CEREBRAL VISUAL IMPAIRMENT, VISUAL DEVELOPMENT, DIAGNOSIS AND REHABILITATION

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CEREBRAL VISUAL IMPAIRMENT, VISUAL DEVELOPMENT, DIAGNOSIS AND REHABILITATION

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Editorial: Cerebral visual impairment, visual development, diagnosis, and rehabilitation

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Editorial on the Research Topic
Cerebral visual impairment, visual development, diagnosis and rehabilitation

Introduction

Cerebral (or cortical) visual impairment (CVI) is a verifiable visual dysfunction(s) that cannot be attributed to any potentially co-occurring ocular condition (Sakki et al., 2018). CVI can manifest in many ways including varying degrees of reduced visual function (i.e., acuity, fields, etc.), as well as visual perceptual functions depending on which part of the brain is impacted (Chokron et al.). Despite the potential long-term ramifications on a child's development and quality of life, there remains an urgent need for evidence-based assessments, diagnostic protocols, and interventions for children with CVI. This special issue includes 18 manuscripts from which three major themes emerged: 1. Current challenges in receiving an accurate and timely diagnosis of CVI, 2. Strides toward identifying risk factors, screening tools, and biomarkers for the multidisciplinary diagnosis of CVI across multiple age ranges, and 3. The potential impact of interventions on outcomes and quality of life in children affected by CVI.

Theme 1: Current challenges in receiving an accurate and timely diagnosis of CVI

As highlighted by Chokron et al., the prevalence of CVI is increasing worldwide, including industrialized and developing nations. Despite the increasing recognition of CVI, distinguishing the consequences of visual dysfunctions from neurodevelopmental conditions, including autism spectrum disorder, attention deficit disorder, and dyslexia, remains challenging. Consequently, the aberrant behaviors may not be recognized as being due to a visual disorder and may therefore be misdiagnosed. The authors highlight the need to provide additional information and training to clinicians for differentiating CVI from other neurodevelopmental or specific learning disorders.

Chokron et al. also provide compelling evidence for the negative consequences that CVI can have on development, including motor function, social interaction, and learning. A comprehensive multidisciplinary assessment may assist to optimally plan intervention and habilitative strategies, which might afford additional opportunities for neuroplasticity. The deleterious effects of a delayed diagnosis are further presented in the study by Goodenough et al.. Through a series of semi-structured qualitative interviews the authors probe how CVI impacts all aspects of everyday life. These interviews emphasize how receiving a diagnosis of CVI can substantially transform the child's ability to access their environment. However, CVI may fail to be recognized, preventing the patient from accessing supports and services for the visually impaired. Recently published guidelines may be useful to gain access to supports (Boonstra et al.).

Theme 2: Strides toward identifying risk factors, screening tools, and biomarkers for the multidisciplinary diagnosis of CVIs

Historically, CVI has been mainly a diagnosis of exclusion, with no standardized diagnostic procedures and guidelines. Subsequently, Boonstra et al. performed five literature searches to determine the level of evidence supporting the use of specific assessments for the diagnosis and referral in CVI. The outcome of searches on medical history and the use of questionnaires, as well as ophthalmological, neuropsychological, neurological, and genetic assessments are presented. These outcomes suggest that specific evaluations can be used to identify those with CVI or at risk for CVI, depending upon the individual patient's age and developmental level.

Parents of children with CVI frequently report a desire for early screening and diagnosis. Along these lines, Kooiker et al. investigated whether it was effective to screen 1 year old preterm children for visual processing dysfunctions (VPD) using neurological history and eye tracking. At 1 year of age, 38% of the children examined were at risk for a VPD, with an increase in abnormal visual orienting functions at the age of 2 years, suggesting that some individuals demonstrate a delayed onset of their visual dysfunctions. On the other hand, evidence from Galli et al., suggests that in children with cerebral palsy (CP), signs of CVI may be more common in younger children as compared to older children. However, this may be in part due to differences in the specific CVI assessments in each study, with the later focusing more on ophthalmological characteristics as opposed to visual perception in the study of Kooiker et al.. Additionally, Wilton et al. provide evidence for potential CVI in children with Down Syndrome, suggesting the need for screening in neurodevelopmental and genetic disorders. Together, these studies provide further evidence supporting the need for early and repeated screening of high risk groups for CVI (including preterm birth, CP, and neurodevelopmental and genetic disorders) before or until at least school age, so that no child is mis- or un-diagnosed and can get the support needed early in life.

Reduced visual acuity and abnormal looking patterns are often the first signs in children that warrant a visual examination by an eye care professional. In their retrospective chart review study, Raja et al. sought to determine whether the discrepancy in visual acuity as measured by preferential looking tests (PLT) and visual evoked potentials (VEP) could serve as a potential biomarker for CVI. The results suggest that VEP acuity exceeding PLT acuity by one or more octaves may be a biomarker for CVI, although this needs to be confirmed in a prospective study in a secondary sample.

It is increasingly recognized that children with normal or near normal visual acuity can have a diagnosis of CVI and present with higher visual dysfunctions as a consequence of brain injury, maldevelopment, or genetic disorders, as well as other causes (e.g., Chokron et al.; Chandna et al.). Unfortunately, CVI in children with good visual acuity often remains undiagnosed. Chandna et al. sought to determine the spectrum of higher order visual dysfunctions in children with CVI and good visual acuity using a 51-item inventory. They propose a subset of 11 questions that may be particularly discriminating for identifying CVI in patients with good visual acuity.

Individuals with CVI frequently demonstrate increased visual latency, requiring more time to perform visual tasks (Barsingerhorn et al., 2018, 2019). In this issue, Tanke et al. investigated the use of the developmental eye movement test (DEM) as a diagnostic aid for CVI. They suggested that, in combination with crowding assessment, the DEM may be a useful addition to the assessment battery.

One of the higher order visual dysfunctions commonly seen in CVI involves motion perception. New evidence from van der Zee et al., suggests that children with brain damage may be at an increased risk of isolated and combined motion perception problems, including global motion, speed of motion, or motion-defined form and this was independent of cognition.

In another article, van der Zee et al. also reported on the correspondence between dorsal and ventral stream dysfunctions, finding a higher proportion of dorsal stream dysfunctions (e.g., challenges with motion perception, visual attention, and visuomotor tasks) in those presenting with ventral stream dysfunctions (e.g., object recognition) as measured by the L94 (as compared to those without object recognition impairments). Of the dorsal stream dysfunctions evaluated, motion perception, and visual attention were more frequently impacted than visuomotor skills. Together, these studies suggest that evaluations should include at minimum an ophthalmological assessment, as well as evaluations of both dorsal and ventral stream visual functions.

The value of MRI in the diagnostic process remains contentious. Sakki et al. sought to determine the association between brain lesions visible on MRI and the level of visual dysfunction in two subgroups of patients with CVI. No anatomical correlates with specific visual dysfunctions were identified, but the authors concluded that neuroimaging may prove valuable for assisting in the diagnosis and identification of those at risk for CVI due to brain injury to the visual processing networks in the brain.

Additionally, ocular imaging tools may be useful for investigating CVI. Lennartsson et al. sought to determine the relationship between brain injury and retinal degeneration. They reported on differential patterns of visual field restriction and OCT (optical coherence tomography of optic nerve head) found across subgroups of CVI, corresponding to diffusion tractography measures.

Eye tracking is becoming increasingly implemented as a potential diagnostic aid for CVI, particularly as it can be implemented in patients with limitations in mobility or verbal communication. In addition to the article by Kooiker et al., eye tracking technology was also used by Mooney et al. in their study. Their "visual ladder" approach for detecting, quantifying, and comparing eye movements may enable a robust and rapid quantification of visual impairment in patients with CVI, including those who have limited verbal abilities. This is important because it is only through objective, quantifiable measurement that one can determine the impact of rehabilitation strategies.

Another feasibility study in this special issue by Almagati and Kran describes a method combining synchronous (remote) and asynchronous assessment and data collection in a pediatric low vision clinic setting. The asynchronous components included recruitment, pre-assessment information, the Flemish CVI questionnaire, Vineland-3 comprehensive parent questionnaire for assessment of age equivalent, and vision function tests, such as contrast sensitivity. The synchronous components were administered *via* Zoom telehealth and included assessment of visual acuity *via* FrACT electronic software and assessment of visual perceptual batteries *via* the CVIT 3-6. This hybrid approach may prove beneficial for both the clinic and research setting, particularly when evaluating individuals who are physically remote from the clinic/research site. They also demonstrate that this approach is indeed possible in the CVI population.

Theme 3: The impact of interventions in CVI

Two articles in this issue focused on a longitudinal evaluation of CVI outcomes following intervention. The first, by Jimenez-Gomez et al., was a retrospective chart review. Their goal was to identify outcome predictors for CVI severity as well as factors associated with a change in their grading scale (based on visual function). The majority of patients in this study had limited functional use of vision (they demonstrated no blink to light or could not fixate and follow), limiting the generalizability of the results across the CVI spectrum.

The effect of intervention was also evaluated by Duke et al.. Their randomized clinical trial sought to determine whether individualized visual support strategies, derived from the insight question inventory, a structured history tool as also investigated by Chandna et al., could improve quality of life outcomes beyond that observed in standard therapy. The results suggest that, although there was no change in generic QoL scores, there was a small but significant improvement in speech and communication subscale following a 6-week intervention period. Further research in this area over a longer timeframe is required.

Conclusion

This Research Topic provides new evidence supporting the diagnostics and rehabilitation of children with CVI. New techniques such as time-related tests with optotypes, eye tracking, OCT, and MRI have been useful to gather evidence in children with multiple disabilities. A more standardized multidisciplinary battery of assessments that may be used for screening, assessment, and diagnosis of

CVI across various underlying conditions will result from further investigations. Applied research on visual acuity measurement appropriate to developmental age as well as other objective measures, such as visual fields, OCT, and MRI, will enable us to increase diagnostic possibilities such that no child with CVI is left undiagnosed and left without access to services in order that they may reach their full potential.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Behavioural Features of Cerebral Visual Impairment Are Common in Children With Down Syndrome

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It is widely recognised that children with Down syndrome have a broad range and a high prevalence of visual deficits and it has been suggested that those with Down syndrome are more likely to exhibit visual perception deficits indicative of cerebral visual impairment. This exploratory study aims to determine the prevalence of behavioural features suggestive of cerebral visual impairment (CVI) occurring with Down syndrome and whether the visual problems can be ascribed to optometric factors. A cohort of 226 families of children with Down syndrome (trisomy 21), aged 4–17, were invited to participate in a validated question inventory, to recognise visual perception issues. The clinical records of the participants were then reviewed retrospectively. A five-question screening instrument was used to indicate suspected CVI. The majority of the 81 families who responded to the questionnaire reported some level of visual perceptual difficulty in their child. Among this cohort, the prevalence of suspected CVI as indicated by the screening questionnaire was 38%. Only ametropia was found to have a significant association with suspected CVI, although this increased the correct prediction of suspected CVI outcome by only a small amount. Results suggest that children with Down syndrome are more likely to experience problems consistent with cerebral visual impairment, and that these may originate from a similar brain dysfunction to that which contributes to high levels of ametropia and failure to emmetropise. It is important that behavioural features of CVI are recognised in children with Down syndrome, further investigations initiated and appropriate management applied.

Keywords: Down syndrome, cerebral visual impairment, CVI, visual perception, refractive error, dorsal stream, ventral stream

INTRODUCTION

This study set out to estimate the prevalence of behavioural features associated with cerebral visual impairment (CVI) among children with Down syndrome (DS) and to identify whether a child's reported behavioural features are related to optometric deficits. This information could help better understand a child's needs and tailor more appropriate and accessible educational strategies.

CVI is one of the most common causes of visual impairment (Kong et al., 2012; Philip and Dutton, 2014; Solebo et al., 2017), responsible for 27–48% of childhood visual impairment in developed nations (Rahi and Cable, 2003; Kong et al., 2012; Chong and Dai, 2014). Difficulties met by children with CVI vary greatly but have been shown to reduce quality of life even in less severe cases (Sakki et al., 2021). Problems arising from CVI in children without DS have been related to the widely accepted model of two visual pathway streams. Damage to the posterior parietal lobes affects dorsal stream functions such as processing the whole visual scene, visually guided movement and perception of motion. This can cause difficulty handling crowded scenes, difficulty seeing moving objects, impaired visual attention and difficulty negotiating steps and uneven flooring (Dutton and Jacobson, 2001; Dutton et al., 2004; Dutton, 2010). Damage to the temporal lobes affects ventral stream functions and results in difficulties with recognition, manifesting as difficulties recognising faces, facial expressions, objects or abstract drawings and difficulty with orientation and route finding (Dutton and Jacobson, 2001; Dutton et al., 2004; Dutton, 2010).

Common causes of CVI include hypoxia, brain injury or infection, metabolic disorders, seizure disorders and *in utero* drug exposure (Philip and Dutton, 2014; Pehere et al., 2018). For many children, visual impairment occurs as a trait of, or in conjunction with, a multitude of complex systemic diseases (Flanagan et al., 2003; Rahi and Cable, 2003; Bodeau-Livinec et al., 2007; Rahi et al., 2009). It has been suggested that there may be an association between CVI and DS (Little et al., 2007, 2009).

CVI can be difficult to diagnose as its symptoms can exist in varying combinations and severities (Dutton, 2010) and many of its characteristics can overlap with other conditions. The known association between CVI and other complex systemic conditions may also present challenges in visual examination.

Children with DS are also at risk of ocular pathology and vision problems such as reduced best corrected visual acuity, poor accuracy of accommodation, a high incidence and magnitude of refractive error with a less successful emmetropisation process, a higher incidence of strabismus, cataract, epiphora and reduced contrast sensitivity compared to typically developing children (Courage et al., 1994; Cregg et al., 2001, 2003; Stephen et al., 2007; Zahidi et al., 2018).

MATERIALS AND METHODS

A total of 221 children with DS aged 4–17 years were invited to take part; 37 when attending the School of Optometry & Vision Sciences to participate in ongoing research (for which written consent was obtained), and 184 who attended the School clinic between 1st November 2016 and 1st November 2018, by means of a letter sent to parents. Parents were invited to complete an online questionnaire, and its completion was taken as consent for the study.

CVI Criteria

The online questionnaire was created using the 51-question inventory by Dutton (2010), that explores difficulties experienced by children in everyday tasks that are vision-dependent. The questionnaire used a scale of qualitative responses; "Never" (score (1), "Rarely" (2), "Sometimes" (3), "Often" (4), and "Always" (5). An option of "Not Applicable" was available and if selected, was removed from the analysis. A positive result (a score of 4 or 5) on three or more of questions 2, 18, 19, 24, and 27 was used as a positive screening for suspected CVI. This 5-question screening tool was determined by those difficulties commonly reported in children with CVI and rarely in those without (Dutton, 2010) and is a reliable diagnostic screening tool (Macintyre-Beon et al., 2012; Philip et al., 2016) with a good construct validity; sensitivity of 81.7% and specificity of 87.2% (Gorrie et al., 2019).

Optometric Data

Retrospective review of participants' clinical records was conducted and eight factors which could impact on the incidence of behavioural features of CVI were identified: age, gender, corrected visual acuity (binocular LogMAR), ametropia (best vision sphere of the least ametropic or fixing eye), magnitude of astigmatism (of least astigmatic or fixing eye), strabismus (present or not), accommodation (accurate or not), nystagmus (present or not).

Ethical Approval

This study was part of a wider longitudinal study in children with DS and had ethical approval from the National Institute for Social Care and Health Research Ethics Service (08/MRE09/46, amendment 5, 7th July 2016).

RESULTS

Population Characteristics

A response rate of 36.7% was achieved; 81 responders. The gender and age of the respondents were compared to those of all invited participants. Gender (55.6% female) and age (4.4–17 years, mean 9.9 years) did not differ significantly from the invited population ($\chi^2 = 0.86$, $p > 0.05$ and $t = -1.53$, $p > 0.05$, respectively).

Participants had a mean binocular visual acuity of 0.29 LogMAR (standard deviation, SD = 0.19), recorded using a variety of tests, based on the child's age and abilities: Cardiff Acuity Test, Crowded or Uncrowded LogMAR Kay Picture Test, Crowded or Uncrowded LogMAR Kay Acuity Test and the Keeler Crowded or Uncrowded LogMAR Visual Acuity Test.

Ten children (12.3%) in the study population had nystagmus and 13 children (16%) manifest strabismus (10 esotropia including 6 fully accommodative, two exotropia, and one vertical tropia).

Accommodative ability was recorded using dynamic retinoscopy; 39 children accommodated accurately, 39 had under-accommodation (all wore multifocal spectacle correction) and three children had inconclusive results.

Choice of refraction method was based on clinical need: static, Mohindra or cycloplegic retinoscopy. The best vision sphere of the least ametropic eye (fixing eye in strabismus) was recorded. There was no correlation between ametropia and age; Pearson, $r = 0.04$; $n = 81$; $p > 0.05$ ($p = 0.72$). The distribution of refraction is shown in **Table 1**.

TABLE 1 | The number of responders falling into each refractive error category.

Refraction	Definition	Number *n*	Percentage % (total *n* = 81)
Emmetropia	−0.75 D to +2.75 D	20	24.7
Hypermetropia only	> +2.75 D	13	16.0
Myopia only	>-0.75 D	1	1.2
Simple astigmatism	One meridian ametropic and the other meridian emmetropic	20	24.7
Hypermetropic Astigmatism	Both meridians hypermetropic	22	27.2
Myopic Astigmatism	Both meridians myopic	5	6.2

The refraction is for the least ametropic or fixing eye.

CVI

Of the 81 children, 31 screened positive for suspected CVI; a prevalence of 38.3%. This report uses the term suspected CVI to mean a positive classification according to the five-question criteria.

Total Score

The raw total score for each participant was attained by summing all question responses and was expressed as a percentage of the total questions applicable for that participant. Both groups were normally distributed (**Figure 1**). The minimum score would be 20% (every question recorded as "Never" and awarded one). No child had a minimum score. The mean total score for children with suspected CVI was 59.5% (SD = 10.5%, range = 41.2–78.8, Shapiro-Wilk $p > 0.05$) and the mean for children without suspected CVI was 44.1% (SD = 10.3%, range = 24.0–67.8, Shapiro-Wilk $p > 0.05$); the difference was significant ($t = 6.286$, $p < 0.001$).

Positive Score

The positive score for each participant was attained by summing the number of positive responses (Often or Always) and expressed as a percentage of the total applicable questions. Of children with suspected CVI, the mean number of positive responses was 36.7% (SD = 17.7%, range = 8.3–76.5%), compared to 13.5% (SD = 11.1%, range = 0–47.1%) among children without suspected CVI. The difference was significant ($t = 7.269$, $p < 0.001$). The range of positive responses is shown as a continuum in **Figure 2**, illustrating the large overlap between those children with and without suspected CVI.

Individual Questions

Figure 3 shows the number of participants whose parents responded positively to each question and therefore highlights the questions that most frequently elicited positive responses and the weighting of suspected CVI and non-suspected-CVI responses for each question.

The 10 questions most frequently eliciting positive responses ("Often" Or "Always") were "Does your child":

2. Have difficulty walking downstairs?

15. Have difficulty seeing things which are moving quickly, such as small animals?

18. Have difficulty catching a ball?

19. Have difficulty seeing something which is pointed out in the distance?

26. Sit closer to the television than about 30 cm?

27. Find copying words or drawings time-consuming and difficult?

29. Find uneven ground difficult to walk over?

37. Find it difficult to keep on task for more than 5 minutes?

38. After being distracted, find it difficult to get back to what he or she was doing?

43. Have difficult behaviour in a busy supermarket or shopping centre?

There were several questions that elicited positive responses equally between children who met the criteria for suspected CVI and those who did not (e.g., 47; Does your child mistakenly identify strangers as people known to them?) and some questions that were responded to positively by large numbers with and without suspected CVI (e.g., 27; Does your child find copying words or drawing time-consuming and difficult)?

There were five questions that elicited responses *only* from children with suspected CVI, although numbers were small:

8: Does your child leave food on the right or left side of their plate?

12: Does your child bump into door/frames or partly open doors?

45: Does your child have difficulty recognising close relatives in real life?

46: Does your child have difficulty recognising close relatives from photographs?

51: Does your child have difficulty recognising familiar objects, such as the family car?

Optometric Factors and Suspected Cerebral Visual Impairment

Each factor was tested independently to determine any association with positive screening outcome for CVI. Continuous factors were tested using a Mann Whitney *U*-Test; categorical factors with a χ^2 test. The raw data for each categorical factor were inspected for outliers. Two data points with refractive errors of −12.00 D and −7.25 D were more than 1.5 × IQR away from the mean and were removed from the analysis.

Of these eight factors, only absolute refractive error (equivalent sphere) was found to be significantly different between those with and without suspected CVI ($p = 0.010$) with two outliers removed. The higher the refractive error, the more likely was a child to screen positive for CVI. To determine whether refractive error is a suitable predictor for the incidence of suspected CVI, a univariate logistic regression was performed. The outcome of the logistic regression is given in **Table 2**.

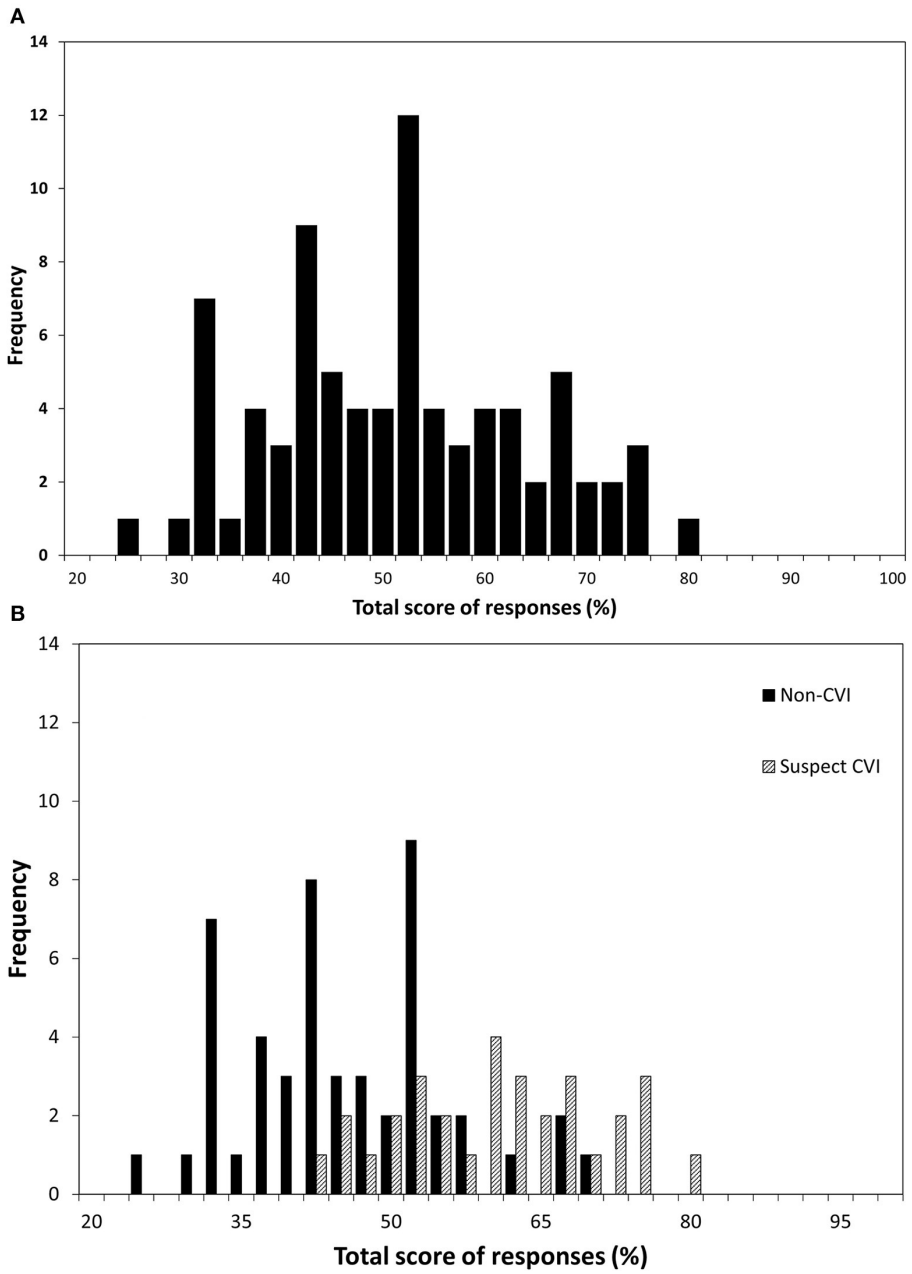

FIGURE 1 | The frequency distribution of the total raw scores in 81 children. The x-axis shows total score expressed as a percentage of applicable questions for **(A)** all children and **(B)** children divided into "suspected CVI" and "non-CVI" according to whether the child screened positive on the five-question CVI screening tool.

However, the model was only able to correctly predict suspected CVI in 62% of cases, compared to the null model's 60.8%.

DISCUSSION

In this sample of children, parents reported a high prevalence of visual perceptual problems including many that have not been previously described in Down syndrome, and that are consistent with cerebral visual impairment. A continuum of CVI-associated behavioural features was observed, in which 93.8% of children exhibited at least one CVI-associated symptom and, overall, 38.3% of children could be classified as suspected CVI, based on the five-question screening criteria. Since sampling bias is possible, the prevalence was calculated, assuming that, at one extreme, all non-responders would screen negative for CVI and, at the other extreme, all non-responders would screen positive for suspected CVI. This reveals that th prevalence of suspected

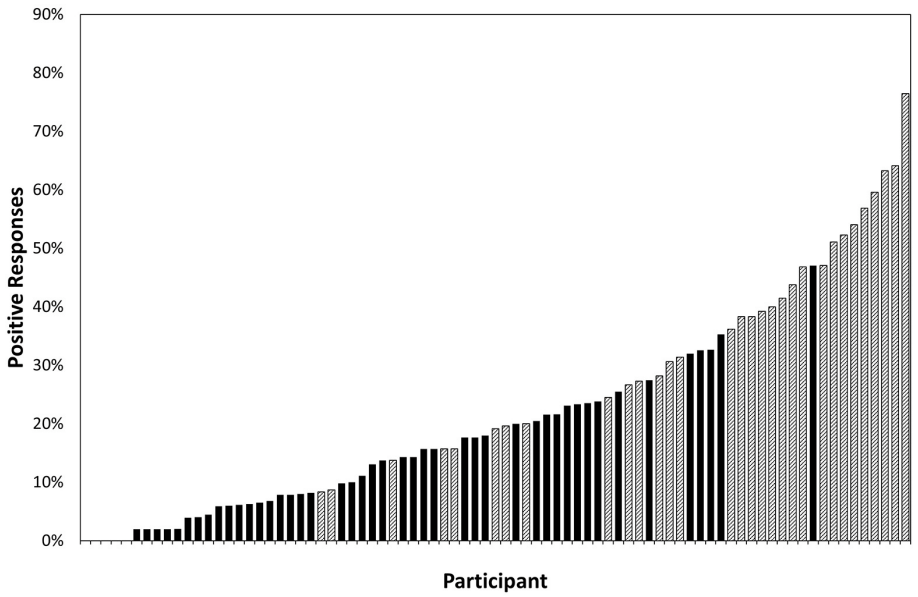

FIGURE 2 | The percentage of questions (excluding those reported as "not applicable") to which each of 81 participants responded positively (a score of four or five on the question inventory) ranked by increasing number of positive responses; crosshatching represents the participants who fitted the screening criteria for suspected CVI and solid fill represents the participants who did not.

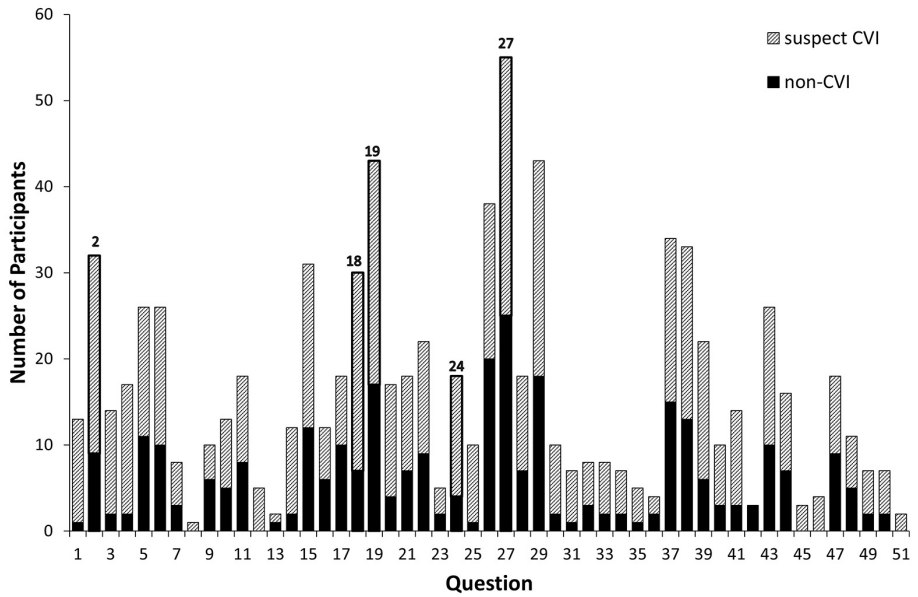

FIGURE 3 | The number of participants (81 in total) who responded positively to each question; crosshatching represents the participants who fitted the screening criteria for suspected CVI and solid fill represents the participants who did not. Questions 2, 18, 19, 24, and 27 are the diagnostic questions used in the CVI screening tool and are outlined.

CVI in a population of children with DS lies within the range of 13.7–77.9%.

Due to differing definitions and diagnostic criteria, a prevalence of CVI in a general population of children is unknown but a recent cross-sectional study using the same five screening questions suggested that at least 3.4% of mainstream primary school children (age 5–11 years old) exhibited at least one symptom of CVI (Williams et al., 2021). Another review, using a different question inventory, also showed a continuum, and visual perceptual difficulties in up to 3.9% of typical 13–14 year olds (Williams et al., 2011). The current study therefore indicates a higher risk of CVI-related difficulties among children with

TABLE 2 | Outcome of logistic regression.

Factor	β	SE β	Wald's χ^2	df	p	Odds ratio (95% CI)
Constant	−1.461	0.487	9.006	1	0.003	NA
Refractive error	0.340	0.137	6.104	1	0.013	1.404 (1.073–1.839)
Test			χ^2	df	p	
Overall model			6.757	1	0.009	
Hosmer & Lemeshow (Goodness-of-fit)			8.700	7	0.275	

All statistics were calculated using SPSS v25.0 (IBM Corp. Armonk, NY, USA). Further descriptive measures of goodness-of-fit given by Cox and Snell $R^2 = 0.082$, Nagelkerke $R^2 = 0.111$.

DS. Positive responses were given to 45 out of 51 questions, suggesting a wide range of symptoms.

The continuum of responses demonstrated in **Figure 2** shows that there is no clear cut-off between children who can be deemed to have suspected CVI and those who cannot. The total score of all children with DS is normally distributed, as opposed to the skewed distribution among typical children (Williams et al., 2011) suggesting that the majority of children with DS exhibit some level of visual perceptual dysfunction.

The full 51 question inventory has been shown to elicit some positive responses from children with autism spectrum disorder (ASD) (Dutton, 2010), but the five question diagnostic criteria have been specifically chosen to represent difficulties associated with dorsal stream dysfunction and have no overlap with the Social Communication Questionnaire, designed to recognise ASD (Gorrie et al., 2019).

Over 50% of this population responded positively to questions 19, 27, and 29 (of which, 19 and 27 are part of the five diagnostic questions), which all represent dorsal stream function. Whilst each question will not be equally likely to elicit a positive response amongst a typical population, it is clear that the most common behavioural features amongst this cohort are related to dorsal stream function. It is more common to find dysfunction of the dorsal stream with an intact ventral stream (Dutton, 2010) but the pattern of responses shown in this study may expose specific impairments related to children with DS.

The use of the diagnostic 5 questions divides the data into two normal distributions (see **Figure 1**), with considerable overlap but different means. This raises the question as to whether the five-question screening tool is appropriate for children with DS or whether alternative questions may result in a more precise distinctions. For example, there are grounds to consider excluding question 27, which elicited a positive response from most participants, and which may represent a characteristic of learning disability in this population. On the other hand, five questions were scored positively only for children with suspected CVI, including ones relating to face recognition. It has already been observed that isolated ventral stream dysfunction is rare and is often combined with difficulties relating to dorsal stream dysfunction (Dutton, 2010). A particular deficit in processing faces in children with DS has been previously described (Wishart and Pitcairn, 2000). The findings in this study suggest that this difficulty with facial recognition may be part of a wider range of impairments relating to CVI. However, the numbers identifying poor face recognition were very low, so these and the other exclusive questions may not be suitable for a screening tool specific to children with DS. Further research is clearly needed to explore identification of a deficit of CVI origin and not related to other impairments, such as learning disability or mobility.

Gender

Male predominance has previously been recognised amongst the DS population and the male to female sex ratio in children with DS has been reported as 1.23 (Kovaleva et al., 2001). Although the current analysis sample has an uncharacteristically high proportion of females, there does not appear to be any gender bias in responders and gender does not appear to be influential on suspected CVI outcome.

Optometric Measurements

The relatively high prevalence of nystagmus, reduced acuity, strabismus and accommodative deficits reported here are consistent with other studies. Analysis showed that none of these functions was predictive of suspected CVI and they are therefore unlikely to be causal factors of the behavioural features. A recent study of children with a diagnosis of CVI and with a variety of risk factors (not including DS) reported that almost half had normal visual acuity (Sakki et al., 2021), confirming that CVI should never be assumed to be limited to children with poor acuity (Dutton, 2021).

Longitudinal studies have demonstrated a failure of the emmetropisation process in children with DS and that large refractive errors tend to either remain stable or increase with age (Haugen et al., 2001; Cregg et al., 2003) in young children, although no large changes to the spherical component of refractive error occur over the age of 4 years (Al-Bagdady et al., 2011). Thus, refractive errors in this study's population of 4–17-year-olds can be considered stable and this was confirmed by Pearson correlation.

Absolute refractive error was the only optometric factor to be significantly different between those with and without suspected CVI. The odds of screening positive for CVI increase by approximately 40% per dioptre of absolute spherical equivalent and children with over 5D of refractive error are more likely to screen positive for CVI than not. However, a model based on refractive error increases the likelihood of correctly predicting suspected CVI by only a small amount. The association between

CVI and refractive error among other groups of children does not appear to have been investigated.

Limitations

Although effort was made to select a random sample, some level of bias is likely present since all invited children were existing patients of Cardiff University's Special Assessment Clinic and may have already been experiencing some sort of visual difficulty. Information such as ethnicity, level of education and income were not collected. No participant had a diagnosis of brain injury, but childhood medical history was not obtained; this could be informative in terms of exposing the underlying cause of behavioural features, such as subtle oxygen deprivation.

Implications

It is clear that visual perceptual difficulties are common amongst children with Down syndrome and that further work needs to be done to understand the origin of the difficulties. Visual perception difficulties have been identified as a potential cause for academic underachievement (Williams et al., 2011), and as children with DS are considered visual learners (Yang et al., 2014) recognition of possible CVI is important in ensuring that these children can access education tailored to their requirements (Dutton, 2021). The findings in the current study would suggest that generally, children with DS tend to exhibit more problems with visual perception than might be expected.

Cognitive impairment is a characteristic of Down syndrome and many of the problems occurring in children both with and without suspected CVI may be attributable to the cognitive impairment. However, the impact of CVI on performance on tests of cognitive ability, which often involve the use of visual attention, spatial orienting, visual perception and visual motor skills (Moore et al., 2002) has not, to our knowledge, been explored. If CVI is present and unrecognised, it may be that a child's cognitive function is at risk of being underestimated.

General Conclusions and Summary

The majority of children with DS aged 4–17 years in this study experienced some level of visual perceptual difficulty and 38.3% met the screening criteria for suspected CVI.

Whilst children with DS are known to have a high prevalence of visual deficits, this study has shown that only refractive error is an indicator of the likelihood of CVI-related behavioural features. It appears likely that CVI is the explanation for the frequent visual perception impairments in children with DS and that further investigations are warranted. Optometric deficits are unrelated conditions that often coincide within this group.

Further research is clearly warranted into the aetiology of the visual perceptual problems that appear so prevalent in children with DS, and the likelihood of a diagnosis of CVI. According to Sakki et al. (2021) "the economic, social, and personal burden of CVI is high, with adverse effects of coexisting disorders increasing the burden further." It is essential that visual problems associated with CVI are explored in the assessment of children with DS, and that difficulties are not simply considered to be due to the learning disability or to inappropriate behaviour. Targeted strategies can be helpful in ameliorating the effects of CVI (McKillop and Dutton, 2008; Tsirka et al., 2020), and these should be considered for any child with DS who exhibits difficulties.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the National Institute for Social Care and Health Research Ethics Service (08/MRE09/46, amendment 5, 7th July 2016). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

JMW supervised the study and contributed to the write-up. GW carried out substantial data collection and did the bulk of the analysis and write-up. RW acted as statistical advisor for the study, did some of the statistical analysis, and contributed to the write-up. VV-N devised the methodology, carried out a proportion of the data collection, and contributed to the write-up. RE carried out a proportion of the data collection and contributed to the write-up. All authors contributed to the article and approved the submitted version.

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Bridging the Gap: Parent and Child Perspectives of Living With Cerebral Visual Impairments

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Cerebral Visual Impairment (CVI) is an umbrella term which includes abnormalities in visual acuity, or contrast sensitivity or colour; ocular motility; visual field and the conscious and unconscious filtering or processing of visual input. Children with CVI have specific needs and problems relating to their development from infancy to adulthood which can impact on their wellbeing. Recent research indicates the complexities of living with CVI but there remains limited information of the full impact of CVI on families' everyday lives. The qualitative interviews reported here explored families' experiences to discover the impact of CVI on all aspects of everyday life. Parents and children (aged 6–18) were invited to participate in semi-structured interviews, either face to face, by phone or video call between January 2018 and February 2019. Topics covered everyday practicalities of living with CVI, focusing on challenges and what worked well at school and home. Interviews were audio-recorded and subject to thematic analysis to look for patterns across the data. Twenty families took part in interviews, with eight children/young people within those families contributing interviews of their own. Four themes were developed from the interviews: (1) Assessment and understanding implications of CVI, (2) Education, (3) Family life, (4) Psychological wellbeing and quality of life. The interviews provide valuable insights into the impact of living with CVI and highlight the need for more awareness of the condition among professionals in both health and education settings.

Keywords: cerebral visual impairment, children, qualitative, vision, visual impairment

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INTRODUCTION

Damage or poor function in areas of the brain related to vision can lead to cerebral visual impairment (CVI) (Dutton, 2003; Fazzi et al., 2007; Philip and Dutton, 2014). Cerebral visual impairment may include loss of peripheral or central visual fields; loss of control over eye movements; difficulty seeing at low contrast and difficulties with visual recognition of objects, shapes or people.

Cerebral visual impairment in children manifests in various ways; including being unable to find things in a cluttered scene; bumping into things; inability to copy from the class whiteboard to their own workbooks or difficulty controlling their eye position effectively to keep focussed on a task (Philip and Dutton, 2014). In primary school aged children, when not fully recognised and understood, these difficulties may be interpreted as lack of understanding, clumsiness or

inattention, or as social and communication difficulties particularly if the child has developmental problems (Swift et al., 2008).

CVI has been reported as the main cause of childhood vision impairment in high income countries and as on the rise in low-income countries (Lueck et al., 2019; Teoh et al., 2021). Our recently published study on the prevalence of CVI in primary school age children suggested that CVI may affect as many as 3.4% of children, with the majority of these already identified as needing extra help at school (Williams et al., 2021). Children with developmental problems and disabilities, who tend to have higher rates of CVI, also have increased risks of additional mental health problems such as anxiety and depression (Davies et al., 2013).

Recent work with families where children and young people have visual impairments demonstrates the importance of listening to and understanding families', children's, and young people's experiences (Tadić et al., 2015; Liebermann et al., 2017; Anderson et al., 2019). Two surveys (initial and follow up) of parents of children with CVI, demonstrated persistent difficulties with obtaining a diagnosis and access to appropriate support (Jackel et al., 2010; Jackel, 2019). The aim of the current study was to understand the broad impacts of CVI for families using qualitative interviews. Our findings contributed to the development of an intervention in English primary schools to support children with CVI, and a set of core outcomes for future researchers to consider when designing interventional studies.

This study was part of the CVI Project[1], a 5-year programme of work involving interlinked studies which aim to increase understanding about CVI and how best to help affected children.

MATERIALS AND METHODS

Parents of children and young people with a diagnosis of CVI, given by a professional, were eligible to participate. Children/young people (CYP) aged 6–18 years were also invited provided their parent/carer or a trusted adult was present for the interview.

Diagnoses of CVI were inclusive, we did not assess children or young people for CVI but accepted parental understanding and report that their child had been given this diagnosis by a professional.

To ensure a range of ages and physical capabilities, purposive sampling identified younger children (6–11 years old) and older (12–18 years old) young people, and those with or without a diagnosis of cerebral palsy.

Families were recruited via: Specialist Teachers for Vision Impairment (QTVIs); The WESC Foundation Specialist Centre for Visual Impairment, Exeter, and the CVI Society – a UK parent support group for families of children with CVI[2]. Recruitment was supported by inviting initial contacts to snowball information to other interested groups and individuals.

Interviews within qualitative research provide the opportunity for in-depth exploration of participants' experiences of their world. Semi-structured interviews while guided by interview topic guides allow for flexibility, offering the participants time and space to discuss and develop the areas that are important to them within the interview structure (Ritchie and Lewis, 2003; Green and Thorogood, 2018). Topic guides and interview methods for this study were developed collaboratively with the CVI Project parent and professional research advisory groups and the Family Faculty at Peninsula Childhood Disability Research Unit at University of Exeter Medical School[3]. Both groups of advisors represented a wide range of experience, including ophthalmologists, orthoptists, special educational needs teachers; community paediatrician and educational psychologist, researchers, and a range of families who had children with CVI and other neurodisabilities.

Families contributed ideas for which areas of daily life to investigate, including asking families to talk about their experiences of living with CVI including what their children enjoy and what they avoid as a way of discovering possible difficulties and how these are addressed and in practical terms offering parents and their children maximum flexibility in timing and mode of interview.

Parents' interviews focussed on day-to-day life for families living with CVI, covering school, home, family and health and wellbeing; practicalities of living with CVI; past support received and what would help in the future.

Children's and young people's interviews covered what they enjoyed about school, home, family life and hobbies; support at home and school including what they liked about this support. Where appropriate, creative activities were offered to help elicit the views of children, including drawing, colouring, and tablet-based art activities. Care was taken to be sensitive to the children's and young people's needs during the interview including being aware when their behaviour might indicate that they wanted to pause or stop.

Following the first interview, the research team reviewed both the interview transcript data and the practicalities of the interview process, to confirm that the topics and approach were flexible and gave families the best opportunity to share their experiences.

Interviews were conducted according to participants' preference either face to face in a location chosen by them; by telephone, or video call, and the audio was recorded with participant's verbal and written consent. For children and young people's interviews, consent was obtained from parents, and children and young people agreed that they would like to take part.

Interview audio recordings were transcribed verbatim, anonymised, checked for accuracy, and imported into NVivo V.11. Braun and Clarke's 6 stage approach to thematic analysis was applied to the transcripts (Braun and Clarke, 2006). This included: initial familiarisation with the data allowed for submersion in the topic area; systematic coding across the transcripts to identify data relevant to each node; nodes were then collated into relevant themes and then the nodes within each theme were revisited to check the goodness of fit within

[1] www.thecviproject.co.uk

[2] www.CVIsociety.org.uk

[3] http://www.pencru.org/getinvolved/ourfamilyfaculty/

each theme and coded extract. Initial analysis was carried out by two researchers who studied the interview data alongside the interview topic guide to identify the nodes and themes within the interviews. The first two transcripts were independently coded by two researchers to cross check the coding and early development of themes. Themes were discussed until a consensus on the description of key themes and subthemes was reached.

RESULTS

Twenty families took part in the interviews. Within these families, eight children and young people contributed interviews of their own. As multiple approaches to recruitment were used, it is not possible to report how many people were exposed to the study invitation or calculate a response rate. The majority of participating families lived in England (16), with fewer from Scotland (1), Northern Ireland (2), and Eire (1). **Table 1** summarises the ages of the children/young people described in the parent interviews, and whether parents described their child as having cerebral palsy or registered as partially sighted/blind.

Twenty parent interviews were completed between January 2018 and February 2019. Seven parent interviews were by telephone, 13 face to face. One parent was interviewed both by phone and contributed again within her child's face to face interview. Of the 8 children/young people interviewed, 1 was by video call, 1 telephone and 6 were face to face. Parent interviews lasted 45 min -2 h, child/young people's interviews were expectedly shorter, lasting a maximum of 30 min. Additional diagnoses for the children, as reported by parents, included: premature birth; cerebral palsy; chromosomal abnormalities; epilepsy; foetal alcohol syndrome; global developmental delay; and autism. Four children/young people were registered as partially sighted or blind.

Themes

Discussions flowed across the interview topic areas, interweaving experiences from home and school presenting a comprehensive picture of the impact of CVI on families' everyday lives. A brief topic guide can be found in **Supplementary Material A**.

The four key themes and associated subthemes generated are summarised in **Table 2**, and described below with illustrative quotes. Children's quotes are included wherever possible, more often representing older children's/young people's experiences as they were better able to reflect on how their visual challenges affected everyday life. Conversations with younger children provided insights into what they enjoyed or found difficult in everyday life, with their contributions often leading to further discussion and interpretation by their parent. A table with additional illustrative quotes for each theme can be found in **Supplementary Material B**.

Key themes

1. Assessment and understanding implications of CVI
2. Education
3. Family life
4. Psychological wellbeing and quality of life.

Assessment and Understanding of Implications of CVI

Recognition of CVI as a diagnosable condition

Parents reported that CVI was not always recognised as a "real" condition, without this recognition parents described challenges accessing the support that their children needed.

> "*But a lot of paediatricians don't believe that CVI is diagnosed, it's a non-diagnosis for them, so that's an issue in itself." Parent 012*

Parents also described how receiving a diagnosis of CVI could transform the environment for their child.

> "*So the only thing that let us down was the ophthalmology department. . .I had to explain every single time that [child]couldn't communicate very well, almost just feel like you're being fobbed off. One woman actually shouted at [child] because she wasn't doing what she was told. . .*
>
> *Researcher: What was it she couldn't do?*
>
> *Just the tests they were asking her to do, her attention was that of a gnat, so me and my husband sat down trawling through papers and papers on Google, and came across thankfully [name of professional] and then she's been our saviour, took [child] to [clinic], literally first meeting [professional] asked all the questions, she asked me the questions first, [child] walked in she was like she's got CVI, and that was it: [child] sleeps in the top bunk, because we put a tunnel over it, so when she's in her bed there's nothing over and that made a massive difference. We made a sensory room under the stairs. . .a little space to go where she had music, and she put lights on. All toys more tactile so that she could actually get out and play with them, she didn't want to play with anything, because everything for kids is visually bright and lovely, take that way, give it a bit more tactile and not so bright and yeah she plays." Parent 017*

Professional knowledge

Parents wanted all professionals assessing their child to fully understand possible impacts of CVI so parents could access the information and support that they and their child required.

> *"very few people, doctors, professionals, look at his vision impairment from a neurological perspective I feel, it's all about can he see this, well yes he can actually see it, he knows it's there, but whether his brain can convert that into any meaningful message or whatever it needs to be I don't think the professionals that we are in touch with understand CVI enough for that". Parent 010*

> *"It's been really nice, [Sense* worker name] do a home visit, and just having that chance to talk to somebody who understands vision and the visual problems, because you don't get that from a hospital appointment about their eyes, because you're just testing them aren't you? But it is really important really to have. . . those visits from [Sense worker] and the Guide Dogs** I can draw on them and that, but[if] I'd never had them that would be quite a big gap I think, and the Great Ormond Street neuro and psychological assessment. . . this guy had never met my kids before, he had them for an hour, he totally sussed them out in that hour. He seemed to have such a good grasp of what their difficulties were and what their strengths were. So having some sort of assessment like that is important because you want to understand what's going wrong, and I think CVI is quite difficult to unravel and understand. It's not like with vision you've got. . . with long and short sighted you've*

TABLE 1 | Ages of the children described in the parent interviews and reported diagnosis of cerebral palsy or registered as partially sighted/blind.

Ages of children who were the focus of parent interviews	Number of children in each age group	Child's Gender		Cerebral palsy diagnosis reported by parent	Registered Blind or partially sighted reported by parent	Number of children interviewed in each age group
		M	F			
3–5 years	2	1	1	0	1	0
6–11 years*	13	8	5	6	2	4
12–17 years*	7	4	3	2	1	4
Total	22	13	9	8	4	8

*In 2 families there was more than one child with CVI.

*got numbers haven't you to tell you this is exactly how short sighted they are, and if they're hearing impaired you know exactly which hertz they can hear, but with CVI it's not that straightforward.". Parent 027*Sense: a UK charity which supports people living with complex difficulties. https://www.sense.org.uk/about/.

**Guide Dogs: a UK charity that provides support for people with sight loss. https://www.guidedogs.org.uk/about-us/.

One young person suggested her condition should be redefined so that professionals would understand the challenges she faced:

"If I was a doctor, I would change it to CCI, cerebral cognitive impairment. . ..There's something called LD, a learning disability, and there's no such thing as CCI though, because it's not just about what you see stuff, it's about how you think, how you process stuff, how you understanding what people are saying to you." CYP 006

Assessment

Early screening or assessment was described as vital to identify and manage CVI immediately any visual processing issues were suspected. Parents also emphasised the importance of incorporating "functional vision" testing within comprehensive assessments where their child's behaviour or additional diagnoses might suggest CVI was present.

"I think that's the key thing because there's so much confusion between autism and CVI specifically because of the poor eye contact, and it seems to be as soon as there's anything wrong with the child they get labelled autistic because that's all people know. So I think the early screening is really important because if he had been misdiagnosed all the wrong strategies would have been put in place." Parent 028

In addition, parents noted the difficulties that arose when individual assessments were completed in isolation, highlighting the need for improved communication between all professionals involved with the child and family.

We need to have people working together. That's the biggest problem she has had all her life is that none of these professionals sit down in a room to discuss. . ..we've had physio, okay this is to do with walking, we've had a physio recommend she carries bags on her sticks, now primarily we're talking someone with balance issues, that's like me giving you shopping bags to ride a bicycle with. We need to get people sitting in a room all talking to each other, because one aspect impacts another, impacts another. . ..We have EH [Education Health Care Plans] stating she needs occupational therapy, stating she needs physio, and you've got them all working singularly. It's ridiculous, why is that so hard? Parent 006.

Education

Discussions about education (at home and within school/college settings: specialist and mainstream), demonstrated the multifaceted nature of the families' experiences. These experiences highlighted the importance of staff understanding CVI; the education assessment process; parents' involvement in their child's education and child's/young person's experiences of their educational settings.

Knowledge

Parents wanted schools to understand CVI and how it affected their child's learning and school life. Particularly how additional

TABLE 2 | Themes and subthemes.

Themes	Subthemes
Assessment and understanding implications of CVI	
	Recognition of CVI as a diagnosable condition
	Professional knowledge
	Assessment
Education	Knowledge
	Assessment
	Additional diagnoses
	Learning and adaptations
	Training
	Specialist support
Family life	
	Information
	Support
	Life at home and the outside world
	Key people "enablers"
	Supporting independence
Psychological wellbeing and quality of life	
	Reduction of anxiety
	Meltdowns
	Increased social inclusion
	Reduction in frustration
	Self-esteem

diagnoses might compound CVI; benefits of individualised adaptations to support learning and the importance of training for all staff and professionals working within schools.

> *"I would like to see the VI service incorporate CVI, I think it's crucial, because there are probably so many children who would benefit from it, and because it's not a known thing I think a lot of things that children with CVI could be put down to other stuff, like sensory processing stuff, or ADHD. So there's a lack of awareness amongst professionals, be they teaching or things like speech and language therapy". Parent 026*

Assessment

Parents reported visual needs assessments were often lacking, or not given enough priority in evaluation of support needs.

> *"One of my main frustrations is about people not knowing about CVI, never having heard of it, not understanding it. For example, at [school] they have a speech and language therapist who has done a report on [child] and it takes into account sensory stuff about distractibility and stuff, but nothing about CVI, because they don't know anything about it." Parent 026*

Additional diagnoses

Where additional diagnoses were present, parents felt visual processing was not always given enough weight or attention. Recognition by educational professionals that CVI may occur in conjunction with other conditions was deemed essential so that all aspects of development and learning were addressed in support planning.

> *". . .people hear a word cerebral palsy and they stop looking, and they think that's fine, they write off his intelligence, I've[also] been told that because I have been looking for more diagnosis, I am making him more disabled." Parent 009*

Learning and adaptations

Parents emphasised the significance of recognising the implications of CVI for children's learning experiences and progress across the whole curriculum (academic, social, and behavioural). Appropriate individualised adaptations were considered crucial for children/young people to thrive, and when present, parents reported positive differences in their child's learning and emotional wellbeing.

> *Researcher: "What sort of things you would say are key?"*
>
> *"The school give her time out, they are fully aware of this CVI. . ..her VI teacher is really keen to make sure that she works, so they have decluttered, everything is very sparse, they put [child] in certain positions that she can see. . ..she's got her workspace which is just plain, and with computers and white boards and when she's in the class they won't use certain boards because they don't think it will help her." Parent 017*

Young people also described the value of appropriate adaptations. This quote from a young person, who is not registered blind, indicates how modifications have helped her.

> *"So another thing is that I don't really read conventionally as in I don't read like use my eyes to read, I get text to speech on the computer, or I use the headphones to listen to the book." CYP 006*

Training

Parents considered all professionals should be trained to recognise how CVI might affect every aspect of the curriculum; reporting that some teachers had not heard of CVI and were thus unable to provide the support required.

> *"Training the schools so they have a better understanding of how to adapt resources and what they can do to help. . .. . ..Yes, if I had a magic wand in an ideal world yes it would, it's everyone, because the TAs [teaching assistants] are the ones that work one to one with the children, so they need it, but the teachers need it as well so they know what to get the TAs to do." Parent 028*

Specialist support

Visual/sensory support teachers were recognised as vital in supporting teaching staff and providing helpful information.

> *"we have really good support from the VI team, they say look this young person needs all this paperwork enlarged, he needs a specific font and specific bold, so the VI teacher was asking [for] the teachers work so she could take it away to get it enlarged. . ..and bring it back so he was actually able to read it." Parent 025*

Parents viewed their relationships with schools as fundamental to their child's progress. Input included practical contributions, e.g., making and supplying adapted learning materials or in some cases, reducing or giving up work to create the time and resources to advocate for their child.

> *"I feel we were lucky that I took extra time off work with [child's name], I spent hours, I coordinated getting some consistency and information sharing for [child's name]. If I hadn't happened to know how to do that, I don't think it would have happened." Parent 012*

Parents described the value of visiting schools to talk to teachers and their child's class about how CVI might impact their child.

> *"I went into his class to do a talk. . ..saying if you want to interact with him you need to come closer, say his name, and then be in front of him, they learnt a lot when I did the talk, because I was able to explain in a suitable format for eight-year-olds that also meant the teacher and the TAs understood a lot more about what was difficult for him." Parent 004*

Following this, the parent noted:

> *"the child's teacher felt after [parent's talk] his friends were more tolerant, and one of his friends came and got round to be in front, and I thought it's obviously clicked with them." Parent 004*

Young people also described support that helped their learning and other school-based activities including developing skills to support life beyond school.

> *"Yeah, because [mobility officer] just helps me go through things, and just being normal and using things people use, and it just helps me break free" CYP 025.*

Family Life

Family life discussions focussed on information and support perceived necessary for their child to reach their full potential. In addition to "assessment," "information," and "understanding of CVI" described in Theme One, in Theme Three parents

emphasised issues more specific for their child to thrive within their family and community.

Information

Parents wanted detailed information of how CVI might affect their children's interactions with their world, not just at diagnosis but at key developmental stages. Information leaflets, videos, or online information, support groups or social media were described as facilitating access to information.

> *"Something upfront to say your child has CVI, this is what it means in terms of physical layout, and this is what it means in terms of content of curriculum, here are things that may help, or if there was three guides one for school, one for home and one for out and about, and these are the things that may help you, these are the equipment you may need, or these are the things that you should request, that would have been very useful." Parent 015*

Support

Enabling parents to make necessary adaptations within the home and community was described as essential. Adaptations included physical alterations as well as enablers/carer support to take children out or to play with them at home. Home visits by specialists including IT support; occupational therapists and QTVIs were viewed as beneficial.

> *"the community VI teacher organised someone to come to our house and look at his IT stuff…. we had some support and help in arranging the desktop icons, the colours and stuff to best suit him as far as we can." Parent 010*

Physical changes to the home facilitated access and independence. For example, one family moved to a bungalow as their child could not manage stairs. Others reported using location stickers or bright tape to identify door openings or routes through the house; introducing cupboards to reduce/hide visual clutter and putting up "tents" to allow for some "down" time when their children got tired.

> *"In terms of CVI, we printed out big red dots, and I asked him where he wanted them stuck round the house, and you do actually see him sometimes tracking to where they are, he uses them to navigate by." Parent 004*

Life at home and the outside world

As part of accessing the outside world, parents described the importance of other people understanding the nature and variability of CVI. For example, for children with additional diagnoses, using a wheelchair for part of the day helped to "preserve" vision for later activities. Support to enjoy local community facilities such as play parks and cinemas was also important, both for the child with CVI and their whole family helping to maintain "normal" family life and activities.

> "*sometimes… actually we transferred him to sit in his wheelchair for a bit because it preserves his vision for longer in the day, we know that because he's got the physical and the visual tiring going on, if he tires himself out too much, we know that everything deteriorates*". *Parent 004*

> "*Yeah, every part of that jigsaw needs to fit so that every part of that child's network understands this, they get that holistic view, and CVI should be a part of it, absolutely should be a part of it.*" *Parent 013*

Key people "enablers"

Active involvement and good relationships with professionals including QTVIs, ophthalmologists with knowledge of CVI and occupational therapists were reported as essential and in some cases transformational.

"*I am lucky I wasn't happy, and I found [QTVI name]…….via the Internet, Google, just basically I was [looking for] an ophthalmologist for children who can't communicate, I didn't know anything about CVI at that point, 'I need somebody who can deal with a child who has got learning difficulties.' Thank God I did, because without [name] we would never have a diagnosis.' Parent 017*'*We have got the paediatrician she is one of the best ones around in the county, she's brilliant. I say I want something [clicks fingers] it's done within… brilliant…we were struggling with [child's] walking, but I don't know whether that is visual as well as a mix with her over supple limbs, but she shuts off, and the paediatrician said, "Would you like a pushchair?" I was like well I don't know whether it would make a difference, but within two days I had pushed her, and my God it did make a difference, it's like a comfort blanket for her. So she will walk quite happily, but when something is too much, whether it's over crowded, she's in this pushchair and she is a different child, she is back to [child's name] again." Parent 017*

Supporting independence

Understanding the social world including recognising family and friends; encouraging friendships and negotiating the outside world were all considered important facets of developing independence. These were often facilitated by parents themselves, but additional specific support was also described.

> *Researcher: "Is the person from the 'Guide Dogs' trying to help with his independence?*
>
> *Oh yes, at the moment, they found that if he wears a baseball cap that helps apparently, helps keep him focused when they are out." Parent 009*

Psychological Wellbeing and Quality of Life

Parents and young people highlighted how their psychological wellbeing and quality of life could be affected by CVI. Parents described the importance of reducing anxiety, increasing social inclusion, reducing frustration, recognising causes of "meltdowns"/tantrums; and increasing self-esteem. Parents acknowledged that some issues their child faced were not solely due to their visual difficulties but involved interactions with other conditions including cerebral palsy or autism.

Reduction of anxiety

Parents recounted how their child's anxieties affected their ability to access many aspects of everyday life, within both community and educational settings

> *"when they were doing activities like something crafty, she would find that really stressful because they did everything on the floor, and that didn't help her at all, she had no defined space. She was*

worried about being able to find her equipment again if she had to get up and go and get something, that was really stressful for her." Parent 007

Meltdowns

Parents explained meltdowns often occurred at home when their child had "held everything together at school" or when they just felt overwhelmed coping with the activities of everyday life.

"I think school do that less well, and that's why we get the meltdowns, as he gets more tired, like any child would, he's got extra factors going on." Parent 004

"He said a few things like that, there's clearly some kind of link between the loud noise and disturbing his vision and things.. . ..he was coming home [from school] and having massive meltdowns, because he is exceptionally good at masking and appearing to be okay and managing, he would hold it together at school absolutely." Parent 012

Increased social inclusion

Parents expressed the importance of enabling increased participation in social activities at home, in local communities and at school. Successful activities included horse riding, football, swimming, carriage driving, and access to community facilities such as shops and local parks. Support from family and external agencies was described, the latter seen as particularly beneficial for older young people's independence.

"he has a personal assistant, and she takes him out and she's well aware of his needs. So, he has some good quality time with her, she takes him to the cinema, or bowling, or walking or to the park, or to the pub just for a meal." Parent 025

One young person also reported how support from a mentor had increased their ability to handle social situations:

Well basically in the other school, I had a mentor and she helped me to come out of my shell a lot more, and by going through a booklet and saying what to say and what not to say, and basically that gave me that confidence. CYP 025

Reduction in frustration

Reasons for frustration included not being able to join in with everyday activities, challenges for learning and difficulties with social interactions. Reducing frustration was often the goal for strategies to support the child.

"he was a bright child but couldn't access the schoolwork, because it was too cluttered, it was written work,. . . it was everything he can't do, and his behaviour was because he was getting frustrated, and he was getting angry, and they weren't helping." Parent 009

"[Name] cannot travel independently outside of the home. She is unable to read a bus timetable or plan a bus route or navigate herself to her bus stop. This causes frustration, isolation, limits her ability to be socially included and impacts her self-worth and self-esteem." Parent 006

Self-Esteem

Parents and older young people described how self-esteem was affected by experiences of managing everyday life with CVI.

This is another thing that's coming through all the time, she's identifying this or her difficulties, as stupidity, and that's really sad' Parent 006.

"The first thing now is I get accepted as a person, I am not treated like a young child, I am treated like me. But because of the [special] school I'm in even the students they understand me as a normal person. . .and now my self-esteem keeps getting up every time." CYP 025

DISCUSSION

The semi-structured interviews offered parents flexibility to discuss the breadth of their experiences together with describing more detailed aspects of living with CVI. A strength of this study is that young people with CVI were also invited and encouraged to participate where they could, providing valuable insights and perspectives of how their condition affects everyday life.

Parents emphasised the importance of all professionals involved with their child recognising and understanding the complexities of CVI. Linked to this, parents reported that having a diagnosis of CVI within a comprehensive assessment enabled their access to appropriate interventions and support within education and community settings. Some parents reported the difficulties and frustrations of being left to seek out knowledge about their child's visual difficulties themselves, which were then compounded by professionals (health and education) not accepting this knowledge. Where no diagnosis was offered, or they were offered what they perceived as incorrect or incomplete explanations for their child's difficulties, parents described how their children/young people were missing out on opportunities that might otherwise be available to them, with the attendant effects on family life.

A recent review of quality of life in parents (whose children had a range of visual impairments) concluded that that parents require better and more extensive information and guidance to understand the diagnosis of their child's condition, more information about resources and services available and support to manage and adjust to the situation' (Lupón et al., 2018). McDowell (2020) also notes how crucial timely, accurate and informed diagnosis is to enable parents to become advocates for their child (McDowell, 2020).

Parents' experiences of their child's journey through education highlight the gaps they observed in knowledge, assessment and provision of appropriate settings and adaptations. Our study involved a self-selected group of informed parents, who were active in bridging the gaps in provision. However, this leaves open the possibility of a significant inequity for families without the support, resources, and capacity to do the same for their own children. Future research should investigate the potential for inequalities in provision.

Children and young people described their experiences of school, and how appropriate adaptations enhanced or enabled their access to education including the benefits of small teaching hubs, adaptations within the classroom including using tablets and access to appropriate teaching assistant support. Families underlined the importance of all professionals

involved with their child understanding the interactions of additional diagnoses with their CVI so that both could be managed effectively.

Accounts of home life including barriers and facilitators to accessing the community and developing independence, along with social inclusion stressed the importance of these aspects of everyday life to parents and young people. Our findings echo other research with young people who have visual impairments and other childhood disabilities, for example the importance for young people of social inclusion and appropriate adaptations to support independence and participation (Foley et al., 2012; Tadić et al., 2015). Our interviews also revealed some strategies that children had developed for themselves to manage their visual environment, including a young girl who changed for PE next to the boys so that she could identify her clothes more easily and a young person who took out most of the "clutter" from her bedroom to moderate her environment.

Children's and young people's psychological wellbeing, particularly the importance of understanding and recognising and managing anxiety and frustration was raised across many aspects of everyday life. Parents described the significance of misreading or misunderstanding their child's behaviour by those around them including teachers, as this could lead to increased distress and "meltdowns" particularly in younger children. For older young people important aspects of psychological wellbeing included not being judged, being accepted as "themselves" and having appropriate support at home and in education to manage challenges faced by CVI and additional diagnoses. Other studies where young people express their concerns and experiences report similar findings including frustration at being restricted in some school activities (Khadka et al., 2012), anxiety about asking for help (Rainey et al., 2016) and lack of understanding from others of visual impairment, especially when it is not an obvious impairment (Tadić et al., 2015). In our study, parents and young people emphasised the importance of self-esteem including the importance of "feeling normal" not being classed as "stupid."

Many of the families in this study were involved in national support groups or support organisations for families, and children with CVI, and could therefore be characterised as having a greater awareness of the issues raised in the interviews Full demographic information, including socioeconomic status and ethnicity were not collected at the time of interview. For future work it would be important to include a larger sample of families, including inviting those from a wide range of ethnicities and all socioeconomic groups, in order to explore and assess their experiences of CVI in everyday life. The themes reported highlighted many similarities within families' experiences of everyday life despite the wide geographical area and range of additional diagnoses. Our findings resonate with families' experiences reported in earlier work (McKillop et al., 2006; Jackel et al., 2010; Jackel, 2019) indicating the continued nature of challenges families still face.

Involving children and young people in exploration of how CVI might affect their everyday lives provided valuable insights into their lived experiences at home and at school. The interviews were designed to include as many children and young people as wanted to participate. Eight children/young people took part in individual interviews. In another four interviews, the children were present some of the time, and joined in with the family interview when encouraged to by their parent/s. The children and young people who took part in individual interviews always had a parent present, and it is possible that this affected their responses. Recent qualitative research that suggests it is important to note that children's and young people's concerns are not the same as those reported by their parents and professionals (Rainey et al., 2016). Further work to explore children's and young people's experiences of CVI would be valuable.

In conclusion, our interviews demonstrate the value of listening to parents, children, and young people as they describe the wide-ranging impacts of CVI on every aspect of their lives, and how they address the issues that they face daily.

Our interviews provide important first-hand accounts of the impact of living with CVI. Parents described in detail their perspectives of how they enable and support their children to participate in all aspects of their daily life, often bridging the many gaps that they have identified in health care, education, and support.

Our study highlights the need for comprehensive joined up services, where effective communication between families, schools and health professionals, and continuity of support could provide more families with the help they need. A first step toward this would be to increase professionals' awareness of the possibility of CVI and provide appropriate and timely access for families to comprehensive and multidisciplinary assessments that can identify visual issues.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are not available, as we do not have consent from families who took part in this study to share these for other research purposes.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the University of Bristol Faculty of Health Sciences, Research Ethics Committee (FREC) reference: 58441 December 12, 2017. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

CW devised the study with support from AP and TG. Interviews were carried out by TG, coding and analysis by TG with support from AP. Themes and structure of the final analysis were agreed by all authors. The manuscript was drafted by TG with significant contributions from AP and CW. All authors have agreed this final submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnhum.2021.689683/full#supplementary-material

Supplementary Material A | Topic guides for parent/carers and young people.

Supplementary Material B | Additional illustrative quotes for each theme.

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BRIEF RESEARCH REPORT
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Implications of a Remote Study of Children With Cerebral Visual Impairment for Conducting Virtual Pediatric Eye Care Research: Virtual Assessment Is Possible for Children With CVI

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The Pandemic of 2020 impacted conducting in-person research. Our proposed project already had an asynchronous online component but was later morphed to add a synchronous online component, thereby eliminating the need for in-person assessment. The project compares the results of various tests between a group of children with Cerebral Visual Impairments (CVI) (N = 4) and an age-matched sample of children without CVI (N = 3) from a pediatric low vision clinic. This model was trialed with a small convenient sample of typically developing children in the same age range (N = 4). Given the positive feedback, recruitment for the larger study was done *via* encrypted e-mail rather than through traditional mailing. The asynchronous components included recruitment, pre-assessment information, the Flemish CVI questionnaire, Vineland-3 comprehensive parent questionnaire for assessment of age equivalent, and vision function tests, such as contrast sensitivity. The synchronous components were administered *via* Zoom telehealth provided by necoeyecare.org and included assessment of visual acuity *via* the Freiburg Visual Acuity and Contrast Test (FrACT) electronic software and assessment of visual perceptual batteries *via* the Children's Visual Impairment Test for developmental ages 3–6-years (CVIT 3–6). Our virtual testing protocol was successful in the seven participants tested. This paper reviews and critiques the model that we utilized and discusses ways in which this model can be improved. Aside from public health considerations during the pandemic, this approach is more convenient for many families. In a broader perspective, this approach can be scaled for larger N studies of rare conditions, such as CVI without being confined by proximity to the researcher.

Keywords: cerebral visual impairments, pediatric eye research, assessment, synchronous, asynchronous

INTRODUCTION

Telehealth refers to the use of digital modalities to access information which in turn allows the clinician to provide healthcare services remotely. These remote means typical fall under video calls (real in-time/synchronous audio and video communication), audio calls and asynchronous/email communication with the patient (Board on Health Care Services and Institute of Medicine, 2012). Technological advancement facilitated the development of telehealth. The first technology-assisted remote diagnosis took place in 1948 where a radiology photograph was sent *via* telephone across a distance of 24 miles (Gershon-Cohen and Cooley, 1950). The birth of the internet expanded the use of telehealth *via* creating a global communication network. Caffery et al. (2019) reviewed 78 articles of tele-ophthalmic models of eyecare. They reported that the majority of services were either for general eyecare or emergency services. The authors also demonstrated that tele-ophthalmology is feasible for screening, consultation and follow-up care of various ophthalmic conditions. The novel global acute respiratory syndrome, that result in the Coronavirus Disease of 2019 (COVID-19) pandemic, caused a spike in telehealth medical services. Telehealth services complied with the Center of Disease Control (CDC) quarantine and social distancing guidelines. Now, multiple venues/platforms are available which are compliant with Health Insurance Portability and Accountability Act (HIPPA). These include Zoom for Healthcare (©Zoom, Inc. San Jose, CA, United States), VSee (©Sunnyvale, CA, United States), and Doxyme Pro (©LLC, Salt Lake City, Utah, United States). While telehealth medicine may have some benefits over in-person delivery of medical services, in which it is convenient, cost-effective especially for routine examination, it is limited in the scope of care provided, licensing and insurance coverage. In response to the COVID-19 pandemic, human subjects research has either shutdown/paused or adapted necessary changes to accommodate safe clinical practice (Mourad et al., 2020). This paper describes adaptation of a model for both synchronous and asynchronous data collection for a pediatric eye care research project. This approach may be particularly valuable for gathering large group data for clinically significant but rare conditions, such as CVI.

RESEARCH DURING THE PANDEMIC

The current pandemic greatly impacted the research processes which pushed researchers to find innovative ways to move forward with remotely based research models while adhering to rigorous research practices. This required major protocol and procedural changes. In recruitment, written consent changed to electronically obtained consent. In addition, internet access automatically became an inclusion criterion. We had originally planned to conduct a study to evaluate visual perceptual abilities in children with cerebral visual impairments (CVI) vs. children with ocular and/or ocular-motor disorders only *via* two CVI tools (Vancleef et al., 2020). Sakki et al. (2018) defined CVI as a verifiable visual impairment which is not attributed to anterior visual pathway pathology and/or ocular disorders. However, in-person research was no longer feasible due to public health considerations during the pandemic. We developed and trialed a virtual model in a small sample of typically developing young children. The feasibility of the remote applicability of the synchronous component: the FrACT and the CVIT 3–6 and the asynchronous component: The Flemish CVI questionnaire and the Vineland-3 Comprehensive parent questionnaire was evaluated. The pilot study consisted of four participants ages 3–5 years old, success was defined as successful completion of research tasks in at least 75% of participants. Upon review of the pilot data, we determined to proceed with the same approach for the CVI study. The CVI study had a total of seven participants, four of which had a previous diagnosis of CVI. The diagnosis was made at NECO center for eye care at Perkins by Drs. Barry Kran and Nicole Ross. Caregivers provided digital copies of signed informed consent and assent in accordance with the Declaration of Helsinki. The experiment protocol was approved by the institutional review board of New England College of Optometry. Description of material and method is provided below.

METHODS

FrACT Visual Acuity Version 3.10.5

The FrACT is a validated electronic software which was mainly developed for research purposes in order to obtain more precise acuity measurements (Bailey and Lovie-Kitchin, 2013). The acuity test optotypes are letters presented with a fixed number of trials (Bach and Schäfer, 2016).[1] The presentation sequence follows an adaptive staircase method to determine threshold (Bach, 2006). Schulze-Bonsel et al. (2006) found that visual acuity results of ETDRS and FrACT closely agree.

The visual acuity of the child was measured binocularly while the participant was wearing their habitual distance correction. The caregiver was instructed to have a millimeter ruler and a tape measure to calibrate test distance for the FrACT Visual Acuity test. A printable millimeter ruler was attached to the invite email.[2] To assess visual acuity we used the Landolt-C Acuity. Although the FrACT Landolt-C has eight possible orientations, a two-forced choice method Up/Down (vertical) was utilized. We eliminated orientations with Left/Right (horizontal) components due to recent experience during telehealth visits which found the vertical two-forced choice method to be more effective, efficient, and more likely to maintain patient interest than the four-choice paradigm.

CVIT 3–6

The CVIT 3–6 is an objective assessment tool that uses a simple matching paradigm to assess the child's visual perceptual abilities. We followed the same procedure guidelines provided

[1]https://michaelbach.de/fract/

[2]https://www.readers.com/blog/wp-content/uploads/2016/07/Rea-PrintableSizeRuler.pdf

by Vancleef et al. (2019). Although, the investigators performed this test in an in-person setting. This test was accessed by the examiner with the internet link[3] and shared with the participant's caregiver and the participant *via* Zoom for Telehealth screensharing. In order for the investigator to observe the child's responses during testing, aside from the camera in the device the child was viewing, an auxiliary smart device (e.g., cellphone or tablet) was utilized positioned appropriately by the child's caregiver for the examiner to have an additional view of the child during testing. The instruction given to the participant was to match an object with the object in a set of three alternatives. Any indication of a response was accepted: simple pointing to the matching object, tapping on the object on the screen, or a verbal response, or using the computer mouse. The examiner ensured that the participant responded to all test trials by friendly encouragement. Breaks were allowed after completion of the first domain and the number of breaks were recorded at the end the test. Scores were recorded for participants who successfully completed the test. The highest possible score is 70. Scores lower than 53 are considered below normal and possibly indicative of CVI. The CVIT 3–6 automatically calculates the overall score and constructs a graphical representation of scores across 14 subtests.

The Flemish CVI Questionnaire

This is a validated questionnaire which consists of 46 binary closed-ended questions completed by the child's caregiver (Ortibus et al., 2011a,b; Itzhak et al., 2020). The information from this survey is useful for characterizing behavioral difficulties, particularly regarding vision for action, vision while moving, and spatial orientation, which provides evidence for the possibility of CVI. The parent checks the most appropriate response for each item. The possible responses are: agree, disagree or NA (not applicable). Under normal circumstances, the questionnaire is available as a hard copy and is filled by the caregiver. Due to the virtual nature of this study, Redcap, a secure web forum for creating and managing online databases and surveys, was used to obtain a digital version of the questionnaire that can be accessed remotely.[4] The finished online version of this questionnaire was reviewed and approved by Nofar Ben Itzhak, MSc and Els Ortibus, Ph.D. through personal communication.

The Vineland-3 Comprehensive Parent/Caregiver Form

The Vineland-3 is a standardized measure of adaptive behavior, that is, the things that people do to function in their everyday lives (Sara et al., 2016). It is available in digital form which provides two delivery options: on-screen administration and remote-administration *via* email invites. The Vineland-3 is designed for mental health specialists, educators, and other professionals to use. It automatically generates a simple scoring and interpretive report eliminating the need for interpretation by certified/specialized personnel. Ability measures focus on what the examinee can do in a testing situation while the Vineland-3 focuses on what they actually do in daily life. The Domain Level tests four adaptive behavior domains, Communication, Daily Living Skills, Socialization, and Motor skills. Because it is a norm-based instrument, the examinee's adaptive functioning is compared to that of others of their age. Age equivalent scores are derived from the subject's measured raw scores in reference to the normative sample median. The electronic Vineland-3 was completed by the subject's caregiver *via* a computer or a smartphone. Developmental age equivalence was derived from the Vineland-3 results to assign the participant to the appropriate age group. We utilized bootstrapping (a resampling method) around the median of the raw scores reported of the four adaptive behavior domains to obtain the developmental age.

RESULTS

Parents and caregivers of all participants were able to follow calibration instructions with ease. The FrACT visual acuity test was completed, instruction and explanation times included, in under 30 min. **Table 1** shows individual acuity levels in the CVI and non-CVI groups respectively. Reported acuity levels are those obtained *via* the FrACT during the study and previously measured visual acuity obtained *via* reviewing the participant's medical file.

Summary of data collected in the three assessment tools (CVIT 3–6, Flemish questionnaire, and the Vineland-3) are provided in **Table 2**. Results of the Vineland-3 are shown as age equivalent values in months. Chronological age is also shown on the table to give the reader an idea of the discrepancy between chronological age and age equivalent in the two groups. One participant in the CVI group could not completed the CVIT 3–6 as tasks became more difficult (indicated as NA in **Table 2**).

DISCUSSION

Results of our small n study support the feasibility of adapting virtual models in data collection for various pediatric eyecare research projects. The FrACT visual acuity test calibrates for both screen size and distance from screen. In this project, the caregiver provided the measurements of both the calibration line (for screen size) and the distance from the screen. The researcher then entered that information into the settings screen prior to testing the child, thereby ensuring measurement accuracy. While the FrACT acuity system was validated for in office assessment (Bach, 2006), its use for remote assessment was not evaluated. In **Table 1** we show VA levels of participants as indicated on their medical file vs. on the FrACT. However, it is worth noting that VA levels on file do not serve as a control since some were updated years ago and/or used symbol charts and not optotypes. For the future, we recommend a validation study of the use of the FrACT in this manner.

Although the CVIT 3–6 was performed remotely, it closely followed the same procedure suggested by Vancleef et al. (2019) with only one exception which is the child was observed

[3]https://psytests.be/clinicians

[4]https://redcap.neco.edu/redcap/surveys/?s=M9FXR9NC48

TABLE 1 | Summary of participants medical history and clinical characteristics.

Subject	VA on file (logMAR)	VA type	FrACT VA (logMAR)	Diagnoses and medical history	Ocular history
1	0.42	Symbol acuity*	1.2	CVI, Tuner syndrome, foveal hypoplasia, premature birth	Pendular nystagmus, derivational amblyopia
2	0.30	Symbol acuity	0.15	CVI, borderline microcephaly, hypotonia, full-term birth, global developmental delay	Left intermittent exotropia
3	0.40	Symbol acuity	0.88	CVI, FOXP1 syndrome, autism, PVL, developmental delay	Nystagmus, high hyperopia, astigmatism, partially accommodative strabismus
4	0.30	Letter acuity**	0	CVI, presumed *in utero* stroke, motor and language delay	Right visual field neglect
5	0.18	Symbol acuity	0.15	Full-term birth, Autism	Anisometropic hyperopia
6	0.18	Symbol acuity	0.04	Unremarkable, full-term birth	Exophoria
7	0.18	Symbol acuity	0.18	Left unicoronal craniosynostosis, speech delay	Anisometropic astigmatism, amblyopia

**Symbol acuity: Lea symbols. **Letter acuity: Snellen E.*

TABLE 2 | Summary of collected data in all participants.

Subject	Flemish percent abnormal (%)	CVIT 3–6 score	Age equivalent (months)	Chronological age (months)	Diagnosis
1	8.66	42	73	40	CVI
2	11.36	65	39	61	CVI
3	12.87	NA	21	67	CVI
4	6.28	61	66	69	CVI
5	1.88	68	75	91	Non-CVI
6	0	62	52	49	Non-CVI
7	0	64	30	57	Non-CVI

via cameras. That said, the child's attention may impact data collection. Since the child is in a familiar environment during their regular days, they might express less interest in following the clinician and in this case the investigator's instructions. Especially that a digital screen is the sole means of communication. Environmental distractors included the use of toys or food (e.g., candy) by the caregiver as encouragement for the child during the test. Furthermore, technical issues can slow down the process which could negatively impact the child's interest.

The Vineland-3 already had the option for remote asynchronous data collection. Its automatic generation of easily understood reports allow for this tool to be utilized by educators and professionals. Parents were encouraged to reach out to the principal investigator for any questions they might have filling out the questionnaire, particularly since the Vineland-3 is a lengthier and more comprehensive questionnaire. In the trial study which included mostly children of the faculty at New England College of Optometry, one parent reached out for clarification regarding the questionnaire. However, none of the caregivers in the CVI study had done so. This is one limitation of remote administration of questionnaires as it is expected that caregivers are less motivated to ask questions when completion the Vineland-3 without immediate access to the research.

We piloted the virtual version of this project during the summer of 2020. Patient recruitment occurred in the fall and early winter of 2020 and finally in January 2021. The low response to participation is postulated to be related to the combination of access to devices, stress of managing the household's access and use of devices for school and work and otherwise caring for their children while being employed. It is anticipated as the pandemic wanes, there will be more flexibility to participate in remote studies, such as this one.

Remote testing is a cost-effective approach to improve timely access to care and early screening for CVI, especially in remote rural areas that might not have access to in-person care facilities. However, our study is limited by the low number of participants recruited. Furthermore, The adopted approach is limited to families who have access to digital devices and to a stable internet connection.

In conclusion, this study shows that virtual testing of young patients using complex tools is feasible in pediatric eye research. The model we adapted is more convenient for many families. In a broader perspective, such model can be scaled for larger studies of rare conditions, such as CVI without being confined by proximity to the researcher.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the NECO Institutional Review Board. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

RA: design of the manuscript, writing, and editing. BK: writing and editing. Both authors contributed to the article and approved the submitted version.

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ORIGINAL RESEARCH
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Clinical Assessment of Visual Motion Perception in Children With Brain Damage: A Comparison With Base Rates and Control Sample

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Aim: In this study, we examined (1) the presence of abnormally low scores (below 10th percentile) in various visual motion perception aspects in children with brain damage, while controlling for their cognitive developmental delay; (2) whether the risk is increased in comparison with the observation and expectation in a healthy control group and healthy population.

Methods: Performance levels of 46 children with indications of brain damage (M_{age} = 7y4m, SD = 2y4m) on three visual motion perception aspects (global motion, motion speed, motion-defined form) were evaluated. We used developmental age as entry of a preliminary reference table to classify the patient's performance levels. Then we compared the percentages of abnormally low scores with percentages expected in the healthy population using estimated base rates and the observed percentages in the control sample (n = 119).

Results: When using developmental age as reference level, the percentage of low scores on at least one of the three tasks was significantly higher than expected in the healthy population [19/46, 41% (95%CI: 28–56%), p = 0.03]. In 15/19 (79% [95%CI: 61–97%] patients only one aspect of motion perception was affected. Four patients performed abnormally low on two out of three tasks, which is also higher than expected (4/46, 8.7%, 95%CI: 2.4–20.8% vs. 2.1%; z = 2.61, p < 0.01). The observed percentages in the patient group were also higher than found in the control group.

Interpretation: There is some evidence that children with early brain damage have an increased risk of isolated and combined motion perception problems, independent of their performance IQ.

Keywords: motion perception assessment, global motion, motion defined form, motion speed, performance age, PIQ, Performance IQ

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INTRODUCTION

Many aspects of a child's (normal) development, such as emotional, cognitive, social, and physical development, are interconnected. From birth onward, a child starts to integrate different sensory modalities, such as hearing and seeing, to interact with its surroundings. When focussing on visual processing, good visual acuity resolves small details of a retinal image, and the extent of

the visual field supports the development and interaction between the oculomotor system and the visual world. Next, brain networks are formed for visual perception, i.e., the ability to recognize and interpret visual aspects of the surrounding environment. During normal development, the development of visual functions depends on the integrity of the eyes and extensive brain networks. If brain damage is present or brain development is hampered, the development of one or more visual functions might be disrupted. The child might be less able to recognize object representations (Vuilleumier et al., 2002; Atkinson et al., 2003; James et al., 2003; Eger et al., 2007), and/or faces (Atkinson et al., 2003), it might have problems with visual attention (Pollmann et al., 2003; Marini and Marzi, 2016), visuomotor integration (James et al., 2003), and/or motion perception (Sunaert et al., 2000; Braddick et al., 2001; Marcar et al., 2004; Stiers et al., 2006; Klaver et al., 2008), even when visual acuity and the visual field developed normally. If one or more of these visual functions are impaired due to brain damage or brain dysfunction a child can be diagnosed with cerebral visual impairment (CVI) and can be considered visually impaired. The presence of (congenital) visual impairment or blindness puts a child's development of social, communication, cognitive, and motor skills at risk (O'Donnell and Livingston, 1991; Dyck et al., 2004; Brambring, 2007; Houwen et al., 2007, 2008; Tadić et al., 2010) and therefore early intervention and habilitation is considered important.

The importance of motion perception, the ability to recognize and interpret dynamic visual information, is clearly illustrated by the case study of an adult with acquired brain damage (Zihl et al., 1983): LM was unable to visually control the changing fluid level while pouring a drink, to read other persons intentions while they walked through the room and to cross a road. Additional studies in monkeys and human adults suggest that the ability to perceive motion might indeed influence the level of performance on daily activities. A study in monkeys (Born et al., 2000) suggest that the perception of global motion, the segregation of moving objects from the background and fixating and following an object relies on the integrity of the middle temporal area (MT). Global motion perception and smooth pursuit seem essential in humans playing ball sports, i.e., being able to track and predict a ball's course before catching or hitting it (Land, 2006). Car driving performance seems to be related to multiple motion perception abilities, the performances on a motion-defined form task and a 3D speed discrimination task (Wilkins et al., 2013) and a global motion task (Wood, 2002).

Although these studies suggest a meaningful relation between motion perception abilities and daily activities, motion perception assessment with computerized tasks is currently uncommon in clinical practice. Motion perception tasks with accurate norm values seem not yet available for clinical use. The use of computerized motion perception tasks could have advantages: they not only have quantitative outcomes, i.e., perception thresholds, but also allow to establish the presence and severity of the motion perception impairment. Outcomes of these tasks could be related to performance levels on tasks of daily living. Prior to this, motion perception tasks must be studied in controls and patients, adults and children to set reliable normal limits and to establish whether patient groups are at risk for motion perception deficits.

In the last decades some motion perception studies were done in children. These studies suggested that motion perception deficits are associated with various developmental disorders, e.g., autism, developmental dyslexia, Williams syndrome (WS) and hemiplegia (Gunn et al., 2002; Braddick et al., 2003), Fetal alcohol syndrome (FAS) (Gummel et al., 2012), prematurity (Jakobson et al., 2006) and early brain damage, such as periventricular brain damage (PVL) (Guzzetta et al., 2009). Studies in children with cerebral palsy (CP) or periventricular brain damage (PVL) suggest that various aspects of visual motion perception, i.e., motion-defined form and global motion, can be impaired after early brain damage (Gunn et al., 2002; Jakobson et al., 2006; Guzzetta et al., 2009). Because different studies addressed different aspects of motion perception in isolation, it is currently not known whether various aspects of visual motion perception are impaired in individual children with early brain damage.

Children with congenital or acquired brain damage seem not only at risk for motion perception deficits, but also have lower performance and verbal IQ scores (Bava et al., 2005). Our recent study on the relation between performance IQ (PIQ) and motion perception outcomes in children with brain damage (Van der Zee et al., 2019) showed that non-verbal cognitive intelligence partly explained visual motion perception performance. This means that motion perception scores reflect a patient's global non-verbal cognitive level, in addition to a possible specific visual motion perception disability. To study the presence of motion perception deficits, one should at least control for a child's non-verbal cognitive level. Currently, a limited number of studies in motion perception controlled for intellectual disability and/or developmental delay by matching individual patients to individual controls or matching patients and controls on group level (Atkinson et al., 2003; Reiss et al., 2005; Del Viva et al., 2006). In clinical neuropsychological assessment, these methods are not suitable, because of the assessment of individual patients and the common use of sample-based reference tables. To uncover specific motion perception problems, i.e., disentangle general effects of the established non-verbal cognitive impairment from motion perception problems, Stiers et al. (2001) have been suggesting an applicable method: the use of the developmental age (DA), the median age equivalent of (non)verbal intelligence subtests, as entry of the reference table. The lack of control for cognitive delays, the use of the patient's chronological age (CA) as reference level in neuropsychological assessments might also lead to a profile with more abnormalities and an increase of the number of false positive results (Stiers et al., 2001), resulting in overdiagnosis. The extent of the risk of overdiagnosis is currently unknown.

In this study, we evaluate whether children with brain damage have isolated or multiple motion perception weaknesses by testing three aspects of visual motion perception: global motion, motion speed, motion-defined form. When multiple tasks are used, finding an abnormally low score is less uncommon than in a single task assessment (Crawford et al., 2007). If children with brain damage are at risk for motion perception deficits,

then the percentage abnormally low score should be significantly higher than the percentage of abnormally low scores found and/or expected in the healthy population. We studied this in 2 ways: 1. We compared the percentages abnormally low scores (score $< 10^{th}$%) between our control and patient group, 2. We compared the percentage abnormally low scores of the patient group with the estimated base rate of the healthy population.

MATERIALS AND METHODS

Participants

Control Group

The control group consisted of 119 typically developing children (54 boys, 65 girls) with no indication of neurological or visual impairments and normal or corrected to normal visual acuity. Controls were recruited through primary schools in the Netherlands ($n = 79$) and Belgium ($n = 40$). At the time of motion perception assessment, their chronological age ranged from 3y6m to 7y10m ($M = 5$y5m, $SD = 1$y0m).

Patient Group

To participate in the current study patients had to have (signs of) brain damage, sufficient verbal skills to communicate verbally with the test administrators and a best corrected decimal visual acuity equal to or higher than 0.1 (US notation 20/200 or 1.0 logMAR) to be able to see the dots of the motion perception stimuli. The children were recruited through rehabilitation centers in the Rotterdam area (Rijndam Rehabilitation Centere and Royal Dutch Visio) and the Leuven University Hospital, Belgium.

The patient group consisted of 46 children (23 boys, 23 girls) with indications of brain damage, brain malformation, or clinical indication of visual perceptual impairment. At the time of motion perception assessment, their chronological age ranged from 4y1m to 14y6m ($M = 7$y4m, $SD = 2$y3m).

The studies were approved by the Ethics Committees of the Erasmus Medical Centre (MEC-2006-056) and the Leuven University Hospital. Informed consent was obtained for all participants from their parents or guardians.

Procedures

Medical History and Orthoptic Assessment

Data on gestational age, etiology of the brain damage and imaging results (CT and/or MRI) and recent orthoptic assessments were gathered from available medical records. If no recent orthoptic assessment was done, the child was invited for an orthoptic assessment. Visual acuity with up-to-date refractive corrections (lenses or glasses), visual field, eye movements and binocular vision were assessed by trained professionals (orthoptists). The tests used were matched with the capabilities of the child: e.g., detection visual acuity tests like Landolt C (indicate the open side of the ring) or Teller Acuity Cards (locate the side with stripes) were used in illiterate patients. Visual field was mainly assessed with the confrontation visual field exam (Donder's test).

Developmental Age Assessment

In the current study, the developmental age at the time of IQ-assessment (DA_{IQ}) was defined as the median mental age determined by multiple subtasks of a test measuring performance IQ or non-verbal skills (Stiers et al., 2001). This procedure consisted of multiple steps after the standard IQ assessment: 1. Converting the patient's raw IQ subtest scores to age-equivalents using the appropriate tables in the manual, e.g., you have results on 6 subtests and get the following age-equivalents 54, 57, 43, 52, 83, and 96 months 2. Determining the median of the age-equivalents, the median of the previous example lies between 54 and 57 and is 55.5 months. This is the DA_{IQ}. 3. If there was a time-lag between IQ and motion perception assessment, we determined the developmental age at the time of motion perception assessment (DA_{mot}) using the follow formula: $DA_{mot} = (DA_{IQ}/CA_{IQ})^{*}CA_{mot}$. Note that this procedure can also be used if multiple Performance IQ subtests are done, but no PIQ can be determined.

To minimize the burden on the patients we decided to use recent intelligence results when available. If not available, we only studied non-verbal intelligence, because only non-verbal cognitive ability, and not verbal cognitive skill, is predictive of perceptual performance (Ito et al., 1996, 1997; Stiers et al., 1999). Although the use of a single intelligence test is preferable, the broad age range in the patient group and the cognitive consequences of the brain damage made this impossible. Data of four Intelligence tests were used: the Snijders-Oomen Non-verbal Intelligence Test—Revised (SON-R), the Wechsler Preschool and Primary Scales of intelligence —Revised (WPPSI-R), the Wechsler Intelligence Scale for Children—Revised (WISC-R) and Wechsler Intelligence Scale for Children-III (WISC-III). All four have normative data for the Dutch speaking population of Belgium and the Netherlands. The correlation between SON-R IQ and WPSSI-R PIQ is 0.93 (Moore et al., 1998) and WISC-R PIQ is 0.79 (internal report), the correlation between WISC-R PIQ and WISC-III PIQ is 0.79 (Oosterbaan et al., 2006) therefore we considered these tests interchangeable for the performance age estimation.

Motion Perception Assessment

All controls ($n = 119$) and the Dutch patient group ($n = 17$) were tested at the children's primary schools. The Belgian patient group ($n = 29$) was studied at the Leuven University Hospital. In the Dutch group, motion perception tasks were presented in the order: motion-defined form, global motion, and motion speed. In the Belgian group tasks were administered in random order.

Task administration was done by trained senior psychology students or neuropsychologists. Tasks were presented on a 15-inch CRT monitor attached to a laptop. Participants were placed in front of the screen at approximately 40 cm.

Motion Perception Tasks

All stimuli (see **Figure 1** for examples of the stimuli) consisted of white dots on a black background, with a resolution of 640 × 480 and refresh rate 25 frames/s.

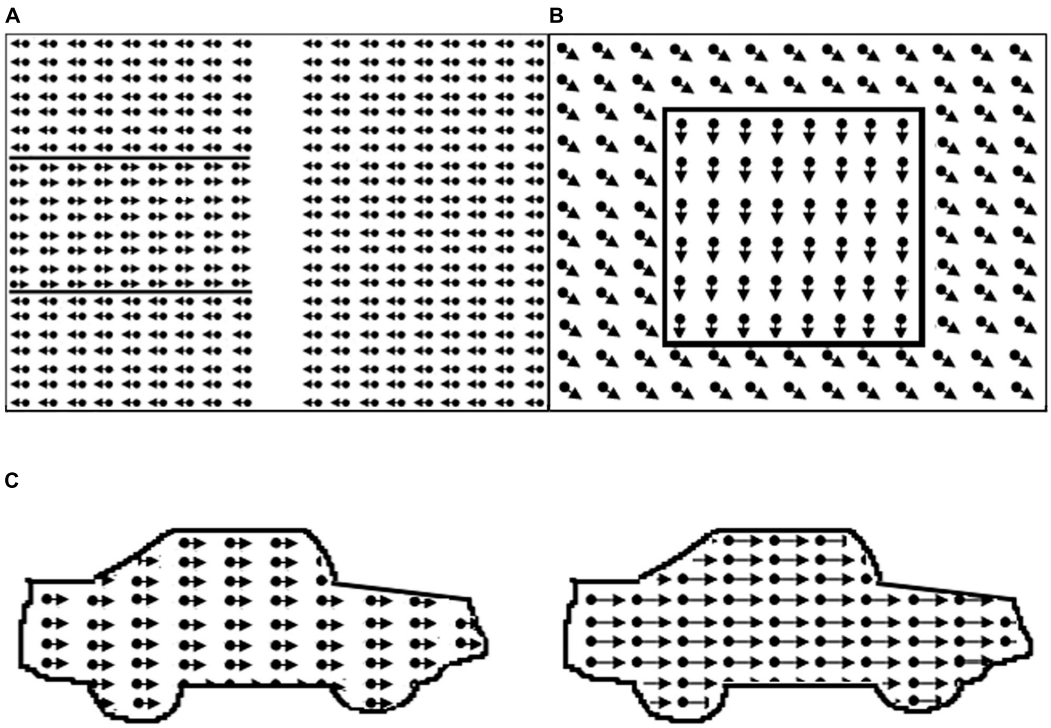

FIGURE 1 | Illustration of motion perception tasks. In the real task borders are not defined by lines. **(A)** Global motion task with target area on the left; **(B)** motion-defined form task, example item square; **(C)** motion speed: dots in right car move faster.

Before each task, example stimuli were used to familiarize participants with task elements and verify that they understood the task.

Global Motion (GM)

The global motion stimulus consisted of two random dot kinematograms (size 14.7 × 22.4 deg) containing 1103 white dots (dot size 0.07 deg, limited lifetime 130 ms), presented next to one another with a distance between them (size 3.3 deg). A variable proportion of dots in each kinematogram oscillated coherently in horizontal direction (reversal time 330 ms, velocity 6.7 deg/s). In the middle of one of the random dot kinematograms there was a horizontal strip (size 14.7 × 7.5 deg), where the coherent dots oscillated in the opposite direction. Because the proportion of coherent dots was constant throughout the random dot kinematograms, the strip could not be located by tracing the movement of single dots.

Participants were instructed to help a lost person find his way in the snow by pointing at the strip (maximum stimulus presentation time = 15 s, additional answer time 5 s). A correct answer was followed by a beep. A 2 up–1 down staircase procedure was used (starting level 100%, scaling factor 0.33): i.e., a child had to give two correct answers before the proportion of coherently moving dots, or the coherence level was decreased; One incorrect answer resulted in an increased coherence level in the next trial. After 8 reversals the task ended and the mean of the values of the last 4 reversals was used as the psychophysical threshold.

Motion-Defined Form (MDF)

The motion-defined form stimuli consisted of objects hidden in a random dot kinematogram (size 20.6 × 16.0 deg, 5,000 dots, dot size 0.13 deg, lifetime 200 ms, velocity 3.4 deg/s). Each object could be displayed in three successive conditions with decreasing level of difficulty (maximum stimulus presentation time = e. 15 s). In all conditions, the dots outside the contour moved coherently in oblique direction. In the first condition, the dots in the contour of the object moved coherently downwards. In the second condition, the dots in the contour were standing still, and in the third condition there were no dots in the contour. After an object was correctly identified the trial was aborted and the next trial, with a new object, was started. If the object was correctly named or described in the first, second or third condition a score of 1, 0.5 or 0 was noted. If the object was not correctly identified in the third condition the response was marked as inconclusive (INC), and the item was not used in the computation of the visual motion perception score. The motion-defined form score was the mean proportion correct answers on the three tasks. If no score was obtained on one of three tasks, the patient was excluded. Three subtasks, increasing in difficulty, with six objects were presented. Objects in task 1 were: circle, star, bear, banana, heart, and fish; task 2: arrow, kangaroo, boat, guitar, ostrich, and bag; task 3: beetle, seat, airplane, seahorse, car and shoe.

Motion Speed (MS)

The motion speed stimulus consisted of two identical contours of a car (car length approx. 17 deg) filled with leftwards moving

dots (dot density 11 dots/deg^2, dot size 0.07 deg, dot lifetime 120 ms). Participants were asked to indicate the location of the fastest car (presentation time 10 s). A correct answer was followed by a beep. A 2up-1down staircase procedure was used (starting speed difference 17.0 deg/s, scaling factor 0.33, 0.25 from fifth reversal). Two correct answers resulted in a decrease in the speed difference of the dots in the cars, which made the task more difficult, an incorrect answer resulted in an increase in speed difference, which made the task easier After 8 reversals the task ended and the mean speed difference of last four reversals was used as the psychophysical threshold.

Scoring Task Outcomes

We used preliminary reference data from Van der Zee et al. (2019) to evaluate individual patient performance levels, using their developmental age (if lower than chronological age) as entry for the reference table (**Table 1**). If the developmental age was lower than 3y6m, task outcomes were compared to results of the youngest reference group. If the age was higher than 7y11m, task outcomes were compared to the results of the oldest reference group.

Scores below the 10th percentile were classified as abnormally low scores or low performance levels.

Statistical Analysis

We used a two-stage procedure to estimate whether the performance levels of our patient group were abnormally low. First, we estimated the base rate, i.e.,: the percentage of the healthy population expected to exhibit 1 or more abnormally low test scores ($<10^{th}$ percentile, i.e., $z = -1.282$) on the battery of the 3 motion perception tasks. We calculated the correlations between the motion perception task outcomes in the control group and used these outcomes for the Monte Carlo simulation method described by Crawford et al. (2007) to determine the base rate. Second, we used the estimated base rate as a fixed number and used the binomial test to determine whether the observed percentage of abnormally low scores exceeded the base rate. A one-sided alpha ≤ 0.05 was considered significant.

To determine whether the observed percentage of abnormally low scores in the patient group exceeded the observed percentage of abnormally low scores in the control group we used the independent-samples proportion test. A one-sided alpha ≤ 0.05 was considered significant.

RESULTS

Medical History and Orthoptic Assessment

The etiology of brain damage was brain malformation in 3 children, hypoxic-ischemic encephalopathy in 21 cases (18 periventricular leukomalacia, 3 intraventricular hemorrhage), perinatal asphyxia in 5, intracranial hemorrhage in 1, hydrocephalus in 1 and acquired brain injury in 6 (4 trauma, 1 meningitis, 1 tumor). Of the 9 patients in whom no or normal imaging results were present, 3 had a genetic disorder (Velo-Cardio-Facial syndrome; Beckwith Wiedemann syndrome; 46XY + m), 5 had neurological signs such as cerebral palsy, 1 had visual problems not explained by ocular abnormalities and 1 was born dysmature probably due to prenatal drug exposure.

Nineteen out of 46 children (41%) had been born prematurely (gestational age < 37 weeks): 1 extremely premature (gestational age < 28 weeks), 12 very premature (gestational age 28–32 weeks) and 6 moderate to late premature (gestational age 32–37 weeks).

Five patients had ocular abnormalities other than refractive errors or oculomotor dysfunctions, like nystagmus, saccadic dysfunction, convergence abnormality and horizontal oculomotor apraxia. In 22 children, suboptimal or low visual acuity and/or visual field abnormalities were found. Eight had low vision (decimal visual acuity 0.1–0.3, i.e., US notation 20/200–20/63 or 1.0 – 0.5 logMAR) and could therefore be considered visually impaired and 8 children had a subnormal

TABLE 1 | Reference table, based on a study in 119 typically developing children (Van der Zee et al., 2019).

	Global motion coherence level			Motion speed difference (deg/s)			Motion defined form proportion correct		
	Age in years			Age in years			Age in years		
	3y6m–4y8m	4y9m–5y9m	5y9m–7y10m	3y6m–4y8m	4y9m–5y9m	5y9m–7y10m	3y6m–4y8m	4y9m–5y9m	5y9m–7y10m
n	31	39	45	25	34	31	31	43	43
Best	0.19	0.18	0.10	1.85	2.43	0.78	0.93	0.97	1.00
p75	0.34	0.37	0.27	7.14	4.63	2.89	0.78	0.89	0.94
p50	0.46	0.43	0.32	13.74	6.31	4.40	0.64	0.82	0.89
p25	0.69	0.55	0.42	22.53	13.41	7.19	0.50	0.76	0.81
p10	0.78	0.69	0.46	23.80	20.00	12.49	0.45	0.63	0.74
p05	0.80	0.74	0.56	23.80	21.53	19.87	0.33	0.59	0.70
Worst	0.83	0.74	0.64	23.80	22.53	20.96	0.28	0.54	0.64
*95%-CI p*10	2–26	3–25	4–24 *	3–31 *	3–27 *	2–26	2–26	4–25 *	4–25 *

*Percentiles for global motion, motion speed and motion defined form task in different age groups. 10th percentile (p10) outcomes were used as cut-off values for abnormally low scores. * 95% CI indicates the precision of the percentiles (range of healthy population that could be excluded using the cut-off values). For this sample, it was calculated for the nearest percentile above p10 giving a whole number of participants excluded.*

visual acuity for their age (decimal visual acuity 0.5–0.8, i.e., US notation 20/40–20/25 or 0.3–0.1 logMAR). In 7 children a slow or late response was found in one side of the visual field, in 1 child a late response was found in the lower visual field, 2 children had a concentric visual field loss, but one side was more affected then the other and 1 child had a scotoma in the right visual field.

Information on neurodevelopmental and (neuro-) ophthalmologic conditions can also be found in **Tables 2** and **3**.

Developmental Age Assessment

SON-R was used in 17 patients, WPPSI-R in 23 patients, WISC-III in 5 patients and WISC-R in 1 patient. In 6 patients subtasks were done but no Performance IQ was reported. In the remaining 40 patients PIQ ranged from 48 to 121 ($M = 78$, $SD = 20$, $n = 40$). The available data was sufficient to estimate the developmental age in all patients. DA_{IQ} ranged from 2y4m to 8y1m (M = 5y3m, SD = 1y5m). The mean time lag between the assessment of non-verbal intelligence and the administration of the motion perception tasks was 2.65 months (SD = 3.48). DA_{mot} ranged from 2y5m to 8y2m (M = 5y4m, SD = 1y5m).

TABLE 2 | Presence of neurodevelopmental conditions in patients with confirmed or suspected brain damage.

Neurodevelopmental conditions	Patient group ($n = 46$)	
	n	%
Etiology		
Asphyxia	5	11
Hypoxic-ischemic encephalopathy (HIE)		
Periventricular leukomalacia (PVL)	18	39
Intraventricular hemorrhage (IVH)	3	7
Malformation	3	7
Hydrocephalus	1	2
Intracranial hemorrhage (ICH)	1	2
Acquired brain damage (8 months–2.5 years)		
Tumor	1	2
Trauma	4	9
Meningitis	1	2
Genetic	3	7
Unclear	6	13
Neonatal Condition		
Prematurity (Gestational age < 37 weeks)	19	41
Performance IQ (PIQ)		
Normal IQ (> 84)	11	24
Borderline (71–84)	12	26
Mild retardation (50–70)	10	22
Moderate retardation (< 50)	6	13
Unknown	6	13
Motor disorder	**30**	**65**
Spastic cerebral palsy		
Hemiplegia	7	15
Diplegia	7	14
Quadriplegia	3	7
Undefined	1	2
Non-spastic cerebral palsy		
Athetoid	2	4
Ataxic	1	2
Mixed cerebral palsy	2	4
Bipyramidal syndrome	4	9
Developmental delay	3	7

The bold values are the total numbers beloning to the main category.

TABLE 3 | Presence of (neuro-)ophthalmologic conditions in patients with confirmed or suspected brain damage.

(Neuro-)ophthalmologic conditions	Patient group ($n = 46$)	
	n	%
Refractive error	**9**	**20**
Anisohyperopia	2	4
Myopia	1	2
Hyperopia	2	4
Hyperopia gravior (≥ + 6D)	2	4
Pseudoaphakia	2	4
Retinopathy of prematurity		
Stage I or II	2	4
Optic disc abnormality	**5**	**11**
Pale appearance	2	4
Smaller than normal	1	2
Optic nerve atrophy (posttraumatic)	2	4
Strabismus	**14**	**30**
Manifest	10	20
Intermittent	2	4
Latent	2	4
Oculomotor dysfunction	**7**	**14**
Nystagmus		
Manifest	2	4
Latent	1	2
Undefined	1	2
Saccadic dysfunction	2	4
Convergence abnormality	1	2
Horizontal oculomotor apraxia	1	2
Visual field defect	**11**	**24**
Scotoma	1	2
Mixed (hemi and altitude)	2	4
Hemianopsia	6	13
Concentric, one side more affected	2	4
Other ophthalmologic conditions	**5**	**11**
Bilateral cataract	2	4
Posterior embryotoxon	1	2
Septo-optic dysplasia (SOD)	1	2
Choroidal coloboma + peripheral fundus abnormality + intact optic nerve	1	2

Outcomes Motion Perception Assessment

To estimate the base rate with the Monte Carlo simulation method (Crawford et al., 2007) we first used the motion perception data of the control group to estimate the correlation between the motion perception tasks. The Pearson correlation

between GM and MDF was −0.39, the correlation between GM and MS was 0.22 and the correlation between MDF and MS was −0.42. The estimated percentage of the healthy population that would have 1 or more abnormally low scores was 27.9%. Two or more abnormal scores was expected in 2.1% of the population and 3 abnormal scores in 0.0% of the population.

Of the patient group 8 patients completed 1 task, 17 completed 2 tasks and 21 completed 3 tasks. **Figure 2** shows the visual motion perception scores of the patient group relative to the scores in the reference sample. Nineteen out of 46 patients (41.3%, 95%CI: 28.0–55.7%) had an abnormally low score on at least one of three tasks. This was significantly higher than expected in the healthy population (41.3% vs. 27.9%; $z = 1.88$, $p = 0.03$). This points toward an increased risk for motion perception problems in the patient group, independent of their performance IQ. Fifteen patients scored below the 10th percentile on a single task. Four patients scored abnormally low on two out of three tasks, which was also higher than expected (4/46, 8.7%, 95%CI: 2.4–20.8% vs. 2.1%; $z = 2.61$, $p < 0.01$).

All 25 patients, which included only 1 Dutch patient, that completed the motion speed task, scored normally on this task (0/25 = 0%, 95%CI: 0.0–13.7%, vs. 10%, $z = -1.33$. *ns*). Ten patients had an abnormally low score on the global motion task (10/42, 23.8%, 95%CI: 12.9–38.1% vs. 10%, $z = 2.73$. $p < 0.01$) and 13 patients on the motion-defined form task, which was significantly higher than expected on a single task (13/38, 34.2%, 95%CI: 19.6–51.4% vs. 10%, $z = 4.70$, $p < 0.01$).

Mean DA_{mot} of the 19 patients with an abnormally low score on any of the tasks was slightly, but not significantly lower than that of patients with normal scores (5y4m ± 1y10 years vs. 5y6m ± 1y1m; $t = 0.32$, $df = 26.9$, *ns*), because it included 4 children with a developmental age under 3 years. Although a developmental age below 3 years did not always result in a low performance level (1 patient scored normally on the global motion task), exclusion of these patients reduced the percentage of abnormally low scores from 10/42 (23.8%) to 7/38 (18.4%, 95%CI: 7.7–34.3%) for the global motion task and from 13/38 (34.2%) to 10/35 (28.6%, 95%CI: 14.6–46.3%) for the motion-defined form task. For global motion the percentage was not different from the expected percentage in the healthy population (18.4% vs. 10%, $z = 1.46$, *ns*). For motion-defined form the percentage was still significantly higher than expected in the healthy population (28.6% vs. 10%, $z = 3.38$, $p < 0.01$).

In the control group 31 of 119 (26.1%, 95%CI: 18.8–34.4%) had an abnormally low score on at least one of three tasks. The independent samples proportion test indicated that the observed percentage in the control group was significantly lower than in the patient group (26.1% vs. 41.3%; $z = -1.91$, one-sided $p < 0.03$). In the control group 3 participants (2.5%, 95%CI: 0.7–6.6%) scored abnormally low on at least 2 tasks. This was significantly lower than in the patient group (2.5% vs. 8.7%, $z = -1.77$, one-sided $p = 0.04$).

Additionally, we explored the characteristics of the patients with abnormally low scores. There was no clear pattern of increased risk for visual motion perception weaknesses associated with any of the etiological categories of brain damage. Low performance levels were found in the following etiological categories: hypoxic-ischemic encephalopathy (6/21, 28.6%, 95%CI: 12.9–49.7%); acquired brain damage (3/6; 50.0%, 95%CI: 16.7–83.3%); genetic (2/3; 66.7%, 95%CI: 17.7–96.1%); unknown (3/6; 50.0%, 95%CI: 16.7–83.3%); other (4/10, 40%, 95%CI: 15.3–69.6%). There was a significant association between low performance levels on the visual motion perception tasks and the presence of low vision ($\varphi = 0.33$, $p = 0.03$) or the presence of remarkable peripheral visual field outcomes ($\varphi = 0.37$, $p = 0.01$). It should be noted that these visual conditions were not sufficient to account for the reduced performance on the visual perception tasks. The lowest visual acuity value measured was 0.17 and one patient with this acuity scored normally on the motion defined form task and motion speed task, while another patient with this acuity scored normally on the global motion task.

DISCUSSION

In this study on motion perception abilities in 46 children with indications of brain damage we assessed whether there is some indication that these group is at risk for motion perception deficits. In current sample we found more abnormally low scores than in our control sample. The observed percentages were also higher than would be expected in the general healthy population. Current results indicate that children with early brain damage have an increased risk for isolated and combined motion perception deficits, while controlling for their non-verbal cognitive level.

Incidences of abnormally low scores (below the 10th percentile) were increased for the global motion task (10/42, 24%) and the motion-defined form task (13/38, 34%), but not for the motion speed task. Importantly, only a small percentage of the patients with impaired motion perception (4/19, 21%, 95%CI: 7.6–42.6%) were impaired on both tasks, indicating that different neural networks are damaged in this patient group. Abnormally low scores were not limited to hypoxic-ischemic encephalopathy, and were also found in other etiological categories of brain damage.

The found incidences were lower than those reported in other studies of neuropediatric populations with comparable cut-off criteria. This difference is most likely due to the more rigorous control for non-verbal performance level in the present study. MacKay et al. (2005), for instance, reported an incidence of 8/19 (42%) of impaired global motion scores in very low birth-weight children with a verbal cognitive ability within the normal range, and age-matched controls. Similarly, in the study by Jakobson et al. (2006), 21/43 (49%) children born preterm and with mild periventricular brain damage scored below 2 standard deviations from the mean in age-matched controls. However, their average performance IQ was almost 20 points lower than that of the controls. It is likely that these incidences, at least in part, also reflected reduced non-verbal cognitive ability.

The use of developmental age as reference level is not only likely to reduce the number of diagnosed problems in groups and individual children, but it will also help

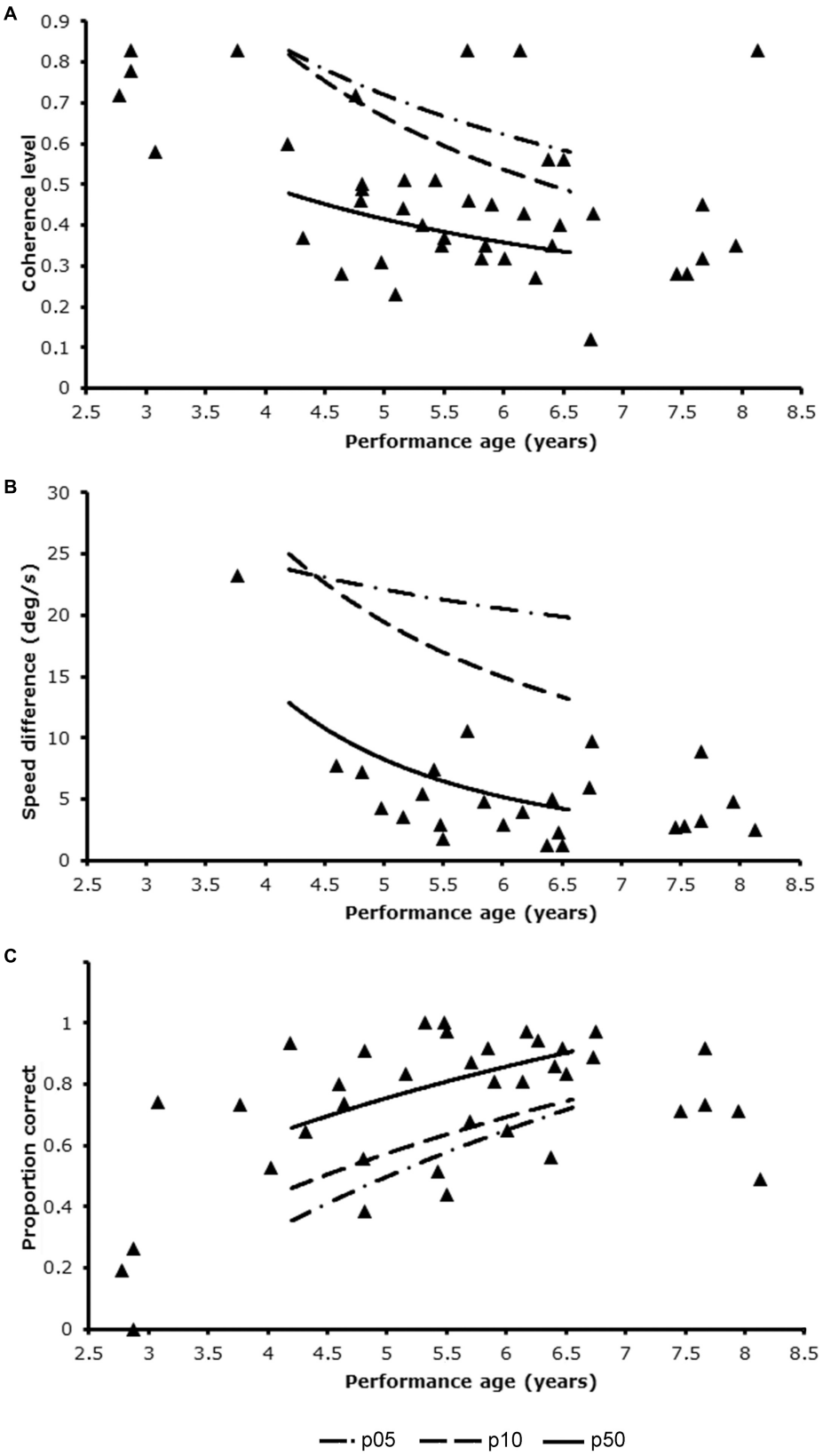

FIGURE 2 | Patients' performance levels in relation to the trendlines for p05, p10, and p50 of the reference group using developmental age as entry for reference table. **(A)** Global motion task; **(B)** motion speed task; **(C)** motion defined form task.

neuropsychologists in clinical practice to uncover specific problems and weighing the effect of different neuropsychological factors on the child's (dis)abilities. Determining and knowing a child's relative strengths is very important, especially in case of training or support.

The method currently used, the use of the extrapolated median age-equivalent based on PIQ subtests (Stiers et al., 2001), is applicable in clinical practice, even if the IQ-test is not completed. Current method is still quite laborious, another quicker method commonly used in clinical practice is DA = (IQ/100 × CA) (Caplan et al., 2015). *Post hoc* analysis suggested that for the individual patient the way of controlling for cognitive delay matters: we found a mean difference between our DA based on age-equivalents and the DA based on PIQ of 0.7 months (SD = 6.2 months) and a range of −16 and 13 months). This means that in several cases a child would be compared to another reference group, possibly with other conclusions.

Another point of attention is that the IQ test used in current study are now outdated. Future studies must make clear whether Perceptual Reasoning subtest performance levels on the WISC-V can also be used to control for cognitive delay. The technical report on the WISC-V gives a correlation 0.74 between WISC-III PIQ and the Perceptual Reasoning Index (PRI) of the WISC-V, which seems reasonable.

It should also be noted that the reliability of the preliminary reference cut-offs is still limited. To set normal limits more precisely, larger samples of typically developing children are needed. Another limitation of our study is that the heterogeneity of the patient population does not allow to delineate specific etiological conditions of risk for visual motion perception disability. Also, evidence for the clinical relevance, i.e., the relation between outcomes of these motion perception tasks and problems in daily life, is still missing. Currently, clinical relevance is primarily based on publication of a single case study, that of patient LM (Zihl et al., 1983). More extensive research on carefully selected patient samples is needed. At this time, motion perception tasks should only be applied as additional observational tools in children with brain damage that have typical problems, for example difficulties in traffic participation.

It is not clear why no weaknesses were observed on the motion speed task. It might be a result of a bias in compliance due to the fixed order of presentation in the Dutch patient group, with motion speed task last: only 1 patient in the Dutch group completed the motion speed task. To avoid this bias in future studies, tasks should be administered in random order. Another possible explanation might be that this was the only task that allowed for a low-level comparison of stimulus features, whereas the other tasks all required a higher level of integration of the moving dots to find the correct answer. Unlike speed discrimination, motion-defined form and global motion required the child to find or identify an object from a limited amount of visual information. This relies on the functioning of more complex networks, the engagement of attention, search and hypothesis testing operations that are associated with frontal-parietal networks (Pollmann et al., 2000; Corbetta and Shulman, 2002). The integrated functioning of posterior visual and anterior executive areas thrives on long-range connection fibers, which may be affected by early brain damage or brain malformation (Ortibus et al., 2012). Additionally, performance levels on the motion speed task might be less dependent on the integrity of primary visual cortex (V1) due to the higher dot speeds used, and might mainly depend on the direct route from the retina to the superior colliculus and pulvinar to the prestriate cortex (Ffytche et al., 1995). The common involvement of V1 in visual acuity, visual field (Duncan and Boynton, 2003) and motion processing (Ffytche et al., 1995) of the global motion and motion-defined form task, might also explain why we found significant correlations between these measures. We suggest, that at least a low-speed task (<6 deg/s) which activates V1 before V5, and a high-speed task (>15 deg/s) which activates the colliculo-prestriate cortical route, should be developed and studied for different motion aspects (Ffytche et al., 1995), in order to study the integrity of different neural networks and the relation with visual acuity and visual field outcomes.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committees of the Erasmus Medical Center (MEC-2006-056) and the Leuven University Hospital. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

PS and LL conceived the study, designed the study design and procedures for the study in Belgium. YZ, PS, and HE adjusted the design for the current project, drafted, revised, and prepared the manuscript. PS, LL, and YZ significantly contributed to procedures and execution. YZ and PS interpreted the data. All authors gave final approval for the submitted manuscript.

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REVIEW
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Cortical Visual Impairments and Learning Disabilities

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Medical advances in neonatology have improved the survival rate of premature infants, as well as children who are born under difficult neurological conditions. As a result, the prevalence of cerebral dysfunctions, whether minimal or more severe, is increasing in all industrialized countries and in some developing nations. Whereas in the past, ophthalmological diseases were considered principally responsible for severe visual impairment, today, all recent epidemiological studies show that the primary cause of blindness and severe visual impairment in children in industrialized countries is now neurological, with lesions acquired around the time of birth currently comprising the commonest contributor. The resulting cortical or cerebral visual impairments (CVIs) have long been ignored, or have been confused either with other ophthalmological disorders causing low vision, or with a range of learning disabilities. We present here the deleterious consequences that CVI can have upon learning and social interaction, and how these can be given behavioral labels without the underlying visual causes being considered. We discuss the need to train and inform clinicians in the identification and diagnosis of CVI, and how to distinguish the diagnosis of CVI from amongst other visual disorders, including the specific learning disorders. This is important because the range of approaches needed to enhance the development of children with CVI is specific to each child's unique visual needs, making incorrect labeling or diagnosis potentially detrimental to affected children because these needs are not met.

Keywords: learning disability, assessment, differential diagnosis, CVI, occipital

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INTRODUCTION

Vision is fundamental to learning. Sight guides our limb and body movements. It also provides access to a vast range of information, and facilitates social interaction. Children are not only continually learning these skills, they also learn through these developing abilities.

Cortical or cerebral visual impairments (CVIs) include a wide range of visual dysfunctions that can impair learning and social interaction. The present review describes CVI and provides examples helpful to a range of professionals dealing with children with learning disabilities including pediatricians, child psychiatrists, and child neuropsychologists. Learning disabilities refer to brain conditions impairing the capacity to learn in several areas, for which the cause has yet to be identified. A learning disorder or difficulty is commonly "diagnosed" in children presenting significant delay in their development of several functions. Formal diagnoses include intellectual disabilities, specific learning disorders (affecting reading, writing, and mathematics) but also motor learning disorders (American Psychiatric Association, 2013). Crucially, these are often associated with neurodevelopmental conditions, making it urgent to identify and diagnose the underlying causes, and risk factors. This review offers an overview to consider how the diagnosis of CVI can potentially explain, at least in

part, a wide range of learning difficulties, which can be overcome by appropriate management and educational strategies made accessible to the affected child.

THE DIFFERENCES BETWEEN TYPICAL VISION AND CORTICAL OR CEREBRAL VISUAL IMPAIRMENT

Picture a first-year schoolboy coming home from school, running into the kitchen, climbing onto a chair, and reaching into a tin for a biscuit. What part does vision play? He mentally envisions within his frontal territory what he wants to do and how (Buckner et al., 2008). He rapidly uses visual memory to navigate to the kitchen (Sanguinetti and Peterson, 2016). His eyes focus automatically by means of the lenses accommodating. His retinae turn the incoming imagery into unique patterns of electrical activity, with each glance capturing new imagery to integrate into a seamless pictorial flow (Churan et al., 2018). The optic nerves continuously transfer these signals via his lateral geniculate bodies to his occipital lobes, where analysis of the structure of the scene, in terms of extent, clarity (acuity), brightness, contrast and color takes place within about a tenth of a second (Lesniak et al., 2017), while the adjacent middle temporal lobes capture the flow of movement of the scene (Zihl and Dutton, 2015).

This processed information is immediately transferred to the temporal lobes via a bundle of nerve fibers on each side, called the inferior longitudinal fasciculi known functionally as the ventral stream (Bauer et al., 2015) dealing with local, detailed, visual processing, wherein a match with the coded library of past imagery brings about recognition of the tin. At the same time, the occipital lobes pass the processed image data to the posterior parietal lobes, via the superior longitudinal fasciculi (Bauer et al., 2015), functionally known as the dorsal stream dealing with global visual processing. This process is supported by the middle temporal lobes (which supplement the kinetic flow of the moving scene), and the deeper brain structures, the posterior thalamus and superior colliculi (Ptito et al., 2008), which together bring about non-conscious 3D mapped mental emulation of the scene, facilitating visual search and visual guidance of movement. There is evidence that the mapping of sound localization takes place in the same brain region (Thaler et al., 2016).

This mental visual construct enables the chair to be located and dragged to the right place, climbed onto, and the biscuit retrieved. The boy also recruits his cerebellum to modulate the timing of his actions, as well as his balance (or labyrinthine system) to climb onto the chair. In the inner ear there are balance receptors. Minute lumps of calcium linked to nerve endings to detect gravitational forces, act as plumblines, integrating with his vision (Jayakaran et al., 2018) through his semi-awareness of the horizontal edge of the kitchen wall cabinet, automatically ensuring his stability. In essence, through this highly efficient real-time process, the boy's mind processes a continuously flowing emulation of the surrounding moving scene, mapped to his body, enabling him to recognize, and integrate and interact with his surroundings.

Disturbance of any element of these complex mental visual processes can occur in a range of patterns of CVI, unique to each child. These need to be identified, characterized and profiled to provide matched habilitational approaches designed to cater for each element of the resulting visual and associated disabilities.

Definitions, Epidemiology, Etiology of Cortical or Cerebral Visual Impairment

Definitions

Cortical or cerebral visual impairment can be defined as "a verifiable visual dysfunction, which cannot be attributed to disorders of the anterior visual pathways or any potentially co-occurring ocular impairment" (Sakki et al., 2018). This broad consensus definition embraces the wide range of damage or dysfunction of the neural pathways, centers and networks involved in visual information processing. Children with CVI have been sub-classified into those who show selective visual perception and visuo-motor deficits, those with more severe and broader visual perception and visuo-motor deficits, and those with profound visual impairment (Lueck and Dutton, 2015b; Sakki et al., 2021).

These disorders compromise any of the following aspects of visual function in a range of combinations: central vision, peripheral vision (in all or part of the visual field), movement perception, gaze control, visual guidance of movement, visual attention, attentional orientation in space, visual analysis and recognition, visual memory and spatial cognition. Affected young children "know" their vision to be "normal," yet the educational, developmental, and emotional personal and social impact of living with unreliable perception is commonly profound.

Epidemiology

In epidemiological terms, CVI has become the leading cause of major visual impairment in industrialized countries (Kong et al., 2012). This change can be linked to improvement in the survival rates of children born prematurely and/or those with neurological damage, as well as better prevention of visual deficits of ocular origin. CVI in children is common, potentially affecting at least 3.4% of children but many affected children go unidentified (Cavezian et al., 2010a; Williams et al., 2021). The proportion of children with learning difficulties attending special schools who have CVI is high (Black et al., 2019) and may be greater than 50% (Williams et al., 2021).

Etiology

As with other neurodevelopmental conditions (e.g., autism spectrum conditions, learning disabilities, ADHD), children born with complex neurological conditions are at risk of developing CVI. Indeed, complications of premature birth and perinatal cerebral anoxia (or hypoxia), are the most frequent causes of CVI (Fazzi et al., 2009). Other common etiologies include head injury, stroke, brain infection and genetic neurodevelopmental disorders (Lueck and Dutton, 2015a). CVI results from lesions affecting the posterior visual pathways, the optic chiasm, lateral geniculate bodies, optic radiations, primary visual cortices, the middle temporal lobes (serving movement perception) and the visual association areas. The visual functions of these structures

can be affected to varying degree, either in isolation or in a variety of combinations. When the thalamus is involved, the lack of vision tends to be profound (Ricci et al., 2006). Moreover, the resulting visual impairment may be exacerbated by disorders of eye movement control (Fazzi et al., 2009; Boot et al., 2010; Ortibus et al., 2011; Lueck and Dutton, 2015b). CVI is therefore an umbrella term referring to visual deficits not specifically related to ocular, optic nerve or chiasmatic damage, but to pathology behind the chiasm, in particular affecting the visual brain areas involved in integration, identification, analysis and interpretation of static and moving visual information, as well as in visual control of directed movement in the environment.

Typical clinical features of CVI may be manifest in a child, despite undetected brain signatures. Even adults with visual field loss following stroke, can show normal MRI brain imaging in 30% of cases (Zhang et al., 2006a,b; Kelly et al., 2021), as can around 12% of children with Cerebral Palsy (CP) (Robinson et al., 2009; Towsley et al., 2011). It is therefore important to acknowledge that a report of a "normal" brain MRI in a child with neurovisual impairment does not exclude the diagnosis of CVI.

The term "minimal (or mild) brain injury" is sometimes used to refer to brain dysfunction in these children. Yet the consequences of the resulting visual difficulties and their impact on learning are far from "minimal" having far-reaching implications for the child's learning, motor, cognitive and social development (Chokron and Dutton, 2016) with the effects on quality of life being akin to those of lack of primary visual functions (Mitry et al., 2016).

Optical, Ophthalmological and Neurological Disorders Associated With Cortical or Cerebral Visual Impairment

Cortical or cerebral visual impairment can occur in isolation or in association with eye or optic nerve damage (Jacobson and Dutton, 2000; Fazzi et al., 2007). Moreover, around 50% of children with CVI have refractive error or impaired focusing (hypoaccommodation), necessitating spectacle correction (Pehere et al., 2018), so all such children need to have their range of accommodation checked (by dynamic retinoscopy) and must be refracted and have their post-refraction vision checked with their salient spectacle correction for both near and distance to plan their habilitation.

Lesions affecting the optic radiations lead to detectable ganglion cell absence in predictable retinal areas owing to a process known as retrograde transynaptic degeneration (Lennartsson et al., 2014) with lack of the optic nerve fibers causing optic atrophy or optic disk cupping which can be misdiagnosed as glaucoma (Jacobson et al., 2020), when brain injury occurs in later pregnancy (Jacobson and Dutton, 2000) or optic nerve hypoplasia, as a sequel to earlier injury (Zeki et al., 1992).

Children with CVI are frequently observed to have oculomotor disorders, difficulties in visual fixation or visual pursuit, hypometric saccades, or a disorder of gaze strategy (Stiers et al., 2002; Fazzi et al., 2004), as well as nystagmus due to periventricular leukomalacia (Jacobson et al., 1998; Tinelli et al., 2020). These conditions are associated with reduced visual performance.

Some children with CVI show academic success similar to their typical peers, while others show significant learning disabilities. Early brain damage is commonly diffuse, so tends to affect multiple brain functions, leading to associated neurological disorders including epilepsy, intellectual disability and CP, which can compound the deleterious effects of CVI on development (Lowery et al., 2006; Duke et al., 2020). Several studies have been conducted in children with CP to identify and characterize their associated CVI (Stiers et al., 2002; Fazzi et al., 2004; Pehere et al., 2018). These investigations have shown that children with CP commonly have difficulties in visuo-perceptual, visuo-spatial and visuo-constructive activities, regardless of their level of visual acuity (West et al., 2021). The severity and patterns of the deficits closely correlate with the extent and distribution of reduction of white matter as well as impairment of the dorsal stream pathway, interfering with attentional, spatial and motor aspects of visual cognition as well as with global visual processing (Fazzi et al., 2004; Duke et al., 2020). MRI tractography has shown that when the inferior longitudinal fasciculi in periventricular temporal lobe white matter are affected, the ventral stream dysfunctions alter detailed visual processing and in this way, visual recognition (Ortibus et al., 2012), and when the superior longitudinal fasciculi are affected, the resulting dorsal stream dysfunctions impair visual mapping of the visual scene, leading to simultanagnostic vision limiting visual search, with lack of accuracy of visual guidance of movement (optic ataxia) (Bauer et al., 2014) (see below for a detailed description).

Patterns of Cortical or Cerebral Visual Impairment

Many patterns of visual disorder can be seen, with each affected child having their own unique form of vision (Philip and Dutton, 2014). Depending on the topography and extent of the pathology, the deficit may impair any aspect of visual function affecting central vision, peripheral vision (in all or part of the visual field), movement perception, gaze control, visual guidance of movement, visual attention, attentional orientation in space, visual analysis and recognition, visual memory and spatial cognition, as well as central vision, the visual fields, visual analysis, visual exploration, visual attention, or visual memory (Kelly et al., 2021), in any combination, or degree. Recognition or visual memory of an object, a face or a place, the act of processing a set of stimuli or a complex scene, or difficulties directing movement or gesture under the control of vision, can be impaired in a variety of combinations. When the optic tracts, lateral geniculate bodies, optic radiations, or primary visual cortices are affected by a lesion, the resulting CVI manifests as lack of vision for all or a portion of the visual field.

Considering central vision, corrected visual acuities of children with CVI can be normal, subnormal or profoundly impaired. Contrast sensitivity perception is often significantly impaired (Good et al., 2012), while anomalous light brightness appreciation is a likely cause of photophobia, but the effects of CVI on perception of color have yet to be systematically studied.

Observed visual field deficits range from cortical blindness (i.e., lack of all visual sensation despite the integrity of the eye)

to scotoma (i.e., lack of visual sensation for a small portion of the visual field). Intermediate disorders include tunnel/tubular vision (i.e., concentric reduction of the visual field), or its opposite, retention of peripheral vision (i.e., loss of the central visual field, while the peripheral visual field is preserved), homonymous lateral hemianopia (i.e., loss of the contralesional visual field), or quadrantanopia (i.e., loss of a visual quadrant). Lower visual field impairment due to periventricular leukomalacia (often associated with premature birth or CP) can be peripheral or complete, or manifest as degraded clarity in the lower visual fields (Jacobson et al., 2006; Tinelli et al., 2020), and it can be combined with dorsal stream dysfunction, leading to a major deficit in global visual processing. These different disorders may exist as such or be observed successively in the same patient who may show a degree of recovery over time (Guzzetta et al., 2001b; Watson et al., 2007; Werth, 2008).

The lower visual field impairment (which if peripheral, may not be detected by classical central visual field testing) is characterized by adaptive strategies of walking with the head down, tripping over obstacles, reluctance to jump off a bench, holding onto clothing of an accompanying adult (while pulling down) to provide tactile guidance for the height of the ground ahead when walking over uneven ground, going down stairs by running the heel down the riser, and probing the ground ahead with the foot to check whether a floor boundary is a step or not (Lueck and Dutton, 2015a). Reaching in the upper intact visual field is often more accurate than in the lower visual field, when it is impaired. The accompanying dorsal stream dysfunction often leads to distress in crowded and noisy locations, inability to find an object in clutter, or a friend in a group, or to read, unless peripheral text is masked. While looking away from a face into an uncluttered area when listening to someone speaking, to facilitate auditory attention is also common (Zihl and Dutton, 2015; Dutton et al., 2017).

Expansion of the lateral ventricles into temporal lobe white matter in children with hydrocephalus can implicate a pattern of evident ventral stream dysfunctions, such as impaired processing of visual details, impaired visual recognition of faces and facial expressions, as well as difficulties with navigation, and object and word recognition. Shunted hydrocephalus, leading to CVI in 50% of cases, is a cause of this pattern of vision (Houliston et al., 1999; Andersson et al., 2006).

Children with quadriplegic CP can be similarly but more profoundly affected. Complete lower visual field impairment from severe posterior parietal injury, combined with hemianopia from asymmetric cerebral hemisphere injury, may culminate in a single intact upper visual field quadrant of intact vision only. This needs to be sought out and optimally utilized for communication and learning. Associated severe dorsal stream pathology due to bilateral posterior parietal pathology can result in apparent blindness owing to additional probable Balint syndrome (see section "Cortical or Cerebral Visual Impairment, Visuo-Motor Coordination and Gesture Production"). Yet, elimination of all visual and auditory "clutter" by enclosing such children in a monochrome "tent" for a succession of half hour periods can lead to visual behaviors gradually becoming manifest for the first time, even in older children, which can later be sustained even outside the tent (Little and Dutton, 2015).

Semiology of Cortical or Cerebral Visual Impairment in Children

Cortical Blindness, Visual Field Defects and Blindsight

Lesions in the optic tracts, lateral geniculate nucleus, optic radiations or primary visual cortex result in loss of vision in all or part of the visual field (depending on the location and severity of the lesion). The observed visual-field defects range from cortical blindness (i.e., loss of all visual sensation despite the integrity of the eye) to scotoma (i.e., loss of visual sensation in part of the visual field). Moderate impairments include tunnel vision (i.e., a concentric reduction in the visual field; see **Figure 1**) or conversely, peripheral vision (i.e., loss of central vision only). Some children are born with these impairments, whereas others acquire them at a later stage (Lueck and Dutton, 2015b).

Visual-field defects among children are defined by a loss of visual sensation in all or part of the visual field. Unfortunately, there is little public awareness of visual-field defects and they are not usually tested for clinically, whereas, curiously, ocular damage is diagnosed and treated early on. Thus, there is a profound lack of knowledge on cerebral visual deficits in children. Unfortunately, in pediatric patients the sequelae of neonatal cortical blindness are far too frequently diagnosed late [often around the age of 10, by which time the child has already completed several years of school, and sometimes after testing for a pervasive developmental disorder (PDD)] (Lueck et al., 2019).

In terms of signs and symptoms, the initial phase of cortical blindness typically involves loss of all conscious visual sensation as well as loss of the blink reflex to light or to visual threat. Children with such deficits behave as if they are blind, avoiding obstacles and people; they cannot even make basic distinctions between light and dark or between motion and stillness. However, this situation only lasts a few weeks: the child eventually recovers basic visual function, although this can be limited to a diminished visual field, where they only detect high-contrast or moving visual stimuli. Due to delayed diagnosis, children who suffer cortical blindness are often examined only several years after onset of their lesion. They exhibit a less classical set of signs and symptoms than do adults in the acute phase. However, despite the time that has passed since lesion onset, these children typically show a lack of interest in visual stimuli and have marked difficulties in fixing their gaze on such stimuli.

For children who have grown up with cortical blindness that they acquired during the neonatal period but who are evaluated only at an older age, the term *cortical blindness* is generally inappropriate (Watson et al., 2007; Werth, 2008). In these children, the sequelae of cortical blindness manifests as partial bilateral visual field defects such as tunnel vision (perception within a 10–20° concentric area in the central visual field) or peripheral (absence of perception in the central visual field) often accompanied by other visual cognition disorders such as simultanagnosia, visuo-motor ataxia, disorder of orientation of attention in space (Kelly et al., 2021), as well as disorders

of visual recognition of objects and/or faces. Children with profound CP suffering from cortical blindness who are first seen with visual difficulties years after the onset of their deficit (owing to lack of screening at birth) present a less clear picture than that of the adult in the acute phase of bilateral occipital infarction. Even long after presentation, a reduced interest in visual stimuli can be observed, with great difficulty in mobilizing gaze toward visual stimulation. In spite of this, light and sound stimuli presented in the dark can trigger eye movements or visual fixation, which is often not evident in ambient light. It is important to note that, similar to adult patients, children with CVIs can also exhibit a dissociation between their abolished conscious perception and a type of non-conscious perception, known as *blindsight*, which enables them to avoid obstacles and process visual information in their blind visual field without being aware of doing so (see Weiskrantz, 2004 for an extensive discussion on this phenomenon). According to Tinelli et al. (2013), conversely to children with acquired lesions and CVI, residual unconscious processing of position, orientation and motion of visual stimuli displayed in the scotoma of children with congenital lesions and CVI (Tinelli et al., 2013). We have occasionally seen children with sustained bilateral occipital lobe infarction, who sometimes manifest appropriate responses to smiles suggestive of affective blindsight (Celeghin et al., 2015). Other children can show remarkably good mobility despite their very low vision, probably due to intact middle temporal lobe function causing the Riddoch phenomenon as described in adults (Arcaro et al., 2019), allowing them to distinguish moving stimuli in the blind visual field (Boyle et al., 2005; De Agostini et al., 2005; Tinelli et al., 2013). Unfortunately, these visual field impairments can be completely missed, partly because the child is unaware of his deficit, and partly because the disorder is not visible to the clinician, and can only be identified by seeking it out (Pawletko et al., 2014).

Visual Cognition Deficits

Ventral and dorsal stream disorders give rise to more complex perceptual conditions, as described below.

Ventral stream dysfunction

Ventral stream dysfunction tends to result from temporal lobe pathology, leading to impaired visual analysis, visual recognition and route finding, while dysfunction of the middle temporal lobes can lead to impaired perception of movement (or dyskinetopsia), degrees of which are common in children born prematurely, especially if they have periventricular leukomalacia (Guzzetta et al., 2009).

Visual and spatial imagery disorders are commonly seen in clinical practice (for review see Tanet et al., 2010). These can be highlighted through tasks such as producing and copying geometric figures, arranging cubes, solving puzzles and mental imagery tasks (i.e., "visualizing a representation" needed to answer a question about the characteristics of the object). These approaches have yet to be systematically described in the literature.

Visual recognition disorders (known as visual agnosia in adults) are the result of damage to the occipito-temporal region and are not related to impaired verbal skills. Because learning visual information is almost impossible, the child has difficulty interpreting what is seen, but retains recognition through another sensory modality (e.g., touch). The most frequent recognition difficulties concern images and objects (Tanet et al., 2010; Pawletko et al., 2014). However, these difficulties may also concern faces and sometimes even reading and spelling (for review see Fazzi et al., 2009).

Dorsal stream dysfunction

Dorsal stream dysfunction results from posterior parietal pathology limiting parallel processing of multimodal mental mapping of the surroundings owing to attenuation of the superior longitudinal fasciculi (Bauer et al., 2015). This impairs visual exploration and limits attention through simultanagnostic vision (difficulty recognizing objects when presented simultaneously but with preserved ability to recognize them separately). It also impairs the dorsal stream non-conscious mental mapping of motoric space, leading to inaccurate visual guidance of movement (optic ataxia, which is characterized by the difficulty directing voluntary acts under the control of vision) leading to impaired visuo-motor coordination (Atkinson and Braddick, 2020). When severe, this manifests as Balint syndrome, which together with unilateral spatial neglect (also known as neglect or hemifield inattention) have been described in children (Gillen and Dutton, 2003; De Agostini et al., 2005; Drummond and Dutton, 2007; Philip et al., 2016).

Balint syndrome comprises three main clinical signs (Rizzo, 1993). First, what Balint called "psychic paralysis (or apraxia) of gaze" which refers to an inability to voluntarily redirect gaze to a nominated target. Second, simultanagnosia which corresponds to a restricted field of visual attention and finally, optic ataxia, that is a major deficit of visuo-motor coordination. Balint Syndrome is observed following bilateral parietal brain injury, but each of the features may be evident in less extensive lesions such as those resulting from subtle posterior superior periventricular leukomalacia, often associated with premature birth (Saidkasimova et al., 2007). This form of CVI is the commonest variant we have observed (Dutton et al., 2004).

Unilateral spatial neglect, most often evident when it affects the patient's left-side as it tends to be more severe on this side, is characterized by difficulties in reacting to, or acting upon stimuli presented in the hemispace contralateral to the brain lesion. This deficit, in which the patient behaves as if half of space on one side does not exist, can be observed in visual and manual activities (e.g., searching and reaching), but also at the locomotor level (e.g., showing a tendency to turn only toward the non-neglected side) (De Agostini et al., 2005). Clinically, head and eye rotation to the left does not compensate for the resulting left sided inattention, but body rotation does, indicating that the posterior parietal map of the surrounding environment is egocentric (Chokron et al., 2007).

Blurred vision or lack of visual field due to CVI may also impair visuo-motor coordination because the low vision is insufficient to allow movement to be accurately visually guided, giving a false impression of clumsiness. Typically, affected

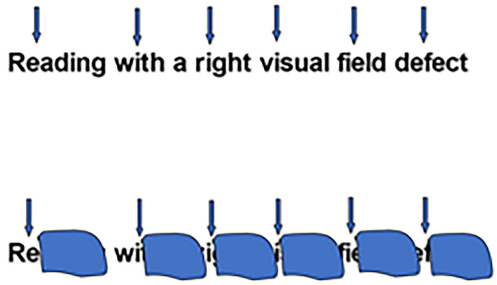

FIGURE 1 | Reading with a right sided visual field defect. **Above:** Upper arrows denote the position of the fovea with respect to the word when reading. **Below:** position of the right scotoma overlying the word when reading.

children's performance of gesture and action are more accurate when tactile and kinesthetic input is used in favor of vision (for review and discussion see Stiers et al., 2002).

BEHAVIORAL EXPRESSIONS OF CORTICAL OR CEREBRAL VISUAL IMPAIRMENT IN CHILDREN

Not only are the CVIs not clearly visible because the ocular system appears normal, but also, children growing up with CVIs due to ante- or neonatal injury have no way of knowing their vision is not "normal." This is not a genuine anosognosia, or a lack of awareness, but an actual inability for the child to recognize her vision is disordered. This means that CVI is not consciously symptomatic. As a result, CVI often goes unidentified. Rather the deleterious consequences on behavior, learning or interactions alert parents, teachers and clinicians that something is amiss. This undoubtedly explains why this disorder is under-diagnosed and why it can be confused with other conditions such as autism, coordination acquisition disorders or learning disabilities (Chokron and Dutton, 2016; Chokron et al., 2020). In turn, the existence of undiagnosed CVI also explains the inflation of other default diagnoses in these children, such as behavioral or learning disorders (Lueck and Dutton, 2015b; Zihl and Dutton, 2015). **Table 1** summarizes a number of situations in which CVI can only be indirectly expressed (Chokron and Dutton, 2016).

Cortical or cerebral visual impairment can take various forms and is expressed in daily life in multiple ways, hindering development, social adaptation, learning and social interaction (Chokron and Démonet, 2010). Most often, clinicians and parents focus on these highly evident manifestations, which are the consequences of CVI, but not on the CVIs themselves. For example, a child can be mistaken for suffering from dyslexia if there is consequent difficulty reading, or as having developmental coordination disorder if fine visual-motor coordination interferes with tasks, without recognition that CVI is the origin of the reading or motor difficulties.

Cortical or Cerebral Visual Impairment and Learning Disabilities

No-one can learn from information they cannot perceive. Children with impaired vision are unaware of what they do not see. Visual deficits due to CVIs likely impair learning in many children worldwide, simply because their visual needs are not being catered for. We all adapt to the circumstances we find ourselves in, and children with CVI, (whether or not their CVI has been identified) are no exception. If we cannot see something, we cannot respond to it. If an event is stressful, frightening or objectionable, we react emotionally to it, but when we have the capacity to overcome circumstances, we adapt our behavior accordingly. Children with CVI are no different and manifest the self-same patterns of behavior, as the natural consequences of the way they perceive their worlds, which of course is their normal. Such conditions may be seen as "behavioral disorders," when in fact they are signatures for the now well-known underlying diagnosis of CVI. Indeed, vision plays an essential role in the development of sensory-motor and cognitive abilities (Atkinson and Braddick, 2007; Chokron and Dutton, 2016). It provides the facility to coordinate all the sensory-motor systems (Fraiberg, 1977). Visual experiences are the first involved in the development of mental representations (Warren, 1994; Fazzi et al., 2010), which will later be crucial for the development of concepts and abstraction. Vision also allows the child to learn through imitation, a process essential to human development.

Although studies on the impact of CVI on the development of young children are rare, there is a large literature on the effect of ophthalmologic visual impairment on development. Studies conducted in blind children, for example, report a marked delay in all areas of motor development compared to sighted children (Fraiberg, 1977; Sonksen, 1993). In a very similar way, children with multiple neurological disorders, such as those with CP, often manifest delay in postural development (Fraiberg, 1977), as well as difficulties in acquiring object permanence, which can be interpreted as a marker of the level of cognitive development (Fazzi et al., 2011). In children with CVI, the problem is even more complex because their perceptual disorders are most often defined and "diagnosed" without questioning their origin, nature or severity.

While there is no question of attributing all learning or behavioral disorders to visual function disorders, it is obvious that, conversely, given the role of vision in development, children with CVI are at significant risk of developmental disorders affecting the entire cognitive and social sphere, as described below. It is therefore crucial to establish the differential diagnosis between CVI and learning disorders, even if this has yet to be rendered systematic policy. Indeed, apart from neuropsychological disorders directly related to neurological injury, CVIs are likely to hinder the development of different skills and learning, as well as interfering with the way the child interacts with the world. It is common to observe that a child suffering from CVI involving visual field, visual attention, or visual analysis, commonly manifests learning, behavioral and/or social interaction disorders as a consequence (Jacobson and Dutton, 2000; Fazzi et al., 2009;

Pawletko et al., 2014). Impairments in these functions may manifest as difficulties in reading, in coordination and in social interaction.

Cortical or Cerebral Visual Impairment and Reading

Word identification during reading is possible thanks to the great clarity of our central vision, served by the foveal zones of the retinae. However, reading also involves the use of clues in the para-foveal zones, i.e., in the area adjacent to the central visual field. A visual field disorder affecting all or part of the para-foveal field will therefore inevitably alter the quality of reading (see **Figure 1**).

In fact, homonymous hemianopia is accompanied by a considerable slowdown and hesitancy in reading fluency as well as anomalies in the amplitude and latency of ocular saccades toward the two visual fields (contra and ipsilateral) (Fayel et al., 2014). On the other hand, several authors have shown the role of attention in reading skills, and even more so in learning, for which it has been shown that visual attentional skills are among the prime predictive factors (Plaza and Cohen, 2007). Thus, a massive attention deficit such as unilateral spatial neglect may be accompanied by neglect dyslexia, where reading errors will involve the neglected (usually left) part of the text and/or words (Laurent-Vannier et al., 2003; Lee et al., 2009; Chokron and Cavezian, 2011). Although reading disorders are not systematically associated with signs of unilateral spatial neglect, children with left-sided neglect may omit or substitute the left part of a text, the beginning of sentences, and have great difficulty returning to the line (Ellis et al., 1987).

Another attentional disorder that may impair reading skills is simultanagnosia. This deficit, in which the patient sees only singular elements, can limit the ability to group the letters seen, and consequently prevent the correct grouping of letters to make up the word.

Finally, CVI can also alter reading and learning due to the presence of a disorder in the recognition of spelling material. Apart from letter-by-letter reading that seems to be acquired, this recognition disorder seems to make it impossible to build up the lexical stock (by inability to recognize syllables and/or words) and is the cause of difficulty in learning to read. It is interesting to note that the case reported by O'Hare et al. (1998) shows that such a form of alexia may exist in children and that it may be the direct consequence of an occipital lesion.

Cortical or Cerebral Visual Impairment, Visuo-Motor Coordination and Gesture Production

Processing of visual information plays a key role in the design, control and execution of movement, especially manual skills (Costini et al., 2014a). Indeed, vision serves as the first support for learning postural control, and it is only at the next stage

TABLE 1 | Main behavioral expressions of CVI in children.

Behaviors	Possible visual explanations
Failing to look the speaker in the eyes (lack of eye contact) but looking to the side. *Diagnostic confusion with a severe interaction disorder (e.g., autism).*	Simultanagnostic vision Visual field deficits (e.g., tunnel vision) Cortical blindness
Fragmented vision of the world, loss of the target, panicky fear of being lost or not being able to find a parent. Fear of approaching people and crowded places. *Diagnostic confusion with a severe interaction disorder (e.g., autism).*	Visual field deficits (e.g., tunnel vision) Simultanagnosia Balint Syndrome Visual extinction
Not seeing an object in front or in the near visual field. Often moving the head and eyes to compensate for the blind visual field. May hold head tilted down Neglecting a part of the visual information (e.g., eating from only part of the plate, writing on only part of the page). *Diagnostic confusion with an attention deficit disorder, clumsiness or a practical problem.*	Visual field deficits Spatial neglect
Difficulties to visually control a gesture, graphic clumsiness, difficulties in copying, clumsiness for gestures requiring fine visual-motor coordination (e.g., Picking up a very small object on a textured mat yet can run into an approaching obstacle when distracted by talking). *Diagnostic confusion with a practical disorder or a coordination acquisition disorder.*	Visual field deficits Deficit of ocular movements control Visual exploration deficit Visuo-manual coordination deficit (optic ataxia) Balint Syndrome and dorsal stream dysfunction
Not recognizing large letters but perceiving very small letters. *Incomprehension by family and school. (It can be incorrectly diagnosed as functional visual impairment.)*	Global visual perception deficits. Simultanagnosia Visual field deficits (e.g., tunnel vision)
Misuse of objects, difficulties with autonomy (dressing, eating, looking for a specific object) *Diagnostic confusion with intellectual disability or autism.*	Visual recognition deficit Simultanagnosia Optic ataxia
Difficulty analyzing a set of visual stimuli on a page. When reading, inability to process all letters, syllables or words. *Diagnostic confusion with dyslexia.*	Refractive error Dysfunctional accommodation Low visual acuities Eye movement disorders Simultanagnosia–Balint Syndrome Visual extinction
Difficulty constructing and evoking a mental image. *Recognition difficulties, lack of mental imagery, difficulties drawing from memory.*	Visual memory defect
Impossibility to follow rapid movements (e.g., fleeting facial expressions, rapid demonstrations, movements made by babies or animals). Difficulty in appreciating distances and fear of being struck by an object or person. *Isolation in the schoolyard and diagnostic confusion with an interaction disorder (e.g., autism).*	Dorsal stream dysfunction Dyskinetopsia Visual motion processing deficit Spatial orientation deficit
Getting lost, not recognizing known places. *Search for rituals to avoid disorientation and withdrawal (e.g., autism)*	Spatial orientation and spatial representation deficits Place recognition deficit
Getting lost when aligning numbers in an operation, lack of a numerical mental line, difficulty in visualizing order of magnitude and time. *Diagnostic confusion with dyscalculia*	Spatial organization and coordination disorder Spatial neglect Dorsal stream dysfunction Balint Syndrome

of learning that the child comes to use tactile and vestibular information (Guzzetta et al., 2001a). Consequently, a CVI may alter an individual's psychomotor skills in the form of optic ataxia (Hay et al., 2020) and can easily be confused with a practical disorder or dyspraxia (Chokron and Dutton, 2016). At the same time, just as unilateral spatial neglect has been associated with motor difficulties such as akinesia or hypokinesia in adults, current evidence suggests that CVI in children, and in particular unilateral spatial neglect, are most often associated with motor neglect as well as with praxis disorders (Gaudry et al., 2010; Chokron and Dutton, 2016). In addition, optic ataxia is defined as a specific difficulty in directing a ballistic gesture under the control of vision. This disorder therefore specifically affects visuo-manual and visuo-motor coordination and is characterized by difficulties in directing voluntary and coordinated acts under the control of vision (Gillen and Dutton, 2003), particularly for pointing and grasping activities.

Finally, it should be noted that the term "visuo-spatial dyspraxia" has tended to render the differential diagnosis between dyspraxia and CVI almost impossible to achieve. Indeed, visuo-spatial dyspraxia (Mazeau, 2005) includes a certain number of CVIs (reduction of visual field, attention and spatial organization disorders) which are themselves thought to be responsible for gestural clumsiness (Costini et al., 2014a,b). Indeed, in children with CVI, the use of vision may interfere with motor achievement, whereas verbal instructions or performing a task without visual control tends to improve performance (Mazeau, 2005; Chokron and Dutton, 2016), which may explain why children with CVI often choose to reach to the side of where they are looking. At present, it is therefore necessary to review the concept of "visuo-spatial dyspraxia," since logically, visuo-spatial disorders alone can explain motor awkwardness. Therefore, as recently proposed by some authors (Costini et al., 2014b), the term "visuo-spatial dyspraxia" should no longer be used in children with clear visual and/or spatial cognitive impairments that may alter their gestural production. Instead, in these children, it is essential to assess neurovisual and gestural disorders independently, with and without visual control (i.e., eyes open or closed), and to reserve the term "practical disorders" only for children whose gestural production is similar under both conditions.

Cortical or Cerebral Visual Impairment, Social Interactions and Emotional Reactions

In the healthy individual, social interactions are based not only upon the exchange of verbal information but also non-verbal information, especially cues mainly expressed through eye contact, gestures and facial expressions. Even in the context of typical development, it is more difficult for a child than for an adult to analyze and give meaning to facial expressions that convey emotion, but this is even more difficult for those with a CVI. From the first months of life, the visual system thus allows the development of tools that are indispensable for interactions with others (Chokron and Streri, 2012). These include the implementation of purely visual communication and then joint ocular attention, which informs the baby from the age of 9 months (Baron-Cohen et al., 1997) about the location and direction of the individuals in front of him. According to Itier and Batty (2009), joint attention, or shared attention of two individuals on the same object, is one of the prerequisites for the development of Theory of Mind, which allows us to make causal inferences about the behaviors of others, being mature around the age of 4–5 years (Mitchell and Lacohee, 1991).

There is a particular challenge for parents who have to interact with a child whose CVI they are frequently unaware of. Indeed, parents of a child with ophthalmologic visual dysfunctioning are warned of future visual difficulties at an early stage and can adapt their behavior accordingly, by using auditory or haptic modalities instead of visual ones. On the contrary, in the child with a CVI, lack of knowledge of the disorder by the medical profession, the family and the child herself, does not allow the stakeholders to interpret the child's particular behavior in terms of a potential visual cause, and therefore take appropriate action to cater for the causative visual disabilities (McConnell et al., 2021).

Interacting with a child who does not look at you, does not follow you with her eyes, does not recognize you, and does not smile in response to your smile, without being able to relate this set of behaviors to disorder of visual function, is extremely difficult, and likely to alter early relationships. Unlike the visually impaired child with ocular disorders, whose healthy occipital cortex will progressively reorganize itself to process other sensory information to compensate for the visual disorder (touch to see, air friction analysis, echolocation etc.) (Martin et al., 2016; Norman and Thaler, 2019), the child with CVI does not have healthy unused cortical areas that can directly compensate for the visual function disorder. Adaptation to the CVI cannot therefore take place spontaneously, but is dependent upon targeted customized adapted education and re-education, which can only be put in place once the diagnosis and characteristics of the underlying visual disorder have been established.

Numerous studies have shown that blindness or severe congenital visual dysfunctioning are frequently accompanied by autistic features (with a much higher occurrence than that observed in the general population), raising the question of the link between visual dysfunction and autism (Jambaqué et al., 1998; Sonksen and Dale, 2002). In a very similar way, Garcia-Filion and Borchert (2013) have recently found a considerably higher prevalence of autism spectrum conditions in a population of visually impaired subjects, being up to 25%, compared to the estimated occurrence of 0.6% in the general population. A recent study by Jure et al. (2016) confirms this hypothesis. All these studies strongly suggest that it is not the etiology of blindness that seems to be the cause, but rather the absence of visual perception from birth or very early in life.

Cortical or cerebral visual impairment can interfere with any or all aspects of visual processing, from detection to attention, orientation, exploration, search, spatial localization or recognition of objects, scenes, places or faces (Kelly et al., 2021). As a result, disorders of cerebral visual cognition such as those impairing face recognition, perception of facial expressions, gestures, movement, and the environment in general also hinder development of social and emotional interaction by impairing many of the processes necessary for communication, including acquisition of related language skills (Pawletko et al., 2014).

Although rarely mentioned in the literature, autistic-like conditions may exist in children with CVI and *vice versa* (Freeman, 2010; Tanet et al., 2010; Fazzi et al., 2019). These manifestations can lead to the official diagnosis of PDD despite the known presence of a brain lesion and neurovisual symptomatology. The question of differential diagnosis between sequelae of the spectrum of CVI to cortical blindness and PDD is thus increasingly being raised (Jambaqué et al., 1998; Freeman, 2010; Tanet et al., 2010; Pawletko et al., 2014; Chokron and Dutton, 2016; Fazzi et al., 2019) and it is now necessary to inform practitioners how to elicit the differential diagnosis between these conditions.

Some children with CVI may underestimate or overestimate certain facial expressions, especially negative ones, such as fear, anger or disgust, or confuse them with each other. Some children with facial recognition problems (e.g., prosopagnosia) may sometimes misrecognize, and so behave with strangers as if they know them, or conversely, fail to react appropriately to people they know, such as friends, and even siblings or relatives (Fazzi et al., 2009). These face recognition disorders can lead to serious problems in social interaction, especially if they are misunderstood by others, who interpret the lack of reaction as disinterest and not as a visual disorder, resulting in a genuine interaction difficulty. For some children with CVI, these difficulties in recognition and analysis can be so severe and disabling that they can lead them to isolate, reinforcing the image of withdrawal seen in autistic syndromes. According to recent studies (Freeman, 2010; Pawletko et al., 2014), CVIs have such a significant impact on social skills that it can lead many affected children to be misdiagnosed as having PDD, Asperger syndrome or autism (conditions now labeled under the autism spectrum term) (Jambaqué et al., 1998; Fazzi et al., 2019).

It therefore seems essential to be able to search early and systematically for CVIs in at risk children, in order to be able to treat them as quickly as possible, and avoid the occurrence of interaction and/or cognitive and/or behavioral disorders (Lueck and Dutton, 2015b; McConnell et al., 2021). The ability to make the best possible differential diagnosis between CVI and autism would also help to identify the most appropriate targeted intervention for each child, to bring about salient school adaptations, while providing useful parental guidance to optimally stimulate and teach these children as effectively as possible (Fazzi et al., 2019).

IMPLICATIONS FOR EARLY DETECTION OF CORTICAL OR CEREBRAL VISUAL IMPAIRMENT IN CHILDREN

The recognition of CVI in children is vital to offer parents, educators and stakeholders, management advice aimed at optimizing motor, cognitive and social development as well as school learning. The need to recognize visual function disorders, whether they are ophthalmological or neurological in origin, is now well established (Fazzi et al., 1999) and must result in the implementation of early interventions to improve the future for these children (Chokron and Dutton, 2016; Rossi et al., 2017; Chang and Borchert, 2020).

Unfortunately, in children with a CVI, a large number of behavioral manifestations can be neglected or misinterpreted if visual disorders of central origin are not considered nor taken into account (Lueck and Dutton, 2015a). At present, failure at school leading to relational difficulties is likely to be systematically interpreted in terms of specific cognitive or behavioral disorders, without consideration of CVI, particularly in the children whose visual acuities are normal (Lowery et al., 2006; Pawletko et al., 2014). At the start of schooling, is often the focus upon the child's activities, rather than the adequacy of their supporting visual processing, that can delay diagnosis (Cavezian et al., 2010b). The situation for children with additional associated neurological or ophthalmological disorders is equally problematic (West et al., 2021). In particular, the visual pathology can be "the tree that hides the forest." In this scenario, the child who is already being followed-up for ophthalmic disorders, may not necessarily be subject to a complementary neurovisual assessment (Ego et al., 2015; Lueck and Dutton, 2015b; Chang and Borchert, 2020; McConnell et al., 2021). The diagnosis of CVI is crucial, as this can impact the child's whole development and their future, because the diagnosis can be confused with other conditions, thereby delaying or even preventing appropriate care. The diagnostic approach includes in-depth structured history taking, precise visual assessment and regular evaluation of those affected to identify the condition, assess the evolution and best adapt management to cater for specific needs at school (Ysseldyke et al., 2009; Salvia et al., 2013; Chang and Borchert, 2020). The assessment process thus varies according to the goal, to identify and characterize other disorders, implement targeted interventions, and make decisions concerning the provision of optimal appropriate educational or vocational services (McConnell et al., 2021).

CONCLUSION

The neuropsychological approach combined with structured history taking for CVI allows us to finely describe visual function disorders as well as to characterize their deleterious effect on cognitive, social and motor development. Optimal management (that we are not covering here) is founded on this finely profiled description, and aims at truly enhancing all the capacities of detection, discrimination, analysis, memory, and visual attention, as well as the processes involved in the mental organization and representation of space (Zihl and Dutton, 2015; Chokron, 2018; Chang and Borchert, 2020; McConnell et al., 2021), complemented by skilled teaching of parents and teachers about the unique visual difficulties of each child, and the salient actions that they need to take. Future research in this field will aim to standardize both assessment and management, tenable collection of comprehensive data on the subject, and dissemination of diagnostic and rehabilitative methodologies for the dynamic assessment and management of CVI to bring about optimal learning and development. While awaiting the

dissemination of these tools, clinicians must finely assess the visual skills of children, taking care to distinguish between primary disorders on the one hand, and their consequences on the overall cognitive sphere on the other, thus avoiding diagnostic confusion, particularly with autism and intellectual disability. This is crucial as it allows distinction between PDD/ASD and/or intellectual disability as a consequence of a primary CVI. A better understanding or such etiological mechanisms is central to propose appropriate solution as early as possible and to spread knowledge on CVI to all professionals caring for children (McConnell et al., 2021).

Twenty years ago, CVI in children was rarely considered or mentioned. Recently, this condition in its many forms has been extensively researched. It is to be hoped that the coming years will see optimal diagnosis and management, especially for children born in a high-risk context (prematurity, neo-natal hypoxia, and neo-natal stroke and non-accidental head injury) for whom targeted screening for CVI is likely to prove effective and worthwhile.

AUTHOR CONTRIBUTIONS

SC: design of the manuscript, writing, and editing. KK: editing final draft. GD: writing and editing. All authors contributed to the article and approved the submitted version.

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BRIEF RESEARCH REPORT
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Pre- and Postnatal Damage to the Retro-Geniculate Visual Pathways Cause Retinal Degeneration Predictive for Visual Function

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To increase the understanding of the relationship between structure and function in individuals with damage to the brain from different stages of maturation of the visual system, we examined 16 teenagers and young adults. We used diffusion-weighted magnetic resonance imaging (MRI) and fiber tractography of the optic radiation (OR) and optical coherence tomography (OCT) of the peripapillary retinal nerve fiber layer (pRNFL) and the ganglion cell layer + inner plexiform layer (GC+IPL) in the macula. Visual field (VF) function was assessed with the Humphrey Field Analyzer (HFA). Injuries to the immature OR were associated with thinning of the pRNFL and GC+IPL, and corresponding VF defects irrespectively of timing of the lesion. However, in cases with bilateral white-matter damage of immaturity (WMDI) we noticed a well preserved central VF despite a very thin GC+IPL. We speculate that this is due to plasticity in the immature visual system. Similar results were not noticed among cases with unilateral damage, acquired pre- or postnatally, in which the central VF was affected in most cases. OCT has proved to be a valuable targeted tool in children with damage to the retro-geniculate visual pathways, and that focal thinning of the GC+IPL predicts VF defects. This brief research report includes a review of four previously published papers. In addition, we present one new case and apply a recently developed classification system for CVI. The classification was applied on cases with bilateral WMDI to investigate its relation to retinal structure.

Keywords: cerebral visual impairment (CVI), optic radiation, retinal degeneration, plasticity, visual system, brain development, optical coherence tomography, visual field defect

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INTRODUCTION

The increased survival rate of infants with critical illness prenatally or in the neonatal period, prematurely born or born at term, and of children with later acquired brain injury, has led to an increase in the prevalence of cerebral visual impairment (CVI) in children (Hatton et al., 2007; Ozturk et al., 2016). Early identification of children with CVI is the prerequisite for early intervention (Kooiker et al., 2020). The development of protocols to assess visual function early in life, of methods to document visual attention based on eye tracking tasks

(Kooiker et al., 2016), and of structured history inventories are essential in the identification of children with CVI (Houliston et al., 1999; Hellgren et al., 2020). Sakki et al. (2021) recently presented a classification system, grading perception, visuomotor, and visual acuity dysfunction, in CVI. A similar severity gradient was shown in co-occurring cognitive and neurodevelopmental deficits. The primary cause of CVI in children is damage affecting the retro-geniculate visual system (pathways and processing structures). Large cupping of normal-sized optic disks associated to white-matter damage of immaturity (WMDI) was described in the 1990's. Retrograde *trans*-synaptic degeneration (RTSD) of ganglion cell axons was suggested as the cause of this ocular sign of interruption of the optic radiation (OR) (Jacobson et al., 1997). Not only WMDI, a pattern of lesion arising in the early third trimester, but also brain malformations from the first or second trimester, and focal infarcts and hypoxic-ischemic encephalopathy from term age and later acquired lesions of multiple etiologies, may cause CVI.

New imaging techniques to map the primary injury and its relation to the retro-geniculate visual pathways and the possibility to document thinning of the macular ganglion cell layer caused by RTSD are tools that may facilitate identification of children with injuries to the retro-geniculate visual system. Structural evidence of injury to the visual pathways and secondary retinal degeneration may predict visual field (VF) defects and pose a high risk of visual dysfunction within the spectrum of CVI. However, secondary loss of ganglion cells may not be present in individuals diagnosed with CVI because of visual cognitive-perceptual dysfunction only, presenting with normal visual acuity and normal VF function.

Evaluation of the Visual Structure and Function With Magnetic Resonance Imaging and Optical Coherence Tomography

Contrary to cerebral palsy (CP), correlations between findings on magnetic resonance imaging (MRI) and visual dysfunction has not been investigated extensively in CVI caused by early brain injuries. Injuries to the retro-geniculate visual pathways can be evaluated on MRI and include lesions in the OR or the visual cortex. Injuries to the immature OR are commonly caused by WMDI (Flodmark et al., 1989), focal infarcts (Mercuri et al., 1996) or watershed infarcts. Brain malformations can also involve the OR (Jacobson et al., 2010). However, the full extent of lesion involvement is difficult to judge on conventional MRI but can be improved with diffusion-MRI fiber tractography (Lennartsson et al., 2014, 2018; Merabet et al., 2016). With streamline fiber tractography, the OR can be generated by seeding streamlines in the lateral geniculate nucleus (LGN) and using ipsilateral targets in the medial occipital lobe (Lennartsson et al., 2014, 2018). The OR-tract can be evaluated by comparison to the expected anatomy of the geniculo-striate projections. Quantitative parameters of the OR-tract can be analyzed, e.g., to infer on the mechanisms of injuries. Associated lesions to primary injuries in the immature retro-geniculate visual pathways include injuries in the basal ganglia and thalamus, most notably the LGN (Uggetti et al., 1996), and are primary or secondary, depending on the etiology of the early brain lesion. However, involvement of these structures correlates strongly with visual impairment (Mercuri et al., 1997). Thinning of the optic nerves, the optic chiasm and optic tracts indicate secondary neurodegenerative injuries.

Optical coherence tomography (OCT) is a relatively new technique but has been heavily implemented in ophthalmology due to the valuable information it provides. Scanning of the retinal structures only takes seconds and is non-invasive. Minor participation from the patient is required. The patient needs to sit in a head-and-chin rest and keep fixation stable during the measurement. The measurement gives 3-dimensional information of the retinal structures and layer thicknesses and volume parameters with a resolution of 3–5 μm. Several studies have shown that brain injuries affecting the visual pathways cause ganglion cell + inner plexiform layer (GC+IPL) and peripapillary retinal nerve fiber layer (pRNFL) thinning and that the pattern of the GC+IPL correlates well with the location and extent of the brain injury and predicts the pattern of the VF defects (Jindahra et al., 2009; Keller et al., 2014). Despite this, OCT is not well explored in pediatric neuro-ophthalmology. Instead, the clinicians often need to rely on other ophthalmic examinations and MRI. One important tool is VF examination, but to achieve a reliable result when examining children or individuals with cognitive and physical difficulties can be challenging. The examination is time-consuming and demanding. Which method to choose needs to be adapted in relation to age and ability to co-operate. The level of participation can influence the result and lead to a high test-retest variability. An objective measure with high repeatability, like OCT, that strongly correlates with VF function is therefore valuable.

Aim

To increase the understanding of the relationship between structure and function in individuals who present with visual impairment, caused by damage to the brain from different stages of maturation of the visual system, we examined teenagers and young adults with pre- or perinatal brain damage. We also examined a few individuals with brain damage acquired later in childhood. This text is a review of four published studies (Lennartsson et al., 2014, 2018; Jacobson et al., 2019, 2020) in which we analyzed VF function in relation to GC+IPL topography. In addition, we looked at the relation between the severity of CVI and the secondary retinal degeneration presented under "Additional analysis and one additional case." We aim at highlighting OCT as a tool to identify children at risk for VF defects, and for CVI, early in life to make adequate habilitation possible.

REVIEW OF METHODS

Study I–IV

The basis for our investigations has been the structuro-functional organization of the visual system, specifically the retinotopic organization of retino-striate visual pathways

(Wärntges and Michelson, 2014). This has made it possible to link primary retrogeniculate injuries with secondary retinal structural changes, and their resulting VF deficits.

Diffusion-weighted MRI (dMRI) and fiber tractography was used to investigate the OR and to assess lesion involvement to the tract (studies I–IV) (Lennartsson et al., 2014, 2018; Jacobson et al., 2019, 2020). In study II, our investigations were refined by inclusion of retinotopic functional MRI (fMRI) mapping. This made it possible to map the location of the cortical visual areas and separate OR into its ventral and dorsal parts of connections to the upper and lower VFs, respectively (**Figure 1**).

Optical coherence tomography (OCT) was used to measure the pRNFL (study I) and GC+IPL in the macula (studies II–IV). Visual field function was assessed with the Humphrey Field Analyzer (HFA) (studies I–IV) using Sita Fast 24-2 (testing 24° temporally and 30° nasally) and Goldmann perimetry (study I). The result from the functional and structural examinations has been mapped for each subject in order to study how the pattern of VF defects associates with the GC+IPL topography.

REVIEW OF RESULTS

Study I

In our first study (Lennartsson et al., 2014), we investigated seven young adults with CVI caused by WMDI and various degrees of VF deficits with spared function in the central 5° of the VF. WMDI, particularly periventricular leukomalacia, has a predilection for peritrigoneal white matter resulting in characteristic bilateral homogenous dysopias in the lower VF, indicating involvement of the superior portion of the OR. White matter fiber tractography was used to map and assess injury involvement of the OR. OCT was used to measure the pRNFL to detect signs of RTSD in the retina after brain injuries. The study confirmed that only cases with lesional involvement of the superior portion of the OR, as assessed from white matter fiber tractography, displayed commensurate reductions in the pRNFL on OCT, and corresponding VF defects. The strong correlation between pRNFL and VF sensitivity, and the relatively thinner axon layer in the superior quadrant of the optic nerve head corresponding to the damage in the superior portion of the OR, gave evidence of the occurrence of RTSD after brain injury.

Study II

In the second study (Lennartsson et al., 2018), we showed that, indeed, there were strict topographical and quantitative correlations between the injury in the OR and the thinning of the GC+IPL. We also found that the GC+IPL topography had a stronger predictive ability of the VF function compared to pRNFL results. Further, the ratio of the mean thickness of the GC+IPL in the superior and inferior sectors significantly correlated with the dMRI parameters of axial and mean diffusivities in the dorsal OR, but not in the ventral OR. We interpreted those results as evidence for RTSD. Moreover, with retinotopic fMRI mapping we investigated the central 11° VF. This generated coherent and reliable V1 cortical activation maps in all subjects, with no difference between subjects and controls. This confirms that all WMDI cases, including cases with injury to the OR and RTSD with thinning of GC+IPL, had apt cortical responses within the central 11° VF.

Study III

Having identified the mechanism of RTSD in CVI caused by WMDI, we proceeded to investigate injuries with different timings. In a smaller case-study, study III (Jacobson et al., 2019), we included six young adults with pre-natal and post-natal injuries occurring at different times. Again, fiber tractography was used to identify the parts of the OR which were affected by lesions, and OCT of the GC+IPL was used to detect secondary retinal changes. In all subjects, RTSD were found to cause thinning of the neuro-retinal structure regardless of the injury timing. This study further confirmed the importance of looking for GC+IPL asymmetry to be able to predict the pattern of the VF defect based on OCT, especially in cases with a physiologic thick GC+IPL or pRNFL layer to start with, and in whom focal thinning may be missed when compared with the normative data base.

Study IV

The convincing results, i.e., that OCT can detect focal retinal RTSD, made us consider its use as a targeting tool to identify individuals with CVI causing VF defects. We addressed this in our study IV (Jacobson et al., 2020), in which we investigated ten subjects with spastic CP, a patient group with high risk of injury to the OR. Using our established method of fiber tractography of the OR and OCT of the GC+IPL, we found, again, focal thinning of the GC+IPL in cases with damage to the OR, resulting in VF defects. In individuals without injuries affecting the OR, we found no focal GC+IPL thinning or VF defects.

Based on these results from studies I–IV, we suggested that children presenting with symptoms of brain damage should generously be examined with OCT early in life. As reliable perimetry is extremely difficult to achieve in pre-school aged children, OCT could serve as a targeted test to identify VF defects in young children (3–4 years of age) making early identification of children with CVI possible.

ADDITIONAL ANALYSIS AND ONE ADDITIONAL CASE

The material included in this additional analysis is presented in **Table 1** and all subjects are linked to previous studies.

We applied the recently developed scale for subgrouping of individuals with CVI suggested by Sakki et al. (2021). The subgrouping is based on the severity of visual dysfunction: A1 with selective visual perception and visuomotor deficits, A2 with more severe visual perception and visuomotor deficits and variable visual acuity, B with lower function and significant visual acuity reduction compared with A. All individuals with bilateral WMDI from studies I and IV (eight) were subgrouped.

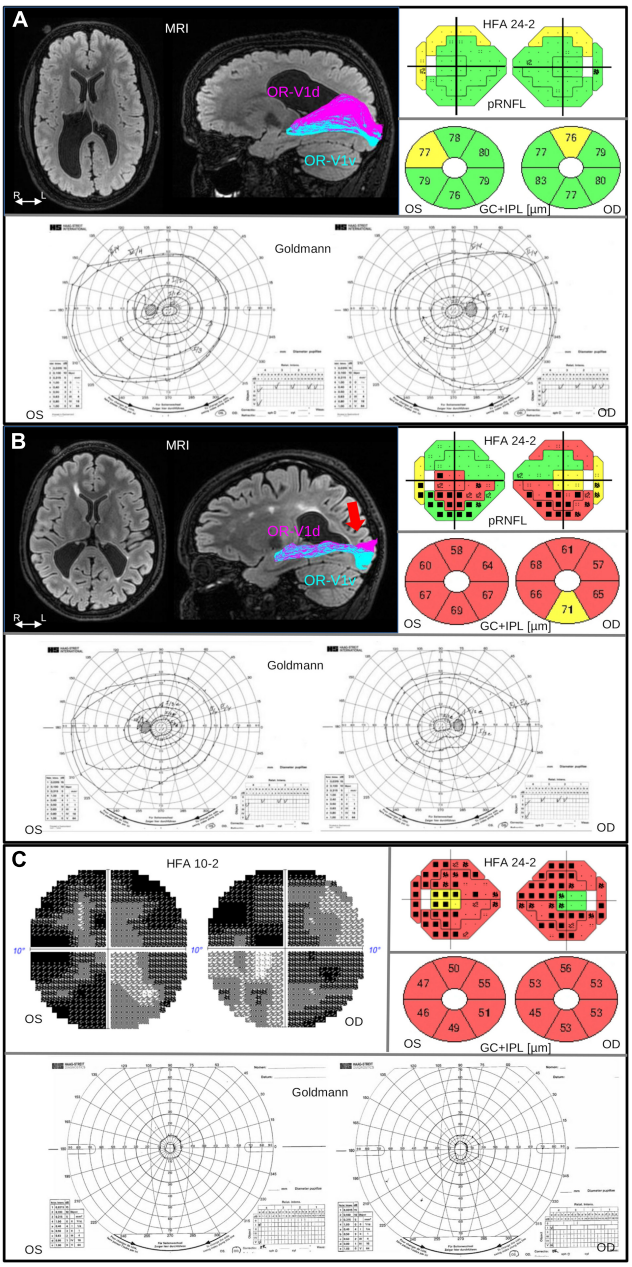

FIGURE 1 | Brain injuries were examined with MRI, with salient findings illustrated on axial FLAIR image (left). Injuries to the OR were investigated with fiber tractography, with results overlaid on a sagittal FLAIR image (right), dividing the OR into parts OR-V1d (magenta) and OR-V1v (cyan) projecting to the dorsal (V1d) and ventral V1 (V1v) fMRI activation maps, respectively, described in Lennartsson et al. (2018). The pRNFL and GC+IPL thickness was measured with OCT. The pRNFL result is visualized in colors together with the results from VF examination using HFA 24-2 and GC+IPL is shown in donuts below. Color code green indicate normal, yellow; borderline and red; abnormally thin. The color codes are automatically generated and based on the reference data in the software of OCT. Visual field function was examined with Humphrey Field Analyzer (HFA) and Goldmann perimetry. The colored visual field maps show VF sensitivity (Sita Fast 24-2) in relation to corresponding pRNFL thickness. Normal VF sensitivity is represented by small single black dots, defects are shown as gray or black squares (black = deeper defect). Goldmann was performed in order to examine the peripheral VF. **(A)** Case 2 in **Table 1**: 19-year-old, born at GA 26 weeks, with bilateral perinatally acquired WMDI (R > L). Suffering from mild left-sided spastic CP, and dorsal stream dysfunction. VA is 1.0 (logMAR 0.00), no strabismus, and sub-grouped as CVI A1. MRI image shows bilateral WMDI (R > L) with periventricular WM reduction, especially posteriorly and on the right side. Fiber tractography shows normal ORs bilaterally, here illustrated with the right OR with separation of the OR-V1d and OR-V1v, dominating the superior and inferior portions of OR, respectively. OCT showed pRNFL and GC+IPL thickness values within normal range. The VF sensitivity and the outer borders were normal. **(B)** Case 7 in **Table 1**: 25-year-old woman, born at GA 33 + 0. She presented with early onset left esotropia and nystagmus. At 4 years of age VA was subnormal in both eyes and large cupping of the optic disks was noted. She has no CP. VA 0.63 (logMAR 0.20), and dorsal and ventral stream dysfunction and CVI A2. MRI image shows bilateral WMDI with WM reduction of, especially posteriorly, and extensive gliosis in the periventricular WM. Results of the left OR (right) shows abnormal appearance of the OR-V1d projections, sharing the space normally solely occupied by the OR-V1v projections, and fanning in the subcortical white matter (red arrow), presumably the location of the

(Continued)

FIGURE 1 | (Continued)
transient developmental subplate. OCT showed reduced pRNFL thickness, most pronounced in the superior quadrants, and globally thin GC+IPL with asymmetric thickness between the superior and inferior hemifield. HFA 24-2 shows reduced sensitivity in the inferior hemifield. Goldmann demonstrate bilateral homonymous inferior quadrant dysopias sparing the VF within 10°. **(C)** Case 5 in **Table 1**: 30-years old woman born at GA 29 weeks, suffered from ultrasound-verified bilateral intraventricular hemorrhages (grade 3) day 3 post-partum. She appeared to be severely visually impaired already as an infant and had early-onset exotropia and nystagmus and difficulties to maintain fixation. VA 0.25 (logMAR 0.70), and severe dorsal and ventral stream dysfunction. She has left-sided mild spastic CP, a developmental disorder and CVI B. OCT demonstrates severe thinning of both pRNFL, except in the temporal portion and extremely thin GC+IPL with only minimal asymmetry. Goldmann and HFA demonstrate severe concentric VF restriction (tunnel vision) with total loss of function in the periphery. HFA 24-2 shows some sparing of the infero-nasal part of the VF. HFA 10-2 shows minimal function also in the most central part of the VF. OR, optic radiation; R/L, right/left side; WM, white matter; WMDI, WM damage of immaturity; V1, primary visual cortex; R/L, right/left side; VF, visual field; VA, visual acuity; pRNFL, peripapillary retinal nerve fiber layer; HFA, Humphrey Field Analyzer; FLAIR, fluid-attenuated inversion recovery; GC+IPL, ganglion cell + plexiform layer.

TABLE 1 | Cases in the current studies are indexed 1–16.

CASE ID	Previously published	Gestational age at lesion (weeks)	Lesion pattern on MRI (side/s)	No/unilateral/ bilateral CP (GMFCS I-V)	BCVA RE/LE	Mean GC+IPL μmRE/LE	GC+IPL asymmetrytm μm RE/LE	VFI% RE/LE	CVI grading
1	S3 (Figure 1 Case A)S4 (Figure 1 Case 1)	=20 GW[a]	MD (R)	U CP (I)	1.25/1.25	83/82	28/31	84[CD]/90	NA
2	S1 (Figure 7)S2 (Figure 2 Case C)S4 (Figure 2 Case 9)	26-28 GW[b]	WMDI (B, R>L)	U CP (I)	1.0/1.25	79/78	5/4	99/99	A1
3	S1 (Figure 4)S2 (Table 2 Case D)S4 (Figure 2 Case 3)	26-28 GW[b]	WMDI (B)	U CP (II)	1.0/0.63	71/67	14/12	92/91	A2
4	S1 (Figure 6)S2 (Figure 1)S4 (Figure 2 Case 10)	26-28 GW[b]	WMDI (L)	B CP (I)	0.63/1.0	80/84	5/5	100/100	A1
5	No	28-32 GW[b]	WMDI (B)*	U CP (I)	0.2/0.25	52/50	11/9	38[CD]/45[CD]	B
6	S4 (Figure 2 Case 7)	28-32 GW[b]	WMDI (L)	U CP (I)	1.0/1.0	67/70	3/5	98/98	No CVI
7	S1 (Figure 3)S2 (Figure 2 Case B)	32-34 GW[b]	WMDI (B)	no CP	0.65/0.32	65/65	10/11	81/88	A2
8	S1 (Figure 2)S2 (Figure 2 Case A)S4 (Figure 2 Case 4)	32-34 GW[b]	WMDI (B)	B CP (III)	0.4/0.65	68/72	13/11	88/81	A2
9	S1 (Figure 1)S2 (Table 2 Case A)S4 (Figure 2 Case 5)	32-34 GW[b]	WMDI (B)	B CP (II)	1.0/1.0	58/58	15/12	77/74	A2
10	S1 (Figure 5)S2 (Table 2 Case E)	26-28 GW[a]	WMDI (B)	no CP	1.0/0.8	67/64	6/3	98/97	A2
11	S3 (Figure 1 Case B)S4 (Figure 2 Case 2)	26-28 GW[a]	WMDI (R)	U CP (I)	0.63/0.63	67/69	35/31	54[CD]/55[CD]	NA
12	S4 (Figure 2 Case 8)	>34 GW[b]	MCA infarct (L)	U CP (I)	1.0/0.5	86/87	5/5	97/98	NA
13	S3 (Figure 1 Case C)	>34 GW[a]	Watershed infarcts (B, L>R)	no CP	0.9/0.8	76/77	9/8	69[CD]/64[CD]	NA
14	S3 (Figure 1 Case D)S4 (Figure 2 Case 6)	1.5 years	PCA infarcts (B, R>L)	U CP (I)	1.25/1.0	73/68	22/32	23[CD]/27[CD]	NA
15	S3 (Figure 1 Case E)	4 years	Hemorrahgic AVM (L)	no CP	1.25/1.6	88/89	11/10	83/77	NA
16	S3 (Figure 1 Case F)	13 years	Traumatic (L)	no CP	1.25/1.25	88/89	10/11	86[CD]/86[CD]	NA

Previous studies are marked, Study 1 = S1 (Lennartsson et al., 2014), Study 2 = S2 (Lennartsson et al., 2018), Study 3 = S3 (Jacobson et al., 2019), Study 4 = S4 (Jacobson et al., 2020). The injury pattern on MRI is described as MD, WMDI, infarcts of a vascular territory, watershed infarcts, hemorrhagic AVM, or trauma. The lesion side is noted as right/left or bilateral. If a bilateral lesion has a clear side-dominance, then this is stated.

**No MRI was available for Case 5, but neonatal ultrasound showed bilateral intraventricular hemorrhage, a salient finding of WMDI. The lesion pattern can estimate the gestational age at lesion which then indicates, in each individual, if the injury is [a]prenatal or [b]perinatal. In cases with CP, this is noted with unilateral/bilateral and the GMFCS I-V. Visual acuity, OCT measurements of the GC+IPL, and VFI are reported. The GC+IPL asymmetry refers to the difference between the thickest and thinnest GC+IPL sector. For comparison, the mean GC+IPL thickness ranged between 77–94 μm and the asymmetry ranged between 2–7 μm in the control group.*

[CD]Focal VF defects within the 4 central test locations, as examined with HFA 24-2, are marked in the column reporting VFI. CVI grading is done according to Sakki et al. (2021) when applicable.

GW, gestational week; MD, malformations of cortical development; WMDI, white-matter damage of immaturity; M/PCA, middle/posterior cerebral artery; AVM, arterio-venous malformations; R/L, right/left; B, bilateral; U, unilateral; CP, cerebral palsy; GMFCS, Gross Motor Function Classification System; NA, not applicable; BCVA, best corrected visual acuity (decimals); RE/LE, right/left eye; GC+IPL, ganglion cell + inner plexiform layer; VFI, visual field index; OCT, optical coherence tomography; CVI, cerebral visual impairment; HFA, Humphrey Field Analyzer.

To increase the understanding of the relationship between structure and function we have added one new individual (Case 5 in **Table 1**) with bilateral WMDI and more severe visual impairment than the 15 individuals included in the four published studies. The findings are demonstrated in **Figure 1C**, and are further elucidated in the discussion. Results are summarized in **Table 1** and the participation of each case, in more than one study, is stated.

Results

According to the CVI-classification by Sakki et al. (2021), one subject had normal visual function (A0), two were classified as A1, five as A2 and one as B. Three individuals, representative of the groups A1, A2, and B, are presented in **Figure 1** with MRI (when available), HFA and OCT measurements. Three individuals with unilateral (two) or bilateral (one) homonymous VF defects caused by injuries acquired later in life, Study III, were compared to these nine individuals with WMDI (**Figure 2**). These three subjects were not graded, as such children were excluded from the study by Sakki et al. (2021).

Thereafter, correlations between retinal structure and function were plotted with respect to the CVI subgrouping, see **Figure 2**. For comparison, a reference group of 12 healthy young adults was included in the plot. They had all been part of previous studies from our research group (Lennartsson et al., 2014; Nilsson et al., 2016). Inclusion criteria were birth at term, no history of ocular disease and absence of visual complaints. As shown in our previous studies, the GC+IPL thickness and GC+IPL asymmetry (defined as the difference between the thickest and the thinnest sector) in relation to the VF index (VFI) is a valuable way of describing retinal structure and function in relation to the location and extent of damage to the OR. Therefore, these parameters were applied for this purpose.

As shown in our previous studies, there is a strong correlation between average GC+IPL thickness and VFI in the WMDI group (**Figure 2A**). Two subjects in the WMDI group had a GC+IPL thickness within the range of controls and seven had a thinner. Out of these seven, two subjects had a thin GC+IPL layer, but no asymmetry and no focal VF defects.

In the three individuals with injuries acquired later in life, the average GC+IPL was close to, or within the range of controls, in two subjects. However, all three showed a GC+IPL asymmetry outside the range of controls and they all had focal VF defects (**Figures 2A,B**).

In WMDIs with no or CVI grade A1, focal VF defects were absent and no GC+IPL asymmetry was noticed although, one subject had generally thin GC+IPL (**Figures 2A,B**). Among those with CVI grade A2 and B, all subjects had reduced GC+IPL thickness. All but one had GC+IPL asymmetry, this individual has a VF defect only in the periphery, in opposite to the others. The CVI classification separated the subgroups and A2 and B showed to be related to increased GC+IPL asymmetry and focal VF loss (**Figure 2B**).

DISCUSSION

We have, in a series of studies, shown that primary injuries in the OR cause secondary degeneration in the retina, and associated VF defects. The topographically correlating injuries in the retino-striate system are evidence of RTSD and occur irrespectively of the timing of the injuries. Conversely, OCT of the GC+IPL can predict injuries to the OR and should be considered as an early targeted investigation in individuals with CVI, or risk of CVI.

Although retinal RTSD was seen in all individuals with damage to the OR, regardless of timing, there were some differences between groups (**Figures 2A,B**). All bilateral WMDIs had their best-preserved vision in the central VF (Lennartsson et al., 2014). They all had a generally thin GC+IPL layer, and those with moderate VF damage had GC+IPL asymmetry. Among cases with acquired injuries, the average GC+IPL thickness was within the range of controls in two out of three subjects, instead they had a large GC+IPL asymmetry and focal, complete VF defects engaging also the most central part of the VF (Jacobson et al., 2019). Further, GC+IPL asymmetry seems useful to detect focal VF defects in this whole group of patients but also to recognize individuals with CVI grade A2-B related to WMDI.

One subject with bilateral WMDI and CVI grade B had a very thin GC+IPL and severe VF loss without any pronounced GC+IPL asymmetry, most likely due to the "floor effect". This effect is a limitation in measurements of the GC+IPL and pRNFL thickness using OCT and can be described as the point when no further structural loss can be detected despite loss of VF function. Attempts to estimate the floor effect has mainly been done in patients with glaucoma. Bowd et al. (2017) found a floor effect for GC+IPL between 31 and 45 μm and Mwanza et al. (2015) between 49 and 65 μm for the pRNFL. Both studies were based on examination of patient with moderate to advanced glaucoma and used different OCT machines. In the context using OCT to reveal VF deficits related to brain injury it is important to consider that severe loss of axons due to bilateral extensive cerebral damage is unlikely to cause asymmetry, but rather a markedly reduced average thickness in relation to the normality database.

Key elements for the organization of the visual system are the aggregation of the GC projections into eye-specific layers in the LGN, largely achieved by midgestation (Hevner, 2000) and is believed to be a prerequisite for the formation the eye-specific ocular dominance columns in the striate cortex during the second half of gestation (Penn and Shatz, 1999), following the invasion of geniculo-striate axons in the cortical plate at around 23–25 GW (Kostović and Judaš, 2010). This is largely achieved by the preservation of the retinotopic map and has been linked to retinotopically coordinated, spontaneous waves of firing in the retinal ganglion cells over the retina before (Shatz, 1996), and sensory driven activity after, opening of the eyes (Vanhatalo and Kaila, 2006). An adult-like pattern of retino-cortical connection is essentially established at time of normal birth (Kelly et al., 2014). In the fetal human retina, the GC count in the optic nerve shows an elevated plateau from midgestation up until around 30 GW, suggesting an overproduction and elimination of the GC in the immature retina (Provis et al., 1985). In parallel, there

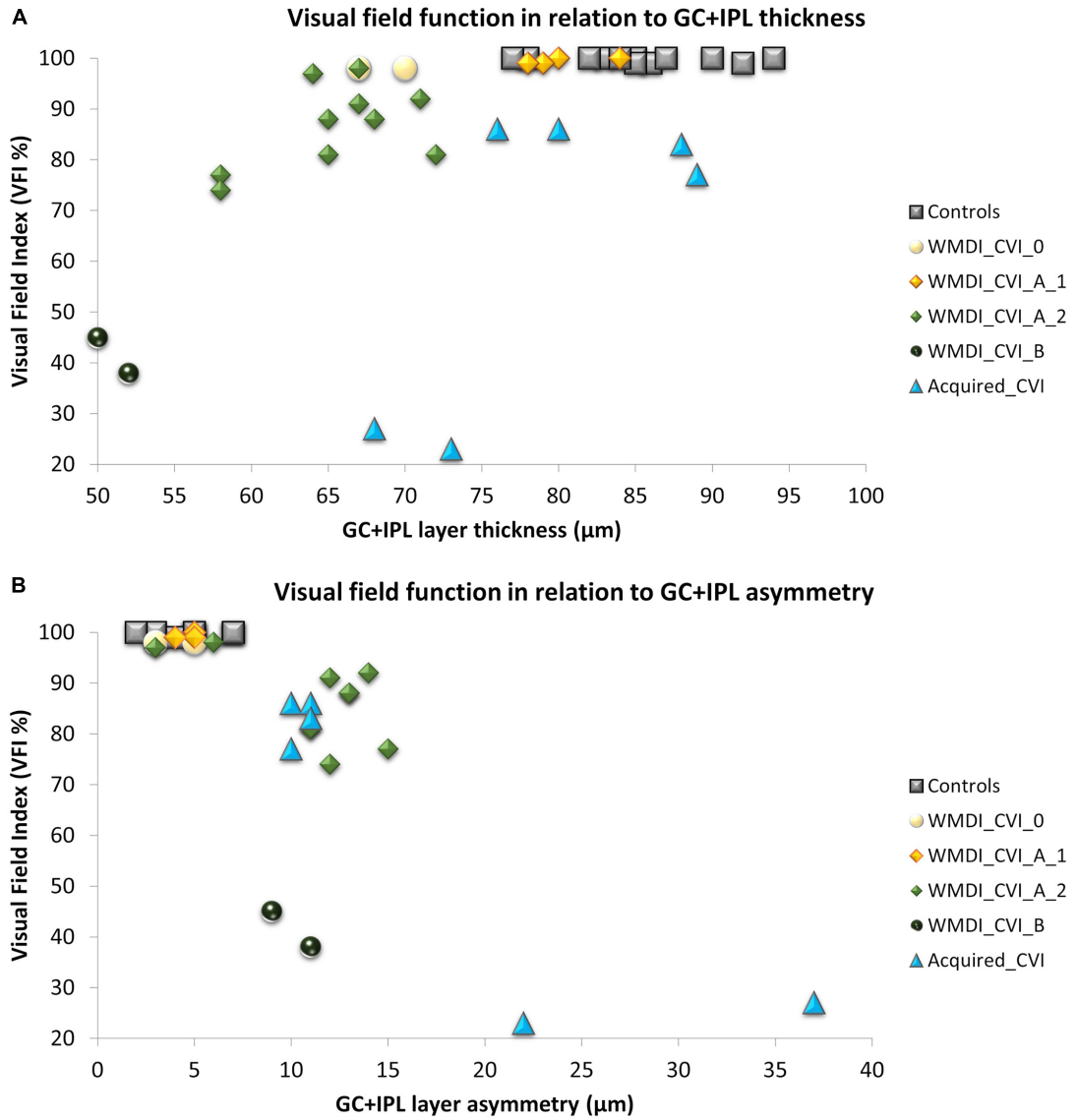

FIGURE 2 | (A) A strong association was seen between retinal structure and function in patients with WMDI. In relation to the range of controls, one WMDI without CVI showed a thin GC+IPL, all grouped as A1 had normal GC+IPL. All subjects in A2 had a thin GC+IPL. Among the three subjects with acquired CVI, one subjects had a thin GC+IPL. **(B)** All subjects with GC+IPL asymmetry had reduced VF sensitivity. CVI subgroups A1 was separated from A2 and B by GC+IPL asymmetry in all but one case graded with A2 who did not have any VF defect or GC+IPL asymmetry. WMDI, white matter damage of immaturity; CVI, cerebral visual impairment; CVI A1, A2, and B are subgroups of CVI severity according to Sakki et al. (2021) "Acquired" includes subjects with CVI due to brain injury after 18 months of age. GC+IPL, ganglion cell + inner plexiform layer.

is a migration of the inner retinal layers and creation of the foveal pit, a process that extends well into the second year of life (Dubis et al., 2012). Taken together, this indicates that dynamic processes are present in the immature visual system, throughout the perinatal and long into the post-natal period.

There is evidence of a better visual recovery after injuries to the immature visual system than after injuries sustained later in life, attributed to its superior potential for plasticity. Our experience is that bilateral WMDIs have spared central VF function within 5° based on perimetry outcome, and spared function within 11° in retinotopic mapping with fMRI (Lennartsson et al., 2018), also when the damage to the OR is comprehensive. When the central VF, in such cases is affected, a total constriction of the VF needs to be suspected. The well-preserved central VF function in bilateral WMDIs, despite thin GC+IPL, may be explained by an early re-organization of the ganglion cells. Could it be, that the normal migration of ganglion cells towards the mid-periphery becomes inhibited to cover up the central vision on behalf of the more peripheral? Interestingly, a time-dependent relationship also exists between injuries during different stages of gestation (Jacobson et al., 2010) and is linked to the different developmental stages of the immature visual system (Guzzetta et al., 2010).

In our studies, we found indications of plasticity in the immature OR (Lennartsson et al., 2018), with displacement of connections to dorsal striate cortex to the space normally solely occupied by connections to the ventral striate cortex (**Figure 1B**). Could it be the result of a compensatory mechanism to preserve the VF map by keeping connections that are normally pruned away? Perhaps as a result of retinal plasticity with an expansion of the receptive fields, and that the plasticity processes in the OR concur to promote central VF function and coverage? This could potentially be addressed by investigating the population receptive fields with functional MRI to map the receptive fields on the visual cortex (Dumoulin and Wandell, 2008).

Altogether, this review includes the results from examination of 15 teenagers/young adults. Only individuals with the intellectual and motor prerequisites to maintain fixation during OCT and capacity to carry out standardized perimetry were invited. One of these 15 did not have CVI. Of the 14 individuals with CVI, three were subtyped as A1 and eight as A2 (Sakki et al., 2021) and three had CVI caused by later acquired retro-geniculate lesions and therefore not sub-grouped. Thus, the studied individuals are not representative of all young adults with pre- or postnatal brain damage as individuals with more severe functional deficits were not invited. We have added one case (**Figure 1C**, case 5 in **Table 1**) with bilateral WMDI and CVI subgroup B, not published before, to highlight the need for further studies to understand the retinal consequences of extensive damage to the immature visual brain. This case is an example of how injury to the immature brain, can cause total loss of the VF function, sparing only the most central part, however, with extremely reduced sensitivity and no high-resolution acuity. Such severely restricted peripheral fields, known as tunnel vision, have mainly been described associated to retinitis pigmentosa and glaucoma. However, we speculate that the few survivors among the GCs in case 5, due to plasticity, and not just by chance, are spared for the very central VF. Van Hof-van Duin and Mohn (1984) described tunnel vision, assessed with confrontation, in association with perinatal hypoxic brain damage in five children.

For individuals with signs of more severe brain damage, such as CP Gross Motor Function Classification System (GMFCS) IV and V and inability to maintain fixation during OCT, there is a need for further development of OCT devices to capture reliable measurements of the GC+IPL. In these groups the risk for severe retinal degeneration secondary to damage to the OR, and severe visual impairment may be considerable, however often underestimated.

A limitation of our studies is the low number of included individuals, and that most of them represent individuals with less extensive brain damage. Future studies with handheld OCT may increase the knowledge about the prerequisites to use vision, for example for communication in non-verbal children with severe CP.

In children with brain damage, focal or general thinning of the GC+IPL indicate deficits in VF function, and a high risk of CVI. However, normal GC+IPL does not eliminate the risk for cognitive-perceptual visual impairment, CVI subgroup A1. OCT has proved to be a valuable tool in clinical pediatric ophthalmology, not only in children with diseases affecting the eye and anterior pathways, but also in children with damage to the retro-geniculate visual pathways.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Swedish Ethical Review Authority (Dnr 2020-06677) Regional Ethical Review Authority Stockholm (Dnr 2013/1114-31/2). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

FL, HMÖ, LJ, and MN contributed to the conception and design of the study, and wrote the sections of the manuscript. FL and MN performed the statistical analysis. LJ wrote the first draft of the manuscript. All authors took part of the data collection and contributed to manuscript revision, read, and approved the submitted version.

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Evaluation of the Relationship Between Preferential Looking Testing and Visual Evoked Potentials as a Biomarker of Cerebral Visual Impairment

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Cerebral visual impairment (CVI) is a leading cause of visual impairment in children in developed countries, but diagnostic tools to detect CVI are limited. We sought to analyze the visual acuity of children with CVI as assessed by visual evoked potentials (VEPs) and preferential looking test (PLT) to determine whether the relationship between the visual outcomes on these two testing methods may serve as a biomarker of CVI. We performed a retrospective chart review of patients with a confirmed diagnosis of CVI and at least one ophthalmological assessment with visual acuity measured by VEP and PLT. Of the 218 patients included in the study, the most common condition associated with CVI was an underlying genetic disorder (36%, 79/218). Treatment for seizures occurred in the majority of the entire cohort of patients (80%, 175/218). Ophthalmic comorbidities included retinal disease in 23 patients, optic nerve disease in 68 patients, nystagmus in 78 patients, and strabismus in 176 patients. When assessed by either VEP or PLT, visual acuity in children with CVI fell below expected norms. At initial and final presentations, VEP acuity exceeded PLT acuity by one or more octaves, and this difference was greater than expected compared with normal visual development. We propose utilizing this quantifiable disparity between VEP and PLT as a biomarker of CVI.

Keywords: cerebral visual impairment, CVI, visual acuity, preferential looking, visual evoked potential

INTRODUCTION

Cerebral visual impairment (CVI) is a leading cause of visual impairment in children in developed countries (Afshari et al., 2001; Good et al., 2001; Hoyt, 2003). CVI has been defined as "verifiable visual dysfunction which cannot be attributed to disorders of the anterior visual pathways or any potentially co-occurring ocular impairment" (Sakki et al., 2018), and recent studies have sought to further clarify the neuroanatomic basis of CVI (Merabet et al., 2017). The number of conditions associated with the development of CVI are myriad and include perinatal hypoxic ischemic injury, genetic disorders, metabolic disorders, infection, trauma, and epilepsy (Merabet et al., 2017). CVI

reflects brain-based visual dysfunction with often normal ocular structures (Lim et al., 2005). Thus, the diagnosis of CVI is often difficult to establish and therefore, biomarkers of CVI are needed.

The purpose of this study was to compare visual measures in children with CVI using two reliable and validated methods of testing grating visual acuity: visual evoked potential (VEP) and preferential looking test (PLT; Birch and Bane, 1991; Bane and Birch, 1992; Good, 2001). The VEP is an electrophysiologic measure of coordinated neural activity elicited by a visual grating stimulus and reflects the integrity of the visual pathway from the retina to the visual cortex (Good et al., 1994). PLT utilizes a forced choice method of visual acuity assessment and relies on higher order visual function. PLT requires that the child not only recognize the stimulus but also process and act on this detection by making a saccadic eye movement toward the stimulus (Hamilton et al., 2021). Based on this inherent difference in methodology, we hypothesize that children with CVI would exhibit reduced visual acuity measures. Further that the disparity between VEP and PLT measures may reflect higher-order cerebral dysfunction and thereby serve as a quantifiable biomarker of CVI.

MATERIALS AND METHODS

This study was approved by the Boston Children's Hospital (BCH) Institutional Review Board and conducted in compliance with the Health insurance Portability and Accountability Act and the tenets of the Declaration of Helsinki. Patients were included by waiver of consent for retrospective data collection.

A retrospective chart review of patient records from January 2005 through December 31, 2020 was performed of patients 18 years and younger at the first visit seen for at least one eye examination in the Department of Ophthalmology at BCH who had undergone VEP (CPT code 95930) and who were coded as having CVI (ICD 10 H47 619, 611, 612 or ICD 9 377.75). Charts were reviewed in detail, and the following inclusion criteria were applied: (1) confirmation of the diagnosis of CVI based on clinical history and examination findings, (2) at least one examination in which VEP and PLT were performed on the same visit. All children included in the study met the proposed criteria for diagnosis of CVI defined as "verifiable visual dysfunction which cannot be attributed to disorders of the anterior visual pathways or any potentially co-occurring ocular impairment" (Sakki et al., 2018).

Data including patient demographic, ophthalmic data, and medical history regarding conditions commonly associated with CVI were collected. Binocular test results for VEP and PLT were recorded for initial and most recent visits, when multiple visual assessments had been made for the same patient. The presence of retinal disease, optic nerve disease, nystagmus, and strabismus was recorded for each patient.

Visual Acuity Procedures

Visual acuity assessment by PLT was performed according to standard clinical practice, and as previously described in detail (Teller et al., 1986; Lim et al., 2005).

Details of the sweep visual evoked potential (sVEP) procedure have been previously described (Fulton et al., 2005; Lim et al., 2005). In brief, sVEP were recorded using the NUDiva system (Norcia and Tyler, 1985; Taylor and McCulloch, 1992). Electrodes were located as follows: the reference electrode was placed at the vertex, a ground electrode was placed on the forehead, additional placements were 3 cm above the inion (Oz) and 3 cm to the left (O1) and right (O2) (Lim et al., 2005). Stimuli consisted of a high-contrast (80%) vertical square-wave grating which was alternating at a frequency of 5.5 Hz with an average luminance of 76 cd/m^2. Gratings were swept from low to high spatial frequency during 10-s trials. The mean of 5 or more sweeps was utilized to estimate visual acuity with a linear extrapolation method determining the spatial frequency that produced a 0 μV response (Lim et al., 2005).

Data Analysis

Visual acuity measures were compared to published, normative data using PLT and sVEP in pediatric patients as a function of age (Orel-Bixler, 1989; Birch, 2006; Leone et al., 2014). PLT acuity was compared to sVEP acuity within patients on a $\log_2$-based or octave scale and their relationship was assessed by determining the Pearson correlation coefficient and a paired student's t-test. Each octave represents a doubling of spatial frequency on the grating acuity (Lim et al., 2005). Longitudinal visual acuity measures in patients with more than one visual acuity assessment evaluating initial and most recent visits were compared using a paired student's t-test. In all cases, $p < 0.05$ was considered the threshold for statistical significance.

RESULTS

The charts of 311 patients who were coded as CVI with a VEP were reviewed. Patients who were older than 18 years at their first visit, in whom a diagnosis of CVI could not be confirmed, and for whom both visual acuity measures were not obtained at a single eye exam were excluded. In total, 218 patients (104 females, 114 males) met inclusion criteria for the study.

Cerebral Visual Impairment Phenotype

The clinical characteristics of this cohort are summarized in **Table 1**. Of the 218 patients meeting inclusion criteria, underlying genetic disease was the most frequent medical condition, affecting 79 patients (36%). Genetic abnormalities included 8 patients (4%) with chromosomal abnormalities; in addition, genetic diagnoses were heterogeneous and included those associated with neurodevelopmental abnormalities and seizures such as Rett syndrome and GRIN associated disorders. Additional comorbidities included a history of prematurity, prematurity with periventricular leukomalacia (PVL) confirmed with magnetic resonance imaging of the brain or computed tomography of the head, congenital brain malformations, perinatal insult, traumatic brain injury during the first year of life, and neurodegenerative disease. The category denoted as "Other" comprised of patients with complex neurological,

TABLE 1 | Clinical characteristics of cerebral visual impairment (CVI) cohort.

	N = 218	(%)
Sex, Female	104	48
Associated Primary Medical Comorbidity		
Prematurity	16	7
Prematurity with Periventricular Leukomalacia	10	5
Genetic Disorder	79	36
Congenital Brain Malformation	36	17
Hypoxic Ischemic Encephalopathy	27	12
Traumatic Brain Injury	11	5
Perinatal Meningitis/Encephalitis	7	3
Perinatal Stroke	8	4
Neurodegenerative Disease	7	3
Congenital Cytomegalovirus or Toxoplasmosis Infection	4	2
Other	13	6
Treatment for Seizure Disorder	175	80
Cerebral Palsy	61	28

TABLE 2 | Ophthalmological characterization of CVI patients.

Age at Testing	**Median (year:months)**	**Range (year:months)**
Age at first visual acuity assessment (*N* = 218)	1:8	0:2–17:10
Age at recent visual acuity assessment (*N* = 152)	6:1	0:11–20:0
Ophthalmological findings	N	(%)
Diagnosis of CVI	218/218	100
Nystagmus	78/218	36
Strabismus	176/218	81
Esotropia	35/176	19.9
Exotropia	140/176	79.5
Hypertropia	1/176	0.6
Retinal disease	23/218	11
Optic nerve disease	68/218	31
Visual Acuity	N	Mean (cycles per degree)
PL acuity at first assessment	218/218	2.0
sVEP acuity at first assessment	218/218	5.5
PL acuity at recent assessment	152/218	2.8
sVEP acuity at recent assessment	152/218	11.2

developmental, and medical histories without a definitive diagnosis or one which did not fall into the categories listed above. Among the cohort, 175 (80%) were treated with continuous medication and followed by neurology for a seizure disorder.

Ophthalmological Phenotype

The ophthalmological profile is outlined in **Table 2**. The median age at first assessment of visual acuity assessment was 1 year 8 months (range 2 months – 17 years 10 months). 152 patients had longitudinal assessments of visual acuity measured by both PLT and VEP methods. The median age at most recent assessment of visual acuity was 6 years and 1 months (range 11 months – 20 years). A subset of patients had ocular abnormalities which included 23 patients with retinal disease and 68 patients with optic nerve disease including optic nerve pallor and hypoplasia. Nystagmus was observed in 78 patients and strabismus was observed in 176 patients; among children with strabismus, the majority had an underlying exotropia.

Visual Acuity

Visual acuity measures for binocular acuity are plotted as a function of age in **Figure 1**. Overall visual acuity measures were worse for patients with CVI compared to age-matched, published normative data (Leone et al., 2014). The overall mean preferential looking acuity in patients with CVI was 2 cpd (range 0.2–12.8 cpd). The mean preferential looking acuity of 1-year old infants in this cohort with CVI was 1.7 cpd (n = 11) compared with a mean of 6.7 cpd (Leone et al., 2014). Only two patients exceeded the mean PL acuity compared with age matched normative data. The majority of patients fell below the lower 95% prediction limit compared with the normative group (Leone et al., 2014). Longitudinal normative data have been published using PLT (Leone et al., 2014). At 33 months old, in the CVI study cohort, mean visual acuity was 2.2 cpd (n = 8) compared with a mean preferential acuity of 12.6 cpd in a population with normal development (Leone et al., 2014).

In the CVI study cohort, the overall mean sVEP acuity was 5.5 cpd (range 0.4–26 cpd). When focused on the subgroup of 1-year old patients in this cohort, the mean sVEP acuity was 4.6 cpd (n = 11) compared with a mean sVEP acuity of 16.9 cpd in normal visual development (Birch, 2006). At 33 months, in the CVI study cohort, the mean sVEP acuity was 9.2 cpd (n = 8). In comparison to age matched normative data, the sVEP acuity for the CVI study cohort fell below the lower 95% prediction limit (Orel-Bixler, 1989; Birch, 2006).

Of the 218 patients evaluated, 152 (70%) had additional measures of visual acuity by PLT and sVEP on subsequent eye visits. The results of acuities assessed by PL and sVEP methods at the patient's most recent visit are seen in **Figures 1C,D**, respectively. At the most recent visit, visual acuity continued to be subnormal when tested by either method. At the final visit, mean PL acuity was 2.8 cpd (range 0.13–15 cpd) and mean sVEP acuity was 11.2 cpd (range 1.2–32 cpd). Compared with the first visit, there was a demonstrable improvement in vision which was statistically significant both for PLT ($p = 0.004$) and also for sVEP ($p < 0.001$).

Figure 2 demonstrates the relationship between PLT acuity and sVEP acuity. Nearly all data points are located above the line of unity, illustrating that visual outcome measured by sVEP exceeds that measured by PLT. Furthermore, the majority of data points lie above the dashed line signifying that sVEP exceeds PL acuity by 1 or more octaves at the first (**Figure 2A**) and most recent (**Figure 2B**) assessment. At first assessment of visual acuity, a moderate correlation was found between preferential looking and sVEP acuities (Pearson correlation, $r = 0.72$, $p < 0.001$). This result was also observed at the most recent assessment of visual acuity (Pearson correlation, $r = 0.48$, $p < 0.001$).

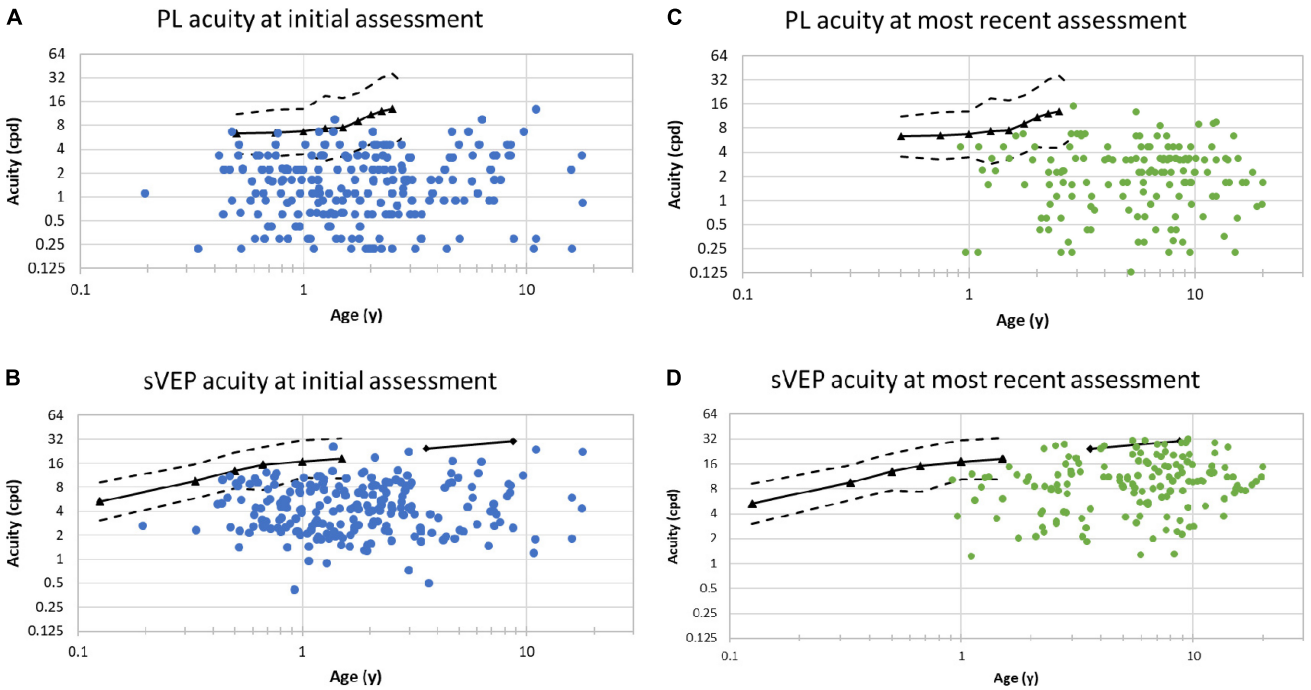

FIGURE 1 | Binocular visual acuities assessed by two different methods at two distinct time points. Acuity (ordinate) is on a $\log_2$ scale and age (abscissa) is on a $\log_{10}$ scale; cpd indicates cycles per degree. **(A)** Preferential looking acuities at first clinical visit. **(B)** Sweep visual evoked potential (sVEP) acuities at first clinical visit. **(C)** Preferential looking acuities at most recent clinical visit. **(D)** sVEP acuities at most recent clinical visit. **(A,C)** Mean normal preferential looking acuity (black triangles) and the 95% limits of normal acuity (dashed lines) based on published results in age matched controls (Leone et al., 2014). **(B,D)** Mean sVEP acuities in typically developing children (black triangles Birch, 2006 and diamonds Orel-Bixler, 1989) based on published findings; the dashed lines represent the 95% limits of normal acuity.

DISCUSSION

Herein, we present binocular visual acuity outcomes in pediatric patients with CVI. To our knowledge, this is the largest study of visual outcome measures in children with CVI. We found that in comparison to normal development, patients with CVI had worse visual acuities when assessed by either method. In most cases, sVEP acuity was better than PL acuity. Longitudinally, although visual acuity did improve, children with CVI continued to demonstrate subnormal vision for age.

The main objective of this study was to assess the relationship between PL and sVEP acuities in patients with CVI. For most patients, we found that sVEP acuities exceeded PL acuities by more than one octave at initial and last assessment. Although in early visual development, VEP acuity is expected to mature more rapidly than PL acuity, this disparity is thought to be on the order of 1 octave in normal development; with visual maturation, the gap between the two measures is anticipated to narrow (Lim et al., 2005). In contrast, we found in children with CVI, the difference between VEP acuity and PL acuity is larger than expected compared with normal development and this continued to be present in spite of visual maturation. Beyond subnormal vision for age by both measures, we hypothesize that both the extent and the persistence of this difference between PLT and sVEP acuity at any given age in the cohort may be a potential indicator of CVI and this warrants further investigation. This profile seen in the CVI study cohort is distinct from normal visual development in which unequal performance on these measures in early visual development (sVEP exceeding PLT) should narrow to more symmetric performance once vision matures normally (Lim et al., 2005). Although it is possible that the comorbidity of cerebral palsy (CP), which occurred in 28% of this cohort, may contribute to difficulty in performance on PLT with respect to oculomotor function, the disparity between the two visual acuity measures occurred in patients with or without CP. Therefore, this disparity between the two measures cannot be explained by CP alone, but likely reflects more global dysfunction in CVI in which there are deficits in visual perception, visual attention, and oculomotor function (Salati et al., 2002).

The results of this study are consistent with previously published reports on the relationship between PL and sVEP acuity in the context of CVI (Good, 2001; Lim et al., 2005; Watson et al., 2010; Olson et al., 2021). In one study of 19 patients with CVI associated with a history hypoxic-ischemic encephalopathy, the authors found the discrepancy between VEP and PL acuity to be greater than one octave in more than half of the patients (Lim et al., 2005). More recently, a similar disparity between PL and sVEP acuities were

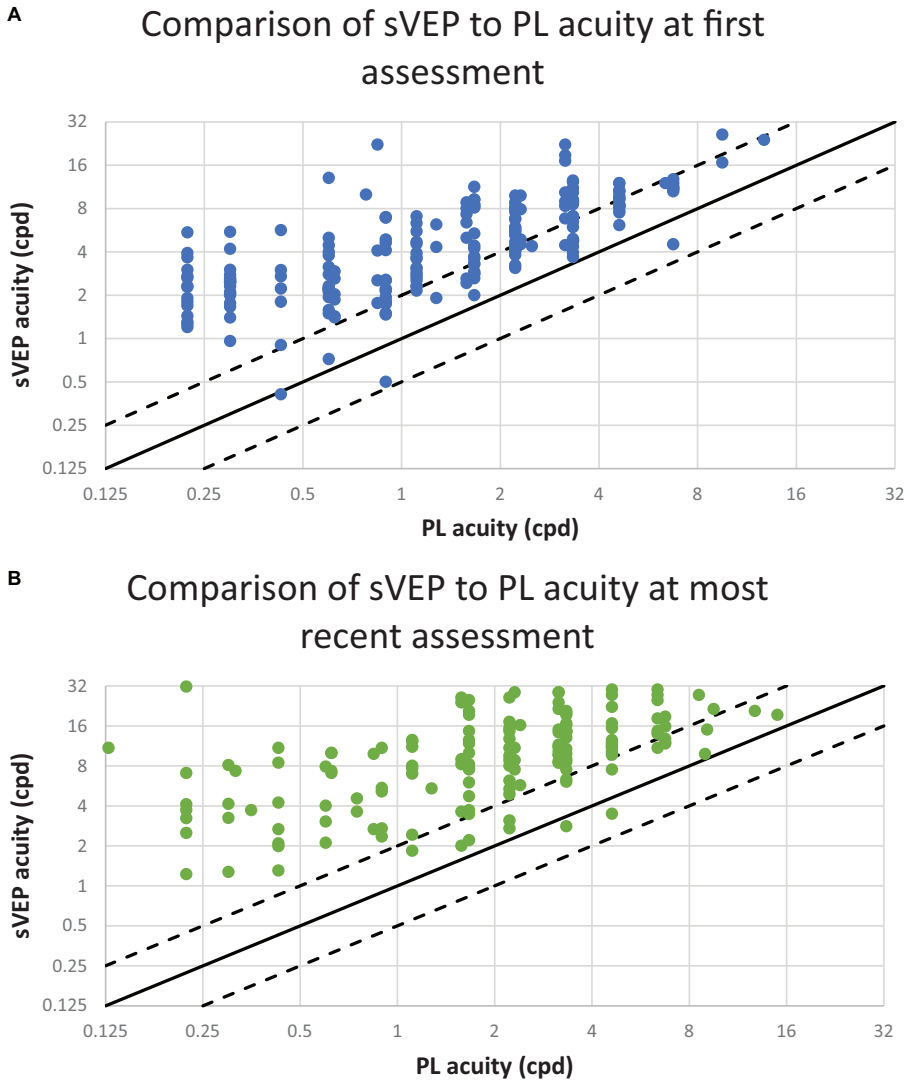

FIGURE 2 | The relationship between preferential looking (PL) and visual evoked potential (VEP) acuities. Each point represents one patient. The diagonal lines have a slope of 1.0. The solid line represents PL and sVEP acuity values in perfect agreement. The dashed lines 1 octave above and below the solid line. The ordinate and the abscissa are a $\log_2$ scale; cpd indicates cycles per degree. **(A)** Visual acuity assessments conducted at the patient's first visit. The results from 225 patients are plotted. **(B)** Visual acuity assessments conducted at the patient's most recent visit. The results from 156 patients are plotted.

described in 11 patients with a genetically confirmed seizure disorder CDKL5 and CVI (Olson et al., 2021). Our study expands on the generalizability of these findings with visual acuity measures from over 200 patients and the inclusion of patients with a diverse range of medical conditions associated with CVI. The study was limited by the requirement for measurement of VEP and PLT at the same visit which may have biased the cohort toward those patients whose visual dysfunction was more profound. Therefore, the applicability of our findings to patients with visual perceptual disorders who may perform optotype acuity testing is uncertain and warrants further investigation.

Diagnosing CVI can be challenging due to its variability in clinical presentation, the presence of additional comorbidities, and the fact that CVI reflects brain-based visual dysfunction. This highlights the need to identify a quantifiable visual profile or visual biomarker of disease to aid in establishing the diagnosis of CVI. In this study, we have shown that visual acuity by PLT and sVEP is consistently lower in patients with CVI across a range of etiologies. Further, the gap in PL and sVEP acuities exceeds what is expected in normal development. Future studies that evaluate the relationship between this potential indicator of CVI and other aspects of functional vision, neuroimaging findings, or cognitive and motor development will allow for a more thorough characterization of the clinical phenotype of CVI and yield insight into areas of accommodation and support for children impacted by this condition.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because they contain identifiable information. Requests to access the datasets should be directed to GH, gena.heidary@childrens.harvard.edu.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Boston Children's Hospital (BCH) Institutional Review Board and conducted in compliance with the Health insurance Portability and Accountability Act and the tenets of the Declaration of Helsinki. Patients were included by waiver of consent for retrospective data collection. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

GH conceptualized the study, analyzed the results, contributed to manuscript preparation, and approval for publication. SR conducted the chart review and analyzed the results. BE conducted the chart review. All authors contributed to the preparation of the manuscript and approval for publication.

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BRIEF RESEARCH REPORT
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The Developmental Eye Movement Test as a Diagnostic Aid in Cerebral Visual Impairment

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The symptoms that characterize children with cerebral visual impairments (CVI) are diverse, ranging from extensive behavioral or physical disabilities to subtle changes that can easily be missed. A correct diagnosis of CVI is therefore difficult to make, but having a wide variety of tests available can be helpful. This study aims to determine if the developmental eye movement test (DEM) can be one of those tests. In this test, a fixed set of numbers has to be read aloud, first in vertical columns and then in horizontal lines. In order to measure differences between children with CVI compared to normally sighted age-matched controls and children with a visual impairment (VI), we determined DEM times, crowding intensities and the reaction time to a large visual stimulus for all three groups. We found that children with CVI or VI need significantly more time to read the DEM numbers than age-matched controls. Additionally, children with CVI need more time than children with VI to read the horizontal DEM, but not the vertical DEM. We also found a significant difference between the children with CVI and the other two groups in the relationship between horizontal DEM performance and crowding intensity. However, for the relationship between DEM performance and visual detection time, no group-differences were found. We conclude that the DEM can be a useful addition in the diagnosis of CVI, especially in combination with information about crowding.

Keywords: cerebral visual impairment (CVI), visual impairment (VI), visual processing speed, diagnostic, developmental eye movement test (DEM)

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INTRODUCTION

The Developmental Eye Movement test (DEM) is a number naming test that was originally designed to measure oculomotor deficiencies without expensive equipment (Garzia et al., 1990). The first two subtests measure the time that a child needs to read two columns of numbers from top to bottom. The third subtest records the time needed to read sixteen rows of numbers from left to right. Although previous studies indicate that comparing the horizontal and vertical DEM scores is not a good method to detect oculomotor deficiencies (Ayton et al., 2009; Tanke et al., 2021), the DEM does reflect clinically relevant factors. For instance, DEM performance relates to the level of academic performance (Garzia et al., 1990; Wood et al., 2018; Hopkins et al., 2019), reading rate

(Northway, 2003; Palomo-Alvarez and Puell, 2009; Facchin et al., 2011; Serdjukova et al., 2016), and speed of visual processing (Ayton et al., 2009; Tanke et al., 2021).

Slower visual processing often occurs in children with cerebral visual impairments (CVI) (Kooiker et al., 2016; Barsingerhorn et al., 2018b). CVI is a visual impairment that is caused by malfunctions in the central visual pathways due to pre, post or perinatal damage to the brain or caused by congenital abnormalities which can lead to visual impairments like difficulties with contrast, depth or recognizing objects (for reviews, see Philip and Dutton, 2014; Lueck et al., 2019). CVI impairments are widely variable and can sometimes be subtle and difficult to detect (Lowery et al., 2006). For example, the visual acuity of children with CVI can range from complete blindness to normal vision. Yet, even children with CVI with a normal visual acuity often show exacerbated visual crowding (van Genderen et al., 2012), a difficulty identifying visual information when it is closely surrounded by visual flankers (Bouma, 1970; Huurneman et al., 2012a). It is because of these wide-ranging features that a wide variety of diagnostic tools is required. This study aims to determine if the DEM can be one of those diagnostic aids for children with CVI.

Previous work has shown that, for normally sighted (NS) children, the DEM scores are positively correlated to fixation duration and visual processing speed (Tanke et al., 2021). However, when looking at cartoons, children with CVI use shorter fixation durations compared to controls and children with visual impairments (VI), but they direct their gaze to a larger area (Kooiker et al., 2016), suggesting that the fixation control of children with CVI is not optimal. Additionally, adults with CVI show a more diffuse search pattern than controls when visual information becomes more crowded (Bennett et al., 2019). During the horizontal DEM, the numbers are inconsistently spaced to minimize automaticity (Garzia et al., 1990). This inconsistent spacing can be challenging for children who use sub-optimal search patterns. We therefore studied the differences in DEM scores and visual information processing between NS children, children with CVI and children with VI. DEM performance, in combination with information about visual processing speed and crowding, can provide valuable information for the diagnosis of children with CVI.

METHODS

Participants

A total number of 158 children aged 5–17 years were recruited. All the children had a visual acuity better than 1.3 LogMAR. For NS children (n = 96, 9.4 ± 2.0 years) and children with VI (n = 33, 9.0 ± 2.4 years), inclusion criteria were normal birth weight (> 2,500 g), birth at term (> 36 weeks), no perinatal complications and normal development. NS children had a linear distant visual acuity of 0.1 logMAR or better, VI children had a visual acuity worse than 0.1 LogMAR. The only inclusion criterium for the children with CVI (n = 30, 9.2 ± 1.6 years) was having the diagnosis of CVI. The diagnosis of CVI was made by ophthalmologists of Bartiméus institute or Royal Dutch Visio, Dutch institutes for the rehabilitation of the visually impaired. After 2019, the Dutch CVI guidelines were applied to obtain the diagnosis (Federatie Medisch Specialisten, 2019). Children with glasses wore them during all tests. For NS children, testing occurred at the children's primary schools. Children with VI and CVI were recruited from Bartiméus (VI; n = 28, CVI; n = 16) or the Royal Dutch Visio (VI; n = 5, CVI; n = 14, for details see Barsingerhorn et al., 2018b; **Supplementary Table 1**).

Informed consent was obtained from the parents of all participants. The study was approved by the local ethics committee Commissie Mensgebonden Onderzoek regio Arnhem-Nijmegen, Netherlands (protocol NL48708.091.14), and conducted according to the principles of the Declaration of Helsinki.

Ophthalmologic Examination

The Freiburg visual acuity test (Bach, 1996) was used to determine the distal visual acuity. For NS children, the uncrowded chart used a fixed inter-letter spacing of at least 30 arcmin, while crowded visual acuity was measured with spacing of 2.6 arcmin. For the children with VI or CVI, crowding was determined binocularly with the LEA version of the *C*-test. The LEA test consisted of the same uncrowded and crowded chart versions as the *C*-test but presented symbols in a larger size range of 0.3–1.7 logMAR.

Crowding intensity was defined as the difference between crowded and uncrowded visual acuities in logMAR (Huurneman et al., 2016c).

Developmental Eye Movement Test

The DEM (**Figure 1A**) consisted of high contrast numbers of 4.9 mm in height (LogMAR 0.71, similar to the paper version of the DEM) that had to be read aloud. For each subtest of the DEM, the numbers were shown all at once. Children first practiced with a DEM pre-test to familiarize them with the task, and to make sure that they could read the numbers. The pre-test was a shortened version of each DEM subtest with randomized ordering of the numbers. Then, children had to name the numbers of test A from top to bottom, one column at a time, as quickly as possible. All the numbers of a subtest appeared on the computer screen as soon as the experimenter pressed the space bar and disappeared when the experimenter pressed the space bar again as soon as the child had read the last number. These start and stop moments were recorded by the software. Test A was followed by test B, which is similar to A but with the numbers in a different order.

The numbers of test C had to be named row by row from left to right, starting at the top left. Horizontal time was taken as the total time to name the first to the last number of test C. For the full list of numbers used and details concerning number spacing and number size see Garzia et al. (1990) and Tanke et al. (2021).

Visual Detection Task

The children also performed a visual detection task (VDT) at the same distance as the DEM to measure the time children needed to respond to a supra-threshold stimulus. In the VDT (20 trials), they had to press a mouse button as soon as they saw the

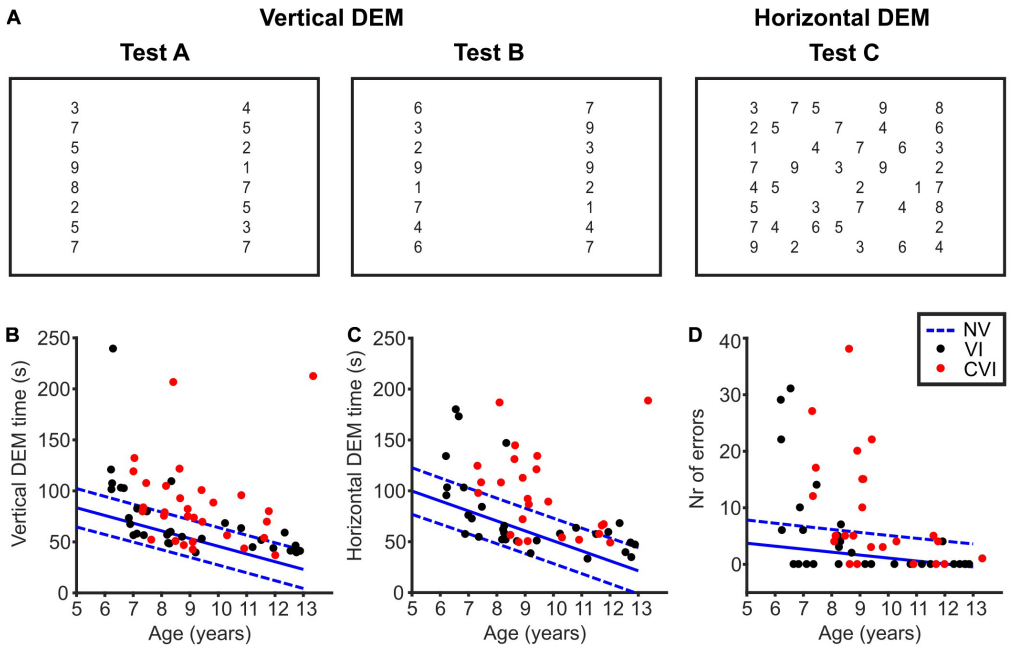

FIGURE 1 | The developmental eye movement test (DEM). **(A)** Overview of the DEM test. Numbers not drawn to scale. Adopted from Tanke et al. (2021). **(B)** Total time needed to read the numbers of the vertical DEM (test A + B) for children with VI (black dots) and CVI (red dots). In blue, the mean (solid line) vertical DEM times of NS children and the corresponding 90% prediction intervals indicated by the 5th and 95th percentile (dashed lines) of the duration distributions. **(C)** Same as for **(B)**, but for the error-adjusted horizontal DEM time (test C). **(D)** Same as for **(B)**, but for the number of errors made during the horizontal DEM.

visual stimulus (a large high-contrast black letter "O," for details see Barsingerhorn et al., 2018a).

Equipment

The stimulus software used at the schools and Bartiméus was written in Matlab (version 2013b) using the Psychophysics Toolbox (version 3.0.12; Kleiner et al., 2007). At Royal Dutch Visio, the stimulus software was written in Python using PsychoPy3 (version 2020.2.10; Peirce et al., 2019). In both versions of the software, stimulus timing and button presses were recorded and stored at millisecond precision. The visual stimuli were presented on a 23-inch LCD screen (Dell, Inc., 1,920 × 1,200 pixels).

Procedure

To assess the visual acuity binocularly, children first participated in the Freiburg visual acuity test (Bach, 1996) administered digitally at 5 meters distance. Then, a paper version of the LEA test was administered at 40-cm viewing distance. Secondly, the computer screen was moved to ∼65 cm viewing distance for the DEM and the VDT.

Data Analyses

The offline analysis was performed and images were created using Matlab (version 2020b).

DEM

Total vertical time was taken as test A + test B. If only test A was completed, vertical time was taken as 2 times test A (Tanke et al., 2021). Time to complete test C was adjusted for omissions and additions (Richman and Garzia, 1987). Repeating a whole line counted as five addition errors. Skipping one-line counts as two omission errors. The time for test A and B was not adjusted for errors because of the limited number of errors made during those tests. The number of errors was determined by adding the number of omissions and additions in test *C*.

$$\text{Adjusted time test } C = \text{Time test C} * [80/(80 - \text{omissions} + \text{additions})]$$

VDT

Mean reaction times were computed after removing atypically long or short reaction times. Trials were excluded if the reaction time deviated more than three times the median absolute deviation from the median after discarding reaction times < 0.1 s.

Statistical Analyses

Correlation coefficients were calculated using Pearson's correlation coefficient, and Pearson's linear partial correlation with age as a confounding variable. Multiple linear regression with age as a co-variable was used to test average differences in DEM times between groups, using group as a categorical variable (model: *DEM*∼ *group* + *age,* Wilkinson notation). Subsequently, we included either the reaction time measured in the VDT or the crowding intensity in the regression to test whether these

factors could account for any additional variability between participants. The power (1–β) of these regression models to detect medium-size effects ($f^2 = 0.15$) at a significance level (α) of 0.05 was > 0.95 (Faul et al., 2007, 2009). Furthermore, a Kolmogorov-Smirnov test showed that both the vertical DEM scores and the horizontal DEM scores were normally distributed. To assess the impact of outliers, robust linear regressions were performed too, but since the results were similar to standard linear regression with equal weights for all data points, they are not reported in this manuscript.

RESULTS

Children were asked to read the numbers of the DEM aloud (**Figure 1A**). All the children participated in both the vertical and the horizontal DEM. However, the horizontal DEM was too difficult for a small number of children (NS, 2/96; VI, 2/33; CVI, 6/30). These children did not read the numbers row by row, but skipped from one row to another on numerous occasions, making it impossible for the experimenter to follow which number was read from which location. We therefore excluded the horizontal DEM scores of these 10 participants. For the other 149 children, scores were correctly documented and the horizontal DEM time was adjusted for the number of errors made (see section "Methods" for details).

Developmental Eye Movement Test Scores and Age

When looking at **Figures 1B,C**, it is implicated that DEM times get better with age. For both the vertical DEM and the horizontal DEM, the relationship between DEM and age for the CVI and VI groups did not differ significantly from the NS children [vertical DEM; VI; $t(126) = 1.06$, $p = 0.29$, CVI; $t(123) = -0.59$, $p = 0.55$, horizontal DEM; VI; $t(122) = 0.36$, $p = 0.72$, CVI; $t(115) = 1.50$, $p = 0.14$, DEM∼age*group]. For all the groups taken together, the slope of the vertical DEM was -6.61 ± 0.85 s/year ($p < 0.001$) and the slope of the horizontal DEM was -9.80 ± 1.30 s/year ($p < 0.001$). This shows that, indeed, DEM performance is age-dependent for all three groups of children. Therefore, age was included in all the regression analyses in this study.

Group Differences in Developmental Eye Movement Test Scores

NS children needed on average 50.3 s (95% CI: 46.6–54.1) to read the numbers of the vertical DEM, and 56.1 s (95% CI: 51.4–60.8) for the horizontal DEM. Children with VI, on the other hand, needed significantly more time [**Figures 1B,C**, vertical DEM; 20.2 s longer (95% CI: 10.3−30.1), $t(126) = 3.44$, $p < 0.001$, horizontal DEM; 18.1 s longer (95% CI: 6.8−29.3), $t(122) = 3.05$, $p = 0.003$, linear regression]. Likewise, children with CVI needed more time than NS children [vertical DEM; 35.4 s longer (95% CI: 24.7−46.1), $t(123) = 6.51$, $p < 0.001$, horizontal DEM; 40.2 s longer (95% CI: 27.7−52.7), $t(115) = 7.34$, $p < 0.001$, linear regression]. In total, 11/33 children with VI and 18/30 children with CVI scored above the 95th percentile of NS children for the vertical DEM. For the horizontal DEM, that was the case for 8/31 children with VI and 15/24 children with CVI. No significant differences were found in vertical DEM scores between children with VI and CVI [15.2 s shorter for VI (95% CI: −4.8−35.2), $t(60) = 1.73$, $p = 0.09$]. However, children with CVI did need more time than children with VI to read the numbers of the horizontal DEM [22.2 s longer (95% CI: 0.7−43.7), $t(52) = 2.53$, $p = 0.015$, linear regression].

This difference between the two patient groups was also seen in the number of errors made during the horizontal DEM. Children with CVI made significantly more errors than children with VI [**Figure 1D**, 4.2 more errors (95% CI:−0.8−9.1), $t(52) = 9.39$, $p < 0.001$, Poisson regression]. NS children made on average 1.4 errors (95% CI: 0.9−1.9), which was significantly less than children with VI and CVI [VI; 3.4 more errors (95% CI: 1.5−5.3), $t(122) = 8.18$, $p < 0.001$, CVI; 7.6 more errors (95% CI: 5.3−9.8), $t(115) = 18.13$, $p < 0.001$, Poisson regression]. A total number of 6/31 children with VI and 10/24 children with CVI scored above the 95th percentile of the control group.

Visual Detection Time

All the children in this study also participated in a simple VDT where a button had to be pressed as soon as a large circle appeared on a computer screen (Barsingerhorn et al., 2018a). An increased reaction time in the VDT indicates that the child needs more time to respond to visual information. NS children took, on average, 347 ms (95% CI: 329−366) to respond to the VDT stimulus. Children with VI needed, on average, 84.4 ms (95% CI: 46.3−122.4) more to respond to the VDT, and children with CVI 187.7 ms (95% CI: 143.7−231.6) more. As described previously, vertical and horizontal DEM times were strongly correlated to visual processing speed for NS children (Tanke et al., 2021).

Figure 2 shows the relationships between DEM performance and VDT for the CVI and VI groups. No significant differences were found between the two patient groups for the regression between VDT and DEM performance adjusted for the effect of age [vertical DEM; $t(58) = 0.07$, $p = 0.95$, horizontal DEM; $t(50) = 0.26$, $p = 0.80$, DEM∼VDT*group + age]. Therefore, the two groups were pooled together in the analysis. A significant relationship was found between VDT and vertical DEM time [$t(60) = 2.74$, $r = 0.33$, $p = 0.008$, DEM∼VDT + age] but not between VDT and the horizontal DEM [$t(52) = 1.54$, $r = 0.21$, $p = 0.13$].

Crowding Intensity

Additional to the VDT, the crowding intensity was determined for most but not all of the participating children (NS; 91/96, VI; 24/33, CVI; 28/30). Children with VI had a mean crowding intensity of 0.18 LogMAR (95% CI: 0.12–0.24) compared to 0.16 LogMAR (95% CI: 0.12–0.21) for the children with CVI. NS children had an average crowding intensity of 0.06 LogMAR (95% CI: 0.04–0.08), and vertical and horizontal DEM times were strongly correlated to the crowding intensity (data not shown; vertical DEM; $r = 0.41$, $p < 0.001$, horizontal DEM; $r = 0.42$, $p < 0.001$). However, since both DEM performance (Tanke et al., 2021) and crowding (Huurneman et al., 2012a) are age-dependent in NS children, the correlation between DEM performance and crowding intensity was lost when age was added

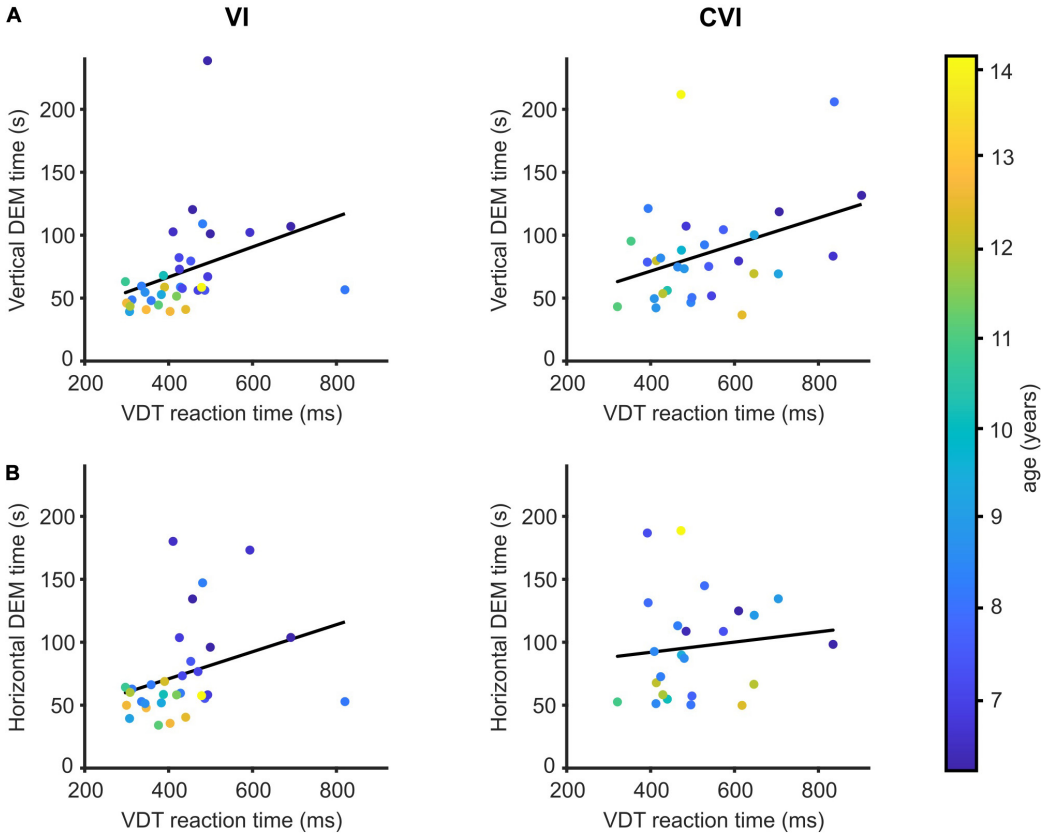

FIGURE 2 | DEM performance in relation to visual detection time. **(A)** Mean reaction time to detect a large visual stimulus compared to the time needed to perform the vertical DEM for children with VI (left) and children with CVI (right). Regression lines in black. Data points are color-coded by age of the child. **(B)** Same as **(A)**, but for the horizontal DEM.

as a covariate (correlation after adjusting for age: vertical DEM; $r = 0.15$, $p = 0.15$, horizontal DEM; $r = 0.19$, $p = 0.07$).

No significant differences were found between the VI and CVI groups for the regression between crowding intensity and vertical DEM performance adjusted for the effect of age [**Figure 3A**, $t(47) = 1.01$, $p = 0.32$, DEM∼crowding*group + age]. With the two patient groups pooled together, no significant relationship was found between crowding intensity and vertical DEM performance [$t(49) = 0.38$, $p = 0.71$, DEM∼crowding + age]. However, for the relationship between horizontal DEM performance and crowding intensity we did find a significant difference between the children with CVI and the children with VI [**Figure 3B** $t(39) = 2.77$, $p = 0.008$, DEM∼crowding*group + age]. A significant relationship between crowding intensity and horizontal DEM was found for children with CVI [$t(19) = 2.20$, $r = 0.45$, $p = 0.04$], but not for the children with VI [$t(19) = 1.47$, $r = -0.32$, $p = 0.16$, DEM∼crowding + age].

DISCUSSION

Our results show that children with CVI and VI need significantly more time to read the numbers of the vertical and the horizontal DEM than age-matched controls. Additionally, children with CVI need more time to read the horizontal DEM than children with VI. We also explored whether visual detection time and visual crowding could explain some of the variability in DEM scores of the patients, and whether these factors played a different role in children with VI compared to children with CVI. We found that individual differences in crowding intensity, but not in visual detection time, explained part of the variation in horizontal DEM scores.

Developmental Eye Movement Test Scores and Age

Vertical and horizontal DEM times improve with age for NS children. The results for the CVI and VI groups were not significantly different from those in the NS group. However, within the group of children with CVI, the correlation between age and DEM performance was not statistically significant (vertical DEM; $r = -0.02$, $p = 0.91$, horizontal DEM; $r = -0.18$, $p = 0.39$). Perhaps, this is due to the relatively small group size. Another possibility is that the developmental age of children with CVI does not match their biological age, and that DEM performance would be better explained by the children's developmental age. Since we could only include children who can

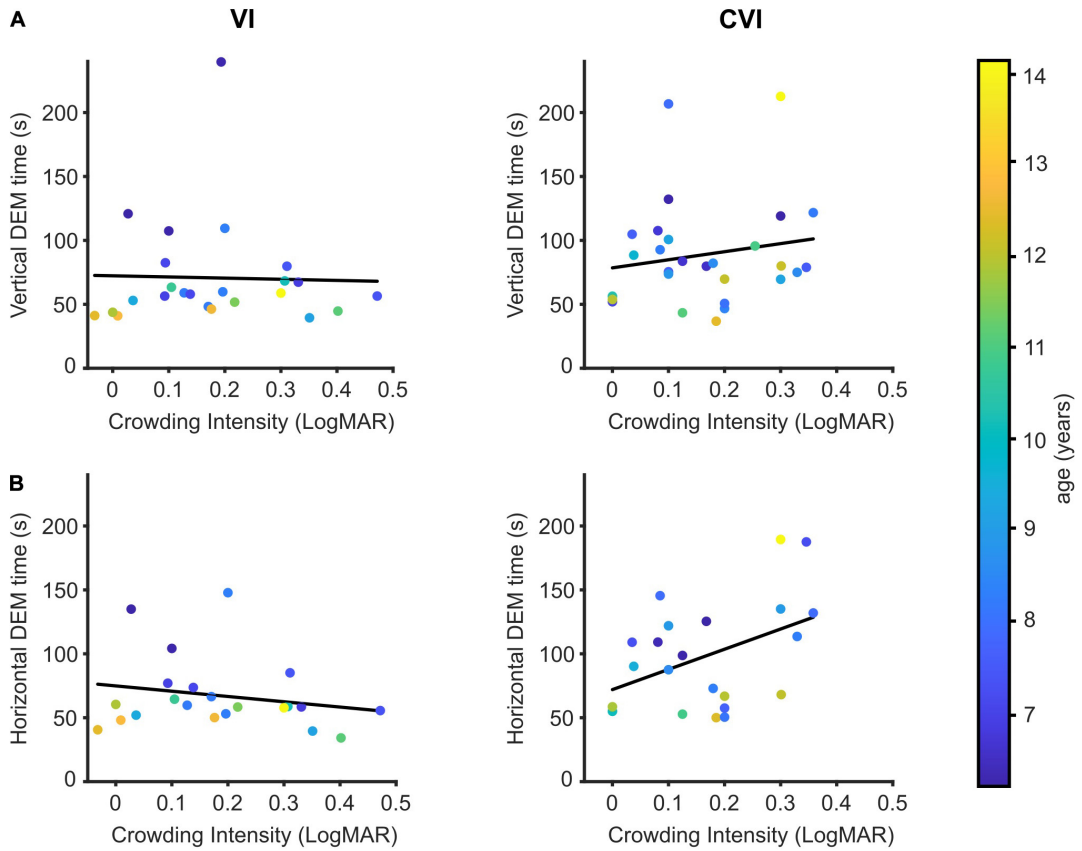

FIGURE 3 | DEM performance in relation to crowding intensity. **(A)** Crowding intensity compared to the time needed to perform the vertical DEM for children with VI (left) and children with CVI (right). Regression lines in black. Data points are color-coded by age of the child. **(B)** Same as **(A)**, but for the horizontal DEM.

read numbers, children with severe developmental impairments were not represented in this dataset. Although children with VI have ocular deficiencies that cause a decreased visual acuity (for details, see **Supplementary Table 1**), their birthweight and development is suspected to be normal (1/33 showed signs of developmental delay). Ten out of the thirty children with CVI, on the other hand, were suspected to show a developmental delay, making the exact developmental age of these children difficult to determine. It is therefore possible that our results underestimate the relation between DEM performance and age.

Developmental Eye Movement Test Performance Differences Between Groups

Children with VI or CVI need more time than NS children to read the numbers of both the vertical and the horizontal DEM. Especially the horizontal DEM was challenging for some of the children with VI or CVI. On average, children with CVI made significantly more errors on this subtest than children with VI. In fact, we may have underestimated this difference: twenty percent (6/30) of the children with CVI were unable to correctly participate in the horizontal DEM even though they had no problems reading the numbers of the vertical DEM. By comparison, only 6% (2/33) of the children with VI and 2% (2/96) of the NS children had so much trouble with the horizontal DEM that their errors could not be scored correctly. This fact alone indicates difficulties for CVI children in recognizing complicating information. DEM scores can be affected by a variety of factors, like academic performance and number naming. For example, two boys with CVI had difficulties recognizing the number seven; they had to count up from four every time. Another possible factor that can influence DEM times is oculomotor behavior; 20/33 children with VI and 8/30 children with CVI experienced some degree of nystagmus (**Supplementary Table 1**). However, reading speed can be nearly normal for people with infantile nystagmus (Barot et al., 2013; Dysli and Abegg, 2016; Huurneman et al., 2016b). Children with CVI need more time to read the horizontal DEM than children with VI. This effect could be due to differences in visual acuity or oculomotor problems. However, oculomotor problems, especially nystagmus, were most frequent in the VI group (**Supplementary Table 1**) and the acuity of children with VI was, on average, worse than that of children with CVI (VI; 0.38 ± 0.23 LogMAR, CVI; 0.17 ± 0.25 LogMAR). Therefore, one would expect poorer performance of the children with VI on the DEM if reduced visual acuity and oculomotor problems were the main predictors of reduced DEM performance. Additionally, no difference was found in vertical

DEM performance between the two groups, which should be equally affected by acuity. Finally, no significant correlations were found between visual acuity and DEM performance (vertical DEM; VI, $r = -0.07$, $p = 0.69$, CVI, $r = -0.17$, $p = 0.38$, horizontal DEM; VI, $r = 0.10$, $p = 0.59$, CVI, $r = -0.34$, $p = 0.10$), indicating that visual acuity alone did not affect DEM performance in our sample. One possible reason for the difference found in horizontal DEM performance between patient groups might be that children with CVI tend to use sub-optimal search patterns (Kooiker et al., 2016; Bennett et al., 2019), which could likely affect horizontal DEM time. Additionally, children with CVI show significantly shorter fixation durations than VI children (Kooiker et al., 2016), which might lead to problems with keeping track of where the last number was found, especially when the next number is not always present in the expected location.

The Influence of Visual Detection Time

DEM performance is correlated to visual processing speed (Ayton et al., 2009; Tanke et al., 2021) and visual processing speed is often reduced in children with VI and CVI (Kooiker et al., 2016; Barsingerhorn et al., 2018b). However, for the relationship between DEM performance and visual processing speed, no significant differences were found between the two patient groups. This would indicate that information about DEM performance in combination with reaction times to a visual stimulus, is not sufficient to clinically differentiate CVI from other visual impairments. When regarding the children with VI and CVI as one group, the mean reaction time to the visual stimulus correlates to vertical DEM performance, but not to horizontal DEM performance. Maybe, the reason why this relationship with visual detection time is only found for the vertical DEM is because the vertical DEM is easier and less affected by additional factors like visual search and oculomotor impairments than the horizontal DEM. Note also that the VDT on its own is not a direct measure of visual processing speed, as the reaction time can also increase as a result of impaired motor skills. Twelve children in the patient groups suffered from a light motor impairment (CVI, $n = 10$, VI; $n = 2$), we therefore recommend combining DEM performance with a task more specifically designed to measure visual processing speed (see for example Barsingerhorn et al., 2018a).

The Influence of Visual Crowding

Both the horizontal DEM numbers, as well as the numbers of the vertical DEM are spaced too far apart to be considered crowded (Huurneman et al., 2012b), indicating that difficulties with visual crowding are unlikely to directly affect DEM performance. Nevertheless, we found a significant correlation between the crowding intensity and horizontal DEM performance in children with CVI, and this correlation was significantly different from the children with VI. Perhaps, this difference was found because crowding limits reading performance (Bricolo et al., 2015; Gori and Facoetti, 2015; Joo et al., 2018), and both reading performance and crowding are linked to plasticity of the visual system (Huurneman et al., 2016a,b; Huurneman and Goossens, 2021).

CONCLUSION

The DEM is a useful addition to visual function tests to diagnose CVI especially in combination with knowledge about the crowding intensity. If a child shows both a longer horizontal DEM performance and a high crowding intensity, this may be an additional pointer to the diagnosis CVI. A slower DEM performance can be an indication that the child is at a disadvantage concerning visual processing speed, but in daily life, this may be compensated for by allowing extra time and by reducing visual clutter.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Commissie Mensgebonden Onderzoek regio Arnhem-Nijmegen, Netherlands. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

AB, JG, and FB designed the experiment. AB performed the experiments at schools and Bartimeus. NT performed the experiments at Royal Dutch Visio. NT analyzed the data and wrote the article with input from AB, JG, and FB. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnhum.2021.732927/full#supplementary-material

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Tracking-Based Interactive Assessment of Saccades, Pursuits, Visual Field, and Contrast Sensitivity in Children With Brain Injury

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Visual deficits in children that result from brain injury, including cerebral/cortical visual impairment (CVI), are difficult to assess through conventional methods due to their frequent co-occurrence with cognitive and communicative disabilities. Such impairments hence often go undiagnosed or are only determined through subjective evaluations of gaze-based reactions to different forms, colors, and movements, which limits any potential for remediation. Here, we describe a novel approach to grading visual health based on eye movements and evidence from gaze-based tracking behaviors. Our approach—the "Visual Ladder"—reduces reliance on the user's ability to attend and communicate. The Visual Ladder produces metrics that quantify spontaneous saccades and pursuits, assess visual field responsiveness, and grade spatial visual function from tracking responses to moving stimuli. We used the Ladder to assess fourteen hospitalized children aged 3 to 18 years with a diverse range of visual impairments and causes of brain injury. Four children were excluded from analysis due to incompatibility with the eye tracker (e.g., due to severe strabismus). The remaining ten children—including five non-verbal children—were tested multiple times over periods ranging from 2 weeks to 9 months, and all produced interpretable outcomes on at least three of the five visual tasks. The results suggest that our assessment tasks are viable in non-communicative children, provided their eyes can be tracked, and hence are promising tools for use in a larger clinical study. We highlight and discuss informative outcomes exhibited by each child, including directional biases in eye movements, pathological nystagmus, visual field asymmetries, and contrast sensitivity deficits. Our findings indicate that these methodologies will enable the rapid, objective classification and grading of visual impairments in children with CVI, including non-verbal children who are currently precluded from most vision assessments. This would provide a much-needed differential diagnostic and prognostic tool for CVI and other impairments of the visual system, both ocular and cerebral.

Keywords: eye movements, contrast sensitivity, TBI—traumatic brain injury, cerebral visual impairment, brain injured children, measurement, psychophysics, visual field

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INTRODUCTION

Visual impairments can have far-reaching implications for performance in numerous domains of perception and action, but many of the most prevalent disorders often elude clear diagnosis or quantification—particularly disorders that disproportionately affect children. Cerebral/cortical visual impairment (CVI) is the most common source of visual impairment in children in developed countries, affecting 30–40% of children with visual disorders (Hatton et al., 2007; Pehere et al., 2018) and more than 10% of children with any developmental disability (Nielsen et al., 2007). It is predominantly the result of perinatal brain injury, such as hypoxia, a genetic disorder, or head trauma (Roman-Lantzy, 2007), but genetic causes have also been identified (Bosch et al., 2016). Though there is not a consensus on the constellation of symptoms that define CVI (Lueck, 2010; Sakki et al., 2018), it is clear that its presentation is diverse, and it is often diagnosed by exclusion after ocular and geniculate sources of impairment are partially or completely ruled out (McConnell et al., 2021).

A refined and quantitative characterization of any given case of CVI can be highly difficult to obtain, as co-morbid communicative and cognitive impairments frequently preclude children with brain injury from participating in standard vision tests (Good et al., 1994; Huo et al., 1999). Whereas neuroimaging techniques hold promise for distinguishing between some manifestations of CVI (Merabet et al., 2016), behavioral assessment methods that require verbal feedback, comprehension of instructions, or sustained periods of attention are not possible for many CVI patients; even children with intact cognition often find conventional tasks too arduous to complete (Witton et al., 2017). Non-verbal alternatives to common tests do exist, such as visual evoked potentials (Leat et al., 2009; Odom et al., 2016) and preferential looking paradigms (Teller et al., 1986), but these methods are less sensitive than verbal tasks (de Faria et al., 1998) and are suitable for only a few dimensions of visual impairment.

Vision tests based on the analysis of gaze hold promise for the improved diagnosis and quantification of CVI (Caplan et al., 2016; Kooiker et al., 2016; Chang and Borchert, 2020, 2021), including more specific impairments such as visual dysfunction or concussion from traumatic brain injury (Samadani et al., 2015; Samadani, 2016; Barker et al., 2017; Armstrong, 2018; Bin Zahid et al., 2020). Brain injury can impair the magnitude and directionality of saccades (Hunfalvay et al., 2019) and limit the perception of motion or the ability to smoothly pursue moving targets in certain directions, even at slower speeds (Suh et al., 2006). These deficits may be accompanied by a pathological nystagmus, which causes involuntary, repetitive motion in one or both eyes (Sarvananthan et al., 2009). Whereas some of these symptoms may be severe and/or frequent enough to measure passively (e.g., a standing nystagmus), any behavioral assessment of higher-order visual function is encumbered by the requirement to infer function through action, such as the analysis of eye position. For example, the assessment of eye movements in response to the presentation of an object (such as a moving finger) is a fundamental component of a clinical vision exam; if a subject can follow a finger, it is inferred that they can see it. The imprecision with which the assessment is made, however, constrains its capacity to grade visual ability. Brain injury can also impair the ability to perceive and/or react swiftly to targets that appear in different parts of the peripheral visual field (Suchoff et al., 2008), but the perimetry tests that are conventionally used to quantify these impairments (Marín-Franch et al., 2018) require prolonged periods of attention and direction that may be impossible for children with brain injury.

Fortunately, the recent deployment of reliable, consumer-based eye trackers permits more rigorous measurement of eye movements, which in turn increases the potential to detect impairments with more sensitivity and reliability than methods requiring judgments by a human observer. Indeed, automated tasks based on eye-tracking can do far more than this: by measuring eye movements that occur in response to more complex stimuli, and using those eye movements adaptively to drive stimulus alterations, these tasks can rapidly measure other dimensions of visual health with no instructions given and no need for verbal feedback. The most useful ocular responses given by patients in these tasks may be *smooth pursuit* eye movements. As pursuits are extremely difficult to produce in the absence of a visible moving stimulus and highly unlikely to match the trajectory of an unseen, unpredictable target, they provide strong evidence of visual perception (Schütz et al., 2011; Spering and Montagnini, 2011; Spering and Carrasco, 2015; Gegenfurtner, 2016). These tasks consequently have extremely low false positive rates; this is a desirable feature for tests in cognitively impaired children, who are likely to require frequent repeated testing to obtain an adequate amount of valid data. Accurate calibration and head stabilization are often problems when using eye trackers to test individuals with cognitive disorders, but these barriers can be at least partially overcome by designing tasks that rely on accurate positional (rather than derivatives of) gaze data as little as possible and using display-mounted trackers on a mobile monitor, respectively.

We constructed a "Visual Ladder" program of computerized tracking-based tasks designed to assess visual functions that are elicited in a clinical visual exam. This computer program was tested in 10 hospitalized children with varying types and degrees of visual impairment, both with and without an independent CVI diagnosis. We measured the spatial dispersion and magnitude of spontaneous saccades and pursuits, visual field symmetry through saccade latency and directness in response to peripheral stimuli, and spatial visual function (i.e., acuity and contrast sensitivity) from the accuracy of tracking responses to moving noise patches. Children were re-tested with a regularity that depended on available flexibility in their in-patient hospital therapy schedule, school schedule, the child's overall health on a testing day, and their willingness to participate on that day. We then computed summary metrics of saccades, pursuits, visual field, and contrast sensitivity for each child to determine if the tasks would enable us to (a) place all children on shared scales for each metric and (b) identify the nature and severity of specific visual impairments.

MATERIALS AND METHODS

Observers

Fourteen children between the ages of 3 and 18 years were recruited between July 2019 and March 2021 through doctor or staff referral from the in-patient population at Blythedale Children's Hospital. The only eligibility criteria were the presence of some form of brain injury or other diagnosed visual impairment, the ability of the child to keep their eyes open, and the ability of the eye tracker to reliably detect their gaze. Four children (with severe impairment or strabismus) could not satisfy this final criterion and were excluded after the first attempted testing session. The gender, age, verbal/non-verbal status, relevant medical history, and clinical vision diagnoses of each child are shown in **Table 1**, along with the length of time over which they were tested and the total number of Visual Ladder sessions attempted. The total span of testing time depended on the length of the child's stay in the hospital and the number of sessions varied with the length of their stay, their condition, and their availability. For simplicity, the children are hereafter referred to from C1 to C10, in an order determined by an approximate *post hoc* classification of increasing overall impairment to aid presentation of their results. Blythedale accepts patients below the age of 21, and although the participant recruited at age 18 (C6) and the participant who turned 18 during the study (C5) were not technically "children," we hereafter refer to all participants as children for simplicity.

Parents/legal guardians of each child gave signed informed consent under an approved Institutional Review Board protocol managed by the Biomedical Research Alliance of New York (BRANY). All able communicative children (determined by doctor), gave verbal assent, signed assent, or signed consent, depending on their age and ability prior to being enrolled in the study. Experimental data were secured and managed with the REDCap database (Harris et al., 2009).

Apparatus

A 27-inch widescreen LCD Dell Optiplex 7760 all-in-one computer running Windows 10 was attached to a mobile trolley using a customized articulated arm. The display was equipped with a Tobii 4C eye tracker (50–95 cm operating distance; 90 Hz sampling rate) with a professional-level license (Tobii Technology, Stockholm, Sweden). Eye tracker data were accessed with the Tobii Pro SDK library, which reports the gaze point on the display for each individual eye and the coordinates of each eye in real space. The raw gaze point data were smoothed with a custom denoising algorithm that avoids smoothing over saccade eye movements. An estimate of mean valid gaze was then computed on each frame by taking the average of both eyes, if both eyes' data streams were valid on that frame, or just one eye if only one eye's data stream was valid on that frame. Stimulus behavior was programmed in Python using the Shady graphics toolbox (Hill et al., 2019), which was also used to calibrate screen gamma, and audio feedback was controlled with the Audiomath toolbox (Hill et al., 2021). Minimum and maximum screen luminance values of 10.0 and 221.1 cd/m^2, respectively, were measured under controlled room illumination with an ILT1700 radiometer (International Light Technologies, Peabody, MA). Observers were measured at a distance as close to 620 mm as possible and our software blanked out the screen and displayed a warning message (which suspended data acquisition) whenever the observer's eyes were closer than 520 mm or further than 720 mm from the screen. At 620 mm, the display subtended horizontal and vertical visual angles of 51.5 and 30.4 degrees of visual arc, respectively. No other form of distance enforcement or head restraint was used, as this was impractical in the hospital setting. A portable battery was used to power the computer while it was moved around the hospital before being connected to an AC outlet for each test.

Stimuli

The Visual Ladder program comprised five tasks:

- **Bubble Burst:** multiple colorful bubbles drift around the screen and pop when fixated upon, which prompts the child to generate a multitude of saccades for assessment;
- **Moving Bubbles:** large bubbles appear one at a time and move along preset paths, which assesses smooth pursuit tracking ability;
- **Field Bubbles:** small bubbles appear one at a time at predetermined peripheral locations, which uses fixation latency to assess visual field sensitivity;
- Our **Gradiate** task, which infers the user's contrast sensitivity function (CSF) by having them track noise patches of varying contrast and noise scale around the screen (Mooney et al., 2020); and
- A **full-screen variant of Gradiate**, in which the same noise patterns cover the screen and move only horizontally, for observers who have difficulty tracking smaller targets.

These five tasks ran automatically in sequence (following a brief practice task) after the program was launched by the experimenter. The sequence is as specified above, except the full-screen version of Gradiate was run before the standard version to place the most difficult task at the end of the sequence. **Figure 1** depicts a screenshot from the practice task and from each of the five experimental tasks. The tasks were designed to appear as "games" and combined real-time visual stimulus manipulation, eye tracker input (including denoising procedures and eye movement classifiers), and engaging audio feedback in the form of music and interactive sound effects. A random music track from a collection of songs was played in the background of each task. The goal was to design positive testing experiences that could feasibly be conducted repeatedly for children, rather than an overly sterile, scripted, or non-interactive experience that could theoretically produce more accurate data but, in practice, fail to motivate participation and hence produce little or no results. Another key to sustained motivation in children is brevity (Witton et al., 2017). Our tasks were designed to act upon gaze information and detected eye movements as rapidly as possible, frequently modifying stimuli in the very next display frame in response, and task time limits and trial counts were refined through pilot testing to avoid fatigue while collecting

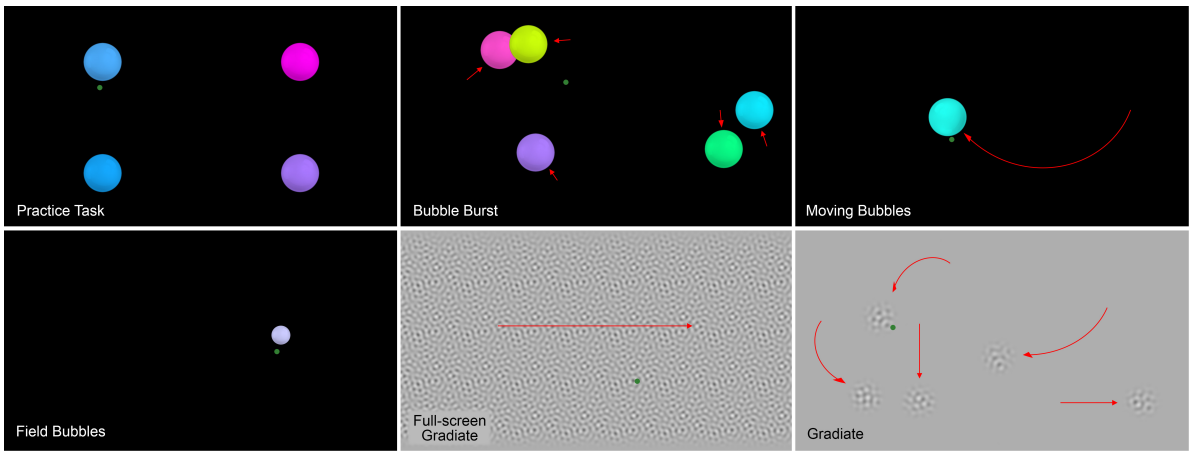

FIGURE 1 | Screenshots of the practice task **(top-left)** and the five Visual Ladder tasks. The green dots and red arrows represent example gaze points and stimulus motion vectors, respectively, and were not visible to the observer during the task.

as much useful data as possible. A detailed description of each task is given below.

In the **practice task**, four randomly colored circular "bubbles" with radius 3° each appeared in the center of one of the display's four quadrants. When the participant's mean gaze fell within 3.6° of the bubble's center (its radius plus a twenty percent buffer) and remained within that radius for a total of 1 s, the bubble "popped" with a pitch-randomized pop sound effect and visible bursting animation. The bubble vibrated with increasing amplitude as it approached this popping time, but this vibration was gradually dampened back toward zero—and progress toward the bubble's 1-s popping timer was gradually lost—if the participant's gaze left the detection radius. Each bubble's color was randomly chosen in hue/saturation/value (HSV) color space by combining a random hue between 0 and 1, a random saturation between 0.5 and 1, and a maximally bright value of 1. Each bubble also had a 10% chance of receiving a color saturation of 0 instead (white). Similar popping bubble stimuli were also used in the first three tasks of the Ladder. When all four bubbles were popped, the first task (Bubble Burst) began.

The **Bubble Burst** task was designed to elicit a relatively unbiased distribution of spontaneous saccades. Five bubbles with a diameter of 6° appeared at random locations on the display and drifted randomly around it at a speed of 4° per second in smooth, curving arcs, overlapping when necessary. A random bright color was chosen per bubble in the same way as the practice task. Whenever a bubble collided with an invisible boundary that excluded the outer 20% of the screen's width and height, it bounced off and moved in the opposite direction. Unlike the vibration-based popping system used in the practice task, each bubble in Bubble Burst was given a random number of "health points" between 10 and 60 and lost one health point per frame in which the observer's mean gaze point was within the 3.6° detection radius of that bubble, audibly popping when its health reached zero. This health-based system was used so that bubbles were easier to pop overall, as the task was designed to encourage saccades rather than assess fixations. Whenever a bubble was popped, a new randomized bubble appeared elsewhere on the display simultaneously to replace it, ensuring that five bubbles were always visible at once. The task ended after a total of 40 bubbles had been popped.

The **Field Bubbles** task was designed to measure response latency to stimuli appearing abruptly at 48 preset locations in the observer's peripheral visual field, similar to a perimetry test (Marín-Franch et al., 2018). These locations appeared at twelve 30° angular intervals along four ellipses whose semi-minor and semi-major axes were both set to 15, 20, 25, and 30% of the display's width and height, respectively. These axes corresponded to 8°-17° eccentricities horizontally and 4°-10° eccentricities vertically.

In each trial, a smaller white bubble with a radius of 1.5° was presented on a black background at one of these 48 locations relative to the observer's current gaze point. Latency was computed as the time from the bubble's appearance until the observer's gaze was within 5° of the bubble's center. The bubble turned slightly green when detected. The task then waited until the observer popped the bubble using the same vibration system as the practice task, but only 0.5 s of continuous gaze within the detection radius was required to pop it. The next trial began as soon as the bubble popped, using the observer's actual current gaze point (rather than the last bubble's position) as its origin. If the observer did not reach the detection zone within 5 s of the bubble's appearance, the bubble disappeared, and a null result was recorded at that location. In this case, the next trial began from the observer's current gaze point.

A randomized queue of all 48 field locations was generated at the start of the task. For each trial, the task iterated over the remaining untested locations and selected the first location that could be presented given the observer's current gaze position (the location of the previous trial's target). If none of the remaining locations could be tested, a dummy "setup" trial was generated at a location no closer than 5° that ensured that the first remaining location in the queue could be tested next. The first trial was also

a dummy trial at a random location at least 5° away from the observer's current gaze point.

The **Moving Bubbles** task was designed to encourage and assess smooth pursuit eye movements. Ten bubbles with a diameter of 6° appeared one at a time and moved randomly around the screen. Bubble color was again randomly chosen in the same way as the practice task, but here, the bubbles followed random paths along a preset grid instead of the random steering motion used in that task. Each bubble started with 20 "health points" before popping, but unlike in Bubble Burst, a health point was only subtracted on each frame in which the observer had been smoothly tracking the bubble's trajectory for at least five consecutive frames. This smooth trajectory match was detected using the same algorithm as Gradiate (Mooney et al., 2020), which is described further below. When the bubble had no health points remaining, it popped, and was replaced by a new bubble at a random location at least 10° away on the display. The task ended when ten bubbles were popped this way. To prevent the task from continuing indefinitely for children who could not pursue the bubbles, each bubble also disappeared 8 s after appearing, and the task itself ended prematurely after five bubbles disappeared this way.

The **Gradiate** task for measuring the CSF was validated previously in healthy adults and children (Mooney et al., 2020). In the task, five windowed circular patches of filtered spatial noise with radii subtending 3° followed random, smooth, non-colliding trajectories at a speed of 5° per second on a mid-gray background. At any given time, the noise pattern in each patch was defined by a particular combination of spatial frequency and contrast, which corresponded to a point in 2D logarithmic CSF space. All five targets began with a spatial frequency of 1 cycle per degree (cpd) and a root-mean-square (RMS) contrast ratio of 0.2, but their appearance progressed along different radial "sweep" vectors in CSF space whenever they were tracked by the observer (a behavior that strongly implies seeing). Tracking was detected using a hybrid algorithm, which requires the observer to exhibit a positional match (i.e., the observer's gaze must be close to the target) and either (a) a smooth trajectory match (i.e., the observer's recent gaze path must match the recent path of the target, modulo current position) or (b) a saccadic match (i.e., the observer must exhibit frequent catch-up saccades toward the target). The saccadic tracking option ensures that observers who have difficulty with smooth tracking, or who can only smoothly track for short bursts, are still able to generate valid evidence of seeing. After sufficient evidence of tracking was collected this way, the stimulus abruptly shifted to its next point along the radial sweep by changing its spatial frequency and (with the exception of one sweep that moved horizontally through CSF space) contrast. Tracking progress was reset for each new step in each sweep to prevent false positives caused by lingering tracking behavior from the previous step. Progress along any sweep was also accompanied by a glockenspiel sound effect to provide positive feedback to the observer. When the observer allowed enough time to pass without tracking any of the five presented targets, five spatial vision thresholds were inferred simultaneously from the targets' final appearance, which can be interpolated to obtain an estimate of the complete CSF. In each session of the Visual Ladder, we measured two repeats of a five-point CSF using this standard version of Gradiate, i.e., two trials containing five moving stimuli each. After the task was completed, a screen appeared telling the observer how many musical notes they had generated during the task, which was highly motivating for several children across their numerous sessions with the Visual Ladder.

We also created a **full-screen variant of Gradiate** that replaces the circular noise patches with a full-screen noise pattern scrolling horizontally at 5° per second. The goal of this task was to measure CSFs in highly impaired children who may find the standard version of Gradiate too difficult for any reason (e.g., difficulty making vertical smooth pursuits, attentional deficits, sensitivity to stimulus crowding). In principle, the full-screen version of Gradiate needs only to elicit a low-level optokinetic nystagmus response (OKN) instead of the more precise, curving smooth pursuits required for progress in standard Gradiate; the same approach has been validated previously in healthy subjects (Dakin and Turnbull, 2016). This variant effectively reduces false negatives—children who can see the stimulus, but are unable to track standard Gradiate patches—at the cost of increasing false positives, as there is no positional component to tracking and it is easier for observers to intentionally or unintentionally (e.g., due to incidental nystagmus) match the velocity of the scrolling pattern. Only one CSF sweep could be measured at a time, but the task otherwise behaved in the same way as standard Gradiate, with stimuli progressing along the same five sweeps in CSF space and a glockenspiel sound played after each successfully tracked sweep step.

To further accommodate impaired children, two additional tools were granted to the experimenter during full-screen Gradiate:

- They had the ability to set the direction of the drifting noise (leftward or rightward) for each child, based on qualitative evidence of an inability to track in one direction. The direction of motion was otherwise chosen randomly for each trial.
- They had the ability to switch the noise pattern with a detailed landscape of cartoon characters scrolling with the same speed and direction. This feature provided a way to practice smooth movement on a larger, more visually pleasing cartoon image than the higher spatial frequency noise stimulus, and to recapture the attention of children who were no longer looking at the screen, or otherwise failing to attend to the task, before switching back to the noise stimulus (a "bait and switch" approach). To prevent lingering tracking of the cartoon from causing false positives, all tracking behavior was disregarded for 2 s after switching back to the noise stimulus.

Only one repeat of a five-point CSF was measured with full-screen Gradiate. As in standard Gradiate, a feedback screen informing the observer of how many musical notes they had produced was shown after the task.

Procedure

Children were tested in their rooms at Blythedale Children's Hospital. Some sat up in their wheelchairs or in their bed to

participate and others were accommodated while lying down according to their physical needs. The display was positioned in front of the child, approximately 620 mm from the child's eyes, orthogonal to their head pose and line of sight, using the articulated arm that was mounted on the mobile trolley. Children were asked to keep still during the procedure to maintain this distance; for all children, the experimenter attempted to account for unexpected head or body movements by moving the display as necessary. The time of day for testing varied both between and within children due to their hospital schedules. Room illumination was not controlled or measured in the hospital, as children were tested in different rooms surrounded by other equipment (often shared with other patients), but direct sunlight was avoided, and curtains were drawn when possible. We have previously shown that variation in artificial room illumination does not significantly impact the results of our contrast sensitivity assessments (Mooney et al., 2018). Children were always awake and fed well before testing and were thus adapted to the photopic conditions of the experiment.

Each Visual Ladder session was preceded by a one-point calibration step and a simple practice task to confirm the eye tracker was detecting gaze. In the calibration step, a white gear subtending 5° appeared in the center of the display on a black background. When the participant's mean gaze point (the average of their left and right eyes' gaze points if both were valid, or just the valid eye) was within 5° of the gear's center, the program assumed that the participant was looking at the wheel and adjusted an internal calibration variable to account for the difference. The gear spun with increasing frequency while the mean gaze point was within this detection radius and slowed while it was not. The calibration step ended, and the gear disappeared, when the gear's rotational velocity reached 1080°/s (approximately 2 s of continuous calibration). This calibration step sometimes took up to several minutes, and gaze was no doubt miscalibrated in multiple sessions (particularly for the more impaired children), but our tasks were designed to be resistant to minor-to-moderate calibration errors. The Field Bubbles task is most reliant on calibration, but participants who could not complete the calibration step were likely to perform very poorly on this task in any case and miscalibration is unlikely to introduce specific directional biases in performance.

While the Ladder proceeded automatically and uninterrupted in most testing sessions, the experimenter had a wireless keyboard with several pragmatic controls available to handle the unpredictable barriers and time constraints that often arose while testing:

- They could toggle a trio of small green gaze marker dots, representing left, right, and mean gaze point on the display, to debug cases where the eye tracker could not detect the child (e.g., due to strabismus or unusual difficulty positioning the screen). These markers were enabled to check the status of the eye tracker, typically during the practice task, and were disabled as soon as the experimenter was satisfied with the setup.
- They could check the gaze distance to make sure the child was close to 620 mm, typically during calibration. Distance was checked as needed throughout the tasks if the child could not remain still for the whole session.
- They could end a task prematurely and skip to the beginning of the next task. Each child's available testing time was sometimes as short as 10 min, and while the Ladder can be completed in that time by a child with only mild or moderate impairment, some tasks (e.g., Field Bubbles) can take significantly longer if every trial is allowed to time out (e.g., due to severe inattention). The ability to skip tasks was added to ensure that impaired children with shorter time slots were able to try later tasks, such as full-screen Gradiate, without having to wait through a long sequence of failures in earlier tasks such as Field Bubbles. Conversely, it was sometimes used to skip full-screen Gradiate in favor of standard Gradiate for children who had previously demonstrated an ability to participate in the latter task but had tight schedules. The experimenter also had the ability to skip the calibration step and practice task for children who could not direct their gaze to specific targets (but who may nevertheless generate useful saccade and pursuit data throughout the program).
- They could toggle the background music on or off at any time. Music appeared in most cases to improve participation and motivate the children, but also appeared in some instances to be a distraction.

As is commonplace for clinical sessions with children, the experimenter freely encouraged them to engage with the procedure and praised their performance, regardless of whether the child was communicative, and interacted freely with communicative children. Rarely, the full testing session was ended prematurely due to the child's time constraints or a medical or behavioral issue that precluded further participation. No cases of severe adverse health effects were attributed to the procedure.

Data Analysis

We identified statistical measures for each task in our Visual Ladder program that can be used to compare observers and identify irregularities without being overly sensitivity to the variable number of times each observer was measured or the variable amount of time each observer took to complete a given session. When analyzing saccades and pursuits, for example, we collapsed eye movements into eight directional bins to ensure that interpretable distributions and means could still be generated by the observers who tended to exhibit fewer eye movements, which could be due to intrinsic behavioral factors or eye tracker noise. The results for one child (C5, who was tested over 9 months) were also treated as a longitudinal case study examining recovery from TBI. To contain the scope of this study, all other metrics were computed over the entire duration of each child's testing period. The primary goal of the study was to establish the ability of the Visual Ladder to produce interpretable results across a heterogenous sample of ten children with diverse medical histories (effectively ten case studies). Statistical tests were hence only used (per participant) to detect broad asymmetries in saccade amplitude—specifically, independent *t*-tests. Our focus was instead on (a) the presence of valid metrics, particularly in non-verbal children, that could be used to aid diagnosis and

quantification of visual impairment, and (b) the detection of patterns that are characteristic of ocular or cerebral deficits in the clinical literature.

RESULTS AND INTERPRETATION

Bubble Burst (Saccades)

Bubble Burst is a relatively unconstrained task that aims to bias saccade distributions as little as possible beyond the innate influence of the display's size and aspect ratio. Bubbles continually appear at random locations as existing bubbles are popped and drift in random directions. We sorted saccades into eight directional bins by computing the angle between the first and last gaze point samples within each saccade, then examined (a) the relative proportion of saccades of any amplitude in each direction and (b) the mean amplitude of saccades in each of those eight directions. Polar plots of these two metrics are depicted for all children in **Figures 2**, **3**, respectively, with values further above each child's overall mean colored increasingly red for visual clarity. Corresponding panels in each figure represent data from the same child; the same is true for all subsequent two-by-five data figures below. The plots permit spatial abnormalities in the distribution of saccades to be identified at a glance, and provide a numerical quantification of saccade behavior that has the potential to both specify a deficit and enable comparisons between subjects.

Several children exhibit patterns that resemble healthy behavior established by the clinical literature: namely, a bias toward more frequent and larger horizontal saccades than vertical, particularly due to the orientation of the widescreen display (Foulsham et al., 2008), and a weaker bias toward larger (though not more frequent) downward saccades than upward (Collewijn et al., 1988). Visually, these biases produce a familiar "bow-tie" histogram in **Figure 2** and (due to the additional downward bias) a "butterfly" distribution in **Figure 3**. Observers C1, C4, C5, C9, and C10 exhibit both of these patterns with varying degrees of symmetry. C4 and C9 also appear to exhibit larger saccades, on average, than the other participants. Observer C3 exhibits near-normative saccades, but with additional weighting in the top-right and bottom-left directions. On closer examination of recorded video, this pattern appears to be due to a tendency for this child to tilt her head to the left relative to the screen regardless of the experimenter's attempts to rotate the screen or ask the child to straighten her posture.

A common symptom of various visual impairments, including those caused by brain injury, is a left vs. right asymmetry in ocular and/or attentive behavior. We used independent *t*-tests to confirm several of the horizontal asymmetries in mean saccade amplitude apparent in **Figure 3** after categorizing every saccade as either leftward or rightward. Each *t*-test compared the mean distance of all leftward saccades to the mean distance of all rightward saccades for a single participant (i.e., hundreds or thousands of samples per test). The tests revealed significant rightward biases in amplitude for C1 ($t = 3.155$, $p = 0.002$), C6 ($t = 6.662$, $p < 0.001$), and C9 ($t = 2.031$, $p = 0.042$), and leftward biases for C2 ($t = -11.392$, $p < 0.001$), C5 ($t = -2.807$, $p = 0.005$), and C7 ($t = -3.667$, $p < 0.001$). Some of these differences are subtle (e.g., C5 and C7) and would likely go undetected without the use of an eye tracker and repeated testing sessions.

Observers C2, C6, C7, and C8 exhibited a variety of other noteworthy patterns in their saccades. C8 had no significant left vs. right asymmetry in mean saccade amplitude, but his histogram indicates that he saccaded more frequently to the

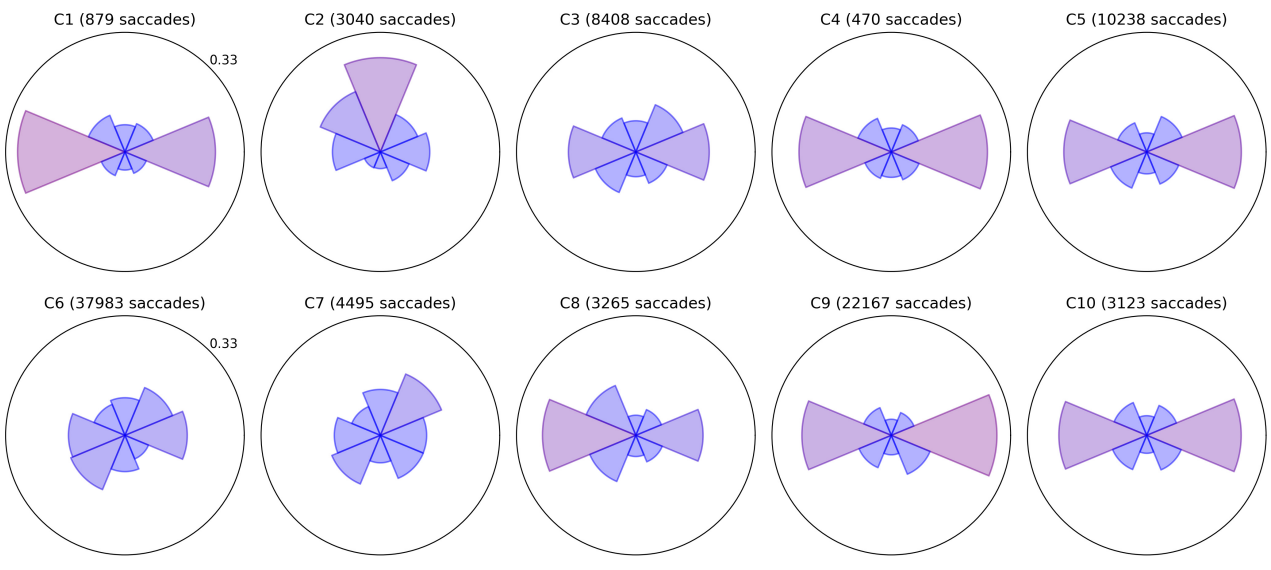

FIGURE 2 | Radial histograms of saccade frequency. Saccades in the Bubble Burst task were binned into eight directions. The upper radial axis limit of each plot is a proportional score of 0.33. The sector bins gradually change in color from blue to red as the proportion for that bin exceeds the mean of 0.125, which allows the more biased directions to be identified at a glance. The participant number and total saccade count are given above each plot.

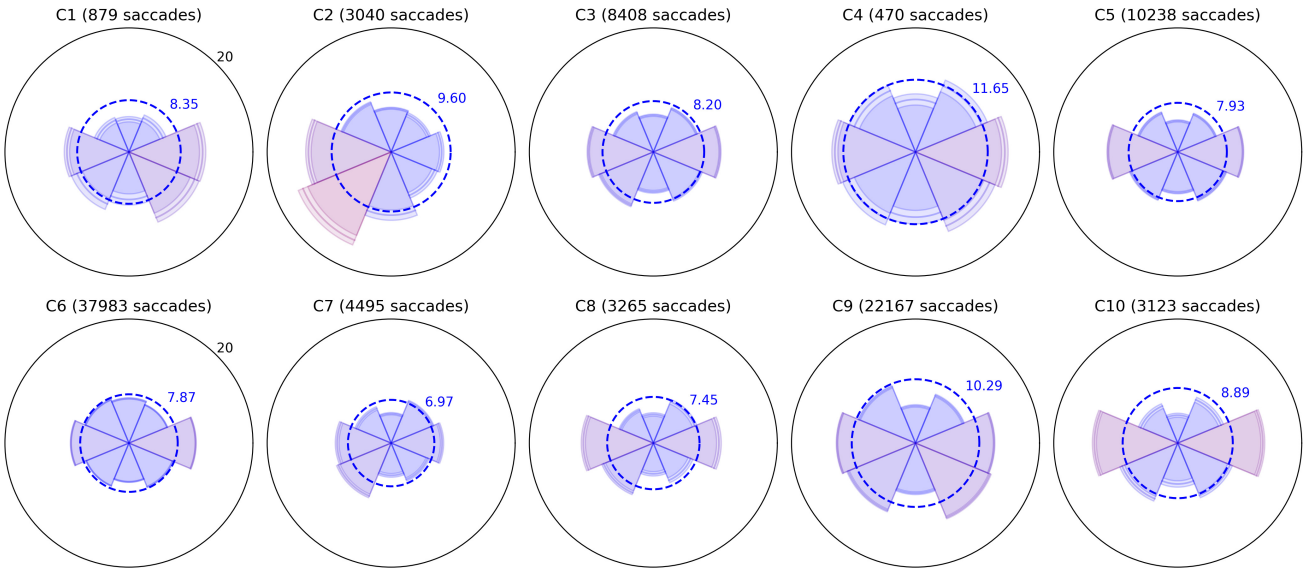

FIGURE 3 | Radial plots of mean saccade amplitude. As in **Figure 2**, saccades in the Bubble Burst task were binned into eight directions. The radius of each sector represents the mean amplitude of all saccades falling in that directional bin. The overall mean amplitude for each child in degrees of visual arc is denoted by the dotted blue ring, and the color of each sector changes gradually from blue to red as the mean amplitude for that direction exceeds the overall mean. The lighter ring segments at the end of each sector represent the standard error of mean amplitude in that direction.

TABLE 1 | Participant information.

Child	Gender	Age (years)	Communicative	Relevant medical history and clinical diagnoses	Testing time	Sessions
C1	M	12	Yes	Large left cerebral ischemic stroke, smaller infarcts in right cerebellum 20/20 vision, previous diplopia	2 months	36
C2	M	12	Yes	Brain tumor (posterior medulloblastoma) 20/30 vision, horizontal nystagmus	4 months	46
C3	F	11	Yes	Complex congenital heart disease, hypoxic ischemic encephalopathy Slow horizontal eye movements; unable to assess acuity	5 months	74
C4	M	16	Yes	TBI, subdural hematomas, encephalopathy from influenza CVI; originally unable to assess acuity, then assessed as 20/25	2 months	18
C5	M	17	No/Yes*	TBI, left subdural hematoma, hypoxia from cardiac arrest Originally unable to fixate/follow and unable to assess acuity, then assessed as 20/25 at end of study	9 months	145
C6	M	18	Yes	Visual impairment from retinitis pigmentosa. Legally blind; possible light perception	6 months	121
C7	F	10	No	Acute cardiac arrest, perinatal hypoxia, optic atrophy CVI; no light perception, no fixate/follow	1 month	15
C8	M	13	No	Perinatal hypoxia, cerebral palsy, Lennox-Gastaut syndrome CVI; no fixate/follow	3 weeks	17
C9	M	5	No	Pelizaeus-Merzbacher disease, neurodevelopmental regression, optic atrophy Upward nystagmus; can fixate/follow with right eye; left eye slow/delayed	2 months	30
C10	F	3	No	Severe global anoxic brain injury, hypoxic ischemic encephalopathy, optic atrophy CVI; no light response	2 weeks	8

**Child C5 was non-verbal for approximately 2 months after enrolling, then regained communicative ability for the remainder of the study.*

left. Observers C6 and C7 exhibited directional histograms that are unusually isotropic, which suggests that the display may not have been visible to them or not well attended. Indeed, C6 is legally blind, and while he verbally reported being able to see some bubble stimuli, his saccades are unlikely to conform to the environment-driven patterns typical in seeing observers. C7 is a non-verbal child with a CVI diagnosis, and her isotropic saccade histogram suggests that she may

have only had minimal awareness of the display or task; this corroborates ophthalmological reports indicating that she has no light perception or fixate-and-follow response (**Table 1**). Finally, observer C2 exhibited a saccade histogram that was strongly biased upward, indicating a pathological oculomotor behavior that will be discussed further below.

Moving Bubbles (Pursuits)

Pursuits were binned into eight directions in the same way as saccades, and corresponding polar plots of directional histograms and mean pursuit distance (computed from pursuit path length) are depicted for all ten children in **Figures 4**, **5**, respectively. The arrow superimposed on each histogram in **Figure 4** represents

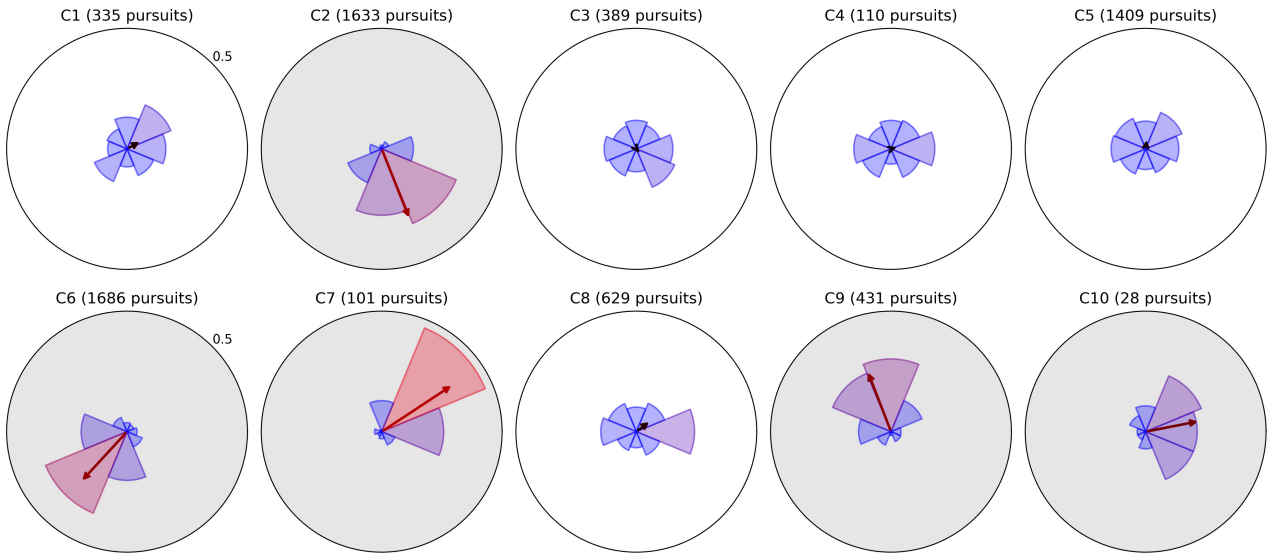

FIGURE 4 | Radial histograms of pursuit frequency and mean bias vectors in Moving Bubbles. Pursuits in the Moving Bubbles task were binned into eight directions. The upper radial axis limit of each plot is a proportional score of 0.5. As in previous figures, the sector bins gradually change in color from blue to red as the proportion for that bin exceeds the mean of 0.125. The participant number and total pursuit count are given above each plot. The arrow originating from the center of each plot represents the Cartesian mean of all pursuits' unit direction vectors, and thus indicates the direction and strength of an overall bias in pursuit direction. The five plots with gray backgrounds exhibit a particularly strong directional bias and have corresponding radial histograms from Field Bubbles shown in **Figure 6**.

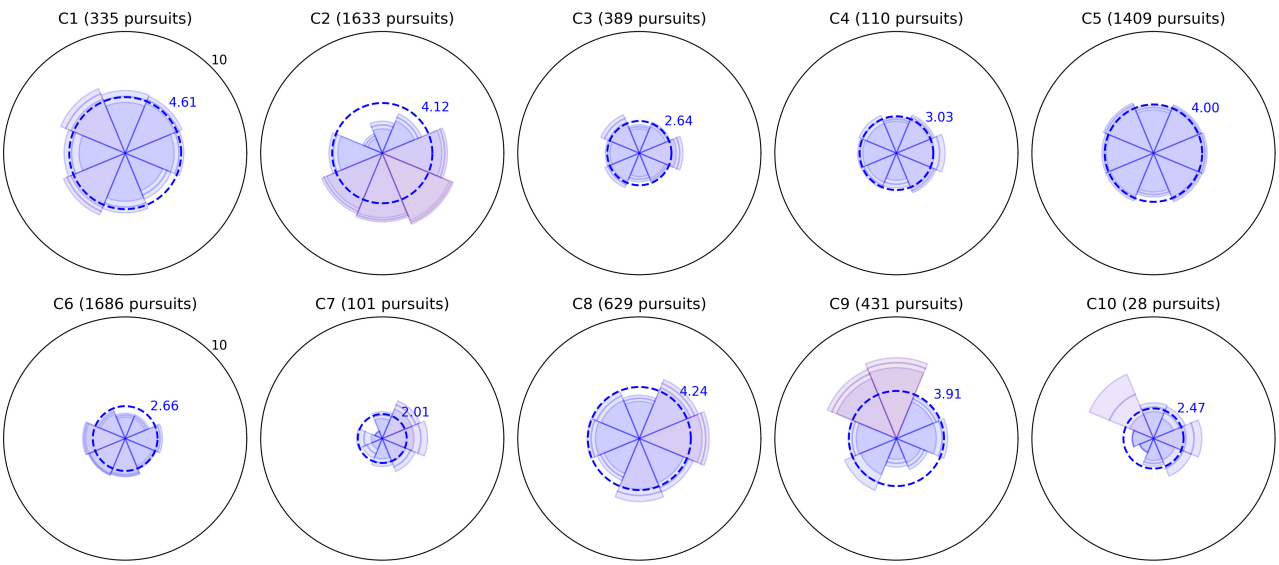

FIGURE 5 | Radial plots of mean pursuit distance computed as path length between the first and last gaze points in the pursuit. As in previous figures, pursuits in the Moving Bubbles task were binned into eight directions and the radius of each sector represents the mean distance of all pursuits falling in that directional bin. The upper radial axis limit of each plot is 10° of visual arc. Overall mean distance is denoted by the dotted blue ring and the color of each sector changes gradually from blue to red as the mean distance for that direction exceeds the overall mean. The lighter ring segments at the end of each sector represent the standard error of mean distance in that direction.

overall pursuit direction bias, computed as the Cartesian mean of the unit direction vectors for all pursuits, and is colored between black and red according to length. As with the saccade plots, these pursuit plots enable a clinician or researcher to quickly distinguish spatial abnormalities in the distribution of pursuits, but also offer more detailed quantification of pursuit ability.

As pursuits guided by the bubble target were equally likely to occur in any direction, we expected the directional distribution and mean distance of pursuits to be relatively isotropic for an unimpaired observer. Observers C1, C3, C4, and C5 fit this pattern, with no directions containing too few or unusually short pursuits, and are hence, less likely to have any severe impairment to their ability to pursue targets. Observer C8 exhibited a small bias toward rightward pursuits in both frequency and distance, but otherwise conformed to a mostly isotropic pattern. Notably, this bias is in the opposite direction to their saccade bias in **Figure 2**, suggesting that they may have a mild tendency to pursue rightward that requires more frequent corrective leftward saccades.

The remaining observers exhibit pursuit asymmetries ranging from large to severe; the directions of these asymmetries are clearly visible in **Figure 4**, and generally correspond to the directions of greatest mean distance in **Figure 5**. It is difficult to infer, from Moving Bubbles alone, whether these asymmetries represent a varying ability to track visible targets in certain directions or a pathological nystagmus that is causing smooth eye movements independently of any stimulus. To determine this, we also analyzed pursuit histograms from the Field Bubbles task for observers C2, C6, C7, C9, and C10 (gray backgrounds in **Figure 4**). Field Bubbles contains no motion at all, and any on-screen pursuits that occur during the task are therefore almost certainly caused by nystagmus. These histograms are shown in **Figure 6**. They are almost identical to the corresponding histograms for all five children in **Figure 4**, which suggests that pathological nystagmus is almost entirely responsible for the asymmetries detected in Moving Bubbles rather than an inability to track moving stimuli in certain directions. The mean bias arrows in **Figure 6** can consequently be interpreted as a precise quantification of the mean direction and spread of each child's nystagmus. Notably, observers C2, C6, C7, C9 exhibited significantly larger saccades in the direction approximately opposite to their nystagmus (see previous section), but only observer C2 appeared to exhibit *more frequent* saccades in the opposite direction to his nystagmus. Observer C10, by contrast, did not exhibit any visible signs of a nystagmus in her saccade data. Notably, of these five children, only C2 and C9 had a nystagmus diagnosed in their ophthalmological report, which suggests that nystagmus in C6, C7, and C10 may not have been discernible to a clinical examiner, may have developed more recently than their clinical exam, or may be transient.

Finally, we note that while there are apparent differences in mean pursuit distance across observers in **Figure 5**, it is difficult to draw inferences from this. Different observers tend to generate different degrees of eye tracker noise, depending on factors such as strabismus, overall movement and attention during the task, the experimenter's ability to position the display optimally, and the child's ability to fully open their eyes. As eye tracker noise can interrupt ongoing pursuit detection, e.g., causing one long pursuit to be broken up into several smaller pursuits, it can have a direct impact on mean pursuit distance for each child. We consequently err on the side of caution when interpreting the clinical relevance of a smaller mean pursuit distance, and instead focus on relative differences across directions for each observer. Our pursuit metrics regardless provide an efficient way to quickly visualize overall impairment, precisely quantify specific deficits, and make comparisons between observers.

Field Bubbles (Visual Field)

We combined all valid Field Bubbles trials (i.e., trials that did not reach the 5-s timeout) at each location for each child and computed mean saccade latency time (**Figure 7**) and the proportion of trials that were completed without first saccading in an incorrect direction (**Figure 8**). In **Figure 7**, a shared color scale is used for the mean latency for each child and target location. Standard error is not shown, but locations with less than three valid trials were excluded from the analysis. The data reveal that observers C1 to C5 found essentially all peripheral targets faster than observers C6 to C10. Observer C6, who is highly communicative but legally blind (i.e., understood the goal of the task and offered extensive feedback, but was expected to have difficulty seeing the stimuli), tended to find the target in a reliably delayed fashion (2–3 s). Observer C7 only reliably generated

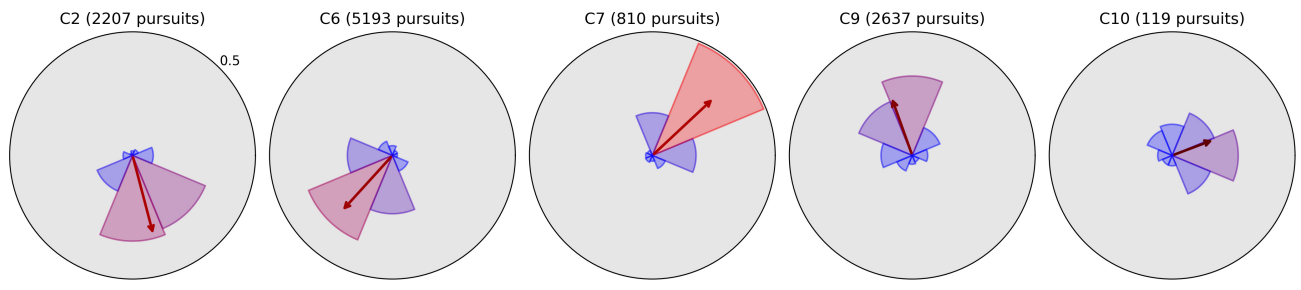

FIGURE 6 | Radial histograms of pursuit frequency and mean bias vectors in Field Bubbles for the same five children whose plots have gray backgrounds in **Figure 4** (the same histograms from Moving Bubbles). All elements have the same meaning as in **Figure 4** and are essentially identical to that figure for each of the five children despite the absence of moving stimuli Field Bubbles, indicating that their pursuits are likely caused by involuntary nystagmus.

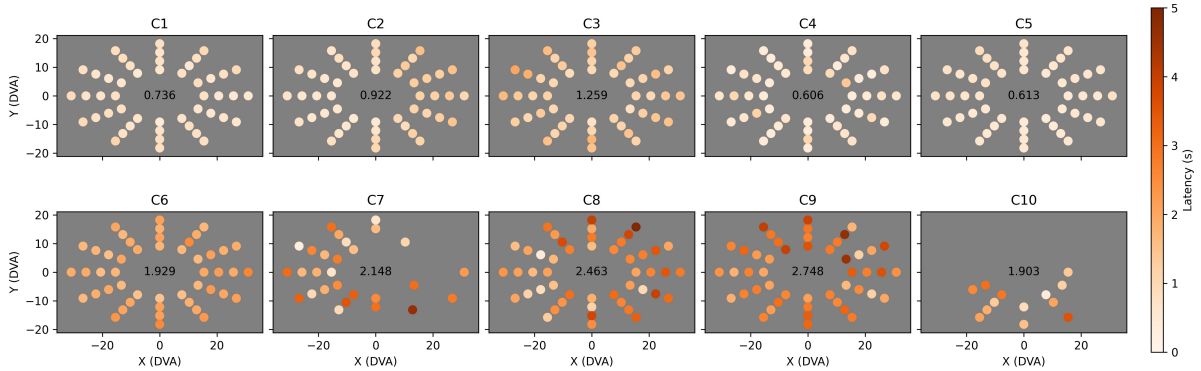

FIGURE 7 | Mean saccade latency across the visual field for each child. Each dot represents the Cartesian coordinates in degrees of visual arc of one of 48 tested locations. The dot's color indicates mean saccade latency for all valid (i.e., completed) trials to that location, provided that at least three valid trials occurred, on a color map shared by all ten observers ranging from zero (white) to five (red) seconds. Locations at which less than three valid trials were completed are left empty (C7 and C10). Overall mean saccade latency is shown in the center of each plot.

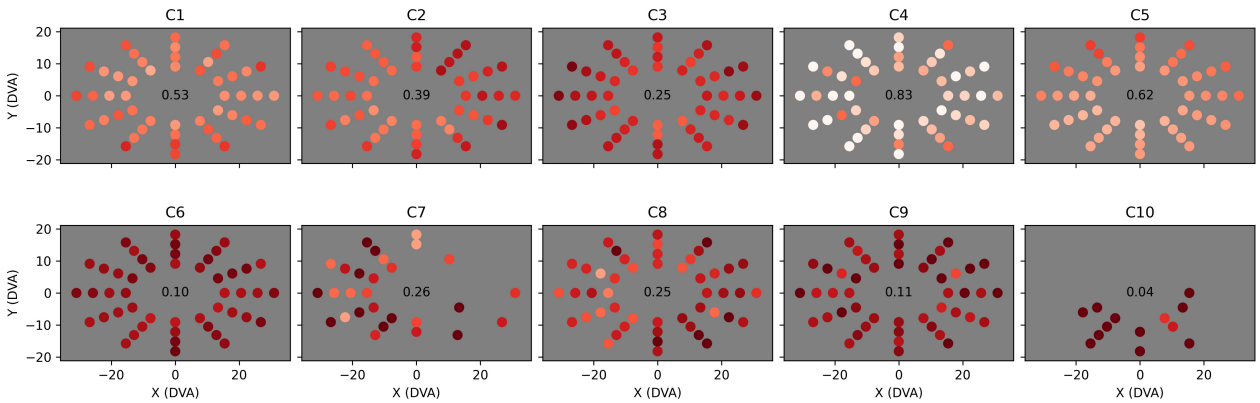

FIGURE 8 | Proportion of saccades to each tested location that were direct. The layout of each plot is identical to **Figure 7**, but the color of each dot now represents the proportion of valid trials at that location that were completed with direct eye movements only (i.e., eye movements that did not stray out of a narrow strip between the start location and the target location), ranging from dark red (0% direct) to white (100% direct). Locations at which less than three valid trials were completed are left empty (C7 and C10). Overall mean direct proportion is shown in the center of each plot.

sufficient data in leftward directions, indicating a potential right-hemifield impairment, and observer C8 was similarly able to find leftward targets faster than rightward targets overall. Their results indicate that visual field deficits may now have the potential to be recognized and quantified in children with brain injury who cannot participate in standard visual field tests. Observer C9 exhibited overall latency impairment but no clear directional bias. Among the less impaired observers, observer C2 reacted more slowly to rightward targets and observer C5 reacted slightly slower to targets in the upper-left field quadrant.

The proportions of trials completed through direct saccades only (**Figure 8**) are potentially more informative than saccade latency. Whereas all trials are potentially useful in identifying certain directional impairments (e.g., directional oculomotor deficits or broad attentional asymmetries), only trials in which the observer saccaded directly toward the target provide strong evidence of localized visual field neglect or a field cut, as any other eye movements will naturally change the target's relative retinal location. These "direct saccade" trials were defined as trials in which the observer found the target while keeping their gaze inside a narrow strip (5° in width) extending from their initial fixation point to the target. The observer was not required to saccade to the target in one eye movement, as this would exclude children who can only reach distant targets through a sequence of small saccades. The data in **Figure 8** confirm that observers C1 to C5 performed better at Field Bubbles than observers C6 to C10 (with C4 performing particularly well) and displayed the same directional impairments for C2, C5, C7, and C8, but in combination with the mean latencies, contain several other implications:

- C3 made fewer direct saccades than the other children with comparably low mean latency. This could suggest a general deficit in attention or perception that the observer made up for with a motivated follow-up search.
- C6 (age 18, verbal, legally blind) made direct saccades in only 10% of trials, with no clear directional bias in either

directness or latency, suggesting that he may have simply saccaded around the display randomly until his gaze collided with the target.

- C9 (age 5, non-verbal) exhibited a similarly low proportion of direct saccades (11%), but had worse latency overall than C6, suggesting that his search for the target may have been less motivated.

The eye tracking-based measures of ocular movements introduced here were designed to quantify the behaviors that are normally used in clinical exams to infer the ability to see in non-communicative subjects. The results show these measures provide the opportunity to grade impairments of visual function in children following brain injury with higher fidelity than is currently practiced.

Gradiate (Contrast Sensitivity)

Observers C1 to C5 were able to track moving stimuli sufficiently well (see **Figures 4–6**) to enable measurements of contrast sensitivity using our Gradiate task. Multiple Gradiate thresholds were measured using a standard version of the task, with five moving noise patches presented at once for tracking. Observers C6 to C10 were only able to generate thresholds with the full-screen variant. The combined results from both versions of Gradiate are shown in **Figure 9**. The top row depicts standard Gradiate CSFs for observers C1 to C5; observers C6 to C10 could not complete even a single trial of standard Gradiate across all sessions, which, while obviously indicative of extensive visual or attentional dysfunction, does bolster our previous conclusion that Gradiate is resistant to false positive responses (Mooney et al., 2020). The bottom two rows (gray background) depict full-screen Gradiate CSFs for all ten children. In all panels, each circle represents one combination of spatial frequency and contrast, and the redness of the circle indicates the proportion of trials in which the observer was able to successfully track that stimulus. For standard Gradiate, both mean CSFs (solid blue lines) and best CSFs (dotted blue lines) are shown. As Gradiate is highly resistant to false positives, the best CSFs (dotted lines) are likely to be valid estimates of the observer's sensitivity under optimal conditions for that child, such as high motivation and rapt attention. For full-screen Gradiate, only the mean CSFs are shown, as this version of the task is more susceptible to false positives and the best scores cannot be safely interpreted as valid. (The irregular lengths of the "best" thresholds in each sweep of this task, compared to the largely correlated lengths in the top row, are strong evidence of some false positives in the full-screen variant.) The number of sessions is shown above each panel. Note that the number of full-screen Gradiate sessions is lower than the number of standard Gradiate sessions for C1, C4, and C5 due to some instances of full-screen Gradiate being skipped by the experimenter to meet the child's scheduling constraints (given their demonstrated ability to complete standard Gradiate).

As anticipated, children who were able to generate data in standard Gradiate (C1 to C5, top row of **Figure 9**) generated similar mean CSFs in the full-screen variant (middle row of **Figure 9**), indicating that the full-screen variant retains Gradiate's validity. However, as was also expected, some children were able to occasionally generate much higher thresholds in the full-screen variant than their best thresholds in the standard variant—particularly C3 and C5, likely because they completed a much

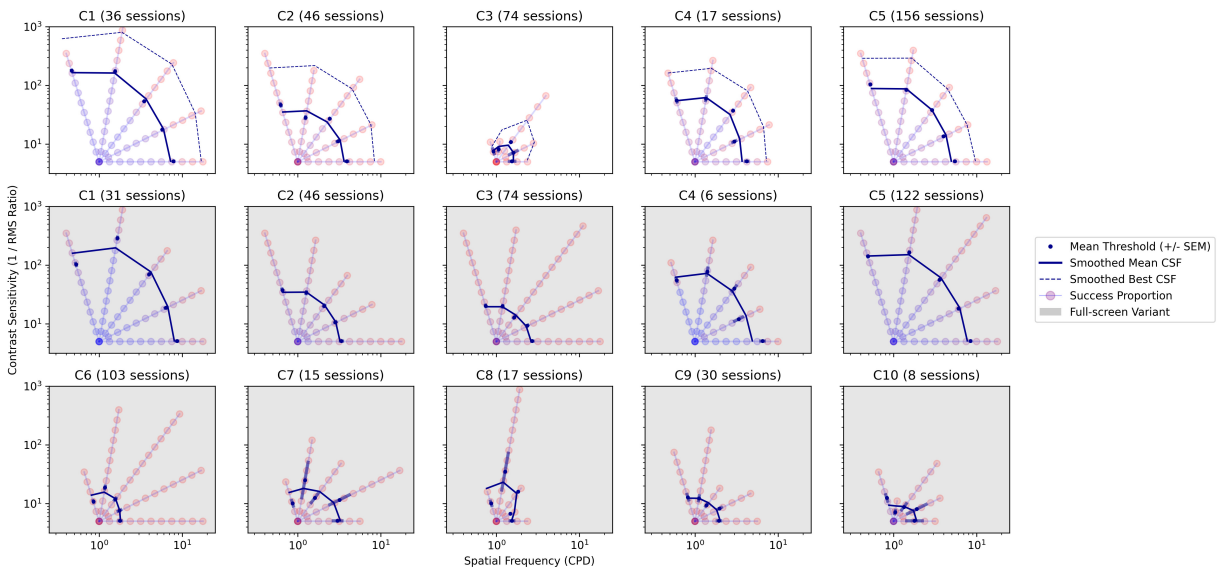

FIGURE 9 | Gradiate CSFs from the standard variant for observers C1 to C5 (top row) and from the full-screen variant for all observers (middle and bottom rows, gray background). The horizontal and vertical axes (both log) represent spatial frequency in cycles per degree and RMS contrast sensitivity, respectively. Each colored circle represents one step in a radial sweep of stimuli progressing outward (and becoming harder to see) from a common origin. The color of each circle varies from red to blue depending on the proportion of presentations of that stimulus in which the observer successfully tracked it (with blue denoting a higher success rate). The solid blue line in each panel is a smoothed CSF interpolated from the mean thresholds of all five sweeps. In the top row, a dotted blue line is also shown representing a smoothed CSF interpolated from the best thresholds of all five sweeps. The total number of sessions for each child/task is shown above each panel.

larger number of Gradiate sessions than the other children and thus had more opportunity to generate more exaggerated full-screen thresholds. Unsurprisingly, the children who were only able to generate data in the full-screen version of Gradiate (C6 to C10) tended to exhibit more impaired mean CSFs. Medical histories indicate that these children are legally blind (C6), lacking in light response (C7, C10), or unable to fixate or follow in at least one eye (C8, C9). None were able to have their acuity assessed by the ophthalmologist—nor was C3, who was nevertheless able to produce a weak CSF with standard Gradiate. Four of these children (all except C8) also exhibited pathological nystagmus (**Figure 6**), which makes tracking-based tasks like Gradiate difficult: the observer will likely find pursuit in arbitrary directions difficult, while also being particularly susceptible to false positives if the velocity of their repetitive nystagmus coincides with the more restricted movement of the full-screen stimulus. As we have discussed in our previous work, it is difficult to make the Gradiate task more accessible to observers with smooth pursuit disorders without increasing the error rate to an unusable extent (Mooney et al., 2018, 2020). The full-screen variant generates higher contrast sensitivity thresholds in general, as the criteria for successful tracking are easier: there is no positional gaze component required and only two directions in which the stimulus can move. It is nevertheless likely that some of the successful tracking exhibited by observers C6 through C10 in full-screen Gradiate is valid—particularly for C10, who tracked the most visible stimuli more reliably (out of her eight sessions) than the other four most severely impaired children. Despite these caveats, we were able to demonstrate that a high-quality measure of spatial vision—among the most informative tests of visual health and impairment—can be obtained in children with brain injury, including those who are impaired in their ability to communicate. Taken together, the results of the Gradiate measures show that all observers, even the child deemed legally blind, have spatial visual function that can be quantified and compared across observers. The use of a full-screen variant of Gradiate is also justified in children who cannot complete the standard five-ball task, since it may have been concluded that such participants had no spatial visual abilities if the full-screen tests were not administered.

Longitudinal Recovery From TBI

Observer C5 was measured over the course of 9 months, following a traumatic brain injury, and completed enough sessions of the Visual Ladder to highlight the Ladder's potential longitudinal use. **Figure 10** depicts monthly metrics from many of the analyses presented above. From top row to bottom row, the metrics are saccade directional histograms, mean saccade distance, pursuit directional histograms, visual field latency, visual field direct proportion, standard Gradiate, and full-screen Gradiate.

The data reveal marked improvement across most metrics. Large asymmetries in both saccades and pursuits disappeared by Month 3, and mean saccade latency in Field Bubbles steadily decreased over the first 6 months. Notably, the proportion of direct saccades in Field Bubbles did not noticeably change after Month 2; furthermore, while an early leftward impairment in field latency disappeared around Month 5, an upward/rightward impairment in latency appeared at the same time and persisted through the remaining months. Most remarkably, the observer's CSF improved consistently over the first 6 months in both the standard and full-screen Gradiate variants, which of all the depicted metrics most directly implies neurological recovery in spatial visual function. The longer recovery time exhibited in the patient's CSF and mean peripheral saccade latency (∼6 months), compared to the quicker recovery of his basic eye movement distributions (∼2 months), reinforces the importance of higher-level visual function assessment in providing a more comprehensive picture of recovery from brain injury. Our data are also consistent with his ophthalmological reports: C5 was unable to even fixate-and-follow in his examinations on arrival and after 2 months, but at the end of our study (when he was discharged) was able to have his acuity measured as 20/25. The important difference is that the Visual Ladder measurements were better able to grade the changes over time. Overall, his results demonstrate that the approach we have developed enables the ability to measure visual impairments in children after brain injury and quantify recovery longitudinally.

DISCUSSION

The study results demonstrate that rapid, intuitive assessments based on eye-tracking have promise for aiding the classification and quantification of visual impairment, including diffuse conditions such as CVI. The outcomes of the Visual Ladder can provide intuitive visualizations for clinicians that allow for rapid detection of broad asymmetries, directional biases, and spatial vision deficits, but just as importantly, they allow numerous types of visual disorder (both ocular and cerebral) to be precisely quantified along multiple dimensions of visual ability. Data are generated efficiently, and our ability to frequently retest the children in the study indicate that our attempt to "disguise" vision assessment behind intuitive game-like tasks was largely successful in sustaining interest and engagement. Below, we highlight three broad outcomes of our study that we find particularly noteworthy.

First, we were able to quantify saccades, smooth pursuits, and contrast sensitivity in children of a wide variety of ages and communicative ability, including a non-verbal child aged just 3 years (C10). This suggests that our game-like approach to assessment is appropriate for both younger and older children and holds promise for the generation of age-specific normative scores in the future. Visual field assessment was particularly difficult for non-verbal children, as it requires more attention that the other bubble tasks or full-screen Gradiate, but we nevertheless observed some broad asymmetries (e.g., a right hemifield impairment for C8) across repeated sessions. Our ability to assess these children with the Visual Ladder and place them on common quantitative scales, despite their other cognitive and communicative deficits, is the most promising takeaway of our study. While the Visual Ladder does not assess many of the higher-level symptoms associated with CVI, such as diffuse attentional impairments, color preferences, and

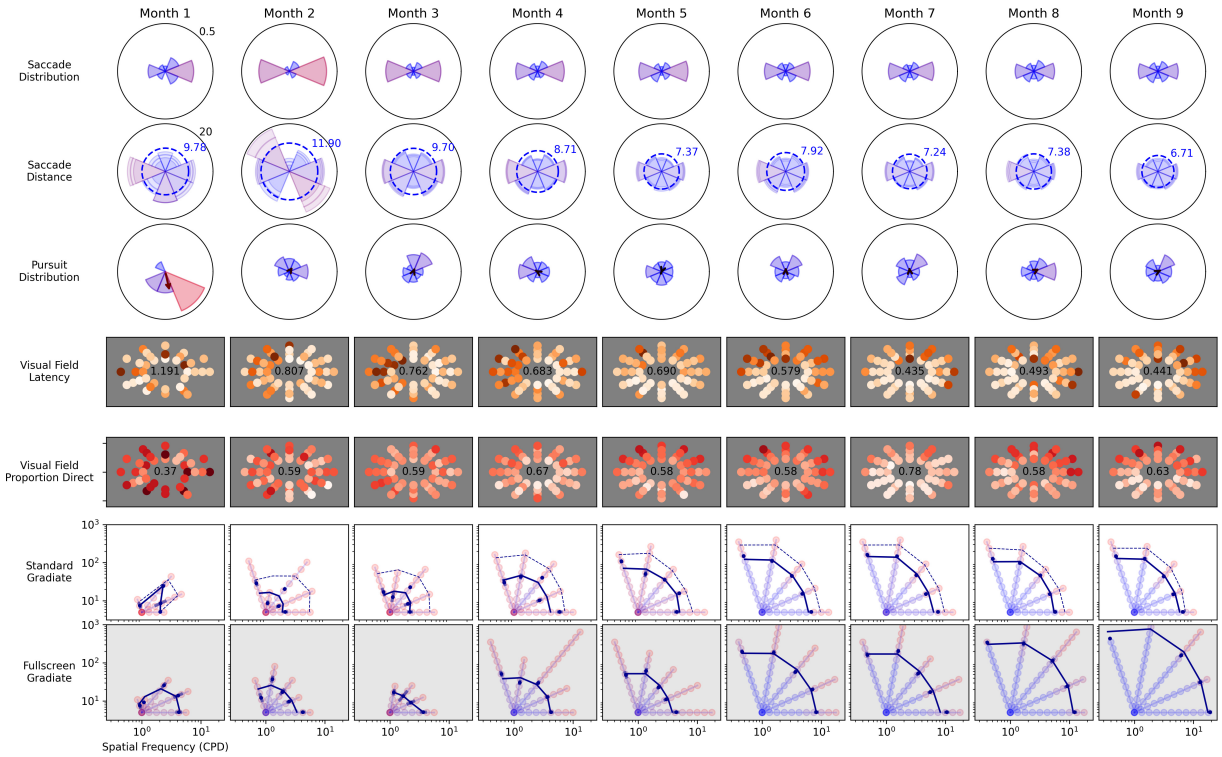

FIGURE 10 | Longitudinal recovery from a traumatic brain injury for observer C5 over 9 months. The child was admitted to Blythedale Children's Hospital approximately 3 months after accident and immediately enrolled in the study. He was non-communicative for approximately 2 months post enrollment. All plot layouts, axes, and units are identical to their corresponding previous figures.

issues perceiving crowded or complex scenes, our in-depth analysis of low-level patterns in eye movements and contrast sensitivity could nevertheless aid clinicians in characterizing CVI or ruling out other explanations for impaired visual function. It is also possible that further analysis of our dataset (e.g., through machine-learning) could reveal statistical fingerprints of disorders such as CVI that are not yet evident to us.

Second, while poor performance on one Ladder metric generally coincided with poor performance on others (seen here most clearly in observers C6 to C10), there are also unique patterns of outcomes across the Ladder tasks that distinguish different participants and affirm the need for a diverse range of quantitative visual tests. Observer C2, for example, performed well in Field Bubbles and standard Gradiate despite exhibiting a strong downward nystagmus, suggesting that his visual deficits may be mostly ocular rather than cerebral. Conversely, observer C3 exhibited relatively normal distributions of saccades and pursuits but had worse overall latency in Field Bubbles than the other verbal children and a highly impaired CSF, which likely indicates that she has intact ocular function but poor spatial vision. The data from observer C6—including his null result for both versions of Gradiate—affirm his status as legally blind, despite evidence of highly motivated participation (e.g., his consistent, though delayed, latency in Field Bubbles). These are patterns that are difficult to extract from any single metric and demonstrate that the Visual Ladder is well-placed to parse some of the numerous and diverse symptoms that can characterize distinct types of visual impairment or even distinct cases of CVI. Identifying the commonalities and dissociations between performance across different aspects of related visual functions—an analytic feat that is not possible without tasks that work for non-verbal children—will likely be fundamental for building a quantitative description of CVI based on objective visual criteria.

Third, observer C4—who was diagnosed with CVI 6 months prior to being enrolled in our study, following a traumatic brain injury—exhibited essentially no impairment across any of our metrics. It is possible that his diagnosis of CVI was based solely on higher-level deficits not measurable by the Visual Ladder, but more likely that they underwent a substantial recovery in the intervening 6 months, similar to the recovery we observed in real time for observer C5 (**Figure 10**). Establishing a regular program of ongoing longitudinal measurement, as we are in the process of doing at Blythedale Children's Hospital, would ensure that we can follow such recovery in detail and enhance our understanding of how outcomes after traumatic brain injury differ from outcomes of other sources of visual disorders.

Our tasks assess an expansive array of visual health metrics across many sessions, and our analysis here is certainly not exhaustive. There are many potential modifications and additional metrics that could provide further insights into visual impairment. We did not, for example, examine the temporal frequency of saccades or pursuits; such metrics are particularly

susceptible to a confounding variation in eye tracker noise, which is typically a larger problem for children with worse impairment overall (due to inattention, difficulty remaining still or maintaining distance, strabismus, etc.). We did not take monocular measurements due to session time constraints and the intolerance or distraction expressed by many children toward eye patching, particularly the non-verbal participants. Separate assessment of each eye is tractable with our approach and would certainly be an important feature to add to our procedure whenever possible in future studies, particularly when measuring visual field health and spatial vision. For clarity, we also divided our analysis of different visual abilities according to the tasks designed specifically to elicit them, but further cross-analysis between tasks (as we did with pursuits in Moving Bubbles and Field Bubbles to identify nystagmus) could reveal more about certain impairments. A more complete picture of overall saccadic ability, for example, can likely be formed from any of our tasks. The full-screen variant of Gradiate could also benefit from further improvements to its false positive rate, such as better classification of tracking behavior that allows stimulus-driven pursuits to be distinguished from incidental nystagmus or random drift. One way to achieve this may be to estimate the direction of any nystagmus from pursuit data in the preceding bubble tasks, as in **Figure 6**, and have the full-screen noise stimulus only scroll in the two directions orthogonal to that observer's nystagmus. We plan to investigate many additional avenues of analysis, both in real-time (to improve interactive stimulus behavior) and *post hoc*, as we continue to refine the Visual Ladder and deploy it in a wider clinical population.

It must also be noted that we were not able to measure all recruited children, despite our efforts in making the tasks as broadly deployable as possible (e.g., designing tasks with minimal reliance on perfect calibration). Four children were excluded from the study after initial testing revealed critical shortcomings in the eye tracker's ability to capture the user's gaze or eye position. These shortcomings were generally caused by strabismus (even when the tracker was set to measure only one eye), scoliosis that precluded proper positioning of the display and tracker, and/or frequent blinking that did not desist over time. Gaze-based assessment, while highly promising overall, is not a panacea: it replaces certain forms of behavioral feedback that are often impaired by brain injury (speech, manual responses, etc.) with another form of feedback that is usually more intact and functionally relevant for vision (eye movements), but certain types of disorders can still impair eye movements to an extent that makes our approach unfeasible. We believe that more of these children will become reachable as (a) eye tracker hardware improves, (b) our algorithms for handling transient gaps in gaze data improve, and (c) we find informative metrics that appear even in the noisiest eye tracking data, all of which we plan to pursue in future studies.

While repeated visual assessment does not automatically constitute a form of therapy, it is natural to consider ways in which the Visual Ladder could be modified to take on a more therapeutic role. It already has several advantages in this regard: the tasks it comprises are goal-directed, interactive, and entertaining, which are important ingredients for a successful program of behavioral treatment. The various tasks also naturally reward progress. More active saccading and pursuit behavior in the bubble tasks leads to more rapid popping, which our participants visibly enjoyed, and faster task completion times. More explicitly, both versions of Gradiate have an ability-driven scoring system built into them (number of musical notes heard); many verbal participants remembered their Gradiate scores and expressed enthusiasm upon surpassing them in future sessions. Gradiate also directly pushes participants into more difficult perceptual territory as they continue to make progress. If the bubble tasks were reconfigured to similarly spend more time at the boundaries of each participant's ability—such as gradually increasing the number of simultaneous bubbles in Bubble Burst, including more trials in high-latency locations during Field Bubbles, or increasing bubble movement speed in Moving Bubbles—they could potentially train participants to improve along the very dimensions of visual function already measured by those same tasks. Anecdotally, hospital staff and patient families have often reported that our repeated visual assessments appear to induce similar levels of stimulation in the children to other therapeutic programs.

The primary goal of the present experiment was to demonstrate that tracking-based assessment can be used to detect, quantify, and compare a variety of fundamental visual abilities, even in non-verbal children with brain injury. Given the numerous and well-known barriers to testing this population, we anticipated a moderate probability of failure, e.g., obtaining mostly null results for most participating children. We consequently did not set out to compare their data to results from an age-matched population of healthy observers. However, having now shown that our approach is promising for impaired children, our priorities for future research are indeed (a) establishing age-matched norms and (b) identifying the metrics that most effectively predict specific patient outcomes, quantify various metrics that are currently (and necessarily) treated as categorical in non-verbal children, and inform choices of actionable therapy. To accomplish these aims, our future studies will involve a larger sample of participants with varying visual disorders, more detailed comparisons of Visual Ladder outcomes with medical history and prognosis, and ongoing collaborations with ophthalmologists and therapists, all with the ultimate goal of refining the diagnosis of diffuse visual impairments such as CVI.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Biomedical Research Alliance of New York. Written or verbal assent and/or consent to participate in this

study was given by the participants and/or their legal guardians, depending upon each participant's age and ability.

AUTHOR CONTRIBUTIONS

SM designed and programmed the experiment, analyzed data, created figures, and wrote the manuscript. NA designed the experiment, recruited the participants, collected the data, and edited the manuscript. GP designed the experiment and edited the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnhum.2021.737409/full#supplementary-material

Supplementary Video 1 | Video demonstrating a segment of all tasks in the order they were presented to participants: Practice Task, Bubble Burst, Moving Bubbles, Field Bubbles, Full-screen Gradiate, and Gradiate. The green marker represents the mean gaze point of the participant (here, an author).

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Conflict of Interest: SM and GP were co-inventors on pending provisional US patent application 62/749,360, which includes the described Gradiate software, pending provisional US patent application 63/167,220, which includes the described trackability of eye movements and pending provisional US patent application 16/661,596 and Patent Cooperation Treaty Application Serial No. PCT/US19/57638, which includes the described methods for evaluating contrast sensitivity and other eye gaze metrics.

The remaining author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Early Screening of Visual Processing Dysfunctions in Children Born Very or Extremely Preterm

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Introduction: Children with early brain damage or dysfunction are at risk of developing cerebral visual impairment (CVI), including visual processing dysfunctions (VPD), which currently remain largely undetected until school age. Our aim was to systematically screen for possible VPD in children born very or extremely preterm from 1 to 2 years corrected age (CA) and to evaluate the effectiveness of early referral.

Method: We included N = 48 children born < 30 weeks from 1 year CA. They underwent a two-step VPD screening based on (1) neurological signs indicative of visual brain damage evaluated by neonatologists and/or pediatric neurologist and (2) a functional assessment of visual orienting functions (VOF) with an eye tracking-based test. If at least one of these assessments was abnormal for their age, the children were classified as a risk of VPD and referred to undergo conventional visual diagnostics: ophthalmic exam and visual function assessment (VFA). At 2 years CA, VOF screening was repeated and neurodevelopment was assessed.

Results: 18 children (38%) were classified as at risk of VPD at 1 year CA. 7 children had abnormal neurological signs, 5 children had abnormal VOF, and 6 children had both. Subsequent ophthalmic exams (N = 14) showed severe hypermetropia in 21% and strabismus in 14%. VFA (N = 10) showed abnormal visual function and behavior in only 1 child. At 2 years CA, the total group showed an increase in abnormal VOF. Whereas the children at risk showed some normalization, the group without VPD risk at 1 year CA showed deterioration of VOF. Neurodevelopmental outcome did not clearly differ between risk groups.

Conclusion: Our findings show a substantial risk of VPD during visual screening (in 38%) at 1 year CA, but relatively few deficits on subsequent conventional ophthalmic exams and VFA. The data suggest that most conventional visual diagnostic methods at

this young age are not related to the established VPD risks. VOF assessment should be used complimentary to these methods. The fact that at 2 years CA the number of children with a VPD risk based on abnormal VOF increased argues for more extensive and continuous screening in risk groups, at least until school age.

Keywords: cerebral visual impairment (CVI), visual processing dysfunctions, preterm children, early screening, neurological risk, visual orienting functions, eye tracking

INTRODUCTION

An increasing number of children has visual impairments due to brain damage or dysfunction, which is called cerebral visual impairment (CVI; Boot et al., 2010; Boonstra et al., 2012). There is currently no consensus on the exact definition of CVI: it is a broad and heterogeneous diagnosis that can include various types of visual dysfunction, depending on the underlying etiology (Ortibus et al., 2019). The problems children with CVI can experience already early in life range from lower-order visual sensory and oculomotor deficits to problems with information processing and higher-order visual perception problems (Dutton and Jacobson, 2001; Stiers et al., 2001). These problems can have a detrimental effect on (later) cognitive and motor development (Sonksen and Dale, 2002). An important aspect of CVI are visual processing dysfunctions (VPD): problems with detecting and processing incoming visual information, which has consequences for directing visual attention to specific locations, objects, or attributes within the visual scene. VPD are thought to reflect impairments in the intermediate stages of visual processing, mediated by both subcortical structures and primary and associative cortical visual areas (Martin et al., 1999). Most children at risk of CVI, and VPD, are enrolled in clinical follow-up programs from birth onward to monitor general health status, cognitive and motor neurodevelopment and for ophthalmic screening (e.g., retinopathy of prematurity, visual acuity deficits). However, no tests are included that monitor the functional impact that VPD may have on the first most critical years of development. The essence of the problem lies in the facts that (a) most tests for higher-level visual processing and/or perception require a certain degree of verbal communication between subject and assessor and (b), that mechanisms of brain maturation cause various higher-level visual functions to start and finish developing at differing ages, complicating their comprehensive assessment at a young age. As a consequence, the higher-level visual dysfunctions within the broad spectrum of CVI, i.e., VPD-related problems and perceptual dysfunction, generally start to be noticed when the functional consequences are beginning to affect social interactions or learning at school, i.e., around 5–6 years of age. It has been argued repeatedly that screening and possible intervention for CVI must take place preferably in the early years of high neuroplasticity, both by researchers (e.g., İdil et al., 2021) and clinicians (e.g., Federation Medical Specialists—CVI Guideline). Because of the methodological issues, many children at risk of CVI miss this window of opportunity. This may be overcome by early screening for VPD as an important hallmark of CVI in children.

When it comes to methods for VPD detection, there have been advances in the early detection of (a risk of) visual problems. Examples are assessment of basic visual functions in neonates as early as 31 weeks of gestation (Ricci et al., 2010), and a functional vision battery with cognitive and integrative aspects, to use between 1 and 4 years of age (Atkinson et al., 2002). These batteries involve various aspects of visual functions and rely on behavioral observations. In addition, a few computer-based methods have been developed, in which observation is combined with tracking the eyes of a child to assess visual orienting functions (VOF) as a proxy for visual attention (de Jong et al., 2016) and visual processing (Pel et al., 2010; Kooiker et al., 2016a). These methods rely on a close coupling between the visual attentional system and the oculomotor system (Munoz et al., 2007; Ross-Sheehy et al., 2017). As the nervous system develops, infant's visual attentional capabilities rapidly develop during the first months in life, and this is apparent when observing simple orienting eye movements toward specific visual stimuli. Eye tracking-based testing can be done in a non-verbal manner to quantitatively assess various characteristics of VOF (compared to normative references), such as visual reaction times, fixation accuracies, and fixation durations. When combined with specific visual stimuli that are known to be separately processed in the brain's visual system, VOF become a proxy for visual processing functions (Pel et al., 2010; Kooiker et al., 2016a).

In previous work, these VOF parameters proved reliable and valid not only in typically developing children, but also in heterogenous populations of children with (a high risk of) brain damage or dysfunction. VPD, as reflected by abnormal VOF, were particularly strongly correlated with signs of brain damage (i.e., visible damage on ultrasound or MRI scans) and a clinical diagnosis of CVI (Kooiker et al., 2014a) and were not related to visual acuity or oculomotor dysfunctions (Kooiker et al., 2014a; Pel et al., 2014). Moreover, abnormal VOF correlated with several aspects of visuoperceptual dysfunctions and daily visual problems in children with (suspected) CVI (Ben Itzhak et al., 2021). An important subgroup of children at risk are children born preterm, i.e., born before 37 weeks gestational age (GA). Because of improved neonatal health care, more preterm born children survive and grow up, even the children born very or extremely preterm, i.e., born before 30 weeks GA. The downside of this increased survival rate is the high risk of acquiring neurological damage with visual attention and processing abnormalities as a result (Atkinson and Braddick, 2007; Dutton, 2013). Previous

Abbreviations: CA, corrected age; CVI, cerebral visual impairment; GA, gestational age; FD, fixation duration; GFA, gaze fixation area; METC, medical ethical testing committee; MRI, magnetic resonance imaging; PAI-CY, participation and activities inventory - children and youth; ROP, retinopathy of prematurity; RT, reaction time; RTF, reaction time to fixation; VFA, visual function assessment; VOF, visual orienting functions; VPD, visual processing dysfunctions.

studies using VOF parameters in children born very or extremely preterm showed abnormal VOF in the form of delayed viewing reaction times in 8–48%, that were related to structural brain damage around birth (van Gils et al., 2020), and to specific perinatal risk factors (Kooiker et al., 2019). Importantly, early VOF delays added to the prediction of later adverse neurodevelopmental outcome at 2 years corrected age (CA) in this population (Beunders et al., 2020).

Based on these recent insights, a logical next step is to use this eye tracking-based paradigm to screen children for risks of VPD 4–5 years earlier than is done in current practice. When this would be successful, it would bridge the gap between scientific findings and current visual (diagnostic) practice. To this end, we set up a prospective study to investigate the potential of early screening of VPD. Given the well-established notion that neuroplasticity is highest early in life, and the fact that other, low-level, visual screening methods showed to be feasible around 1 year of age, we chose to start screening for VPD at 1 year of age. This study is conducted in children born very or extremely preterm to constitute as a model for the larger group of children at risk of VPD due to prenatal or perinatal brain damage.

The aim of the present study was to explore whether systematic screening for possible VPD in children born very or extremely preterm from 1 year CA leads to an accurate selection and whether the age of 1 year is the most optimal age for screening. The following two research questions were addressed:

(1) Do abnormalities found in the early screening of VOF relate to the results of conventional visual diagnostics and daily visual problems at 1 year CA?
(2) How do early VPD risks develop over the course of 1 year and what is their implication for visual and neurodevelopment at 2 years CA?

MATERIALS AND METHODS

Participants

All children who were born before 30 weeks GA and who participated in the outpatient clinical follow-up program of the dept. Neonatology, Erasmus MC-Sophia Children's Hospital, were eligible for inclusion at 1 year CA. Children were excluded from participation based on the following criteria: Visual acuity below 0.05 Snellen equivalent, to ensure visibility of the eye tracking-based assessment; a high chance of epileptic activity during assessment, i.e., more than two attacks in the previous year or when actively using the anti-epileptic Vigabatrin (which may lead to visual dysfunctions; Maguire et al., 2010); retinopathy of prematurity (ROP) of grade 3 or higher assessed by a pediatric ophthalmologist, to exclude severe causes of visual dysfunctions other than VPD. Children were included for participation after receiving written informed consent from their parents or caregivers. The assessments were scheduled to coincide with an existing appointment at the Neonatology outpatient clinic to minimize burden for children and parents. The present study has been approved by Medical Ethical Testing Committee (METC) of Erasmus Medical Center, Rotterdam (MEC-2016-724) and adhered to the tenets of the Declaration of Helsinki (2013) involving research with human subjects.

Demographics

The following information was extracted from the medical records: gender, gestational age (GA, in weeks), birth weight (BW, in grams).

Structural Brain Damage

We obtained cerebral magnetic resonance imaging (MRI) scans that were made at 30 weeks GA or when the child was medically stable (range 29–35 weeks GA) as a part of standard medical care. The MRI scans were scored on brain growth and damage using a modified version of the standardized scoring system of Kidokoro et al. (2013). This included scoring of cerebral white matter (CWM), cortical gray matter (CGM), deep gray matter (DGM), and cerebellum. A modification was made on myelination and thickness of the corpus callosum because of the poor quality of some of the MRI scans. Since the brain measurement are dependent on GA, each scan was age-corrected (George et al., 2017). For a detailed description and visualization of the scoring method and analysis we refer to previous work (van Gils et al., 2020).

Daily Life Functioning

Upon inclusion, parents were asked to complete the Participation and Activity Inventory (PAI-CY 0-2) (Elsman et al., 2017). This questionnaire was developed to identify and monitor the developmental and participation needs of visually impaired children. It is the only available patient-reported visual outcome measure for young children and has satisfactory psychometric properties (Elsman et al., 2020). The instrument comprises items that are categorized in seven domains: attachment, stimulus processing, visual attention, orientation, play, mobility, and communication. Two additional domains, from the first PAI-CY version, were also included because they were relevant for the present study, i.e., sensory functioning and parental concerns. Each item was scored on a 4-point Likert scale with the response options: (0) not difficult, (1) slightly difficult, (2) very difficult, and (3) impossible. An average score per child per category was calculated.

Visual Processing Dysfunctions Screening at 1 Year Corrected Age and Risk Assessment

Screening of VPD consisted of (1) neurological signs indicative of visual brain damage and/or VPD and (2) a functional assessment of visual orienting functions (VOF), evaluated with an eye tracking-based test and compared to age-matched normative references. If at least one type of abnormal VOF (in terms of viewing reaction times; see *VOF assessment*) and/or at least one neurological risk factor was found, the child was classified as having a risk of VPD and they were referred to undergo conventional visual diagnostics.

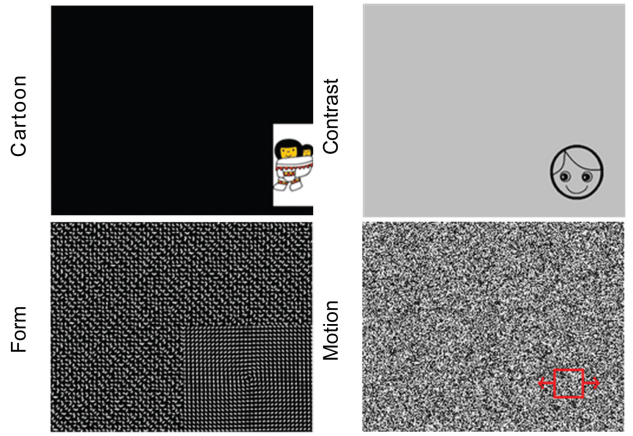

FIGURE 1 | The four stimulus types with various visual content, from left to right and up to down: Cartoon, Contrast, Form, and Motion.

Neurological Risk Assessment

Neonatologists and/or a pediatric neurologist examined the child's medical history for the presence of neurological risk factors for VPD in the context of prematurity (Schalij-Delfos et al., 2000; Ramenghi et al., 2010; Dutton, 2013; Sayeur et al., 2015), i.e.,

- Evidence for moderate to severe brain damage on neonatal MRI scans;
- Cerebral palsy: unilateral, bilateral, hemiplegia, diplegia;
- Infantile strabismus or nystagmus;
- Deviating head circumference (>1 SD in 12 months).

Visual Orienting Functions Assessment

VOF were measured with an eye tracking-based assessment focused on visual attention and processing functions. All tests were performed by trained researchers. The children were seated in front of the 24-inch eye tracker monitor at a distance of approximately 60 cm, either independently, on the lap of their parent or in a pram. No-one received verbal instructions, nor were they restricted in their movements. All assessments were conducted in a quiet room with ambient light conditions and total test duration was approximately 15 min. A 5-point Likert scale was used to monitor the level of attention, fatigue and restlessness/mobility, with option (1) representing "not at all" and (5) representing "all the time."

After a five-point calibration procedure, visual stimuli (images and movies) were presented on the monitor to engage reflexive orienting eye movements of the child, while simultaneously the eye positions were recorded using infrared cornea reflection (Tobii T60 XL or Tobii X3, Tobii Corporation, Danderyd, Sweden). That way, the child's eye movement responses to various types of visual information with different salience levels (i.e., high-salient cartoons and contrast, moderate-salient motion and form; **Figure 1**) were automatically recorded. All stimuli were shown for 4 s. From the eye movement responses, various quantitative parameters were calculated to describe VOF per stimulus, i.e., the percentage of gaze data collected, the number of detected stimuli, the reaction time to fixation (RTF) of a stimulus and its individual variability RTvar. RTF is a measure for the timing of detecting, processing and executing an eye movement to the presented visual information and is the main study parameter (Pel et al., 2010; Kooiker et al., 2016a). In addition, for the high-salient cartoon stimulus two additional parameters were calculated: gaze fixation area (GFA), indicating the size of the fixated area in degrees and representing fixation accuracy; and the fixation duration (FD), indicating spontaneous duration of a child's fixation on a stimulus. Individual parameter results were included when they adhered to the reliability criterion of > 25% of stimuli seen (Kooiker et al., 2014b). For children in whom calibration during the assessment failed, a post-calibration was performed prior to data analyses. For a detailed description of data processing and parameter analyses we refer to previous work (Kooiker et al., 2016a; van Gils et al., 2020).

The child's VOF parameters per visual stimulus were compared with age-related normative data, i.e., developmental trajectories of an existing database of typically developing children born at term aged 0.5–1.5 years (baseline, N = 39) and aged 1.5–2.5 years (follow-up; N = 61). VOF parameter results were classified as normative or abnormal. For the parameters RTF and GFA this was based on the 95% confidence interval around the average (±2 SD) in the age-related norm group. For FD this was based on the 68% confidence interval (±1 SD) around the average of the norm group, because of the large variability in FD in the norm group.

Referral of Children With a Visual Processing Dysfunctions Risk to Conventional Visual Diagnostics

The children who were identified as being at risk of VPD followed the conventional care pathway for children suspected of visual dysfunction. First, they underwent an orthoptic and ophthalmic exam at dept. Pediatric Ophthalmology, to evaluate visual acuity, refractive error and ocular alignment. This evaluation was performed by ophthalmologists and/or research orthoptists. Total duration of the exam was approximately an hour. Next, they were referred to a visual advisory and rehabilitation center to receive standard care, consisting of a visual function assessment (VFA) and, if applicable, a visual intervention program. With the VFA, the following visual sensory and oculomotor functions were assessed using a standardized protocol: ocular alignment and fixation preference, binocular vision, presence of nystagmus, oculomotor function (fixation, saccades, pursuit, motility), convergence, visual acuity, visual field, contrast sensitivity, and color vision. Performance per function was classified as normal or abnormal for the child's age according to norm values per used test. For a detailed description of the assessment and classification per function (see Kooiker et al., 2016b). In addition, an observation of functional visual behavior was performed. The VFA assessments were performed by experienced orthoptists or optometrists and behavioral

therapists. Together they determined the level of visual functioning of the child (Steendam, 2007), ranging from normal visual function to subnormal visual functioning (small degree of functional deficit, borderline), to profound visual dysfunction (clear deficits in visual attention and recognition), or legal blindness (only light responses). All assessments were performed according to a standardized protocol that ensured similar assessments, choice of tests and scoring by the various examiners.

Follow-Up After 1 Year

One year after inclusion, i.e., at 2 years CA, in all included children (with and without VPD risk) the eye tracking-based VOF assessment was repeated. In addition, results from a neurodevelopmental assessment as part of the clinical follow-up of preterm born children were collected. The Bayley Scales of Infant and Toddler Development (BSID-III-NL) were performed by experienced (neuro)psychologists. The cognitive and motor scores and classifications were obtained as indications of overall neurocognitive and motor development, with higher scores indicating better development.

Statistical Analysis

All data were tested for a normal distribution using the Kolmogorov-Smirnov test. This was significant for most parameters, therefore non-parametric tests were performed for the main analyses. Descriptive analyses were used to represent the presence and distribution of participant variables (i.e., demographics, structural data) and results of the VPD screening in the total study population.

To answer research question 1, Wilcoxon Signed-Rank tests were performed in the subgroup of children at risk of VPD, to compare results on the conventional visual diagnostic exams and the PAI-CY results. Additionally, these relations were explored for three different VPD risk groups (i.e., VOF risk, neurological risk, both risks). To answer research question 2, differences in VOF changes and neurodevelopmental outcome at 2 years CA were compared between the children with and without a VPD risk at 1 year CA, using Mann-Whitney *U*-tests. *P*-values < 0.05 were considered statistically significant.

RESULTS

Participants

A total of $N = 48$ children born < 30 weeks GA were included at 1 year CA. **Table 1** shows the demographics and clinical characteristics of the total group. Overall, there was a mild degree of structural brain damage around birth, indicated by a global score of 5 with the Kidokoro method.

Visual Processing Dysfunctions Screening at 1 Year Corrected Age

We found a high risk of VPD in 18 children (38%) at 1 year CA. In 7 children (15% of total) this was based on neurological risk factors, in 5 children (10% of total) this was based on abnormal VOF, and in 6 children (13% of total) both assessments were abnormal.

TABLE 1 | Participant characteristics.

Characteristic	*N* (%) or average (SD)
Gender (boys)	30 (63%)
GA (weeks)	27.9 (1.5; range 24.6–29.9)
Birth weight (gr)	1,088 (246; range 565–1,550)
Structural brain damage (range)	
Global score (0–31)	4.54 (3.28)
CWM score (0–11)	2.64 (1.91)
CGM score (0–8)	0.23 (0.59)
DGM score (0–6)	1.57 (1.60)
Cerebellum score (0–6)	0.79 (0.80)

SD, standard deviation; GA, gestational age; CWM, cerebral white matter; CGM, cerebral gray matter; DGM, deep gray matter.

TABLE 2 | The presence of neurological risk factors for VPD.

Type of neurological risk*	Presence (*N*)
Evidence of brain damage:	13
IVH grade II or III	8
Germinal matrix hemorrhage	2
Venous infarction	3
CNS sepsis	1
Ventricular dilation	2
Meningitis	1
Developmental venous anomaly	1
Cerebral palsy	4
Strabismus	3
Abnormal head circumference	0

**Factors are not mutually exclusive.*
IVH, intraventricular hemorrhage; CNS, central nervous system.

Table 2 shows the presence of neurological risk factors for VPD. Of the 13 children who had evidence of brain damage, in 8 children this was attributable to IVH. Other causes were germinal matrix hemorrhage (2 children), venous infarction (3 children), or ventricular dilation (2 children).

Table 3 shows the overall results of the VOF assessment at 1 year CA. 94% of children had a successful calibration prior to testing. The attention, fatigue and mobility scores were all around 3; indicating scores slightly above average ("now and then"). The percentage of recorded data per stimulus ranged from 56% (Cartoon) to 69% (Motion). The percentage of stimuli seen ranged from 41% (Form) to 79% (Cartoon). The percentage of reaction times (RTs) that could be reliably calculated from all stimulus presentations classified as "seen" ranged from 54% (Cartoon) to 94% (Motion).

Table 4 shows the quantitative parameter results of the VOF assessment per visual stimulus for the total group at 1 year CA. In 12 children (25%) GFA was abnormal and in 7 children (15%) FD was abnormal. The percentage of abnormal RTF values ranged from 6% (3 children;

TABLE 3 | General VOF results in the total group of preterm children at 1 year CA.

Eye tracking feasibility factors	*N* (%) or average (SD)
Calibration successful	45 (94%)
Attention score (1–5)	3.46 (0.9)
Fatigue score (1–5)	2.98 (0.89)
Restless/mobility score (1–5)	3.10 (1.13)
Overall viewing behavior per stimulus	**Median [IQR]**
Cartoon % data	56 [32]
% seen	79 [30]
% RTs	54 [35]
Contrast % data	60 [29]
% seen	75 [25]
% RTs	75 [40]
Motion % data	69 [25]
% seen	75 [50]
% RTs	94 [32]
Form % data	60 [29]
% seen	41 [48]
% RTs	71 [73]

SD, standard deviation; IQR, interquartile range; RT, reaction time.

TABLE 4 | Stimulus-specific VOF parameter values and the concurrent N and % of abnormal results compared to the age-matched normative references, in the total group of preterm children at 1 year CA.

Stimulus parameter	Median [IQR]	*N* (%) abnormal
Cartoon GFA (deg)	1.98 [0.67]	12 (25%)
FD (ms)	1,304 [1,073]	7 (15%)
RTF (ms)	208 [76]	3 (6%)
RTvar (ms)	48 [39]	7 (15%)
Contrast RTF (ms)	432 [122]	6 (13%)
RTvar (ms)	42 [52]	7 (15%)
Motion RTF (ms)	707 [278]	5 (10%)
RTvar (ms)	97 [100]	12 (25%)
Form RTF (ms)	1,098 [450]	4 (8%)
RTvar (ms)	166 [152]	6 (13%)

VOF, visual orienting functions; CA, corrected age; IQR, interquartile range; GFA, gaze fixation area; FD, fixation duration; RTF, reaction time to fixation; RTvar, reaction time variability.

Cartoons) to 13% (6 children; Contrast), and abnormal RTvar values ranged from 13% (6 children; Form) to 25% (12 children; Motion).

Conventional Visual Diagnostics in Children With a Visual Processing Dysfunctions Risk

Table 5 shows the results of the ophthalmic exams and visual function assessments (VFA) that were performed after referral to conventional diagnostic services, separately for the type of VPD risk. Parents of 14 children (78% of the total VPD risk group) agreed with referral to the ophthalmologist. The ophthalmic exams showed moderate hypermetropia in 7 children (50%; considered normal at this age), severe hypermetropia in 3 children (21%), and strabismus in 2 children (14%). Rates of hypermetropia and strabismus were highest in the group with both VPD risk factors.

TABLE 5 | Results of the ophthalmic exam and VFA after referral in the children at risk of VPD, separately for the different types of VPD risks (based on neurological factors, based on VOF, or based on both factors).

Ophthalmic exam (*N* = 14)	Neurological risk (*N* = 4)	VOF risk (*N* = 4)	Both risk factors (*N* = 6)
Moderate hypermetropia	3 (43%)	1 (20%)	3 (50%)
Severe hypermetropia	–	1 (20%)	2 (33%)
Strabismus	–	1 (20%)	1 (17%)
VFA abnormalities (*N* = 10)	**Neurological risk (*N* = 4)**	**VOF risk (*N* = 2)**	**Both risk factors (*N* = 4)**
No stereovision	1 (25%)	0	0
Nystagmus	0	0	0
Fixation	0	0	1 (25%)
Motility	0	0	0
Smooth pursuit	0	0	1 (25%)
Saccades	0	0	0
Convergence	0	0	0
Visual acuity mean (SD)	0.26 (0.11)	0.28 (0.32)	0.20 (0.09)
Visual acuity	0	0	0
Visual field	0	0	0
Contrast sensitivity	0	0	0
Color vision	0	0	0
Level of visual functioning			
Subnormal	–	–	1 (25%)
Normal	4 (100%)	2 (100%)	3 (75%)

Factors are not mutually exclusive. VFA, visual function assessment; VPD, visual processing dysfunction; VOF, visual orienting functions; SD, standard deviation.

Subsequently, parents of 10 children (56% of the total VPD risk group) agreed with referral to a visual rehabilitation center for an extensive VFA. Reasons for not agreeing with referral were that parents did not see any visual abnormalities in their child and/or that they already felt burdened with other medical appointments and assessments. In the group with a VPD risk based on neurological factors, one child did not have stereovision and average visual acuity was 0.26 decimal scale, which is normal for their age. Overall, the children in this group had normal levels of visual functioning for their age. In the group with a VPD risk based on abnormal viewing behavior, average visual acuity was 0.28 and both children had overall a normal level of visual functioning for their age. In the group with both VPD risk factors, average visual acuity was 0.20, slightly lower than in the other groups. One child showed abnormal fixation and smooth pursuit eye movements in combination with fluctuating viewing behavior (i.e., short fixations, many saccades) and as a result was classified with a subnormal level of visual functioning. The other children showed no abnormalities and had normal levels of visual functioning for their age.

TABLE 6 | Results of the participation and activities inventory for children from 0 to 2 years (PAI-CY 0-2), separately for children not at risk and children at risk of VPD.

PAI-CY category average score	Children not at risk of VPD, *N* = 24 (median[IQR])	Children at risk of VPD, *N* = 13, (median[IQR])
Attachment	0 [0–0.5]	0.2 [0–0.4]
Stimulus processing	0 [0–0]	0 [0–0.4]
Visual attention	0.2 [0–0.4]	0.2 [0.1–0.4]
Orientation	0 [0–0]	0 [0–0.5]
Play	0.4 [0–1.0]	0.4 [0.2–0.4]
Mobility*	0 [0–0.6]	0.4 [0.3–0.8]
Communication	0 [0–0.5]	0.5 [0–1.0]
Sensory functioning	1.8 [1.6–2.2]	1.8 [1.5–2.0]
Parental concerns**	1.9 [1.6–2.1]	2.1 [1.8–2.3]

**Sign difference; **trend. VPD, visual processing dysfunctions.*

Daily Life Functioning

A total of 37 parents (77% of total group) completed the PAI-CY 0-2. **Table 6** shows the results per category, separately for children not at risk and children at risk of VPD. Overall, the rate of daily life difficulties as indicated by parents in either group was relatively low. Nevertheless, compared to parents of children not at risk, parents of the children at risk of VPD gave higher scores for attachment, stimulus processing, orientation, mobility, communication, and parental concerns, indicating that more difficulties were experienced in these categories. Only the score for mobility was significantly higher ($U = 86$, $z = -2.0$, $p = 0.043$). The scores on visual attention, play, and sensory functioning where similar between the two groups.

Follow-Up After 1 Year

A total of $N = 43$ children (90% of total group) repeated the VOF assessment at 2 years of age. With regard to changes in general VOF from 1 to 2 years CA, we found that scores on the eye tracking feasibility factors, i.e., calibration, attention, fatigue, and mobility, remained similar. In the total group, the percentage of data recorded decreased for Cartoon and remained similar for the other stimuli. The percentage of stimuli seen by children overall increased (ranging from + 0 to + 25%) and the percentage of calculated RTs remained the same. Compared to the children not at risk of VPD, in the children at risk of VPD the percentage of recorded data increased (ranging from + 4% to + 8%), the percentage of stimuli seen overall also increased (ranging from + 0 to + 38%), and the percentage of calculated RTs remained the same (Contrast and Motion) or increased (+2 to + 8%). However, none of these differences were statistically significant (Mann-Whitney *U*-tests all n.s.).

Table 7 shows the median change in stimulus-specific VOF parameters and the change in the percentage of abnormal parameter values compared to age-based normative references, separately for the total group of included preterm children, the children not at risk of VPD at 1 year CA and the children at risk of VPD at 1 year CA. **Figure 2** shows stimulus-specific RTF values of individual children, at 1 year CA and at 2 years CA.

In the total group at 2 years CA, the percentage of abnormal GFA, FD, and RTF values relative to normative references increased compared to 1 year CA (except for RTF for Contrast), and RT variability decreased. Children who were not at risk of VPD at 1 year CA showed more changes to abnormal VOF parameter values at 2 years CA, whereas children with a VPD risk at 1 year CA showed more normalization (i.e., less abnormal parameter values compared to normative references) at 2 years CA. The decrease in absolute RTF value for Contrast was significantly larger in the group with a VPD risk compared to the group without a VPD risk ($U = 93.5$, $z = -2.26$, $p = 0.024$). The change in absolute RTvar value for Form was also significantly larger in the group at risk of VPD, where it considerably decreased ($U = 19$, $z = -2.24$, $p = 0.025$).

Specifically for RTF values we analyzed individual changes among all children with successful VOF measurements at both ages. For Cartoons, 3% had abnormal RTF at 1 year CA but no longer at 2 years CA, whereas 18% had normal RTF at 1 year CA but abnormal values at 2 years CA. For Contrast, Motion and Form, respectively 21, 2, and 13% had abnormal RTF values at 1

TABLE 7 | Median changes in stimulus-specific VOF parameters and changes in the percentage of abnormal parameter values compared to age-based normative references, separately for the total group, the children not at risk of VPD at 1 year CA and the children at risk of VPD at 1 year CA.

	Total group (*N* = 43)		Children not at risk of VPD at 1 year CA		Children at risk of VPD at 1 year CA	
Stimulus	**Median change**	**Change in% abnormal**	**Median change**	**Change in% abnormal**	**Median change**	**Change in% abnormal**
Cartoon GFA (deg)	+0.3	+10%	+0.22	+16%	+0.10	0%
FD (ms)	−138	+10%	+286	+7%	+538	+14%
RTF (ms)	+18	+9%	+53	+17%	+12	−6%
RTvar (ms)	−18	−8%	−17	−10%	−18	−5%
Contrast RTF (ms)	−63	−5%	−30	+13%	−129	−33%
RTvar (ms)	−6	−8%	−9	+6%	+3	−22%
Motion RTF (ms)	−184	+9%	−214	+10%	−162	+5%
RTvar (ms)	−22	−6%	−26	0%	+46	−11%
Form RTF (ms)	−169	+9%	−162	+17%	−425	−5%
RTvar (ms)	−15	−12%	+18	−17%	−104	−6%

VOF, visual orienting functions; CA, corrected age; GFA, gaze fixation area; FD, fixation duration; RTF, reaction time to fixation; RTvar, reaction time variability.

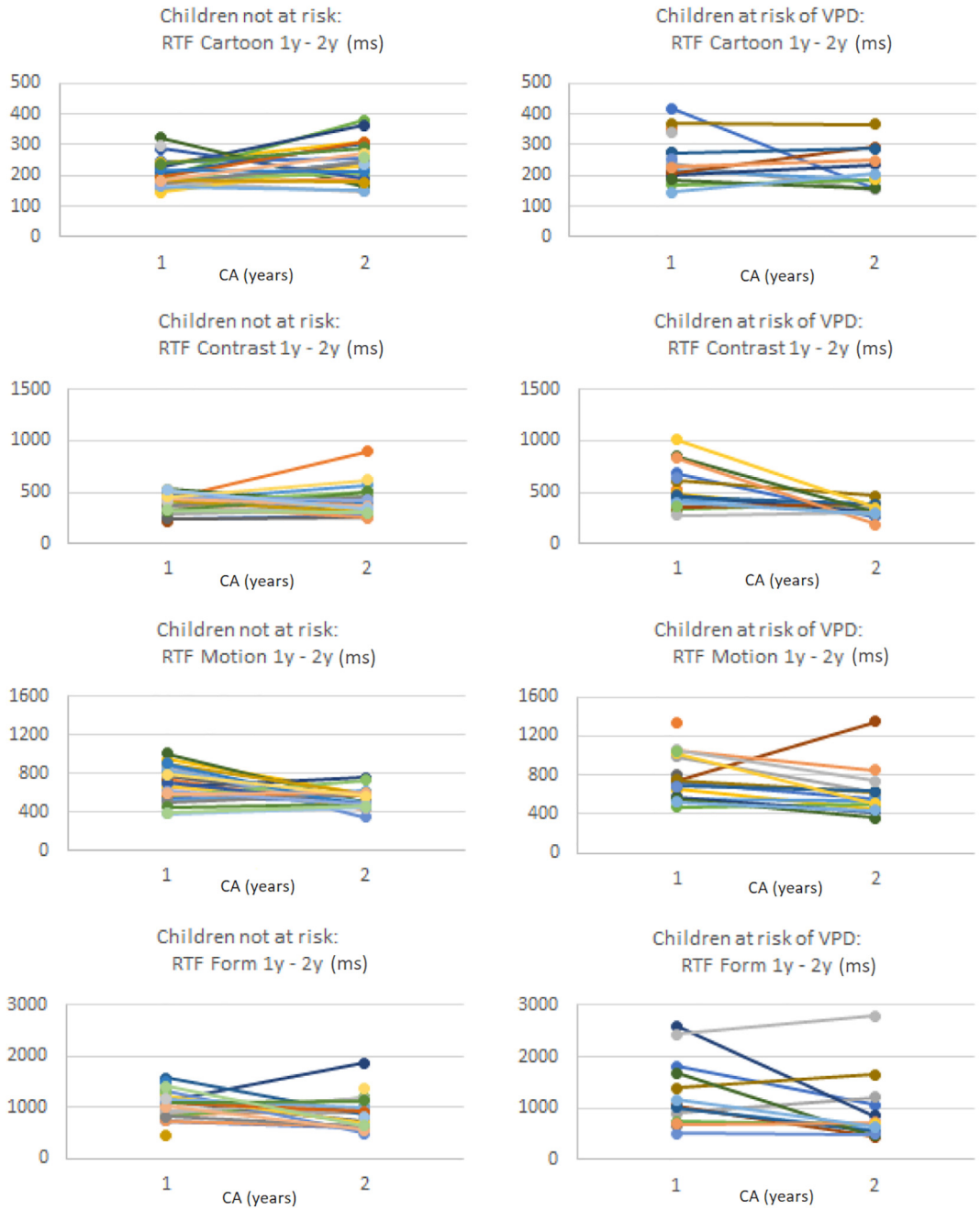

FIGURE 2 | Per stimulus the RTF values (in ms) of individual preterm children at 1 year CA and at 2 years CA, separately for the children without a VPD risk **(left column)** and the children with a VPD risk **(right column)**. Note that values on the *y*-axis differ per stimulus.

year but no longer at 2 years. Another 8, 20, and 23% had normal RTF values at 1 year but abnormal values at 2 years CA.

Neurodevelopmental Outcome at 2 Years Corrected Age

Table 8 shows the results of the BSID-III-NL assessment, indicating the level of neurodevelopmental outcome, separately for the children not at risk of VPD and the children at risk of VPD. No differences were found between the groups on the cognitive and motor scores.

DISCUSSION

The aim of the present study was to systematically screen for possible VPD at 1 year CA in children born extremely preterm (<30 weeks GA), to compare the outcome with conventional

TABLE 8 | Results of the Bayley Scales of Infant Development (BSID-III-NL) assessment (average, SD), separately for the children not at risk of VPD and the children at risk of VPD.

BSID-III-NL category	Children not at risk of VPD	Children at risk of VPD
Cognitive score	101 (10)	105 (7.8)
Cognitive classification	3.1 (0.6)	3.3 (0.5)
Motor score	99 (13)	99 (15)
Motor classification	3 (0.8)	3 (0.7)

SD, standard deviation; VPD, visual processing dysfunction.

visual diagnostics and to evaluate the effectiveness of early referral at 2 years CA. We found a moderate risk of VPD during visual screening (in 38%) at 1 year CA on the account of abnormal neurological signs (15%), abnormal VOF (10%), or both risk factors (13%). Relatively few deficits were found on subsequent conventional ophthalmic examination and VFA. During follow-up at 2 years CA, the percentage of abnormal VOF results increased in the total group, indicating a larger number of children at risk of VPD at this age. Interestingly, this was not related to a VPD risk at 1 year CA.

Screening at 1 Year Corrected Age

The innovative early screening at 1 year CA showed both neurological risks of VPD and functional risks based on abnormal VOF. The type of neurological VPD risk was predominantly based on IVH and other sorts of damage that are relatively common in children born extremely preterm (such as germinal matrix hemorrhages and venous infarctions). With regard to the functional, VOF-based risk assessment we supported with quantitative data that non-verbal eye tracking-based assessments are feasible in children born extremely preterm at this young age. The total group showed high degrees of successful calibration (94%) and average overall attention, fatigue and mobility/restlessness. Overall, we found very acceptable rates of general viewing behavior during the assessment: the percentage of recorded data ranged from 56 to 69%, the percentage of stimuli detected ("seen") from 41 to 79%, and the percentage of RTs that could be reliably calculated out of seen stimuli from 54 to 94%. These parameters are all conditional factors for calculating the stimulus-specific quantitative VOF parameters. If a child has no attention for the test in general (% data), and subsequently does not detect the stimulus-specific target areas (% seen), then no RT can be calculated (% RTs).

The subsequent quantitative VOF analyses revealed that compared to age-matched norms, spontaneous fixation duration was abnormal in 15% of children and fixation accuracy was abnormal in 25%. The percentage of delays in VOF (abnormal RTF values) ranged from 6% (Cartoons) to 13% (Contrast), and high variability in VOF timing (abnormal RTvar values) ranged from 13% (Form) to 25% (Motion). These numbers are comparable to previous results in children born extremely preterm at 1 year CA, and minor differences can likely be attributed to sample size.

After referral of part of the risk group to conventional visual diagnostic services, relatively low levels of ophthalmic and VFA abnormalities were found at this age. Most abnormalities were found in the group with both VPD risk factors (i.e., neurological and VOF-based); where rates of hypermetropia and strabismus were highest, visual acuity was lowest and one child was classified with subnormal visual functioning based on abnormal oculomotor function and fluctuating viewing behavior. The VFA included a structured observation of the child's visual and viewing behavior, which was expected to partly correlate with the eye tracking-based VOF assessment, as both revolve around active viewing and exploration. Surprisingly, in the children with abnormal VOF these abnormalities were not discovered by observation during VFA in most children. This may have to do with the fact that during observation, slighter deviations in viewing behavior are more difficult to notice than when using an automated recording system such as an eye tracker. As a consequence, most cases of abnormal visual function that were found with the screening were of an ocular origin. As expected beforehand, it is reflected by our data that most conventional visual diagnostic methods at this young age do not tap into cerebrally-mediated visual functions such as form- or motion processing. Whereas ophthalmic exams and VFA are necessary to map a child's eye and visual function and deliver information on possible CVI signs such as visual field defects and crowding (see Federation Medical Specialists—CVI Guideline), other methods are needed to gather additional information on a VPD risk. Therefore, the available methods should be applied complementary to get a comprehensive overview of not only visual function but also of functional visual behavior.

Resulting from the relatively few abnormalities that were found with the conventional visual diagnostic exams, and given the relatively good levels of visual functioning in the group of children at risk of VPD, none of the children were in need of visual rehabilitation. In children born preterm at 5.5 years of age, it has also been shown that most did not qualify for visual rehabilitation services, despite some visual dysfunctions (Geldof et al., 2015). However, given the well-established risk of VPD in this population, the question remains whether visual function is indeed better than expected in this group or that these risks are just not sufficiently detected in clinical practice.

Development of Visual Orienting Functions Over Time and Relation With Neurodevelopment

With regard to changes in general VOF from 1 to 2 years CA, we found that both the eye tracking reliability factors and overall viewing behavior remained largely similar. Interestingly, children with a risk of VPD at 1 year CA showed an increased percentage of recorded data and stimuli seen, compared to the children not at risk at 1 year CA. This indicates that overall attention for the test and detection of visual stimuli improved more in the VPD risk group.

With regard to the quantitative VOF parameters in the total group at 2 years CA, the percentage of abnormal GFA, FD, and RTF values relative to normative references increased compared to 1 year CA (except for RTF for Contrast), and RT variability decreased. This implies that the total group of preterm children

at risk of VPD expanded at 2 years CA and confirms previous findings in a larger group of children born very and extremely preterm (Beunders et al., 2020; van Gils et al., 2020). Notably, the children with a VPD risk at 1 year CA showed more normalization of VOF parameters (i.e., decrease in the percentage of abnormal results), opposed to the group not at risk of VPD at 1 year CA who showed less function improvement, resulting in an increase in the percentage of abnormal results. However, the percentage of abnormal results fluctuated within and between the groups. This means that one screening at one particular age is not necessarily indicative. More specific, for the parameter RTF the percentage of children with normative values at 1 year CA but abnormal values at 2 years CA was highest for stimulus types that represent cerebrally-mediated visual processing, i.e., of motion and form information. For the parameter RTvar, indicating individual variability in viewing reaction times, we found a decrease in the percentage of abnormal results at 2 years CA. This is in accordance with normative developmental patterns where viewing behavior parameters become more stable and less variable with age. This also implicates that this specific parameter might be less sensitive to detect abnormalities in risk groups.

Taken together, these findings signal that performing a VOF-based VPD screening should be focused on the established parameters GFA, FD, and RTF. In addition, screening only at 1 year CA is not always indicative for later abnormal findings and is therefore not effective enough.

Neurodevelopmental Outcome

A disturbing question that is familiar to most caregivers of children at risk of VPD is which possible adverse events during development can be expected due to the neurological risks of their child. This warrants close monitoring of (neuro)developmental outcome in a range of domains. In our total study population, neurodevelopmental outcome in terms of overall cognitive and motor performance was quite good, in accordance with previous results (Beunders et al., 2020), and no differences were found based on an early VPD risk. The current neurodevelopmental results give a first indication at 2 years CA, but their meaning is restricted due to low sample size and the relatively low rates of objectified brain damage. However, in a recent larger study in 209 children of the same risk group, we showed that abnormal (delayed) VOF at 1 year of age significantly contributed to the prediction of adverse neurodevelopmental outcome at 2 years of age (Beunders et al., 2020). Other large cohort studies have shown that at 5 years of age, overall neurodevelopmental outcome of children born preterm is characterized by relatively high rates of severe and moderate disabilities, in multiple domains ranging from visual, auditory, and motor function to IQ, behavioral disorders and school assistance, irrespective of GA (e.g., Pierrat et al., 2021). Therefore, the signs of a relation of VOF abnormalities with abnormal neurodevelopmental outcome cannot be set aside and advocate for follow-up at later ages, i.e., at school age.

Implications and Future Directions

One interpretation of the overall results is that the investigated screening for VPD at 1 year CA is not fully effective: not all risks were detected at this age, risk profiles considerably fluctuated after 1 year, and no clear relation with conventional visual diagnostic results or neurodevelopment was found. However, given that the risk group expanded at 2 years of age, it becomes apparent that screening may still be useful, albeit at different or various time points.

An important challenge was to determine the right age to start screening for VPD: when is early not too early? Because this is yet unknown, we chose to start at 1 year CA when basic visual and neurological development has completed and more elaborate and cerebrally-mediated developmental processes emerge (Ricci et al., 2010; Braddick and Atkinson, 2011). At present, we cannot answer the question which age is optimal for screening. However, from the fluctuating and variable VPD risks at 1 and 2 years of age in our study population, it follows that abnormalities can reveal themselves at multiple moments in development. In particular, VOF abnormalities in more basal or lower-order types of visual processing (to Cartoon and Contrast) seem to present earlier (i.e., higher rate of abnormalities at 1 year CA) than visual functions that are more cerebrally mediated, i.e., form and motion processing with increasing rates of abnormalities at 2 years CA. This is in accordance with knowledge on visual developmental trajectories (Braddick and Atkinson, 2011) and argues for a differential screening at 1 year and at 2 years. Possible developmental trajectories include normalization of early VPD risks until reaching school age after a couple of years, consistent delays compared to normative references, or an increase of VPD risk signs over time (i.e., "growing into deficit"). Moreover, our current results and previous work clearly show that, within the group of children born (extremely) preterm, there are certain subgroups with a considerably higher risk of VPD, namely the ones with other visual or ophthalmic conditions, evidence of or a high risk of brain damage (see also van Gils et al., 2020), certain perinatal risk factors related to hypoxia and/or pulmonary dysfunction (Boot et al., 2010; Kooiker et al., 2019). Particularly in these high risk groups it is advisable to accessibly follow further development through continuous yearly screening. This could be achieved by adding visual/VOF tests to existing clinical follow-up (programs) in other developmental domains, and by closely observing the type of risks and possible need for additional information on, e.g., brain imaging. That way, a more individual follow-up and profiling can be achieved. Promisingly, recent diagnostic developments at young ages have led to more advanced resources for structured observations (e.g., evidence-based history taking) and there are increasingly successful efforts of assessing early VPD performance on a task level, focused on visual perception instead of merely detection (Vancleef et al., 2020). This means that already from 3 years of age the possibilities for VPD/CVI tests are improving.

An important, yet open, question is how predictive early, relatively basal disruptions to the visual attention and processing system (mapped by VOF performance) are for later neurocognitive and higher-order visual dysfunctions (such as visual perception problems, impaired school performance in reading or writing). The VOF responses indicate whether and how fast children detect and fixate a specific stimulus, but are independent of (conscious) recognition. From recent work, we

know that there are clear relations between VOF performance and visuoperceptual performance and daily life behavior in children with (suspected) CVI, mainly in the domains of visual (dis)interest, visual spatial perception and object processing (Ben Itzhak et al., 2021). This indicates that integrating VOF measurements into clinical screening procedures has added value as it incorporates aspects conditional to daily functioning and higher-order perception. Also, the presence of abnormal VOF may explain visual behavior such as a limited visual attention span and aberrant gaze behavior often seen in children at risk of CVI. This would be in accordance with guidelines such as the European perspective on CVI (Ortibus et al., 2019) and those published by the ophthalmic society in the Netherlands (Federatie Medisch Specialisten, 2019), that a CVI diagnosis is to be achieved through a multidisciplinary team, covering all previously mentioned aspects of the disorder. It may also add to circumventing the problems regarding the lack of a generally accepted definition on CVI, by focusing on a more operational definition concerning functional impairments in children that can be targets of (re)habilitation (Geldof et al., 2015).

From a research perspective, the next step is to comprehensively follow visual function and behavior up to school-age, both with functional VOF screenings and conventional neuropsychological assessments, to investigate the relation of VOF with the development of CVI-related symptoms and to determine the sensitivity and specificity of abnormal VOF findings for (future) CVI. If this early screening proves effective at school age, the age to start visual rehabilitation may be advanced and early visual development may be improved. Importantly, future research efforts should be directed toward developing VPD assessments to be used early in development.

In general, the ultimate goal is to achieve for all children at risk that when there are concerns about visual and viewing behavior, they enter the visual care chain as early as possible. Even though in many cases a definite diagnosis of CVI cannot be achieved before a certain age, the child and caregivers will benefit from early signaling clear signs of abnormalities that call for visual-developmental support.

STUDY LIMITATIONS

Before the start of the study, it was difficult to estimate the number of children with a risk of VPD in this specific population of children born < 30 weeks at 1 year CA. This number turned out somewhat lower than expected and, along with recruitment and continuation issues, led to a low sample size, especially of the group with VPD risks. This prevented us from being able to statistically evaluate certain detailed questions, e.g., whether the heterogeneity of brain lesions influenced the results. Also, the study population is a relatively vulnerable risk group, particularly because of their young age. Recruiting at 1 year CA may still have been too early in the light of ongoing medical issues and difficulties for caregivers, explaining the relatively high drop-out rate. For all VOF parameters, it holds that the norm group at 1 year of age was smaller than that at 2 years CA, which may have influenced the percentage of abnormal results. It is therefore recommended to expand the youngest norm groups prior to clinical application of the method, preferably to month-based norms given the high rates of functional development at young ages.

Other drawbacks are that visual development was not followed at 2 years CA, as ophthalmic exams and VFA were not repeated. With this set-up we missed children in whom ophthalmic disorders started to present from 2 years of age. Lastly, the children with a risk of VPD based on abnormal VOF that started to emerge at 2 years CA (who did not have that risk at 1 year CA) were not referred to conventional diagnostics at all. All these limitations argue for a longer follow-up to determine the right age for VPD screening and VOF inclusion.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Medical Ethics Testing Committee, Erasmus Medical Center, Rotterdam, NL. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

JS, SS, and IR conceived the study. MK and JP designed the study and procedures. MK, MG, YZ, and JP interpreted the data. MK and MG drafted, revised, and prepared the manuscript. All authors gave final approval for the submitted manuscript and significantly contributed to procedures and execution.

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The Effect of Insight Questions Inventory and Visual Support Strategies on Carer-Reported Quality of Life for Children With Cerebral Palsy and Perceptual Visual Dysfunction in Nigeria: A Randomized Controlled Trial

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Structured clinical history question inventories have previously been used to try and elicit symptoms of perceptual visual dysfunction (PVD) in children with cerebral palsy (CP) in different settings. Earlier studies have suggested that PVD may affect quality of life and specific habilitational strategies, linked to inventory responses, may improve quality of life. Through an RCT, based on a community based sample of children with CP in Cross River State, Nigeria, we aimed to determine if a structured history inventory such as the Insight question inventory (IQI) and associated tailored visual support strategies (IQI VSS) for the management of those children who have PVD, can improve quality of life and is superior to standard therapy. Children with CP were recruited by the key informant method and confirmed by clinical examination. The parent reported IQI was used to identify children with PVD. Primary outcome measures were both Pediatric Quality of Life 4.0 Generic (PedsQL 4.0 Generic) and Pediatric Quality of Life 3.0 Cerebral Palsy (PedsQL 3.0 CP) scale scores. Children were enrolled with a parallel arm allocation to either IQI and IQI VSS or to standard therapy for CP. Children were followed up for 6 weeks with weekly phone call session and the questionnaires repeated at the end of the 6 weeks' period. Results show that the children in the treatment group (n = 191) showed no significantly different change between baseline and follow up in quality of life (PedsQL 4.0 Generic p = 0.943: and PedsQL-CP 3.0 p = 0.287), compared to the control group. There was suggestion of a better improvement (p = 0.035) in the PedsQL 3.0 CP subscale of speech and communication for the intervention group. The use of IQI VSS for the treatment of

PVD in children with CP in this population does not show any superiority over current standard CP management in terms of overall quality of life. However, there was some evidence of improvement in quality of life in the area of speech and communication. Further research and refinement of these management method is required.

Clinical Trial Registration: www.ClinicalTrials.gov, identifier [PACTR20161200188] 6396.

Keywords: cerebral palsy, cerebral visual impairment, perceptual visual disorders, insight questions inventory, visual support strategies

INTRODUCTION

Cerebral palsy (CP), is the most common neurologic and motor disability in children globally (Surman et al., 2006). CP describes a group of permanent disorders of the development of movement and posture causing activity limitation, which are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain (Rosenbaum et al., 2007). The motor deficits are often accompanied by disturbances of sensation, perception, cognition, communication, behavior, epilepsy, secondary musculoskeletal problems and nutrition (Rosenbaum et al., 2007).

World Health Organization, through the International Classification of Functioning, Disability and Health (ICF), clarified the understanding of CP in relation to intervention options and differentiated functioning problems, participation problems and disability. It is suggested that interventions should aim at maximizing a child's independence in daily activities and community participation, while also focusing on optimizing children's environment. In addition, a goal-based approach and (Zihl and Dutton, 2015), patient centeredness based on choice of interventions guided by what would best help the family achieve their goals, is recommended (Novak et al., 2013).

Visual impairment in children with CP varies in nature and severity and its prevalence ranges from 40-50% of children in different studies (Ego et al., 2015). Visual impairment in CP is often directly associated with the same brain injury which causes the motor problems. This is generally termed cerebral visual impairment (CVI) (Sakki et al., 2018), commonly affecting children with CP but also children with other neurodevelopmental diagnoses such as epilepsy and hydrocephalus. CVI can cause problems with 'basic' vision such as visual acuity or visual field or affect 'higher' visual perception or cognitive vision such as ability to see moving targets, to pick out a target of interest from a complex scene, visual control of body movement or object recognition (Dutton, 2011). This latter group of behavioral symptoms of abnormal higher-order visual processing can be termed perceptual visual dysfunction (PVD), part of the CVI spectrum.

It was previously shown in India, Bangladesh and more recently in the United Kingdom (Mitry et al., 2016; Philip et al., 2016; Tsirka et al., 2020), that this latter group of symptoms of higher visual processing problems or PVD are commonly present in children with CP; we have previously published a detailed visual assessment of the children recruited for this trial showing high rates of visual pathology (including 46% PVD measured objectively and 49% CVI, dropping to 16% if optic atrophy excluded) (Duke et al., 2020).

Previous work has suggested that PVD can be effectively assessed by a structured clinical history question inventories, including the insight question inventory (IQI) (Macintyre-Beon et al., 2012; Mitry et al., 2016; Philip, 2017; Tsirka et al., 2020). IQI scores have been shown to have internal reliability, and to discriminate between children diagnosed with CVI and healthy aged matched volunteers (Macintyre-Beon et al., 2012; Philip and Dutton, 2014); they have also been shown to correlate with neuropsychological tests of visual perception (Tsirka et al., 2020), and predict quality of life in children with CP independent of other predictors such as visual acuity and degree of motor impairment (Mitry et al., 2016).

The IQI provides in-depth information about the aspects of daily living activities that children struggle with. The current 52 item inventory, Insight Questions Inventory tests 6 domains of vision namely, visual field, perception of movement, visual guidance of movement, visual search, visual attention, recognition and navigation, which, in addition to visual field, test visual perception, either dorsal (occipito-parietal) stream processing (visuo-motor control, processing moving targets and processing large amounts of visual information at once) or ventral (occipito-temporal) stream processing (person and object recognition).

Previous work indicated that considering dorsal and ventral stream as 2 factors explained 63% of variance of IQI scores between patients (Philip et al., 2016). In addition to diagnostic information, a simple software program links each question inventory response to a specific group of tailored visual support strategies (VSS) appropriate to that question, so that after completing the inventory each child/family has a set of tailored visual support strategies (IQI VSS) for that particular child. An example of the IQI and Visual support strategy can be seen in question 11, which asks "Does your child bump into door frames or partly open doors (left/right/both)"? Corresponding tailored visual support strategies would include suggesting that the caregivers would give extra hints. For example, "There is a door coming up in a few steps." Another recommendation would be to replace doors with a beaded curtain.

A recent hospital based longitudinal study investigated the impact of the IQI VSS linked to the inventory responses on

functional vision and quality of life (Tsirka et al., 2020). Children were followed up 6 months after receiving the IQI VSS and improvements were seen in both qualities of life and functional vision compared with baseline pre-intervention assessments but there was no control group.

We aimed to test whether this approach would be effective for a community based sample of children with CP in Cross River State, Nigeria by means of a randomized controlled trial. We did not screen for CVI or PVD within the CP sample but recruited all children with CP. The rationale for this was that we predicted high rates of PVD detectable with IQI and that, even for those without formal PVD, almost all children with CP would have at least one positive response to IQI and therefore receive at least one IQI VSS. The aim was to test the impact of IQI VSS on children with CP rather than those with CP *and* CVI.

Our previous work has suggested that PVD (measured by IQI) adversely affects quality of life, (Mitry et al., 2016) and that IQI VSS improve quality of life (Tsirka et al., 2020), using the PedsQL 4.0 Generic module which assesses domains of physical activities, social, emotional and school functions. The PedsQL 3.0 CP module, is designed to be used by children with CP to detect changes arising from this condition or factors associated with it, with subdomains which include daily activities, movement and balance, fatigue, pain, school functions, eating and speech (Varni and Said, 2006; Varni et al., 2006; Viehweger et al., 2008). Peds QL 4.0 Generic and PedsQL 3.0 CP assessments can be based on parent report, child reports or proxy reports (Varni et al., 2007; White-Koning et al., 2007). Since PedsQL3.0 CP is specifically designed for children with CP but has not been previously tested in relation to CVI or PVD we decided to use both PedsQL 4.0 Generic and PedsQL 3.0 CP modules as primary outcomes for this trial.

MATERIALS AND METHODS

This was a parallel group, double blind clinical trial, with a superiority design (**Figure 1**). Recruitment took place between December 2016 to December 2018. Details of the trial methodology have been published and are briefly summarized here (Duke et al., 2019).

Participants

This prospective population study was conducted in 18 local government areas in Cross River State, Nigeria. Recruitment took place over 12 months, using the key informant method (Murthy et al., 2014). In the first stage, a population based sample of children suspected to have CP were identified by the key informants with the use of the Ten questions Questionnaire and CP picture chart (Muhit et al., 2007). In the second stage, children had a comprehensive history taken and detailed examination, including neurological examination and confirmation of the diagnosis and classification of CP by a pediatric neurologist who used the diagnostic criteria for CP (Surveillance of Cerebral Palsy in Europe, 2000). Detailed visual assessment was performed and the results have been published including the Insight question inventory for PVD (Duke et al., 2020).

Eligible children were those confirmed to have CP who consented to be recruited into the trial (Rosenbaum et al., 2007). Data on all eligible children address and phone number(s) of carers was entered into a password protected database. Each child was allocated a unique identification number.

Assessment of CVI/PVD

For the purpose of the trial, symptoms of PVD were behaviorally ascertained by the use of the Nigerian Version IQI, a 52-item symptoms based inventory, (**Supplementary Material 1**), derived through linguistic translation of the British version of the insight questions inventory, and which was administered to each carer. There are 6 sections. Responses to each question was in accord with a 5-point Likert scale (1-5) to describe whether a child has problems: never, rarely, sometimes, often or always including "not applicable" respectively. The questions in each section are designed to identify CVI/PVD through asking about visual tasks involving both the dorsal (sections 1-5) and ventral (section 6) visual streams. Any subject who answered "sometimes", "often" or "always" to at least one question (out of 52) would be considered to have PVD and would receive at least one strategy. Questions with more than half of respondents reporting "n/a" were excluded (Mitry et al., 2016).

Assessment of Speech and Communication

The Communication Function Classification Scale (CFCS) assessed the full activity of communication in five levels between a familiar person and the child (Virella et al., 2016). We referred to children as having communication impairment if CFCS was level 4-5. Speech impairment were defined as inability to create or form speech sounds (Strand and McCauley, 2008).

Eligibility Criteria

Inclusion: Children aged 4 to 15 years diagnosed with CP (by a pediatric neurologist who would using standardized diagnostic criteria) of any type or severity. CVI and PVD were not criteria for inclusion before randomization into the study (rational in introduction).

Exclusion: Children beyond the age criteria, with other causes of motor disorders, children whose carers refuse to participate and children with CP who have debilitating illness and require immediate medical care.

INTERVENTIONS

Intervention Arm

The intervention was the application of carer selected tailored IQI VSS (at maximum of 8) based on the "sometimes", "often" or "always" response to the 52 IQI questions which they consider to be the most important, relevant and practical to implement. So if any one of the 52 questions in Insight was responded to as being a problem always, often or sometimes, a group of strategies to help adapt to this particular problem was suggested and explained to the carer. If 6 questions were responded to as

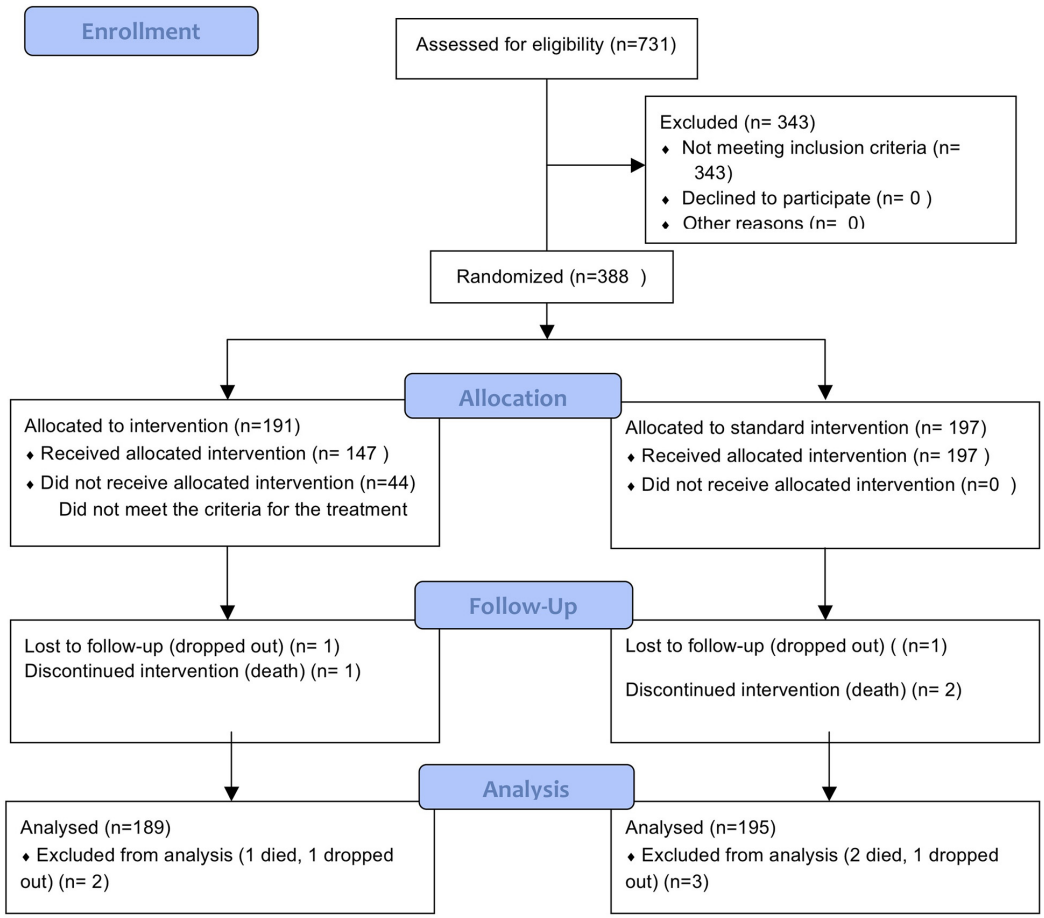

FIGURE 1 | Shows the consort flow chart.

problematic, 6 groups of strategies would be administered to the carer. If more than 8 were responded to, the most relevant 8 problems/strategy groups chosen by the parents were selected for the carer to concentrate on. The strategies were explained at baseline and reinforced with phone calls.

The Standard/Control Treatment Arm

The types of challenges highlighted by the IQI are not assessed or treated routinely in management of CP in our environment, in the control arm, no vision support strategies were given after the IQI had been administered. After the 6 week follow up assessment had been completed, children in the control arm were offered IQI vision support strategies based on their response to the IQI.

Outcome

The primary outcome was change in quality of life, between baseline and follow up, assessed using the PedsQL 4.0 Generic and PedsQL 3.0 CP modules. These outcomes were all compared between the intervention and standard treatment arms at six weeks.

The secondary outcome measure for visual function was the IQI mean scores change/difference from baseline to follow up.

Data Collection Methods

Data forms for socio-demography of carers and subjects were filled and analyzed. The PedsQL 4.0 Generic, PedsQL 3.0 CP, IQI and IQI VSS, and follow up forms were used to collect data. Data were collected at baseline and at the end of follow up after 6 weeks. Data was entered into one Microsoft excel database by a masked medical records officer who was not part of data collection.

Quality of Life– Methodology

The quality of life methodology is described according to the format of the designers. For the PedsQL 4.0 Generic and the PedsQL 3.0 CP modules, the parent's proxy form was used. To create Scale Scores, the mean was computed as the sum score of the items over the number of items answered (this accounts for missing data). If more than 50% of the items in the scale are missing, the Scale Score should not be computed. Imputing the mean of the completed items in a scale when 50% or more are completed was the method used.

The PedQL 4.0 Generic module has 4 subscales which identifies problems with: (1) Physical functioning, (2) Emotional functioning, (3) Social functioning and (4) School functioning.

The PedQL 3.0 CP module has 7 subscales which identifies problems in activities in everyday living, they are:(1) daily activities (2) School activities, (3) Movement and Balance, (4) Pain and Hurt, (5) Fatigue, (6) Eating activity, (7) Speech and Communication.

The school scores were not used as over 50% of children were not in school. To create the Total Scale Score, the mean is computed as the sum score of all the items over the number of items answered on all the Scales.

The higher the score report the better the quality of life.

Sample Size

Unpublished data from a pilot study in Bangladesh was used in the sample size calculation. In this study of 180 children with CP, the visual support strategies showed an impact on quality of life, measured by PedsQL 4.0 Generic of approximately 0.3 standard deviation (SD) (Mitry et al., 2016). Using the Altman nomogram, a sample size of approximately 370 children with CP, with 185 children in each arm, is needed to detect an effect size of 0.3SD with 80% power and at a 95% confidence, allowing for 5% loss to follow up.

Randomization: Sequence Generation

The database of children recruited with information on their unique ID, age, sex and GMFCS was sent to the data analyst in the University of Calabar Teaching Community Medicine Department at the end of the examination per local government area. The randomization sequence was generated by the data analyst (SA) using Stata 11 programming syntax for block randomization of patients into the treatment and control group. Children were stratified and blocked by age groups 4-9 and 10-15 and by Gross Motor Function Classification Score (GMFCS) Levels 1-3 and 4-5.

Randomization: Allocation Concealment

Carers of children where contacted by an independent research clerk who was masked to baseline examination. Carers were invited to visit the same primary health center where the baseline examination was conducted. At this visit, carers assigned to the treatment arm of the trial received the intervention which was explained to them by the social workers while those in that standard arm received counseling on observation of the child's symptoms and a final follow up call.

Implementation/Fidelity

Carers were to identify a maximum of 8 best strategies for implementation and were to conduct the strategies three times daily. Carers were encouraged to start with the selection of 1-3 of the most important strategies to them, to start with and practice the intervention three times a day, and those which could be implemented thereafter were identified and explained with each follow up phone call. Carers were given a list of all the strategies they had selected to study further. To improve adherence and as part of the intervention, carers were contacted by phone call weekly for 6 weeks, to ask about the application of the strategy, the frequency of the application and if there were any side effects. Carers of children in intervention and control arms were unlikely to meet after the baseline assessment and allocation to arms, as each family was discharged individually and no physical group or internet based group was formed.

Blinding/Masking

A different set of social workers conducted the post intervention interviews. Allocation was concealed to the PI and all the members of the examination team who were different from those in the intervention and follow up team.

Follow-Up

The trial period was 6 weeks, during which phone calls were made to monitor the progress of implementation of the visual support strategies, to identify additional new strategies for implementation for the following weeks, and to remind parents to visit the primary health center for the final follow up. Follow-up interim calls were performed weekly for 6 weeks in the intervention arm. The standard treatment arm received a single call at the 6th week as a reminder for the final follow up visit. Final interviews and data collection were conducted in the primary health centers for those that presented and in homes for those that could not present.

Informed Consent

The study was performed in accordance with the Helsinki declaration and approved by London School of Hygiene and Tropical Medicine. A written information sheet was read out and informed consent was obtained from all subjects under 18, from a parent and/or legal guardian.

Statistical Methods

Statistical analyses were conducted with STATA (version 15.1) Analysis of data for parametric or non-parametric distribution was initially done. The *T*-tests was used to detect difference in parametric data with a significance threshold at $p = 0.05$. These were used to compare intervention versus control group and also to assess the relationship between baseline characteristics and the primary outcome measure.

We analyzed by intention to treat (the treatment group was considered as all those randomized to get IQI VSS), per IQI protocol (treatment group considered as those that actually required and received at least 1 VSS) and per VSS treatment (those that actually implemented at least 1 tailored VSS based on parent report) approach (as reported in the phone calls/at follow up), for all primary outcome analysis. Descriptive statistics included means and SDs, and medians and interquartile ranges as appropriate. The number and proportions for categorical variables describing the sociodemographic details of the population by randomization were derived.

The impact of our intervention was measured using the difference in pre and post intervention scores.

The analysis of the IQI that showed responses with >/ = 50% as non-applicable and questions 9,5,15,32,33,34,45,46 were expunged.

Ethical Approval

The study was performed in accordance with the Helsinki declaration and approved by the ethics committees of Cross River State and the London School of Hygiene & Tropical Medicine. A written information sheet was read out. Informed consent was obtained from parents and/legal guardian. Children were referred for health care services as needed.

RESULTS

Participants Flow

A total of 1024 children were identified by key informants, 293(28.6%) were not brought for examination. 731 children were assessed for cerebral palsy diagnosis eligibility, 343(46.9%) did not meet the inclusion criteria for CP and 388(37.9%) were confirmed to have CP; all enrolled into the RCT, no parent declined to participate. 388 children who met the criteria for CP were then randomized; 191(49%) were allocated to intervention while 197(51%) were allocated to standard intervention. Of the 191 that were allocated to intervention, 44(23%) of children did not meet the criteria for requiring VSS treatment as they did not answer, 'always', 'often,' or 'sometimes' to any of the Insight Questions Inventory questions.

Follow up phone calls in the intervention arm was made in the following frequency: week 1: 99(26%), week 2: 96(25%), week 3: 82(21%), week 4: 71(18.3%), week 5: 55(14%) and week 6: 37(10%). However, the key informant method ensured that the key informants knew each child's home and was able to ensure they attended the follow up.

383 (98%) children completed the study protocol, and analyses performed for the primary and secondary outcomes.

Recruitment

Children were recruited per local government area into the study from December 2016, and allocated to an intervention arm or a standard treatment arm (**Table 1**). The study data collection was closed in December 2018.

Baseline Data

Baseline demographic and clinical characteristics of each group can be seen in **Table 1**.

Table 2 shows the distribution of the place of residence and father and mothers' educational status of children with CP. 89% of children were from rural areas, 30% of mothers and 29% of fathers were subsistent farmers.

A total of 331(85.3%) children had speech impairment and 173(44.6%) had communication impairment.

A total of 335/388(86.3%) children had at least one symptom of PVD in this population, 147/191(77.0%) in the intervention arm which required the administration of at least one Insight Questions visual support strategy and 188/197(95%) in the control arm, $p = 0.0012$.

We assessed 6 factors at baseline for their effect on QoL; residence (urban vs. rural), sex (male vs. female), age (< 9 years vs. > 9 years), type of CP (spastic vs. others), GMFCS

TABLE 1 | Sociodemographic and clinical characteristics of the intervention and no intervention arms (N = 388).

Characteristics		Intervention arm		Control arm	
		No	%	No	%
Total		**191**	**100.00**	**197**	**100**
Local government area					
	Abi	3	1.6	2	1.0
	Akamkpa	6	3.1	8	4.1
	Akpabuyo	8	4.2	13	6.6
	Bakassi	6	3.1	5	2.5
	Bekwara	15	7.8	13	6.6
	Biase	8	4.2	11	5.6
	Boki	15	7.8	16	8.1
	Calabar Municipality	7	3.7	3	1.5
	Calabar South	13	6.5	19	9.6
	Ikom	10	5.2	10	5.2
	Etung	7	3.7	8	4.1
	Obanliku	13	6.8	14	7.0
	Obubra	9	4.7	11	5.6
	Obudu	15	7.8	12	6.0
	Odukpani	3	1.8	4	2.0
	Ogoja	25	13.5	19	9.6
	Ugep	8	4.2	8	4.1
	Yala	20	10.5	21	10.6
Residence					
	Urban	21	11.0	23	11.7
	Rural	170	89.0	174	88.3
Sex					
	Male	120	62.8	109	55.3
	Female	71	37.2	88	44.7
Child's age					
	Mean (SD)	9.08	4.0	9.2	4.0
	Median (IQR)				
	<9 years	98	51.3	114	57.9
	9 + years	93	48.7	83	42.1
GMFCS					
	1	35	18.3	35	17.8
	2	80	41.9	76	38.6
	3	22	11.5	32	16.2
	4	30	15.7	24	12.2
	5	24	12.6	30	15.2
GMFCS					
	Ambulatory	137	71.7	143	72.6
	Non-ambulatory	54	28.3	54	27.4
Anatomic					
	Monoplegia	18	9.4	13	6.6
	Triplegia	26	13.6	21	10.7
	Diplegia	10	5.2	9	4.6
	Hemiplegia	70	36.6	80	40.6
	Tetraplegia	67	35.1	74	37.6
CP Type					
	Spastic	137	71.7	134	68.0
	Ataxic	20	10.5	18	9.1
	Dystonic	10	5.2	8	4.1
	Unclassified	13	6.8	19	9.6
	Choreoathetoid	11	5.8	18	9.1

(Continued)

TABLE 1 | (Continued)

Characteristics		Intervention arm		Control arm	
		No	%	No	%
Total		**191**	**100.00**	**197**	**100**
Visual acuity (Mirror Test)					
	Normal	92	48.2	83	42.1
	Visual impairment	99	51.8	114	57.8
PVD(IQI)					
	PVD	147	77	188	95.4
	No PVD	44	23	9	4.6
PVD(tests)					
	PVD	86	48.6	91	51.4
	No PVD	105	51.4		48.6

(ambulatory I-III- vs. non-ambulatory IV-V), and presence or absence of PVD (according to the IQI). Baseline QoL comparisons showed that those with non-spastic CP had a better QoL (mean 43.1 vs. 39.2, $p = 0.0337$ for PedsQL 4.0 Generic and mean 58.2 vs. 48.8, $p = 0.001$ for 3.0 PedsQL CP); also for PedsQL 3.0 CP only, children older than 9 years had a higher mean and better QoL (56.9 vs. 45.4 $p < 0.001$).

There was a baseline difference in QoL between the two arms with the PedsQL 4.0 Generic, with children in the treatment arm having better QoL (42.1 vs. 38.7, $p = 0.0411$).

Numbers Analyzed

Three hundred and eighty-eight children were randomized and 191/388 (49%) allocated to intervention and 197/388(51%) allocated to standard treatment representing the number in the intention to treat analysis.

For the per IQI protocol analysis, 147/191(77%) met the criteria for the IQI protocol administration of intervention, as forty-four children in the intervention group did not have symptoms of PVD in any subdomain and therefore did not get strategies. For the per VSS treatment analysis, there were 91/191(48%) participants randomized to treatment who actually implemented the strategies three times a day.

The mean number of strategies assigned to each family was 3.7(SD 2.9).

The first three choices of strategies with the highest frequencies chosen by parents were to Insight Questions and strategy numbers 17:100/147(68%); If the child has difficulty catching a ball:

❶ Practice catching skills with your child by throwing a balloon to each other. The balloon will move slower than a ball and may be easier for your child to catch.❷ Put a little bit of rice/water in the balloon. The balloon will make a noise as it moves so your child can hear where it is. ❸ Use large, brightly colored balls when playing catch or other ball games with your child.❹ Use balls with sound or light effects when playing catch or other ball games with your child.

Number 4:52/147(35%); If the child appears to 'get stuck' at the top of a slide or hill:

❶ Encourage your child to practice around the house trying to cross small gutters and playing on small play slides and/or by lying on his tummy on a scooter board or skate board. Some children choose to go down slides head first. Do not stop this, but make sure it is safe. Children may do this because the upper part of their field of view is being used in this situation.❷ Give additional verbal information.

Number 37:40/147(27%).

If the child reacts angrily when other restless children cause distraction:

❶ If possible, take other distractions away from your child's work area. i.e., sound, movement.❷ Let your child use head phones or ear plugs so noise does not disturb him.❸ See how your

TABLE 2 | Distribution of the place of residence and father and mothers' educational status of children with cerebral palsy ($N = 388$).

Variables	No	Percent
Fathers age ($n = 353$)	Mean age 42.7(SD 15.5); Median 40;(IQR35,50)	
Mothers age ($n = 373$)	Mean age 34.3(SD 8.4); Median 32 (IQR 29, 40)	
Place of residence		
Urban	44	11.3
Rural	344	88.7
Educational status		
Fathers educational status		
No formal education	19	4.9
Incomplete primary education	7	1.8
Completed primary	56	14.4
Completed junior secondary	15	3.9
Completed senior secondary	129	33.2
Post-secondary education	79	20.4
Post graduate education	2	0.5
Could not be ascertained	81	20.9
Total	388	100
Mothers educational status		
No formal education	17	4.4
Incomplete primary education	16	4.1
Completed primary	81	20.9
Completed junior secondary	26	6.7
Completed senior secondary	150	38.7
Post-secondary education	60	15.5
Post graduate education	1	0.3
Could not be ascertained	37	9.5
Total	388	100
Occupational/Skills		
Mother		
Unskilled (subsistence farmers)	118	30.4
Semiskilled	233	60.0
Civil/Public servant	28	7.2
Professional	9	2.3
Father		
Unskilled (subsistence farmers)	112	28.9
Semiskilled	196	50.5
Civil/Public servant	66	17.0
Professional	14	3.6
Income/month		
Fathers income $n = 353$	Mean $13.4; Median 0; IQR(0, 0)	
Mothers income $n = 373$	Mean $13.1; Median 0; IQR(0, 5.3)	

child gets on sitting at a separate desk at the end of the group. This may give him more space without leaving him out of the group.

Outcomes and Estimation

For the primary outcome analysis, the results of 'intention-to-treat,' 'per IQI protocol' and 'per VSS treatment' analysis did not show any significant difference between intervention and control groups, in change or improvement in the total quality of life in children using either the generic or the PedsQL-CP tool using the unpaired t test. (**Tables 3**, **4** shows the intention to treat analysis, per IQI protocol and per VSS implementation for the Total CP generic and CP scores). Testing indicated that all the data were parametric so *t*-test were used throughout.

Table 5 shows the subdomains of speech and communication, where there was a better improvement in quality of life in the intervention group compared to the control group, analyzed by intention to treat and per IQI protocol. ($p = 0.035$ and $p = 0.006$).

The secondary outcome measure (the Insight Questions Inventory) is reported in **Table 6** as intention-to-treat, per IQI

TABLE 3 | Primary outcome measure, total PedsQL 4.0 Generic scores using intent-to-treat (*N* = 388), per protocol (*N* = 344), per treatment analysis (*N* = 288).

Variable	Intention to treat			Per IQI protocol			Per VSS treatment		
	Intervention arm	Control arm	*P* value (*t* test)	Intervention arm	Control arm	*P* value (*t* test)	Intervention arm	Control arm	*P* value (*t* test)
Total PedsQL 4.0 baseline								0.3234	
N	191	197		147	197		91	197	
Mean (SD)	42.1(SD 19.5)	38.7(SD 18.6)		43.2(SD 18.3)	38.7(SD 18.7)		41.2(SD 17.5)	38.7(SD 18.6)	
Median (IQR)	41.7(25, 56.25)	37.5(25, 54.2)		43.7(27.1, 56.2)	37.5(54.2)		41.7(27.1, 52.1)	37.5(25, 54.2)	
Total PedsQL 4.0 follow up									
N	157	157		125	157		91	197	
Mean (SD)	45.1(SD 22.9)	44.1(SD 21.6)		45.5(SD 21.9)	44.1(SD 21.6)		41.2(SD 17.5)	38.7(SD 18.6)	
Median (IQR)	43.7(27.1, 58.3)	41.7(29.2, 58.3)		43.7(29.5, 58.3)	41.6(29.2, 58.3)		41.7(27.1, 52.1)	37.5(25, 54.2)	
Total PedsQL 4.0 difference			0.943			0.9317			0.100
N	157	157		125	157		81	157	
Mean (SD)	2.3(SD 11.8)	5.0(SD 17.8)		2.3(SD 11.8)	5.0(SD 17.8)		2.3(SD 10.0)	5.0(SD 17.8)	
Median (IQR)	9(0, 0)	0(0, 0)		0(0, 0)	0(0, 0)		0(0, 0)	0(0, 0)	

TABLE 4 | Showing the results for the primary outcome measure on the total PedsQL 3.0 CP scores using intent-to-treat (*N* = 382), per protocol (*N* = 339) and per treatment analysis (*N* = 283).

Variable	Intention to treat			Per IQI protocol			Per VSS treatment		
	Intervention arm	Control arm	*P* value (*t* test)	Intervention arm	Control arm	*P* value (*t* test)	Intervention arm	Control arm	*P* value (*t* test)
Total PedsQL 3.0 baseline									
N	189	193		146	193		90	193	
Mean (SD)	53.5(SD 26.5)	49.8(SD 27.6)		53.9(SD26.3)	49.8(SD27.6)		52.4(SD 26.7)	49.8(SD27.6)	
Median (IQR)	55.5(34.7, 76.1)	45.2(27.4, 74.2)		53(34.7, 76.6)	45.2(27.4, 74.2)		47.6(33.9, 74.2)	45.2(27.4, 74.2)	
Total PedsQL 3.0 at follow up									
N	164	162		130	162		86	162	
Mean (SD)	60.4(SD27.2)	54.4(SD 27.5)		62.3(SD 26.9)	54.4(SD27.5)		61.6(SD 27.8)	54.4(SD27.5)	
Median (IQR)	61.7(42.2, 83)	53, 2(32.2, 77.4)		63.3(43.5, 87.1)	53.2(32.2, 77.4)		64.9(41.9, 87.1)	53.2(32.2, 77.4)	
Total PedsQL 3.0 difference			0.287			0.163			0.908
N	163	161		130	161		86	161	
Mean (SD)	6.3(SD 22.2)	4.9(SD 23.2)		7.5(SD 22.4)	4.9(SD 23.2)		9(SD 9)	4.9(SD 23.2)	
Median (IQR)	0(−2.4, 19.5)	0(0, 13.7)		0(−1.6, 20.1)	0(0, 13.7)		0(−2.4, 27.4)	0(0, 13.7)	

TABLE 5 | Primary outcome measure, pediatric quality of life cerebral Palsy speech and communication subdomain scores for using intent-to-treat (*N* = 310), per protocol (*N* = 247), per treatment analysis (*N* = 227).

Variable	Intention to treat			Per IQI protocol			Per VSS treatment		
	Intervention arm	Control arm	*P* value (*t* test)	Intervention arm	Control arm	*P* value (*t* test)	Intervention arm	Control arm	*P* value (*t* test)
PedsQL 3.0 Speech and communication at baseline									
N	154	156		118	156		71	156	
Mean (SD)	44.1(SD 40)	42.9(SD 41)		42.3(SD 40)	42.9(SD 41)		43.3(SD 41.4)	42.9(SD 41)	
Median (IQR)	37.5(0, 81.2)	31.2(0, 94)		34.3(0, 81.2)	31.2(0, 94)		37.5(0, 93.7)	31.2(0, 94)	
PedsQL 3.0 Speech and communication at follow-up									
N	139	136		110	136		71	136	
Mean (SD)	51(SD 43.1)	42.2(SD 41)		53.6(SD 43.6)	42.2(SD 41)		55(SD 44.4)	42.2(SD 41)	
Median (IQR)	50(0, 100)	25(0, 93.7)		50(0, 100)	25(0, 93.7)		62.5(0, 100)	25(0, 93.7)	
PedsQL 3.0 Speech and communication difference									
N	133	130	0.0350	105	130	0.006	66	130	0.994
Mean (SD)	7(SD 35.2)	−0.64(SD 32)		10.5(35.7)	−0.64(SD 32)		12.4(SD 46.8)	-0.64(SD 32)	
Median (IQR)	0(0, 18.75)	0(0, 0)		0(0, 025)	0(0, 0)		0(0, 31.2)	0(0, 0)	

TABLE 6 | Secondary outcome measure of visual function using the Insight Questions Inventory using intent-to-treat (*N* = 383), per protocol (*N* = 341), per treatment analysis (*N* = 285).

Variable	Per treatment			Per IQI protocol			Per VSS treatment		
	Intervention arm	Control arm	*P* value (*t* test)	Intervention arm	Control arm	*P* value (*t* test)	Intervention arm	Control arm	*P* value (*t* test)
Total IQI score at baseline									
N	188	195		146	195		90	195	
Mean (SD)	1.5 SD(0.5)	1.7 SD(0.7)		1.6 (SD 0.48)	1.7 (SD74)		1.64(SD 0.54)	1.67(SD 0.74)	
Median (IQR)	1.3(1.2, 1.7)	1.4(1.2, 1.9)		1.4 (1.2, 1.7)	1.4(1.2, 1.9)		1.5(1.3, 1.8)	1.4(1.2, 2.0)	
Total IQI follow up scores									
N	188	192		146	192		90	192	
Mean (SD)	1.2 SD(0.62)	1.3 SD(0.8)		1.25 (SD0.57)	1.3 (SD 0.8)		1.36(SD 0.51)	1.34(SD 0.81)	
Median (IQR)	1.3(1.0, 1.5)	1.2(1.0, 1.1.6)		1.2(1.0, 1.5)	1.2(1.0, 1.66)		1.3(1.0, 1.56)	1.3(1, 1, 1.67)	
Total IQI scores of difference			0.322			0.659			0.567
N	188	192		146	192		90	192	
Mean (SD)	−0.27 SD (0.61)	−0.3 SD (0.8)		−0.33(SD 0.6)	−0.30(SD0.8)		−0.29(SD 0.51)	−0.30(SD 0.79)	
Median (IQR)	−0.13(−0.4, 0)	−0.12(−0.4, 0)		−0.15(−0.3, −0.5)	0(−0.1, 0)		−0.17(−0.4 −0.05)	0(−0.17, 0)	

protocol or per VSS implementation. There was no overall difference between intervention and control groups.

Adverse Events

Two patients died in the standard treatment arm and one in the intervention arms of the study due to complications of CP. There were no side effects reported from any group.

DISCUSSION

In this community based RCT, visual support strategies aimed at compensating for visual perceptual problems identified by the Insight Questions inventory (IQI VSS) were not shown to significantly improve the overall quality of life of children. The IQI tool did not function effectively for this population. It did not

elicit sufficient positive responses in children who seemed to have evidence of PVD using some basic objective tests (Duke et al., 2020). Since the IQI VSS depends on such positive responses this would have limited its effectiveness. IQI did seem to be effective, in a similar population in Bangladesh, in eliciting symptoms which did relate to quality of life; and IQI VSS have shown some promise in improving quality of life in a UK hospital based study of children with CVI (Tsirka et al., 2020). Although it has been successful in other studies it should be noted that the IQI questions taken individually are not specific for CVI or PVD: they could be answered positively by children with ocular VI or pure motor impairment.

Further work is required refining this tool for this population including investigation of which questions are appropriate, for children with CP/comorbidities, for families in more rural environments, and for parents with a range of education levels. It is possible that a questionnaire approach is not the best one for this population. Separate from how the IQI performed we did find evidence of under recognition/reporting of visual morbidity by the carers of these children (Duke et al., 2020). In retrospect it could be argued that we should have screened for CVI or PVD before recruiting e.g., perhaps had a cut off requiring a certain number of positive IQI responses to be eligible for recruitment. Our assumption was that almost all children with CP have some level of PVD but this proved not to be the case; almost a quarter did not receive any strategies which resulted in an underpowered trial. The results might have been influenced by chance differences between the 2 groups at baseline. There was a higher proportion of PVD in the control group compared to the intervention group. Also the treatment group had better scores PedsQL 4.0 scores at baseline though this was a small difference and would lose significance after adjustment for multiple comparison.

Another reason for the lack of effect could have been poor adherence to the strategies. The rate of successful follow-up calls dropped substantially across the 6-weeks intervention period, it is possible that parent implementation of strategies decreased and that adherence might have been over reported.

Improvement due to the use of IQI visual support strategies, in the health related quality of life in the CP speech and communication domain was suggested across the intention to treat and per IQI protocol. However, this may be a chance finding as our analysis was not adjusted for multiple comparisons. (Since there were 2 PedsQL modules each with subsections, a threshold value p value of 0.05, for instance, would drop to 0.003) The impact of the VSS on speech and communication needs further investigation before drawing strong conclusions and should be further investigated since a large proportion of children in this population had speech impairment (85%) and 45% had communication difficulties. It is well reported that these are common problems in children affected by CP (Pennington et al., 2004). Various strategies have been tried, but evidence of their effectiveness is limited (Pennington et al., 2004).

A surprising finding was that quality of life seemed to improve more in the control arm than the intervention arm when the PedsQL 4.0 Generic score was used whereas the reverse was true when the PedsQL CP 3.0 module was used. The differences were not significant and may be due to chance but this difference in trend is notable and may be because of the differences in the 2 tools with the CP module being more physical disease focused and easier for parents to relate with their child's problems. Another possible reason for the discrepancy between the 2 PedsQL versions is that the main benefit was seen in the speech and communication domain of the PedsQL 3.0 CP tool which is not present in the generic version. Some children appeared to have a decrease in quality of life in the 4.0 Generic module following the intervention. It is possible that having undergone lengthy assessments and not received any medical treatment or glasses immediately, carers may have felt a lack of intervention or improvement and reflected this in their answers. In addition, they may have thought more (after the first experience of answering the PedsQL questionnaires) about problems children have, so give more negative results second time around, a possible situation of investigation fatigue (this may have also contributed to the lack of improvement in IQI scores in the treatment group, where previous work did find such an improvement) (Tsirka et al., 2020).

Limitations of the Study

A rigorous RCT was conducted in a field where there is little RCT evidence on which to base management of this condition. However, the assessment and intervention tool did not seem to work well in this population, despite having worked well in a range of geographic populations previously. IQI scores and the number of children receiving IQI VSS were smaller than predicted, likely underpowering the trial. More cultural adaptation and piloting would have been beneficial such as checking whether the questions were appropriate (for children with CP/comorbidities, for families in more rural environments and for parents with the education levels noted).

CONCLUSION

The use of the IQI and IQI VSS for the treatment of PVD in children with CP in this population did not show any superiority over current standard measures of treatment. The study suggests that further investigation and refinement of this type of intervention is required for this population. There was a suggestion of a positive effect in the area of speech and communication related quality of life.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by London School of Hygiene and Tropical Medicine Ethics Committee and the Cross River State Ethics Committee. Written informed consent to

participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

RD and RB contributed to conception, design, execution, supervision, analysis and writing of the manuscript. TC and SA contributed to design and execution. MK and KB contributed to design, supervision, analysis and writing. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnhum.2021.706550/full#supplementary-material

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Higher Visual Function Deficits in Children With Cerebral Visual Impairment and Good Visual Acuity

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In clinical practice Cerebral Visual Impairment (CVI) is typically diagnosed by observation of abnormal visually guided behaviors which indicate higher visual function deficits (HVFDs) suggesting abnormal brain development or brain damage in a child with a suitable clinical history. HVFDs can occur even in the presence of good visual acuity and may remain undiagnosed *because* the good visual acuity does not prompt further investigation. This leads to a lack of understanding of the child's visual perceptual difficulties. In a prospective study, we determined the spectrum of HVFDs in a group of children with history suggestive of brain damage or disruption of brain development and an independent diagnosis of CVI in comparison with typically developing children with a structured 51 question inventory, the Higher Visual Function Question Inventory (HVFQI-51) adapted from the Cerebral Vision Impairment Inventory, CVI-I. Here, we show that the HVFQI-51 can detect a range of HVFDs in children with CVI with good visual acuity and clearly distinguishes these children from typically developing children. HVFDs in our study group could mostly be attributed to dorsal stream visual processing dysfunction though the spectrum varied between children. We report on the inclusion of the "not applicable" response option in analysis providing a picture of HVFDs more in tune with the overall disability of each child. We also propose a subset of 11 questions (Top-11) which discriminate between children with CVI vs. behaviors seen in typical children: this provides both a *potential* screening tool for initial assessment of HVFDs and a measure of CVI-related impairment, and needs further validation in a secondary independent sample.

Keywords: higher visual function deficits, screening, questionnaire, good visual acuity, children, low vision, cerebral visual impairment (CVI), structured question inventory

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INTRODUCTION

Cerebral Visual Impairment (CVI) is a heterogenous disorder of brain-based visual impairment resulting from brain injury or disruption of development of retrochiasmatic visual pathways and vision processing regions of brain, commonly occurring during gestation at or around birth. In clinical practice, CVI is typically diagnosed in a child with a suitable clinical history by observation of abnormal visually guided behaviors (i.e., behaviors that rely on normal visual function) that suggest abnormal brain development or brain damage. These behaviors can stem from higher visual function deficits (HVFDs) of visual processing with consequent perceptual deficits, even

in the presence of normal or near-normal visual acuity (Dutton and Jacobson, 2001; Fazzi et al., 2007, 2009; Saidkasimova et al., 2007; Boot et al., 2010; van Genderen et al., 2012; Philip and Dutton, 2014). However, HVFDs, in presence of good visual acuity, often remain undiagnosed because good visual acuity precludes further investigation leading to a lack of understanding of the child's visual perceptual difficulties. The reasons are mainly historical. CVI, previously termed cortical blindness (Marquis, 1934) and later Cortical Visual Impairment (Whiting et al., 1985) was previously diagnosed based on severity of visual acuity loss which limited the understanding of the condition (Hoyt and Fredrick, 1998; Frebel, 2006; Colenbrander, 2010). It is now clear that manifestations of this condition involve more than the occipital cortex and CVI is associated with a spectrum of agnosias indicating presence of HVFDs, oculomotor abnormalities and secondary changes in the optic nerve have been documented (Jacobson et al., 1998; Jacobson and Dutton, 2000; Jan et al., 2001; Salati et al., 2002; Dutton et al., 2004). In the light of these findings, CVI, by consensus, is now termed *Cerebral* Visual Impairment, "a verifiable visual dysfunction which cannot be attributed to disorders of the anterior visual pathways or any potentially co-occurring ocular impairment" (Sakki et al., 2018) with HVFDs synonymous with visual perceptual difficulties (Vancleef et al., 2020). Using visual acuity criterion alone is likely to miss a large proportion of children with HVFDs and a diagnosis of CVI should be based on the combined presence of multiple factors with reduced visual acuity being a contributory but not the defining criteria. Tsirka et al. (2020) using the Insight question inventory for detecting HVFDs in children aged 5–16 years applied the following eligibility criteria for CVI: (i) a confirmed diagnosis of CVI based on a known medical reason for brain injury or dysfunction, (ii) no signs of ocular pathology other than mild optic atrophy (defined by indirect ophthalmoscopy), and (iii) binocular visual acuity of at least LogMAR 1.0 (Snellen 6/60); relegating visual acuity loss to one of the criteria. The diagnosis is based on an assessment of clinical history of predisposing factors, parental reports of visual behaviors suggestive of HVFDs, an ocular examination to exclude a purely ocular cause of the visual impairment (though CVI may co-exist with an ocular condition especially when associated with prematurity such as retinopathy of prematurity, optic nerve hypoplasia; for a review see Fazzi et al., 2007], input from a neurological examination and, when possible, supplemented by other investigations such as neuroimaging. Normal visual acuity and absence or presence of neuroimaging findings no longer excludes a diagnosis of CVI (Stiers et al., 2002; Bassan et al., 2007; Saidkasimova et al., 2007; Fazzi et al., 2009; Ortibus et al., 2009, 2012; van Genderen et al., 2012).

Visually guided behaviors and cognitive processes or Higher Visual Functions (HVFs) are best explained through a functional model of two cerebral networks comprising the dorsal stream connecting occipital V5 (area MT), V3A areas and parietal lobes; and the ventral stream connecting the occipital and inferotemporal (area IT) cortical area (Felleman and Van Essen, 1991; Young, 1992). Visual functions such as motion perception, dealing with complex visual scenes, navigation through three dimensional space and visually guided movements are assigned to the dorsal stream—the "where" or "action" pathway of HVFs; while color, shape, object, word and face recognition are assigned to the ventral stream—the "what" stream of HVFs (Mishkin et al., 1983; Goodale and Milner, 1992; Milner and Goodale, 2008; Goodale, 2013). In early life, the functional morphology of the brain representing the dorsal stream is thought more vulnerable (Braddick et al., 2003) resulting in a preponderance of dorsal stream visual function deficits in CVI (Macintyre-Beon et al., 2013). There is, however, considerable overlap between the two putative streams in the execution of most visual functions such as identification of objects and visually guided motion to reach and grasp (Milner, 2017).

The detection of HVFDs is difficult as young children with CVI cannot self-report and, older children are usually agnostic of their HVFDs as they have not lost an ability—they never developed the function (*they know not what they know not*). In addition, the presence of good visual acuity which often precludes further investigations (Sakki et al., 2018), the lack of readily available tools (Gorrie et al., 2019) or the knowledge and understanding of manifestations of CVI amongst clinicians and teachers (Fielder et al., 1993; Youngson-Reilly et al., 1994; McDowell, 2020) adds to the challenges of identifying HVFDs. However, diagnosing HVFDs is essential since they can cause significant visual disability in everyday activities and education especially, while visual acuity remains largely intact (Mercuri et al., 1998; Dutton and Jacobson, 2001; Fazzi et al., 2007; Saidkasimova et al., 2007; van Genderen et al., 2012).

We chose a structured history taking tool (The CVI Inventory, CVI-I) that was designed to be used by clinicians to record parental observations in order to assess and document HVFDs which might otherwise go unnoticed in children with CVI (Dutton et al., 2010b). Furthermore, based on the responses, the CVI-I provides guidance to implement (re)habilitation strategies for HVFDs. This inventory (51 questions) and its previous version of 52 questions (the Insight Inventory) has been validated in children with CVI with moderate to severe visual acuity loss (Houliston et al., 1999; Dutton, 2011; Macintyre-Beon et al., 2012; Philip et al., 2016; Sakki et al., 2020; Tsirka et al., 2020). Though the diagnosis of CVI was not established by independent criteria in most of the studies except by Macintyre-Beon et al. (2012) (see section "Discussion"), the results were encouraging and further studies were recommended. However, prospective studies on children with an independent diagnosis of CVI and normal visual acuity are lacking at present in the published literature with only one retrospective study (van Genderen et al., 2012) reporting on children with good visual acuity and CVI and with suspected CVI using an abbreviated question inventory, adapted from the question inventory of Houliston et al. (1999). Their results showed CVI remains a clinical diagnosis and their question inventory should only be used to identify "symptoms" associated with CVI. Several other questionnaires and modifications of the questionnaires have been developed and utilized to detect HVFDs in children with CVI (Ortibus et al., 2011; van Genderen et al., 2012; Geldof et al., 2015; Salavati et al., 2017; Ben Itzhak et al., 2019; Gorrie et al., 2019; Fazzi and Micheletti, 2020, and for a recent review see McConnell et al., 2021).

The primary goal of this prospective study was to characterize the range of HVFDs in children with good visual acuity in the presence of an independent clinical diagnosis of CVI compared to a typical group of children. The CVI population with good visual acuity is most at-risk of HVFDs not being identified. We adapted the CVI Inventory (CVI-I) with its 51 questions (Bax, 2010) with permission from the original author Dr. Gordon Dutton, making minor changes and have used the name Higher Visual Function Question Inventory (HVFQI-51) to ensure clarity of purpose: (i) to determine the spectrum of HVFDs in a group of children with a history suggestive of brain damage or disruption of brain development and (ii) not use the HVFQI to diagnose "CVI" in these children; instead we used it in this group of children who were already diagnosed with CVI (van Genderen et al., 2012). We also investigated the most reliable questions in the HVFQI-51 and outline them in a new shortened inventory that may potentially serve as a short screener or as a measure of CVI-related impairment. Further, we sought to determine how best to score the inventory accounting for the responses to the "*Not Applicable*" option (NA), which have not been dealt with in previous publications using this inventory. In our experience, NA is a useful response option since a number of the observed behavior items may not be developmentally appropriate for the age of the child or for other reasons such as comorbid impairments. We allowed the parents to use the NA option and comment on their analysis and utility within the questionnaire.

MATERIALS AND METHODS

Participants

Study participants were recruited through the patient population of the Alder Hey Children's Hospital, Liverpool, United Kingdom (AH). This study received ethical approval NHS Research Heath Authority IRAS ID:193481; REC Reference:16/EE/0062 and abided by the tenets of the Declaration of Helsinki. Informed written consent was obtained from parents and assent from children where appropriate. Children with CVI were recruited after a diagnosis of CVI was established (see section below on CVI diagnosis) from the eye and neurology departments. Typically developing children were recruited from verbal requests largely through parents of children undergoing routine screening in the community and some from colleagues and friends. All participants (parents and assenting children) were naive to the purpose of the HVFQI and the design of the study.

Participants included 33 children with CVI with good binocular visual acuity and 111 typically developing children. The mean age (±SD) of participants was 7.0 years (±2.8) for the CVI group and 8.7 years (±2.8) for the typically developing group. The average crowded Lea Symbol binocular visual acuity was 0.14 ± 0.12 LogMAR for the CVI group with only 3 children with acuity worse than 0.2 LogMAR (but better 0.4 LogMAR) indicating good visual acuity in the presence of a diagnosis of CVI; and 0.14 ± 0.16 LogMAR for the typically developing group (see **Table 1**). Visual acuity in the typically developing group is lower than expected normal acuity reflecting the effect of using crowded acuity charts (Atkinson et al., 1986; Huurneman et al., 2012a,b; Anstice and Thompson, 2014).

Diagnosis of Cerebral Visual Impairment

Diagnosis of CVI was based on an integrated assessment of gestational, birth and developmental history; detailed eye, oculomotor and sensory status examination including cycloplegic refraction (AC, SF; optometrist); detailed neurologic examination and review of neuroimaging for clinico-radiological diagnosis (RK); symptom correlation (AC, RK) and, MRI in almost all (31 out of 33) children (see **Tables 2**, **3**). Typically developing children were declared normal based on detailed history which included detailed birth and developmental history and an eye examination which included normal distance visual acuity, normal ocular and sensorimotor status and, non-dilated retinal examination. Oculomotor status was assessed with cover tests (Cover-Uncover and Alternate-Cover test); assessment of extraocular movements; sensory status was determined with age-appropriate tests for stereopsis (Frisby; TNO; Lang Stereotest) and fusion (Bagolini Striated lenses and Worth 4-dot test) by experienced clinicians (AC and SF).

Question Inventory

The HVFQI comprised 51 questions (HVFQI-51) organized into clusters of questions that seek behavioral evidence of impairment of visual cognition, including putative dorsal and ventral stream dysfunction. The inventory was adapted from the CVI-I (Dutton et al., 2010b; Macintyre-Beon et al., 2012) and following modifications were made. We added instructions on completing the question inventory, a brief explanation of the purpose of the study (but not the purpose of the HVFQI) in accordance with our ethical approval. We also replaced the misprint in question 42 "Do quiet places/open countryside cause difficult behavior?" with "Do quiet places/open countryside result in better behavior?" (changed after personal communication with the author of the original questionnaire Dr. Dutton). The name of the question inventory was changed to HVFQI-51 to reflect the purpose of the question inventory—to document HVFDs and not use it to diagnose CVI.

The research project was explained to the parent or caregiver by the responsible clinician (SF or AC) in a standard format explaining the purpose of the research project and process of completing the QI. Queries were addressed without giving leading explanations or answers. The questions were answered in one sitting. Parents chose a response from a standard 5-point Likert scale (e.g., Never, Rarely, Sometimes, Often, Always). An additional "Not Applicable" (NA) option for each question was chosen only if a particular question could not be answered; for example, child was too young or a physical disability precluded applicability of that particular visual behavior.

Analysis and Exploratory Analysis

Analyses were performed using Python (NumPy and SciPy libraries).[1]

[1]http://www.python.org

TABLE 1 | Clinical characteristics of children with CVI.

ID	Gender	Age	Term/weeks	VAOU	Amblyopia	Ref Error	Strab	ONH OD	ONH OS
1	F	5.75	35	0.00	None	0	0	Mild pallor	Normal
2	F	6.80	Term	0.10	OS	1	1	Normal	Normal
3	M	11.17	Term	0.00	OD	1	1	Normal	Normal
4	M	5.91	27	0.20	OU	1	0	Normal	Normal
5	F	12.51	Term	0.00	None	0	0	Normal	Normal
6	F	14.02	34	0.20	OU; OS > OD	0	1	Normal	Normal
7	M	6.93	34	0.10	OD	1	0	Normal	Normal
8	F	8.51	Term	0.20	OU	1	1	Normal	Normal
9	F	5.78	34	0.20	OU; OD > OS	0	1	Normal	Normal
10	F	5.72	Term	0.20	OU; OS > OD	1	1	Pallor	Pallor
11	F	10.12	27	0.10	OU	1	1	Normal	Normal
12	F	10.18	34	0.10	OU; OD > OS	1	1	Normal	Normal
13	M	11.36	Term	0.20	OU; OD > OS	1	0	Mild pallor	Mild pallor
14	M	8.50	Term	0.10	None	1	1	Temp pallor	Temp pallor
15	F	11.57	33	0.20	OU	1	0	Normal	Normal
16	F	10.66	Term	0.10	OU; OS > OD	1	0	Hypoplasia	Hypoplasia
17	M	9.72	Term	0.30	OU; OS > OD	1	1	Mild temp pallor	Slight temp pallor
18	F	5.67	Term	0.20	OU; OD > OS	1	1	Mild pallor	Normal
19	F	12.14	29	−0.10	None	0	1	Normal	Normal
20	M	4.52	Term	0.40	OU	1	1	Normal	Normal
21	M	10.82	Term	0.00	None	0	1	Normal	Normal
22	F	7.38	Term	0.00	None	1	0	Normal	Normal
23	M	4.44	38	0.10	None	0	1	Normal	Normal
24	F	11.56	Term	0.10	OS	1	1	Pallor	Pallor
25	M	9.09	Term	0.20	OU; OS > OD	0	1	Normal	Hypoplasia
26	F	8.32	Term	0.00	None	0	1	Normal	Normal
27	M	14.53	33	0.00	OS	1	1	Normal	Normal
28	F	8.05	30	0.20	OU	0	1	Normal	Normal
29	F	4.41	35	0.10	None	0	0	Poor views	Poor views
30	M	5.35	Term	0.20	OU	0	1	Normal	Normal
31	F	8.81	33	0.10	None	0	1	Mild temp pallor	Slight temp pallor
32	M	9.27	Term	0.20	OU	0	1	Pallor	Pallor
33	M	9.42	30	0.30	OU	0	1	Normal	Normal

*Gender, age at the time of the test, Binocular Visual Acuity (VAOU; Lea Symbol Test) presence/absence of amblyopia (OU, Bilateral; OD, Right Eye; OS, Left Eye; OS > OD and similar indicates amblyopia in left eye worse than right eye), refractive error (Ref Error) and strabismus (Strab) is reported. (ONH, Optic Nerve Head; temp, temporal) ONH status is reported for each eye separately. We also report neurological diagnoses and MRI findings (see **Table 2**). ONH, Optic Nerve Head.*

Analysis of the Responses, Accounting for the Not Applicable Response

To determine the ability of the HVFQI-51 to distinguish between the two groups (children with CVI and typical children), values of 0, 1, 2, 3, or 4 were assigned to Never, Rarely, Sometimes, Often and Always, respectively. Therefore, higher scores reflect more impairment. A total score was calculated on these *applicable* responses, where answered, for each child; the *average* score for each of the 51 questions and for each group. For example, for a given child, if the number of applicable answers was 48, then the total score would be the average of the values assigned to these 48 questions.

Analysis for the Most Discriminatory Questions

We also wished to determine whether a particular response on the five-level ordinal-response Likert scale when compared against the other responses would endorse a subset of "most discriminatory" questions. The purpose of this analysis was to determine whether a set of fewer questions would lead to a *potential* screening tool, or a potential tool for measuring CVI-related impairment, discriminating from the normal range of behaviors seen in typical children.

For this analysis we employed a series of dichotomy analyses where we split the five-level ordinal responses into binary groupings (**Table 3**; column 1, 2, and 3). It is typical in analysis of a potential clinical tool to reduce the 5-point Likert scores to a dichotomy based on a fixed level for all questions: a response of Yes indicating 'endorsed' and No indicating 'not endorsed' (Houliston et al., 1999, see Dutton's Top-5 in Dutton et al., 2010a), or the level that gives the best performance for a given question. First, the response "0" (not endorsed) was assigned to questions with the Never response and "1" (endorsed) was assigned to questions answered as any one of the four remaining four responses (Rarely, Sometimes, Often or Always);

TABLE 2 | Neurological summary diagnoses and Brain-MRI scan results of children with CVI.

ID	Primary neurological diagnosis	Brain MRI findings
1	16p13.11 deletion syndrome	Normal
2	Cerebral palsy, GMFCS Level 2, asymmetric spastic diplegia	PVL
3	Global Developmental Delay, ASD, mild neurodevelopmental deficits	normal
4	Global developmental Delay, ASD	PVL
5	ASD, ADHD	Not available
6	Neonatal meningitis	PVL
7	Learning difficulties (moderate), ASD	Normal
8	Cerebral palsy, GMFCS Level 3, spastic diplegia	Not available
9	Cerebral palsy, GMFCS Level 3, spastic diplegia	PVL (performed elsewhere)
10	Congenital Achiasma Syndrome (abnormal VEP)	Normal
11	Cerebral palsy, GMFCS Level 1, left hemiplegia	Right frontal porencephalic cyst
12	Severe IUGR, dyspraxia, feeding difficulties, joint hypermobility	PVL
13	Cerebral palsy, GMFCS Level 4, asymmetric spastic quadriplegia, right side more involved	Left frontoparietal porencephalic cyst, hydrocephalus
14	Cerebral palsy, GMFCS Level 2, mild neurodevelopmental deficits	Right frontoparietal porencephalic cyst, white matter volume loss
15	Global Developmental Delay, moderate learning difficulties	PVL
16	Cerebral palsy, GMFCS Level 1, right hemiplegia, mild learning difficulties, newborn HIE Grade 3	Bilateral occipital gliosis
17	Newborn symptomatic hypoglycemia, normal gross neurology	Bilateral occipital gliosis
18	Neurodevelopmental and congenital cardiac malformation syndrome, severe learning difficulties	PVL
19	Social communication difficulties, dyspraxia	Normal
20	Cerebral palsy, GMFCS Level 1, right hemiplegia	Left fronto-parietal porencephalic cyst
21	Neonatal hemorrhagic stroke, normal gross neurology	Right Occipital Gliosis
22	IUGR, ASD	Normal
23	ASD	Normal
24	Cerebral palsy, GMFCS Level 2, right hemiplegia	Left temporo-parietal porencephalic cyst
25	ASD	Bilateral Dilated Ventricles
26	Meningitis, hydrocephalus	Hydrocephalus
27	Normal gross neurology	PVL
28	Cerebral palsy, GMFCS Level 3, spastic diplegia	PVL
29	Fine motor impairment, Behavioral disorder	PVL
30	Cerebral palsy, GMFCS Level 2, spastic diplegia, mild learning difficulties, neonatal meningitis	Bilateral occipital and parietal gliosis
31	Neonatal arterial ischemic stroke	Left parietal and temporal multicystic encephalomalacia
32	Cerebral palsy, GMFCS Level 2, spastic diplegia, traumatic perinatal intracerebral hemorrhage	Right temporal and parietal multicystic encephalomalacia
33	Neonatal Meningitis	Left occipital gliosis and atypical PVL

MRI was not available in child #5 and #8. GMFCS, Gross Mototr Function Classification System; ASD, Autistic Spectrum Disorder; ADHD, Attention Deficit Hyperactivity Disorder; IUGR, Intrauterine Growth Restriction; HIE, Hypoxic Ischemic Encephalopathy; PVL, Periventricular Leukomalacia; VEP, Flash and Pattern Reversal Visual Evoked Potential.

TABLE 3 | Endorsement criteria for the dichotomies.

Dichotomy name (Likert scale score)	Not endorsed: Score of 0	Endorsed: Score of 1
"Rarely", (1)	Never	Rarely, Sometimes, Often, and Always
"Sometimes", (2)	Never and Rarely	Sometimes, Often, and Always
"Often", (3)	Never, Rarely, and Sometimes	Often and Always
"Always", (4)	Never, Rarely, Sometimes, and Often	Always

Dichotomies were named based on the cutoff response level. The 5-point Likert scale score corresponding to the name of the dichotomy name is also provided (range 0 = "Never" to 4 = "Always").

this was called the dichotomy of "Rarely." Next, "0" was assigned to questions answered as Never or Rarely and "1" assigned to questions answered as one of the remaining 3 responses (Sometimes or Often or Always); this was called the dichotomy of "Sometimes"; and so on for a total of 4 cut-off points creating four dichotomies. Each dichotomy was then analyzed (**Table 3**).

RESULTS

Not Applicable Responses

The frequency of NA responses was higher in the CVI group compared to the typical group: median number of 1 (75% quartile at 3 NAs) for the CVI group compared to 0 (75% quartile at 0 NAs) for the typical group; the difference in the number of reported NA responses for a participant was significant (*Mann-Whitney U*, $p < 0.001$) confirming the need to account for the NA response when comparing to neurotypical children to prevent bias.

Applicable Responses

Figures 1A–E show the results of the overall average score for the applicable responses on the HVFQI-51. The full 5-level Likert score result is shown in **Figure 1A** and scores for different cut-off threshold dichotomous scoring methods in **Figures 1B–E**. For all scoring methods, the CVI and the typical group were significantly different (Mann-Whitney U p-values < 0.001): the average scores were higher for children with CVI compared to typical children regardless of which scoring method was used.

The dichotomies based on cut-off thresholds at "Rarely," "Often," and "Sometimes" performed equally well to indicate HVFDs in the CVI group (see **Supplementary Material** for a detailed analysis). Therefore, we chose the top five most discriminant questions from each of these three dichotomy thresholds (in line with Dutton's Five questions; Dutton et al., 2010b); i.e., a total of 15 questions. Four questions occurred in more than one dichotomy threshold. This yielded a total of 11 questions which we will refer to as the "Top-11" (**Table 4**). **Figures 1F,G** shows scores for the Top-11 for each group and also for individuals as a function of age indicating that Top-11 can potentially be used as a screening tool or a CVI-related impairment measure across the age range in children with CVI and good visual acuity, subject to further cross validation studies. Please note that for the questions in Top-11, we chose the cut-off for dichotomy according to which dichotomy level yielded the highest discriminability for that question (see **Supplementary Material**). For our sample of typical children and children with CVI, our Top-11 performs better than the 95 percentiles of randomly chosen sets of questions (with a similar procedure to make the set, or a similar set size); therefore, we suggest that the Top-11 set is a good potential for a screener. Nevertheless, we were limited by our sample size: our sample of typical children and children with CVI may not represent all the variation in the true population of children with CVI or typical children. We therefore caution the reader that we do not have sufficient statistical power to prove that the Top-11 set is the best set of questions for a screener tool; see **Supplementary Material** for more details. Further studies with independent samples are required to validate the Top-11.

Questions With Maximum Discriminability

Figure 2 shows the scores for each question for children with CVI and for the typical group, distinguishing typical children (in blue) from children with CVI (in red) and displaying the variability of HVFDs in children with CVI and typical children. It can be seen that there are marked differences in both the median scores (observed frequency of behaviors) and the variability of scores in individual question items, between and within the CVI and the typical children groups.

For comparison, the seven conceptual categories, defined by Dutton et al. (2010b) as domains of visual cognition, that could be affected by CVI, are marked (C1:Visual field, C2: Perception of movement, C3: Visual search, C4: Guidance of movement, C5: Attention, C6: Crowded/complex scenes, C7: Recognition and navigation). Dutton et al. (2010) attributed C3, C4, and C5 to dorsal stream dysfunction and C7 to ventral stream dysfunction. In accordance with other studies, dorsal stream dysfunction was predominant in our group of children with CVI. For typical children, on average the score was less than 1 for both dorsal and ventral stream domains, i.e., for both they reported "Never" observed. For children with CVI, the average scores on questions attributed to the dorsal stream were close to 2 (i.e., a report of "Sometimes" observed) and for the ventral stream, were close to 1 (i.e., a report of "Rarely" observed). This confirms that behaviors suggesting dorsal stream dysfunction are more frequently reported than ventral stream dysfunction, at least in the group of children with CVI recruited to our study (Mann-Whitney *U*-test showed that the difference between the dorsal and ventral stream dysfunctions was significant in children with CVI; p-value < 0.001).

The Top-11 questions are marked by vertical lines on the horizontal axis in **Figure 2**. Note that the Top-11 questions are not necessarily the question items that give the highest median or mean scores (most frequently observed behaviors) in the group of children with CVI, but rather the most discriminant items from typical children for the corresponding dichotomy threshold. This allows for inclusion of even infrequently observed behaviors suggestive of HVFDs in the group of children with CVI, (such as question item 34, "Does your child find inside floor boundaries difficult to cross?"), which have discriminant value if these behaviors are usually never observed in typical children.

Figures 1F,G suggest that the scoring on the Top-11 (which is based on the criteria in **Table 4**) is clearly different between the typical children and children with CVI so that a threshold may be used to warrant further investigation. The decision on which threshold to use depends on false positive and true positive rates. **Table 5** shows these indices for when the threshold is set variably at 4–8 questions endorsed out of the Top-11 (if all 11 questions are applicable).

Internal Consistency of Dichotomous Scoring With Accounting for Not Applicable Responses

We calculated internal consistency taking into consideration NA responses for the three dichotomies scoring of Rarely, Sometimes and Often (see **Supplementary Material** for reasons why we chose these dichotomies). We used the Kuder–Richardson Formula 20 (KR-20) formula to assess reliability (Equation 1; Kuder and Richardson, 1937) for the dichotomous scoring methods with an adjustment for the NA responses to prevent

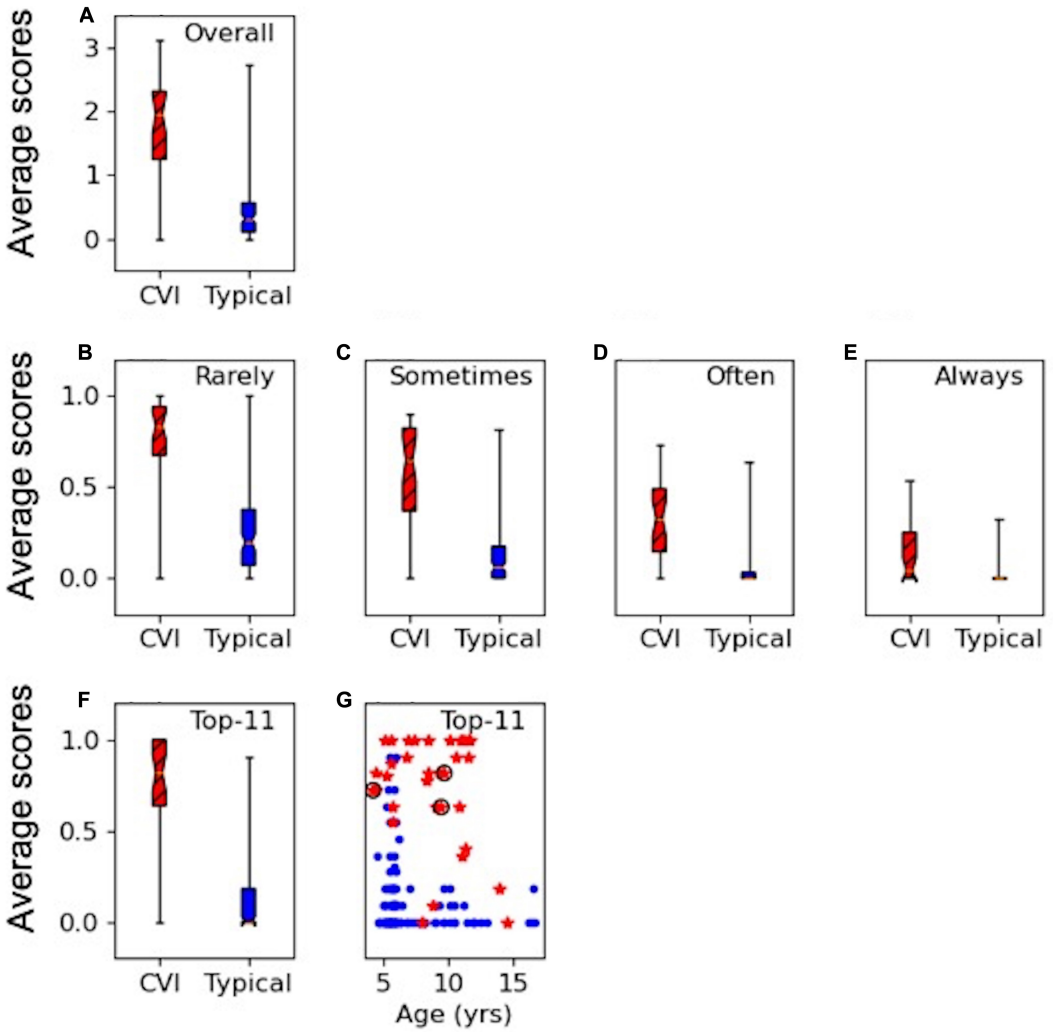

FIGURE 1 | HVFQI-51 scores for CVI (in red and hatched) and typical (in blue) groups. Boxplots show 25th and 75th percentile of group data with the median shown as the narrowest part of the box; whiskers show data range. **(A)** Full Likert overall scores for HVFQI-51. **(B–E)** Scores for HVFQI-51 for "Rarely," "Sometimes," "Often," and "Always" dichotomies (see **Table 3**). **(F)** Scores for the Top-11 subset of HVFQI-51. **(G)** Individual scores for the Top-11 subset of HVFQI-51 for typical children (blue dots) and children with CVI (red stars) as a function of age (in years); data for 3 children whose binocular visual acuity was slightly worse than 0.2 are marked by black rings.

underestimation of internal consistency given that the variance of total scores (σ_t^2) would be underestimated.

$$KR\_20 = \frac{K}{K-1}\left[1 - \frac{\sum_{i=1}^{K} p_i q_i}{\sigma_t^2}\right] \quad (1)$$

Where K is the number of questions. To account for the underestimation related to NA answers, we used an "adjusted total variance" where the "total score" for a given participant is scaled up by a factor of $\frac{\text{Total \# of questions (incl. NA)}}{\text{\# of applicable questions}}$ (Arifin and Malaysia, 2018). Therefore, in Equation 1, ($\sigma^2_{t,\ adjusted}$) was used instead of (σ_t^2). In addition, we calculated p_i as the proportion of endorsed and q_i as the proportion of not endorsed responses for the applicable responses. The adjusted KR_20 for the dichotomy at "Rarely," "Sometimes," and "Often" analysis was 0.978, 0.978, and 0.968, respectively, indicating high internal consistency and reliable scoring for all three dichotomies.

DISCUSSION

Our prospective study confirms that the HVFQI-51 clearly distinguishes the range of visually guided behaviors in children with an established clinical diagnosis of CVI *and* good visual acuity from neurotypical children. Our study characterizes the spectrum of visual perceptual difficulties in this unique cohort of children as largely "dorsal stream" deficits with the most discriminatory questions distinguishing the normal range of visually guided behaviors observed in typical children

TABLE 4 | The Top-11 subset of the HVFQI-51.

Dichotomy cut-off threshold level	Q#	Question	Dutton's Five (2010)	Dutton's conceptual visual cognition domain
Often	19	Does your child have difficulty seeing something that is pointed out in the distance?	+	Complex scene (dorsal stream)
Often	29	Does your child find uneven ground difficult to walk over?		Visually guided movement (dorsal stream)
Often	39	Does your child bump into things when walking and having a conversation		Visual attention (dorsal stream)
Often	2	Does your child have difficulty walking downstairs	+	Visual field/attention to one side
Often	38	After being distracted does your child find it difficult to get back to what they were doing?		Visual attention (dorsal stream)
Sometimes	*2*	*also in Often*		As above
Sometimes	20	Does your child have difficulty finding a close friend or relative who is standing in a group		Complex scene (dorsal stream)
Sometimes	27	Does your child find copying words or drawings time-consuming and difficult	+	Complex scene (dorsal stream)
Sometimes	4	Does your child trip at the edges of pavements going down?		Visual field/attention to one side
Sometimes	*19*	*also in Often*		As above
Rarely	*2*	*also in Often and Sometimes*		As above
Rarely	34	Does your child find inside floor boundaries difficult to cross?		Complex scene (dorsal stream)
Rarely	14	Does your child have difficulty seeing scenery from a moving vehicle?		Perception of movement
Rarely	*20*	*also in Sometimes*		As above
Rarely	6	Does your child look down when crossing floor boundaries?		Visual field/attention to one side

Q# indicates the question number in the HVFQI-51. They include the 5 questions that yielded the highest discriminability for the "Often," "Sometimes," and "Rarely" dichotomies; repeated questions are italicized and cross- referenced. Dutton (2010) suggested 5 questions (Dutton's Five) for screening 3 of which are amongst the Top-11 are in the last column. Two items from Dutton (2010) are not included: 18—does your child have difficulty seeing things which are moving quickly, such as small animals; and 24—does your child have difficulty locating an item of clothing in a pile of clothes.

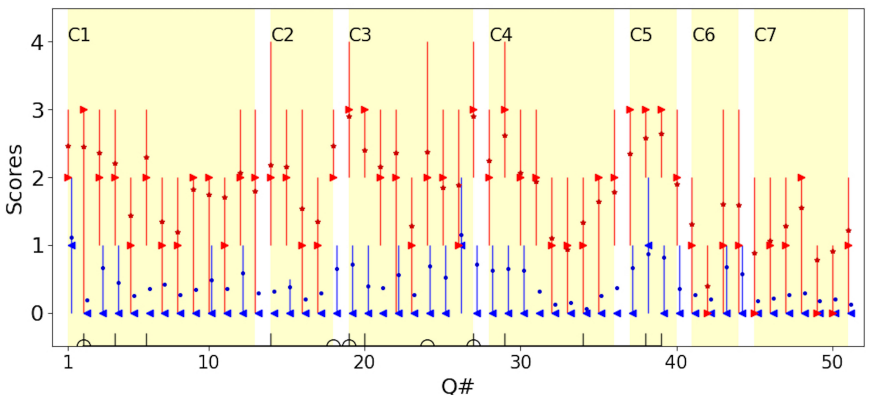

FIGURE 2 | The distribution of scores for each question for children with CVI (red) and typical children (blue). For children with CVI, the median is shown in red right-pointing triangles; the mean is shown in red stars. For typical children, the median is show in blue left-pointing triangles; the mean is shown in blue dots. Error bars represent the 25th and 75th percentiles. To avoid overlapping of the plots, data for typical children is moved rightward by 10% of the unit. C1–C7 mark the 7 categories in Dutton et al. (2010). Questions in the Top-11 (vertical lines) and Dutton's Five (half circles) are marked on the horizontal axis (see **Table 4**).

TABLE 5 | True and false positive rates for the Top-11 in our group of children with CVI and typical children, based on decision threshold.

# of endorsed questions in Top-11	8	7	6	5	4
Decision threshold: The score on Top-11 if all questions are applicable	0.72	0.64	0.55	0.45	0.36
True positive rate (sensitivity%)	66%	79%	82%	82%	88%
False positive rate (100-specificity%)	3%	5%	6%	7%	10%

outlined in **Table 4**. We thus identify a subset of 11 questions, the Top-11, that appear to be most discriminative for HVFDs in children with CVI and good visual acuity compared to typical children. In addition, to ensure an accurate representation of HVFDs within the overall disability, we account for the NA responses within the analysis and suggest

that they be included as a response option and analyzed in further studies.

High internal consistency for questions indicates that they are correlated and the reliability is reflected by the excellent overall value of a minimum of 0.968 or higher as we confirm with our analysis of division of responses along the dichotomy scoring method. High internal consistency has been reported previously in studies using similar and different inventories in children with CVI (Macintyre-Beon et al., 2012; Pueyo et al., 2014; Salavati et al., 2015; Philip et al., 2016; Gorrie et al., 2019). Direct comparisons with other works using a questionnaire to study children with an independent diagnosis of CVI are difficult because of difference in study designs and different question inventories. A similar study, by Macintyre-Beon et al. (2012) used the 51-question inventory (CVI-I) on a similar number of children with CVI (n = 36), established an independent clinical diagnosis of CVI and included a control group (n = 156). There are differences from their study, particularly in their unstated extent of visual acuity loss, their dichotomy of the Likert scale into normal and impaired based on a single cut-off ("Often") value, use of Cronbach's alpha for reliability measured for subgroups of questions (grouped on presumed neurobiologically feasible conceptual domains of visual cognition; i.e., the 7 categories presented; **Figure 2**), rather than individual question items, and no reported analysis of NA responses. Furthermore, Macintyre-Beon et al. (2012) did not present an analysis of the variability of responses between and within typical children and children with CVI in the groups of children in their study, or an analysis of the discriminant values of the individual questionnaire items. Notwithstanding these differences, the HVFQI-51 in our study reports similar high internal consistency indicating that the HVFQI-51 is clearly reliable at detecting HVFDs even in children with good visual acuity.

We suggest the Top-11 is a potentially discriminative tool for measuring HVFDs in children with CVI, i.e., a measure of CVI-related impairment. The Top-11 discriminating question items from our results (**Figures 1**, **2**) covers a range of behaviors suggesting HVFDs as generally reported for children with CVI (Dutton et al., 1996; Bax, 2010; Jackel et al., 2010; Sakki et al., 2018; Gorrie et al., 2019; Jackel, 2019; Lueck et al., 2019). The 11 most discriminating questions elicited HVFDs in awareness of lower visual field, distance viewing, finding objects in environmental clutter, multiple task management (central attention) and motion perception despite good visual acuity in these children. A previous study of children with CVI with a wide range of acuity loss (Dutton et al., 1996) identified simultaneous perception, perception of movement, orientation, recognition and depth perception as being the most frequent HVFDs. These are similar to our cohort with good visual acuity indicating independence of HVFDs from visual acuity measures and reliability of the HVFQI (see **Figure 2**) and, the potential reliability of our derived Top-11 (see **Table 4**) in eliciting HVFDs.

Studying hospital records, using a Flemish question inventory based on work by Ortibus et al. (2011) and Ben Itzhak et al. (2019) suggests object and face processing impairment (ventral stream deficit) visual (dis)interest, clutter, distance viewing, and moving in space were factors that distinguished children with a CVI from a non-CVI diagnosis. Gorrie et al. (2019) used the CVI Questionnaire (Ortibus et al., 2011); a survey with 46 items with Yes/No options for parents. 539 children (age 5–18 years) were included; the diagnosis of CVI was based on parental report. 104 children were reported to have CVI, although data on visual acuity was mostly not provided. Gorrie et al. (2019) used an exploratory factor analysis. The following five factors were significant, with given items contributing to more than one factor: (i) F1, complex neurological problems, (ii) F2, dorsal and ventral stream functions, (iii) F3, visual attention, (iv) F4, influence of a familiar environment on vision, and (v) F5, processing in multi-task activities. Children in our study, on the other hand, had a confirmed CVI diagnosis and had good visual acuity. The sample size in our study was not sufficient for us to perform a factor analysis (51 items, 5-level Likert and NA options). Nevertheless, the Top-11 could cover factor 2, 3, and 5. Further studies are needed with a more diverse and larger cohort of children with CVI to derive underlying neurobiologically-feasible factors in the HVFQI-51 using a data-driven approach; and whether these factors correspond with the theory-driven subgroups of questions in Macintyre-Beon et al. (2012) and the data-driven factors of Gorrie et al. (2019).

The results of our study provide novel information on the range of frequency of observation for each putative HVFD questionnaire item which we note do not necessarily indicate measuring a visual pathway problem, since motor and cognitive problems independent of visual pathways can cause the same behavior. The HVFQI-51 items span a wide spectrum of potential visually guided behaviors, and our study identifies the range of such behaviors in typical children as well as in a sample of children with CVI. It should be noted that it is the conjunction of items and responses rather than the individual item response in isolation that indicates that the child's behaviors are the result of a visual pathway disruption. The information on the range of behaviors suggesting HVFDs in controls (typical children) allows us to compare to the range of frequency of that item in children who are known to be abnormal with CVI, usually combined with other neurodevelopmental comorbidities since a brain network disruption rarely affects visual pathways only. This provides information on how discriminant each item is, and thus how much weight to place on a response in that item when considering CVI-related impairment. It is an essential part of clinical assessment and history-taking in patient populations to know the range of behaviors that are normal or appear to be abnormal in normal children and hence, are not actually abnormal behavior, but simply within the range of normal behavior in the childhood non-clinical population. The discriminant value of each item in the HVFQI-51 is important information not just for using that item or a subset of items (i.e., Top-11) as a diagnostic tool, but also for allowing a quantification of CVI-related impairment (see e.g., Tsirka et al., 2020, who used the Insight inventory for measuring CVI-related impairment before and after intervention strategies). Some question items should have more weight than others in measuring CVI-related impairment, i.e., the items with most discriminant value from normal range of behavior, rather than simply summing the responses across all items equally

irrespective of their discriminant value as done by Sakki et al. (2020) who used the 51-question CVI-I. We propose in effect the Top-11 has these favorable properties: a range of visually guided behaviors across conceptual domains of visual cognition, but importantly discriminate from behaviors seen in typical children. The Top-11 thus has potential as not just a "screener" implying a short diagnostic tool of CVI for individual child-level clinical practice, or as used in large scale epidemiological studies where many hundreds of participants need to be screened, as Dutton's Top 5 has been used by Gorrie et al. (2019), Williams et al. (2021), but also as a *scale* to measure severity of CVI-related impairment in children diagnosed with CVI (in the way the Insight inventory was used by Tsirka et al., 2020). We would re-emphasize that we consider the Top-11 as a potential tool subject to further studies and do not recommend its widespread clinical use yet.

We did not find a significant number of putative ventral stream deficits in our CVI group, though other impairments suggestive of dorsal stream dysfunction are in common with our Top-11. Categorical descriptions are difficult as most HVFDs engage multiple HVFs across both dorsal and ventral streams, other sensory processing and integration with motor commands (Merabet et al., 2017; Milner, 2017). However, based on our study and other reports there are HVFDs common in CVI encapsulated within the Top-11. Further studies are needed to establish the reliability of the Top-11 in a secondary independent sample. As an aid to those studies a threshold which activates taking a detailed HVFQI-51 would be helpful. This threshold will depend on acceptable true and false positive rates (see **Table 5**). A threshold that gives at least 70–80% true positive rate outcome is likely to ensure that at-risk children are not missed (see Ortibus et al., 2011).

van Genderen et al. (2012) chose 12 questions, from a more extensive questionnaire (Houliston et al., 1999), based on problems reported more often in children with CVI compared to children with a suspected diagnosis of CVI. They found the 12-item question inventory with only Yes/No/Sometimes responses not sensitive to diagnosing CVI in children with good visual acuity suspected of CVI. Our Top-11 includes five of their 12 questions (Q# 2, 4, 14, 20, and 29) but also an additional six questions. The differences could lie within the wider set of Likert response for each question, additional accounting for the NA option and a different methodology for endorsing responses in our study to make the Top-11.

We suggest that HVFQI-51, its derivative Top-11 and possibly other similar question inventories, have utility in characterizing the range of functional impairments related to higher visual function affecting the individual child and identifying strategies for treatment. Although these question inventories can be used to support a clinical diagnosis of CVI, these tools are not suitable for diagnosing CVI on their own. This is because these functional impairments, presumptively due to HVFDs, may be present in other conditions, such as developmental co-ordination disorder (Chokron and Dutton, 2016) or autism spectrum disorder, which may be co-morbid with CVI (Ortibus et al., 2019; Chokron et al., 2020; Molinaro et al., 2020). In addition, visually guided behavior may be abnormal because of a dysfunction outside the visual pathway such as a motor pathway (Ghasia et al., 2008; Salavati et al., 2014). For example, tripping on a curb could be due to depth perception problems or a problem with ankle dorsiflexion. This is a particular challenge in children with cerebral palsy and periventricular leukomalacia since they are likely to have both CVI and cerebral motor pathway impairment, the latter defining cerebral palsy. Tools to understand the association and interdependence between visual and motor dysfunction are being developed and used for identifying these aspects (Salavati et al., 2017; Sakki et al., 2021). The HVFQI-51, Top-11 and other question inventories may be used in children with suspected CVI and could form an important complementary role to other clinical evaluation for the assessment of CVI within the context of risk factors and coexisting conditions.

In our study, the diagnosis of CVI was established independent of the HVFQI-51. Though the nomenclature and diagnosis of CVI has a contentious history (Jan et al., 2001; Deonna and Roulet, 2004; Jacobson et al., 2004; Matsuba and Jan, 2006), the diagnosis of CVI in our study essentially remains a clinical one based on a multidisciplinary approach between ophthalmology, neurology and where necessary brain neuroimaging (Dutton and Jacobson, 2001; Signorini et al., 2005; Fazzi et al., 2007; Ospina, 2009; Roman et al., 2010; Lueck et al., 2019; Ortibus et al., 2019; Sakki et al., 2020). Neuroimaging was done in most of our CVI cohort (31/33) and in 7 children the MRI was judged to be normal. Neuroimaging or indeed an abnormal MRI scan is currently not considered essential for diagnosis of CVI (Salavati et al., 2015). Absence of abnormalities on MRI brain scan does not exclude CVI as abnormalities may not be seen due to current limitations of image resolution (Ortibus et al., 2009, 2019) and even a normal MRI brain postdating abnormal neonatal ultrasonography at birth (van Genderen et al., 2012) does not exclude CVI. Some studies have relied on inventories to diagnose CVI and recommend their use for diagnosis (Ortibus et al., 2011; Macintyre-Beon et al., 2013; Philip et al., 2016; Gorrie et al., 2019) or, only on parental reports of diagnosis without corroboratory evidence (Gorrie et al., 2019). The Insight inventory and later CVI-I originally published by Dutton et al. (2010b) though originally developed for children with CVI was never meant to diagnose CVI, only to document cerebral visual dysfunction (Bax, 2010; Macintyre-Beon et al., 2012) which in itself may be a component of other brain-based conditions associated with visual behaviors similar to those with CVI. The ideal diagnostic criteria which encompass this protean condition of CVI have not yet been established (Sakki et al., 2018). Therefore, we have used the term HVFQI-51 (rather than CVI-I) to emphasize that the role of HVFQI-51 (rather than the CVI-I) is to document HFVDs and not establish a diagnosis of CVI as the only measure (van Genderen et al., 2012).

Questionnaires like the HVFQI-51 often comprise questions that may be critical for the purpose but do not necessarily apply to every respondent (Frary, 2003) due to physical or cognitive limitations and often include a "Not Applicable" (NA) response

option. The NA option is useful and extends the applicability to a wider group of children with CVI as they often have a wide spectrum of physical and perceptual deficits. For example, for a child in a wheelchair, questions such as difficulties in "tripping over pavement" and "coming down stairs" may not be applicable. The NA option has been part of previous versions of the inventory (CVI-I and Insight) and was retained for the HVFQI-51. However, in previous studies, NA responses have not been reported (Gorrie et al., 2019); or items with a high rate of NA responses were excluded (Tsirka et al., 2020) not accounted for Gorrie et al. (2019) or not mentioned (Macintyre-Beon et al., 2012; Philip et al., 2016). If NA responses are not accounted for, i.e., counted as not endorsed, the question inventory score will be artificially low, reducing the chance of further investigations for HVFDs. The other extreme is to count all of NA as endorsed which will artificially increase the score for children who may not have HVFDs. A variety of ways to account for the NA response in question inventories have been suggested in the literature (Fayers et al., 1998; Holman et al., 2004). Here, we implement one of the methods, modified specifically for the HVFQI-51 to analyze the NA responses within the total number of questions for each subject allowing us to use all the data (Sakki et al., 2020). We believe this is essential to provide a holistic picture of the child with CVI and importantly to remove any bias when comparing the two groups in our study as NA responses were significantly higher, as expected, in the CVI group compared to the typically developing group.

Our study does have limitations. Dorsal and not ventral stream dysfunction is characterized by our study population. Our clinical cohort of children with CVI and good acuity largely comprised etiologies known to lead to patterns of dysfunction processed through the commonly affected dorsal stream (see Dutton, 2009 for a review) and dorsal stream has been reported to be more vulnerable to cerebral insults during early visual development (Atkinson and Braddick, 2005). Other etiological mechanisms of brain injury such as temporal lobe lesions (encephalitis, tumor, hemorrhage, rare calcification syndromes) may yield a different pattern of ventral stream-related HVFDs.

We provide detail of comorbidities from an independent neurological examination and neuroimaging results. We acknowledge that the questions can also pick up motor (efferent) pathway abnormality rather than visual (afferent) pathway abnormality since many children have comorbid motor problems—either gross motor problems such as cerebral palsy, or milder problems in balance. There are some questions which do not appear to have any motor component, such as finding faces in a crowd whereas others are likely to load significantly on motor problems even if there are depth perception problems or visual field problems such as bumping into objects or tripping on the curb. One study (van Genderen et al., 2012) did find an overlap between HVFDs in CVI and good visual acuity and comorbid conditions with an abbreviated 12 question, 3-choice inventory. Our results for a similar population are different possibly because of design differences and we have employed a 51 question inventory with 5-response options.

Our population of children with comorbid conditions is typical of a clinical population of children with CVI. It is similar to other published studies using either question or assessment inventories documenting HVFDs and visual perceptual problems where comorbidities have been documented (Fazzi et al., 2007; Roman et al., 2010; Chong and Dai, 2014; Gorrie et al., 2019; Ortibus et al., 2019; Ben Itzhak et al., 2020; Chokron et al., 2020; Tsirka et al., 2020). Sakki et al. (2018) and also acknowledge the difficulties and controversy in diagnosing HVFDS in CVI in presence of co-morbidities and further outline a spectrum of HVFDs that relate to CVI similar to those documented in our study. Moreover, HVFQI-51 is designed to ask questions related to visual perceptual problems and not cognitive problems which may be a predominant feature in some of the comorbidities such as autism. Finally, the relatively small cohort of children in our study is offset by the prospective design, an independent established diagnosis of CVI, a population of CVI with near-normal visual acuity and comparison with a control group.

In summary, the HVFQI-51 is a potentially useful assessment tool for characterizing HVFDs in children with CVI when compared to normal children and applicable to similar cohorts with behaviors suggesting HVFDs. The set of Top-11 questions derived from HVFQI-51 has the potential to serve as a screening tool and as a CVI-related impairment measure, feasible to use in routine clinical practice or for larger scale studies. High scores on the Top-11 should instigate more detailed characterization of HVFDs with the longer and more detailed HVFQI-51 which covers a wider spectrum of visually guided behaviors. The HVFQI-51 (and, potentially the Top-11 once validated by further studies with independent samples) can also be applied in clinical practice for evaluating children with a history of brain damage or disruption of brain development where there are concerns at home or school about abnormal visual function but visual acuity is good. Our results confirm that poor visual functioning in normal environments and at school in the presence of good visual acuity or a normal ocular examination should engender a high index of suspicion of the possibility of HVFDs in CVI (Macintyre-Beon et al., 2013; Williams et al., 2021). Williams et al. (2021) using the CVI-I of Macintyre-Beon et al. (2012) reported that in mainstream schools on average one child in a class of 30 children has one or more CVI-related vision problems, with most (79%) being already identified as at-risk, thus delineating a group that may benefit form screening for CVI.

Future work will focus on validation of HVFQI-51 and the Top-11 with a larger set of patients; with a wider set of disabilities and within homogeneous radiological or clinical subgroups (e.g., occipital lobe injuries visible on MRI or children with periventricular leukomalacia); determining usefulness as a screening tool and as a CVI-related impairment measure, and studying the long-term natural history of HVFDs in CVI with and without targeted intervention. Additional separate work is needed to assess the place of question inventories within group of children with disabilities without evident clinically diagnosed CVI and with other tests of visual perception such as visual evoked potentials (Weinstein et al., 2012) and standard neuropsychological tests (Tsirka et al., 2020).

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the NHS Research Heath Authority IRAS ID:193481; REC Reference:16/EE/0062. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AC conceptualized the study and performed the eye examinations. AC and SF collected the data. RK wrote the neurological sections and did the neurological examinations and interpretation of the brain imaging. SG did the data analysis and produced the figures. AC was the lead in writing the manuscript with SG who wrote most of the data analysis section. All authors contributing to the editing and final review of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnhum.2021.711873/full#supplementary-material

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frontiers in Human Neuroscience

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Exploratory Investigation of Brain MRI Lesions According to Whole Sample and Visual Function Subtyping in Children With Cerebral Visual Impairment

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Background: There is limited research on brain lesions in children with cerebral visual impairment (CVI) of heterogeneous etiologies and according to associated subtyping and vision dysfunctions. This study was part of a larger project establishing data-driven subtypes of childhood CVI according to visual dysfunctions. Currently there is no consensus in relation to assessment, diagnosis and classification of CVI and more information about brain lesions may be of potential diagnostic value.

Aim: This study aimed to investigate overall patterns of brain lesions and associations with level of visual dysfunction and to compare the patterns between the classification subgroups in children with CVI.

Methods: School-aged children with CVI received ophthalmological and neuro-psychological/developmental assessments to establish CVI-related subtyping. Other pediatric information was collected from medical records. MRI scans were coded according to a semi-quantitative template including brain regions (right hemisphere, left hemisphere, visual pathways) and summed for total scores. Non-parametric analyses were conducted.

Results: 28 children had clinical brain MRI scans available [44% of total sample, Group A (lower severity of visual dysfunctions) n = 16, Group B (higher severity) n = 12]. Total brain scores ranged between 0 and 18 (Group A mdn = 7, IQR = 0.8–10.0, Group B mdn = 10, IQR = 6.5–11.8) and were widespread across regions. 71 per cent had post-geniculate visual pathway damage. The median total brain and hemisphere scores of Group B were higher than subgroup A but differences did not reach statistical significance. No statistically significant associations were found between brain scores and vision variables (acuity, contrast sensitivity).

Conclusion: This study found a spread of lesions across all regions on the brain scans in children with congenital CVI. The majority had damage in the postgeniculate visual pathways and visual cortex region suggesting this is an area of interest and potentially

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informative for diagnosis. However the subtyping classification did not show differences in number or region of lesions though the trend was higher toward Group B. This study confirms the complex diffuse and variable nature of brain lesions in children with congenital CVI, many of whom have other neurological impairments.

Keywords: cerebral visual impairment (CVI), MRI, subtypes, visual pathway dysfunction, brain lesions, children, neuroimaging, classification

INTRODUCTION

Congenital cerebral visual impairment (CVI) refers to heterogeneous visual dysfunctions of multiple pediatric etiologies that originate in the brain rather than in the ocular structures or anterior visual pathways (Sakki et al., 2018). These include disorders of acuity (discrimination of detail), visual attention, depth and motion perception, object recognition, visual perception, spatial cognition and visuo-motor integration and motor coordination skills. However knowledge of the disordered brain substrate and its relationship with the visual dysfunctions including acuity is still limited though there are exploratory advances (Merabet et al., 2017; Chang and Borchert, 2020). This study intends to consider further the relationship between brain lesions in different regions of the brain and relationship with acuity and contrast sensitivity in children with congenital CVI, using a semi-quantitative coding template for MRI brain scans (Fiori et al., 2014).

Convergent evidence suggests that congenital CVI is associated with widespread diffuse changes in the structural and functional integrity of gray and white matter pathways, including optic radiations from the optic nerves to the occipital cortex; these have been associated with reduced visual acuity and visual perceptual dysfunctions (Ortibus et al., 2012; Bauer et al., 2014; Bauer and Papadelis, 2019; Bennett et al., 2020; Pamir et al., 2021). Thalamic involvement has been associated with severe visual impairment (Cioni et al., 1996, 1997, 2000; Ricci et al., 2006; Ortibus et al., 2009; Merabet et al., 2017). Damage to occipital-parietal areas has been related to impairments in visual crowding (Drummond and Dutton, 2007; Ortibus et al., 2012). Primary visual cortex thickness has been associated with motion perception in children with periventricular leukomalacia (Bhat et al., 2021). Damage to the structure, volume and network integrity of white matter of the inferior longitudinal fasciculus has been implicated in object recognition difficulties (Ortibus et al., 2012). Performance on a task of global motion coherence was associated with integrity of the right superior longitudinal fasciculus in typically sighted children (Braddick et al., 2016) and white matter connections of the visual cortex to temporal cortex in people with CVI (Pamir et al., 2021). Using the coding template for MRI brain scans (Fiori et al., 2014), brain damage scores of global structural, hemispheric and subcortical scores were found to correlate significantly with basic vision disorder in children with cerebral palsy and periventricular leukomalacia (Tinelli et al., 2020).

CVI includes diverse individual profiles of visual disorders of differing degree of impairment which might be grouped according to classification of discrete patterns or subtypes (Fazzi et al., 2007; Boot et al., 2010; Colenbrander, 2010; Philip and Dutton, 2014). Our team has recently demonstrated that a sample of school-aged children with congenital CVI of heterogeneous etiologies had individual profiles of visual dysfunctions that could be classified into three groups; this followed data-driven cluster analysis and statistical grouped comparisons (Sakki et al., 2021). The results suggested a gradient of severity in basic and higher-level visual dysfunctions from Group A1 (least severe) to Group B (most severe) with Group A2 as intermediate, paralleled by a similar gradient in cognitive abilities and motor disorders (Sakki et al., 2021).

Using the original sample of school-aged children with congenital CVI of heterogeneous etiologies (Sakki et al., 2021), the objectives of this study were to undertake a within-group analysis of the overall patterns of brain lesions across different regions of the brain on clinical MRI brain scans and associations with level of visual dysfunction. This included comparison of these patterns between the classification subgroups. According to previous literature it was hypothesized that (1) there would be widespread and variable brain disorders within the sample according to pattern of regional sites and severity (number) of brain lesions, (2) the pattern of brain lesions would differ between the classification groups (Group A and B) with greater severity in Group B, and (3) there would be an association between visual dysfunction (acuity, contrast sensitivity) and brain disorder with greater visual dysfunction associated with greater number of brain lesions. Of exploratory interest was to consider the white matter visual pathways including the post-geniculate visual pathway and visual cortex and occipital-parietal region, with anticipation of frequent brain lesion in these pathways across the whole sample.

MATERIALS AND METHODS

Participants

A cross-sectional observational study was conducted at the single hospital research site in a tertiary pediatric hospital including ophthalmology and developmental vision neurodisability services (research data collection conducted between 2014 and 2017). Convenience sampling recruitment was undertaken in this hospital site and in a second recruitment center in a tertiary eye hospital (with a pediatric department) and through direct parent self-referral. Details of recruitment and ascertainment and consent are available in Sakki et al. (2021) and a flow chart is available (see **Supplementary Figure 1**). All children were seen by the pediatric ophthalmologist (RB) prior to final decision that they met the inclusion criteria of the study. Inclusion criteria

were (1) age 5–15 years, (2) a definite or provisional diagnosis (on the evidence available) of congenital CVI by RB; this was defined as the child meeting at least two of three criteria of (i) pediatric history of early brain injury/neurodevelopmental disorder, (ii) convincing symptoms of functional vision difficulties associated with CVI in daily life reported by parents, and (iii) clinical evidence of visual difficulties on examination that were considered as cerebral in origin and in the context of normal or near normal eye health. All children had an ophthalmology examination undertaken by RB to examine eye health. Exclusion criteria were (1) onset of CVI after 4 weeks after birth (according to age of condition likely to have caused the CVI such as meningitis), (2) visual difficulties caused by abnormal ocular disorder according to ophthalmologist examination (RB) and (3) parental understanding of English insufficient to complete study questionnaires.

A few children who had complex visual, motor and cognitive presentations were assessed by the neurodisability pediatrician (JS) in the multidisciplinary developmental vision neurodisability clinic. Further details of recruitment and inclusion criteria are available in Sakki et al. (2021).

Classification Into Subtypes

Data-driven analyses including cluster analysis of the individual profiles (according to visual acuity, contrast sensitivity, stereopsis, visual perception and visuo-motor integration scores) and statistical comparison (visual acuity, contrast sensitivity) were undertaken. This led to three subgroups (Groups A1, A2, and B), which are briefly summarized here. Group A1 (n = 15) had normal visual acuity and contrast sensitivity range, with selective disorder in visual perception and visuo-motor integration, Group A2 (n = 28) had intermediate acuity reduction (half in the mild-moderate visual impairment range and a low proportion with abnormal contrast sensitivity) and widespread disorder in visual perception and visuo-motor integration, and Group B (n = 20) had the most severe acuity reduction (nearly half with moderate visual impairment or worse and half with abnormal contrast sensitivity). Group B was significantly lower on visual acuity reduction than Group A and external validation showed significant co-occurring ophthalmological (e.g., strabismus) and motor impairment differences between the groups. See Sakki et al. (2021) for further details.

Procedure

Each participant attended a single individual research assessment, where they were examined with both eyes open and best corrected vision. This consisted of basic vision and neuropsychological examination (including verbal cognition, visual perceptual, visuo-motor integration and other neuropsychological assessments, for further detail see Sakki et al., 2021) by the primary researcher (HS), supervised by the clinical neuropsychologist (ND). All assessments included standard clinical visual and psychometric methods leading to standard measurements. Separately and on a different appointment, each child underwent a clinical pediatric ophthalmology examination and orthoptic and optometric assessments (conducted by RB and an orthoptist). Medical case notes were accessed for the details and information relating to the child's pediatric history and any related diagnoses. For this study, structural brain MRI scans available in the child's medical reports were included with parental consent.

The routine ophthalmological examination was conducted by RB and included fundoscopy (with or without cycloplegia according to clinical need), retinoscopy, ocular motility, corneal reflexes, convergence, and visual field assessment. Optical coherence tomography was not used routinely. Fundoscopy was recorded as normal/abnormal, and presence of refractive error was coded. Nystagmus was coded as absent/present. The cover test was conducted and results for each eye recorded at near and distance as symmetrical, exotropic or esotropic. Visual fields were also assessed (see Sakki et al., 2021).

Data Collection Instruments

Vision

Near Visual Acuity

Participants completed the recognition acuity test of Sonksen LogMAR test at 40 cm standard distance (n = 19; Salt et al., 2007). This pediatric optotype acuity assessment provides published developmental normative data to interpret test results up to 9 years, at which age the normative data shows stability and similar values to adult data (Sonksen et al., 2008). Test administration was terminated according to the test standard, when the child was unable to identify two sequential uncrowded optotypes or could only identify fewer than three crowded optotypes in a line. Those unable to perform this letter optotype task by matching completed the 17-card forced choice preferential looking resolution acuity grating test of Keeler Acuity Cards at 38 cm standard distance (n = 7, Keeler Ltd, 2014), with a reversal staircase procedure repeated five times (card 17 = 0.18 cycles per degree, approximating 2.2 logMAR, card 1 = 35.4 cycles per degree approximating –0.08 logMAR). For children who could not produce reliable responses to either test, a broad estimate of acuity level was made from near detection assessment using the Near Detection Scale (n = 2; Sonksen et al., 1991). Administration was terminated when the participant did not show an overt response to the presented stimulus. Scores were categorized according to the World Health Organization, as adapted by Cumberland et al. (2016; "normal": logMAR 0.00–0.20, "near normal": 0.21–0.30 logMAR, "socially significant VI": 0.31–0.49 logMAR, "moderate VI": 0.50–1.00 logMAR, "severe VI": 1.01–1.30 logMAR, "blind": > 1.30 logMAR).

Contrast Sensitivity

The Hiding Heidi Cards (Hyvärinen, 2018), a preferential looking test where the child is presented with two white 23 × 23cm cards at 1 m distance, one of which is a blank control card and the other which contains a schematic face at six contrast levels (100, 25, 10, 5, 2.5, and 1.25%) was administered with a reversal staircase procedure repeated five times. Test performance was categorized as "normal" if the participant responded correctly to the 1.25% stimulus, and "weaker" if they could not.

Other measures of higher vision including visual perception and visuo-motor integration in the main study are not included

here as they were unable to be undertaken by those in Group B (with most severe visual and cognitive disability).

MRI Brain Scan Protocol

Children had received a clinical MRI scan in the hospital MRI scanner as part of clinical routine care. The images were performed on a 1.5T Siemens Avanto scanner, using standard imaging protocol consisting of 3D T1, Axial T2, Coronal FLAIR, DWI and ADC sequences (Saunders et al., 2007). The hospital neuroradiologist (KM) and specialist registrar (GT) scored the clinical brain MRI scans. according to a standard radiological template. Results were then coded by the researcher (HS) according to a modified version of the validated semi-quantitative template from a previous study (Fiori et al., 2014; see **Figure 1**). This template gives summary scores for the hemispheres (left and right, based on frontal, temporal, parietal and occipital lobes), the basal ganglia and brainstem (left and right, based on thalamus, caudate, lenticular, posterior limb of internal capsule), the corpus callosum, and the cerebellum. These summary scores can be summed for a total score. In Fiori et al. (2015) high intra- and inter-rater reliability (0.84–0.93) for the hemispheric and total global summary scores were reported. Evidence for the construct validity of this template has been reported in a sample of children with unilateral cerebral palsy, with motor and sensorimotor hand function measures correlating with contralateral lobal and hemispheric scores (Fiori et al., 2015). This coding template has since been extended to examining functional neuroimaging and white matter structures in adolescents with CVI and visual impairments related to perinatal injury (Pamir et al., 2021).

The coding template permitted investigation of brain regions separately, with higher scores indicating more damage seen on the scan. All regions were summed to obtain a total brain integrity score (range 0–24); hemisphere scores were obtained by summing the lobar and striatum scores of each hemisphere (range 0–10).

Cerebral Lobes

The lobes (frontal, parietal, occipital, temporal) were scored separately. For each lobe, cortical gray matter and subcortical white matter were scored (0 = no abnormality, 1 = abnormality seen) and summed for a lobar score (0–2) for each hemisphere.

Striatum

The thalamus and basal ganglia were coded separately (0 = no abnormality, 1 = abnormality seen) and summed for a striatum score of 0–2 in each hemisphere.

Brainstem

The brainstem was coded as 0 = no abnormality or 1 = abnormality seen.

Cerebellum

The left hemisphere, right hemisphere and vermis of the cerebellum were coded (0 = no abnormality, 1 = abnormality seen), and summed for a cerebellum score of 0–3.

In addition, the visual pathways were coded separately in this study because of the interest in vision. Three regions were considered: the pregeniculate area (optic nerves, optic tracts), postgeniculate area (optic radiations) and visual cortex. Each region was coded (0 = no abnormality, 1 = abnormality seen) and summed for a visual pathway score ranging between 0 and 3.

Data Analysis

Data analysis was conducted using SPSS 26 (IBM Corp, 2019; RRID: SCR_002865). Non-parametric analyses were conducted due to small sample size and skewed distributions; details of tests used are given for each data table. To assess the sample representativeness of the subset with MRI scans, the subset was compared with those without scans according to general pediatric and other factors (recruitment source, weeks' gestation at birth, age, gender, confirmation of CVI diagnosis, presence of movement disorder, verbal cognition, fundal abnormality, refractive error; Mann Whitney-*U*-tests and Chi squared tests). The brain scan scores of the classification or subtype groups (Groups A and B), were investigated and compared (Mann Whitney-*U*-tests and Fisher's exact tests). MRI summary scores were treated as continuous variables and visual pathway scores were treated as binary/ordinal. MRI data were treated as continuous variables in all analyses. Finally, associations between brain MRI scores and vision function variables (acuity—ordinal variable, contrast sensitivity—binary variable) were investigated across the total sample (Mann Whitney-*U*-tests, Kruskal-Wallis tests). Analyses were Bonferroni corrected for four comparisons (significance level set at $p < 0.0125$).

RESULTS

Descriptives

Supplementary Figure 1 gives details of participant ascertainment, numbers and reasons for exclusion and final number participating in the main study and the numbers in this study with brain scans (further details in Sakki et al., 2021). A total sample of 63 children (28 males, 35 females, median age 8 years) (Sakki et al., 2021) was recruited (58 per cent out of the 109 ascertained).

Twenty-eight children had clinical brain MRI scans available for analysis (44% of original study sample). The median age when the clinical MRI scans were undertaken was 2.61 years *(IQR* = 0.04–7.02 years). When comparing participants with and without available MRI scans, no significant differences were found in weeks' gestation at birth, gender, whether or not the CVI diagnosis was definite or provisional (not confirmed), verbal cognition level, presence of movement disorder, presence of fundus abnormalities, refractive error (**Table 1**). The children with MRI scans were significantly younger and more likely to be recruited through the hospital pediatric neurodisability service; the children who were self-referred by parents into the study were less likely to have an MRI report.

Of the subsample with MRI scans, children were classified as Group A1 ($n = 3$), A2 ($n = 13$) and B ($n = 12$) from the original study (Sakki et al., 2021). To permit analysis in this study, Group A1 and A2 were combined to Group A ($n = 16$). There was no significant difference in frequency of whether participants were in Group A or B ($\chi^2 = 1.80$, $p = 0.18$, phi = 0.169).

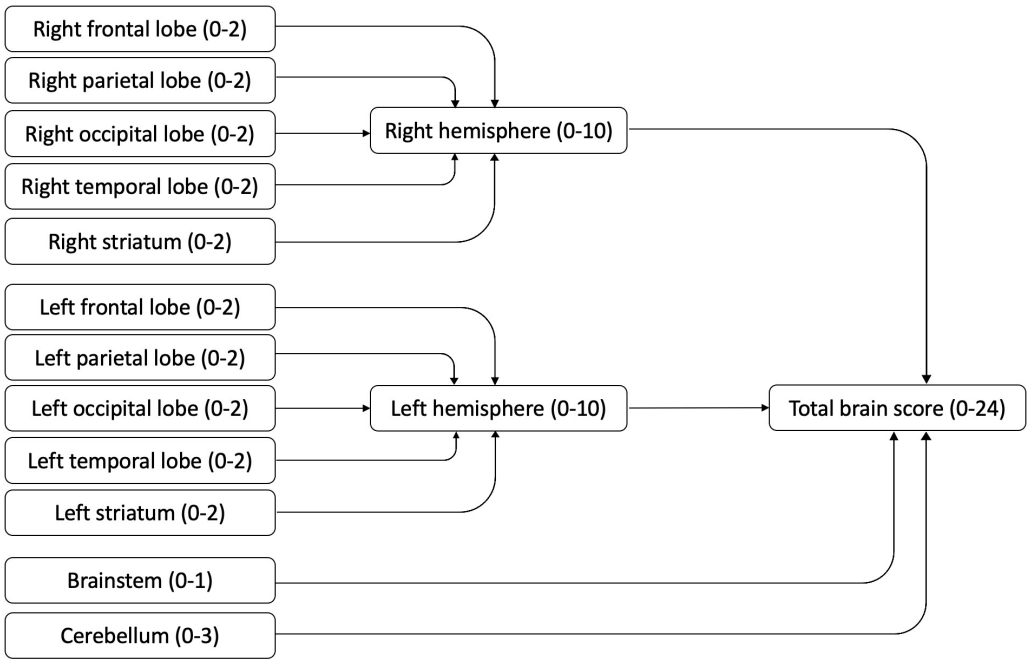

FIGURE 1 | MRI scoring template (based on Fiori et al., 2014).

Region Site and Severity of Brain Lesions

Table 2 shows the MRI data for total and region scores. Participant total brain scores ranged between 0 and 18, with four children showing no apparent abnormalities (14% of MRI sample, Group A $n = 3$). Right hemisphere scores ranged between 0 and 9, left hemisphere scores ranged between 0 and 10, subcortical scores ranged between 0 and 4, and visual pathway scores ranged between 0 and 3.

Approximately half of children (43–54%) showed abnormalities in frontal or temporal hemispheres, or striatum (see **Supplementary Table 1** for score details). Approximately three quarters of participants (71–79%) showed abnormalities in occipital or parietal areas. Cerebellar abnormality was reported in five participants (18%) and brainstem abnormality in four participants (14%).

Examining the visual pathways, five children (18%) showed an abnormality in the pregeniculate pathways, 20 (71%) showed a lesion in the postgeniculate pathway and 8 (29%) showed a visual cortex lesion. Four children (14%) showed no visual pathway abnormalities, 16 (57%) showed lesions in one area (two pregeniculate, 12 postgeniculate, two visual cortex), seven (25%) showed abnormalities in two areas (two in pregeniculate and postgeniculate pathways, five in postgeniculate pathway and visual cortex) and one child (4%) showed lesions in all three visual pathway areas.

Comparison of Brain Lesions According to Classification Group

Table 2 reports the MRI summary scores for and group comparisons between Groups A and B. Although no statistically significant differences were found between Groups A and B in any brain regions investigated, Group A had lower median scores in all brain regions than Group B. There was a non-significant trend for more children in Group B to have postgeniculate pathway damage than in Group A ($p = 0.09$, see **Table 2**). Comparisons of ophthalmological impairments (nystagmus, strabismus) as a secondary analysis also did not reach statistical significance between the groups.

Relationship Between Brain Lesions and Vision Dysfunction

The associations between region and frequency of brain lesion scores (MRI total brain, left hemisphere, right hemisphere, total visual pathway) and vision dysfunction (vision acuity or contrast sensitivity, **Table 3**) were low effects and did not reach statistical significance.

DISCUSSION

This study used a standard template of brain anatomy to examine the clinical MRI scans of a sample of children with heterogeneous confirmed or provisionally diagnosed CVI. The hypothesis that there would be widespread brain disorders within the sample was confirmed. All of the sample, except four children, had identified brain disorder on their clinical MRI scans which could be classified on the semi-quantitative template of Fiori et al. (2014), highlighting that early brain damage is a clinical feature of congenital CVI. As predicted, there were variable patterns across the sample with approximately half of participants showing abnormalities in

TABLE 1 | Descriptive characteristics of the study sample.

General characteristics	MRI subsample (*n* = 28)	No MRI subsample (*n* = 35)	Statistical comparison
Age at assessment (mdn, IQR)	7.65 (6.22–10.50)	10.99 (7.40–13.02)	$U = 322$, $p = 0.02$, $\eta^2 = 0.087$
Gender (male: female)	13: 15	15: 20	$\chi^2 = 0.08$, $p = 0.78$, phi = -0.04
Subgroup (A1: A2: B)	3: 13: 12	12: 15: 8	$\chi^2 = 2.87$, $p = 0.09$, phi = 0.21
Recruitment source			
Neurodisability	1	3	$\chi^2 = 21.82$, $p < 0.001$, $V = 0.59$
Ophthalmology	8	9	
Self-referral	4	23	
Cognitive level, mdn (IQR)	85.5 (50.3–98)	87 (69–99)	$U = 440$, $p = 0.49$, $\eta^2 = 0.008$
Clinical CVI diagnosis confirmed	19 (68%)	18 (51%)	$\chi^2 = 1.73$, $p = 0.19$, phi = 0.17
Fundal abnormality present	10 (37%, 1 missing)	8 (24%, 2 missing)	$\chi^2 = 1.16$, $p = 0.40$, phi = 0.14
Refractive error present	20 (71%)	18 (51%)	$\chi^2 = 2.60$, $p = 0.13$, phi = 0.20
Etiological risk factor for CVI			
Periventricular leukomalacia	9 (32%)	9 (26%)	
Intraventricular hemorrhage	6 (21%)	7 (20%)	
Likelihood of hypoxia/ischemia	6 (21%)	7 (20%)	
Neonatal infection (confirmed)	3 (11%)	5 (14%)	
Neonatal seizures	5 (18%)	1 (2%)	
Hydrocephalus	2 (7%)	3 (9%)	
Genetic (confirmed)	1 (4%)	2 (6%)	
Cerebrovascular incident	1 (4%)	2 (6%)	
Hypoglycemia	2 (7%)	1 (3%)	
Weeks' gestation at birth, mdn (IQR)	36 (27–40)	35 (28–40)	$U = 469$, $p = 0.96$, $\eta^2 = 0.001$
Neurodevelopmental co-occurring condition			
Movement disorder	17 (61%)	12 (34%)	$\chi^2 = 4.37$, $p = 0.04$, phi = 0.26
Current seizure disorder	5 (18%)	7 (20%)	
ASD	2 (7%)	7 (20%)	
ADHD	1 (4%)	2 (6%)	
DCD	2 (7%)	2 (6%)	
Hearing impairment	1 (4%)	1 (3%)	
Dyslexia	2 (7%)	0	

Mdn, median; IQR, Interquartile range; U, Mann Whitney-U test; χ^2, Chi squared test; GMFCS, Gross Motor Function Classification Scale; ASD, Autism spectrum disorder; ADHD, Attention deficit hyperactivity disorder; DCD, Developmental coordination disorder; η^2, eta squared effect size; V, Cramer's V effect size.

the frontal or temporal or striatum areas and approximately three quarters in the occipital or parietal areas. Cerebellar or brainstem abnormalities were present in less than a fifth of participants. The diffuse nature of the regions affected suggests that proportions of the children will have additional neurodevelopmental disorders to CVI; this was reinforced by the finding that over half of the sample have a motor disorder and the proportion below the median are in the mild-moderate intellectual disability range. This corresponds to a population-level study demonstrating that CVI-related vision problems are related to neurodevelopmental disorders, extra educational support and admission to a special care baby unit (Williams et al., 2021).

The findings are similar to previous literature describing widespread brain areas affected in children showing CVI but with a majority showing involvement of the occipital and parietal regions (Cioni et al., 1996, 1997, 2000; Drummond and Dutton, 2007; Ortibus et al., 2009; Merabet et al., 2017). The predominance of lesions in the visual pathways is as anticipated, with over four fifths of the sample showing disorder in some aspect of the visual pathway. Nearly three quarters showed damage in the postgeniculate pathways and over a quarter showed lesions in the visual cortex. Very few children showed lesions in the pregeniculate pathways, confirming that the visual dysfunctions were not attributed to disorders of the anterior visual pathways (Fazzi et al., 2007; Good, 2007; Colenbrander, 2010; Philip and Dutton, 2014). However we found some degree of pregeniculate involvement; this is not uncommon in CVI (Fazzi et al., 2007; Good, 2007; Philip and Dutton, 2014) with ocular features of nystagmus and strabismus quite prevalent in this study (Sakki et al., 2021). Very few children showed absence of visual pathway abnormalities and therefore consideration of these pathways, particularly the postgeniculate pathways, is likely to be of clinical radiological importance that may also be informative for diagnosis.

The second hypothesis that the pattern of brain lesions would differ between the classification groups was inconclusive.

TABLE 2 | MRI brain summary scores and group comparisons.

Summary scores	Median score (IQR)		N children with no abnormality (%)		Statistical comparison
Total brain score (Score range 0–24)					
Total	8 (5–10.75)		4 (14%)		$U = 61.5$, $p = 0.11$, $\eta^2 = 0.092$
Subgroup A	7 (0.75–10)		4 (25%)		
Subgroup B	10 (6.5–11.75)		0		
Right hemisphere score (Score range 0–10)					
Total	4 (2–5)		4 (14%)		
Subgroup A	3.5 (0.5–4.75)		4 (25%)		$U = 66.5$, $p = 0.17$, $\eta^2 = 0.067$
Subgroup B	5 (2–5.75)		0		
Left hemisphere score (Score range 0–10)					
Total	4 (1.25–5)		6 (21%)		$U = 70.0$, $p = 0.24$, $\eta^2 = 0.052$
Subgroup A	3.5 (0–4.75)		5 (31%)		
Subgroup B	5 (2–6.5)		1 (8%)		
Visual pathway scores	**0**	**1**	**2**	**3**	**Statistical comparison[a]**
Total visual pathway, n (%) (Score range 0–3)					
Total	4 (14%)	16 (57%)	7 (25%)	1 (4%)	
Subgroup A	3 (19%)	10 (63%)	2 (13%)	1 (6%)	$p = 0.34$, $V = 0.368$
Subgroup B	1 (8%)	6 (50%)	5 (42%)	0	
Pregeniculate pathway, n (%)					
Total	23 (82%)	5 (18%)			
Subgroup A	13 (81%)	3 (19%)			$p = 1.0$, phi = -0.027
Subgroup B	10 (83%)	2 (17%)			
Postgeniculate pathway, n (%)					
Total	8 (29%)	20 (71%)			$p = 0.09$, phi = 0.388
Subgroup A	7 (44%)	9 (56%)			
Subgroup B	1 (8%)	11 (92%)			
Visual cortex, n (%)					
Total	20 (71%)	8 (29%)			$p = 1.0$, phi = -0.068
Subgroup A	11 (69%)	5 (31%)			
Subgroup B	9 (75%)	3 (25%)			

IQR, Interquartile range; U, Mann Whitney-U test, η^2 = eta squared effect size, V = Cramer's V effect size.
[a]*Fisher's exact test.*

As postulated, Group B (with more severe acuity reduction) had a higher number of lesion sites in the total score and each brain region than Group A, but these differences did not reach statistical significance. The median total brain and hemisphere scores of Group B were higher than Group A. Over ninety per cent of Group B showed damage in the postgeniculate visual pathways, in contrast to only half of Group A, but this difference failed to reach statistical significance. All of Group B had some degree of structural abnormality and spread across all brain regions, whereas a quarter of children in Group A had no brain abnormalities visible on MRI. Together these findings point suggestively toward greater severity of visual disorder and higher prevalence of other neurodevelopmental conditions in Group B (Sakki et al., 2021) but more research with a larger sample is needed in the future. As in Ortibus et al. (2009) and Goodale (2013), there was a small proportion of children found in Group A who had visual perceptual dysfunction on test scores but had normal structural MRI scans.

Although our small sample size precluded comparing brain lesion patterns within Group A (Groups A1 vs. A2), our previous data driven cluster analysis showed that in the; "least severe" group (A1) the visual perceptual disorders tended to be more visuo-motor in nature and potentially indicating "dorsal stream impairment" (Sakki et al., 2021). This would be expected to be associated with occipito-parietal impairments; as three quarters of our sample showed lesions in these regions it is postulated that these brain regions are of significance and diagnostic relevance (Ffytche et al., 2010) but we were unable not compare Group A1 and A2 in this study. More recent interest in adult visual perceptual disorders is exploring how each higher visual function relates to a specific network of cortical locations and white-matter connections which may be *topological* (localized within a cortical area) or *hodological* (connections between areas and where function in one region is altered by changes in another spatially remote region, Ffytche et al., 2010).

In relation to the final hypothesis of an association of brain lesions with visual dysfunction, this was not supported

TABLE 3 | Comparisons of brain summary scores with vision/eye variables.

Vision area	Categories	Total brain	Left hemisphere	Right hemisphere	Total visual pathways
Visual acuity[a] *0 missing*	Normal (0.0–0.2) = 12 Near normal (0.21–0.3) = 2 Socially significant VI (0.31–0.49) = 2 Moderate VI (0.5–1.0) = 8 Severe VI (1.1–1.3) = 3 Blind (>1.3) = 1	$\rho = 0.249$ $p = -0.201$	$\rho = 0.258$ $p = 0.185$	$\rho = 0.129$ $p = 0.512$	$\rho = 0.289$ $p = 0.136$
Contrast sensitivity[b] *2 missing*	Normal = 20 Weaker = 6	$U = 48.5$, $p = 0.481$, $\eta^2 = 0.019$	$U = 49.5$, $p = 0.518$, $\eta^2 = 0.016$	$U = 51$, $p = 0.580$, $\eta^2 = 0.012$	$U = 49.5$, $p = 0.481$, $\eta^2 = 0.016$
Strabismus[c] *0 missing*	None = 4 Exotropia = 14 Esotropia = 10	$H = 2.21$, $p = 0.331$, $\eta^2 = 0.127$	$H = 2.64$, $p = 0.267$, $\eta^2 = 0.107$	$H = 1.49$, $p = 0.475$, $\eta^2 = 0.160$	$H = 2.14$, $p = 0.343$, $\eta^2 = 0.130$
Nystagmus[b] *1 missing*	No = 15 Yes = 12	$U = 86$, $p = 0.844$, $\eta^2 = 0.001$	$U = 98$, $p = 0.961$, $\eta^2 = 0.006$	$U = 76$, $p = 0.489$, $\eta^2 = 0.017$	$U = 81.5$, $p = 0.638$, $\eta^2 = 0.006$

[a] *Spearman rank correlation.*
[b] *Mann Whitney-U test.*
[c] *Kruskal-Wallis test, η^2 = eta squared effect size, V = Cramer's V effect size.*
Significance level corrected for multiple comparisons, set at $p < 0.0125$.

by our evidence. No clear associations were found between regions or numbers of brain lesions and degree of visual acuity and contrast sensitivity. This contrasts with the findings of Tinelli et al. (2020) who reported strong correlations between global brain lesion severity on MRI scans and visual function impairment scores in children with cerebral palsy and periventricular leukomalacia using a similar MRI coding template to the template used in this study. One noteworthy difference is that Tinelli et al. used a single encompassing category of "visual dysfunction" including fixation, saccades, nystagmus, acuity, visual field, stereopsis, color perception, whereas our current study investigated only acuity and contrast sensitivity separately. Our secondary group comparisons of ophthalmological features (nystagmus, strabismus) showed no significant differences. Our study only focused on acuity and contrast sensitivity but it is well established that there are different anatomical substrates for specific aspects of visual dysfunction, such as object recognition impairment with normal acuity but probably a posterior cortical lesion or visual acuity reduction and only a subcortical lesion (Cioni et al., 2000; Ricci et al., 2006; Ortibus et al., 2009).

We were unable to investigate visual perceptual dysfunction across the sample as only the children in Group A had sufficient acuity to undertake these test activities (Sakki et al., 2021). Differences in our findings with Tinelli et al. may result from their focus on a single clinical population and brain lesion site (periventricular leukomalacia) leading to a strong correlation with vision function whereas our study had multiple etiologies and brain lesion sites and no significant correlation with vision.

The evidence of our study suggests diverse widespread and diffuse brain involvement in children who have CVI of heterogeneous etiologies, but many in this sample have other neurodevelopmental impairments too and it is not known whether some of the brain lesion abnormalities are causal or incidental to the visual dysfunctions. Of theoretical interest are the high proportion with postgeniculate visual pathway and/or visual cortex damage and the high proportion with lesions in the occipital-parietal regions. The brain scans were undertaken when the children were on average 2 years old but the visual function data was assessed when the children were school age (broad range of 6–10 years). Early neuroplastic and ongoing neurodevelopmental growth and compensatory processes (such as language development and verbal mediation) may enable some children to have improving acuity or better functional use of available vision (Fazzi et al., 2007; Good, 2007; Guzzetta et al., 2010; Merabet et al., 2017; Pamir et al., 2021). This might explain why Group A and Group B did not differ significantly in brain lesions but other protective factors may be at play in the improved visual acuity levels of Group A.

Clinical structural MRI brain scans may not be sensitive enough to identify differences in white matter connectivity affecting selective visual attention and motion vision which has been shown at experimental research level. Our findings are similar to previous research suggesting that the ability to predict functional outcomes of CVI from the clinical neuroimaging are not at a reliable level (Jacobson et al., 2006; Boot et al., 2010; Chang and Borchert, 2020). However, as neuroimaging techniques develop further, the role of brain anatomical classification may become more relevant (Bauer et al., 2014; Merabet et al., 2017; Bennett et al., 2020; Pamir et al., 2021).

This study analysis had limitations which affects generalizability of findings. Firstly, although the study investigates children with CVI due to different etiologies, the total number of subjects is very small considering the different rare etiologies. A larger heterogeneous sample is needed in the future with adequate sampling of different heterogeneous etiologies to ensure that one group, such as cerebral palsy, is not skewing the data. Secondly, of the sample of 28 children,

only 16 were in Group A and of these four had a normal MRI scan and some subjects enrolled were of provisional diagnosis by the ophthalmologist (and not clinically confirmed by the multidisciplinary team). The variance in Group A may have been skewed by enrollment decisions and the smaller sample size (further divided into two small subgroups) may be underpowered to consider anatomical differences between the subgroups. It is notable that *post hoc* power calculation indicated that a sample of approximately $n = 90$ would lead to statistically significant group differences in the postgeniculate visual pathways. The merging of Group A1 and A2, which were identified in our original study through cluster analysis, may have obscured important variance between the groups. Thirdly, there may have been sampling biases as the MRI scans were undertaken for medical need and children with the MRI scans were skewed to the younger age range and recruited through hospital routes. Although it did not reach statistical significance, nearly two thirds of the MRI sample had movement disorder compared to less than a third of the non-MRI sample, suggesting that this clinical group were more likely to have early brain scans. However, the main etiological factors of periventricular leukomalacia, intraventricular hemorrhage and likelihood of hypoxia/ischemia were of similar proportions as in the original total sample. Fourthly, the high level of pediatric co-occurring conditions and diverse etiologies of CVI with known broader impacts on brain structure (e.g., cerebral palsy, hydrocephalus, cerebrovascular events) may have complicated the analysis and interpretation of the brain lesion patterns. Finally, the study was limited in considering only two and not necessarily the most important aspects of visual dysfunction in CVI—visual acuity and contrast sensitivity; this restriction reflected the only visual measures that could be undertaken across both Group A and B for comparison purposes. The main study included major other areas of visual function including stereopsis, field, visual perception, visuo-motor integration and visual attention, which could not be included in this paper.

This study has demonstrated that there is widespread brain disorder in a heterogeneous sample of school-aged children with definite or provisional diagnosed CVI and that use of a quantitative MRI template (with additional focus on the visual pathways and visual cortex) is a useful means of quantifying and grouping brain lesions in this population. Further analyses according to the classification or subtyping of the sample using the methods of Sakki et al. (2021) would be usefully considered with a larger powered sample and a prospective brain imaging protocol. The multidisciplinary integrated assessment involving ophthalmological, neurodisability pediatrics and neuropsychological assessment of basic and higher visual functions in the context of a neurodevelopmental framework was able to assess each child's functional profile, which formed the basis for the data-driven analyses and the group classifications. This method could be suitably used in the clinic for identifying and diagnosing CVI and establishing the child's individual profile and clinical and habilitation needs. Further research with larger samples of school-aged children with CVI of heterogeneous etiologies or single clinical populations such as cerebral palsy will be valuable to build on these findings.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Fulham National Health Service Research Ethics Committee. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

HS, ND, RB, and JS contributed to conception and design of the study. HS organized the database, performed all other data analyses, and wrote the first draft of the manuscript. HS and JS modified the MRI coding template. KM and GT analyzed the MRI data. ND contributed to the second and final drafts. All authors contributed to manuscript revision, read, and approved the submitted version.

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Age-Related Effects on the Spectrum of Cerebral Visual Impairment in Children With Cerebral Palsy

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Background: Cerebral Visual Impairment (CVI) is a very common finding in children affected by Cerebral Palsy (CP). In this paper we studied the characteristics of CVI of a large group of children with CP and CVI, describing their neurovisual profiles according to three different age subgroups (subgroup 1: infants 6 months–2 years; subgroup 2: pre-school age 3–5 years; subgroup 3: school age ≥ 6 years).

Methods: We enrolled 180 subjects (104 males, mean age 66 ± 42.6 months; range 6–192 months) with CP and CVI for the study. We carried out a demographic and clinical data collection, neurological examination, developmental or cognitive assessment, and a video-recorded visual function assessment including an evaluation of ophthalmological characteristics, oculomotor functions, and basic visual functions. In school-aged children, we also performed an evaluation of their cognitive-visual profiles.

Results: There were signs of CVI in all the three subgroups. Subgroup 1 (62 children) and subgroup 2 (50 children) were different for fixation ($p = 0.02$), visual acuity ($p = 0.03$) and contrast sensitivity ($p < 0.01$), being more frequently impaired in younger children. Comparing subgroup 2 with subgroup 3 (68 children), the older children presented more frequently myopia ($p = 0.02$) while the younger ones esotropia ($p = 0.02$) and alteration in smooth pursuit ($p = 0.03$) and saccades ($p < 0.01$). Furthermore, fixation, smooth pursuit, visual acuity, contrast sensitivity and visual filed ($p < 0.01$) were more frequently impaired in younger children (subgroup 1) compared to the older ones. Multiple correspondence analysis (MCA) confirmed the different neurovisual profiles according to age: younger children with CP showed more signs of CVI compared to the older ones. 34 out of 68 children belonging to subgroup 3 underwent the cognitive visual evaluation; an impairment of cognitive visual skills was detected in 21 subjects.

Conclusion: Younger children with CP showed more signs of CVI compared to the older ones, likely for the physiological maturation of visual system and mechanisms of neuroplasticity. In this direction, we suggest an early neurovisual evaluation to detect any weak visual functions.

Keywords: cerebral visual impairment, cognitive-visual disorders, cerebral palsy, age, children

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INTRODUCTION

Cerebral Visual Impairment (CVI) is the major non-ocular cause of pediatric visual impairment worldwide (Bauer and Merabet, 2019; Ortibus et al., 2019; Philip et al., 2020; Tinelli et al., 2020; Sakki et al., 2021) and it is operationally defined as "a verifiable visual dysfunction, which cannot be attributed to disorders of the anterior visual pathways or any potentially co-occurring ocular impairment" (Sakki et al., 2018; Bauer and Merabet, 2019). In recent years, there has been an increased effort to find a consensual definition of CVI (Kran et al., 2019; Ortibus et al., 2019; Sakki et al., 2021), and to identify a classification system based on clinical severity (Philip and Dutton, 2014; Sakki et al., 2021). Sakki et al. (2021) used cluster analysis to derive a medically based CVI classification, identifying three different profiles: (A1) selective visual perception and visuomotor deficits; (A2) more severe and broader visual perception and visuomotor deficits, and variable visual acuity; (B) unable to perform psychological testing (significant visual acuity reduction). The three subgroups showed profiles progressively more severe from Group A1 to Group B also for refractive errors, strabismus, nystagmus and the level of motor impairment with the majority of children belonging to Group B with Cerebral Palsy (CP). It is widely known that CVI is frequently observed in CP (Fazzi et al., 2007). We have found a great variety in its prevalence among studies (from 16 to 70%) according to the sources of clinical information used (for example direct observation, telephone questionnaires), to the different definition of visual impairment, to the methodological heterogeneity (for example different tests used for assessing the cognitive visual disorders), and to the visual parameters taken at clinical assessment (Ego et al., 2015; Duke et al., 2020; Philip et al., 2020; Tinelli et al., 2020).

The co-occurrence of CVI and CP is related to the fact that the lesions to motor pathways, particularly periventricular leukomalacia, are anatomically close to visual pathways (Fazzi et al., 2012; Tinelli et al., 2020).

The clinical spectrum of visual problems in children affected by CP is extremely broad, ranging from mild to severe, and including ophthalmological, oculomotor, basic visual function, cognitive-visual disorders (CVDs) (Fazzi et al., 2007; Castelli and Fazzi, 2016; Merabet et al., 2016; Maioli et al., 2019; Baranello et al., 2020; Bennett et al., 2020). In children affected by CP, the severity of visual impairment seems to correlate with the severity of motor deficits (Dufresne et al., 2014). Fazzi et al. (2012) describe different neuro-ophthalmological profiles according to the type of CP. Children with tetraplegic CP showed the greatest visual impairment, presenting markedly reduced or not assessable visual acuity, highly impaired or absent oculomotor functions, and high percentage of ocular abnormalities. Diplegic CP was characterized by moderately reduced visual acuity, altered contrast sensitivity, absent stereopsis, impaired oculomotor abilities, refractive errors and CVDs while children suffered from hemiplegic CP presented slight reduced visual acuity, reduced visual field (frequently unilateral), altered stereopsis, less frequent oculomotor involvement, and refractive errors. Tinelli et al. (2020) also suggest a relationship between brain lesion severity and visual function in children affected by CP: visual acuity, visual field, stereopsis and color perception were compromised in presence of a cortical damage, while oculomotor functions in presence of a subcortical damage. Therefore, to date authors have focused on profiling the spectrum of CVI according to the type of CP (Fazzi et al., 2012) or to etiology, location, timing and extent of brain lesions (Guzzetta et al., 2001; Bennett et al., 2020; Tinelli et al., 2020).

Although visual functions progressively mature during the first years of life in healthy subjects (Luna et al., 2008; Lewis and Maurer, 2009; Helo et al., 2014), only few studies evaluated the visual profile in children affected by CP according to age, reporting inconsistent results. Ego et al. (2015) hypothesized a spontaneous improvement of oculomotor functions, quantitatively assessed, in a cohort of children with CP, while Tinelli et al. (2020) found no correlation between the age of CP subjects and the Visual Total Score (Tinelli et al., 2020) obtained from the sum of oculomotor (fixation, following, saccades, and nystagmus) and perceptual signs (acuity, binocular visual fields, stereopsis and color perception); for each item, the authors gave a score of 0 if "not compromised" or of 1 "when there is an impairment." However, the visual dysfunctions considered in Visual Total Score can occur independently and their sum may hide potential underlying associations. Finally, literature data on visual function outcome in children with CVI caused by heterogeneous etiology (such as cerebral nervous system malformations, infections, injuries or seizures) reported an improvement of visual acuity, ranging between 32–83% (Matsuba and Jan, 2006; Handa et al., 2018) and contrast sensitivity (Watson et al., 2007).

Profiling the visual development of patients affected by CVI and CP is a crucial starting point to ameliorate their follow-up. Understanding the developmental trajectories of each impaired visual function may allow health professionals to: (1) define the type and the timing of rehabilitation, directing resources toward those functions that have till the possibility for improvement and, at the same time, preventing them from being further compromised; (2) advance the awareness and understanding of mild spectrum of CVI that can go unrecognized until it interferes with learning and daily life activities; (3) improve counseling offered to families regarding the developmental trajectories of each impaired visual function.

Our hypothesis is that the clinical spectrum of CVI can modify during the first years of life and that the youngest children can present more signs of CVI in terms of visual dysfunctions compared to the older ones. In fact, in literature we found data that attests that age-related visual development is due to maturation of brain anatomy and function (Luna et al., 2008). Moreover, visual deficits caused by early brain damage could be influenced by adaptive neuroplasticity that, especially during the first years of life, modulate the natural history of children suffering from CP and CVI (Ismail et al., 2017; Sabel et al., 2018; Fiori et al., 2019).

The aims of our study were: (1) to detail the neurovisual profile (that means ophthalmological, oculomotor and basic visual functions) of a large group of children affected by CP according to three different age subgroups (subgroup 1: infants 6 months–2 years; subgroup 2: pre-school age 3–5 years; subgroup 3:

school age > 6 years), (2) to compare age subgroups. Finally, (3) we wanted to know whether cognitive visual functions in the oldest age group were different from reference values and whether the presence of cognitive visual disorder was related to the IQ values (FIQ, VIQ and PIQ). We divided the sample into these three age subgroups based on visual anatomical and functional aspects. Gross anatomical structures, although constructed before birth, continue to develop into childhood, together with the maturation of neural circuits of the visual cortex (Kovács et al., 1999). Specifically, some authors suggest the hypothesis that synaptogenesis in human visual cortex reaches a peak between 8 months and 2 years and is followed by a long period of synaptic pruning to reach adult levels later in childhood (Siu and Murphy, 2018). A similar trajectory is seen in dendritic refinement, with a peak at 5 months and adult levels by 2 years (Siu and Murphy, 2018). Many anatomical features (as cortical thickness, synaptogenesis, horizontal, and interlaminar connections, for details see the review of Siu and Murphy (2018)) are already adult-like at this stage, but vision continues to mature well beyond the first years of life. In fact, lower visual functions (such as visual acuity) reach adult level between 3 and 5 years of age, while higher level visual function (such as figure-ground discrimination and visual attention) complete their development in adolescence (Dutton, 2003; Ortibus et al., 2019). However, the precise age of maturation may vary significantly depend on test design (e.g., because of potential validity issues), that in turn hinders estimations of function development and on the visual experience of the child. Finally, literature data report that the time windows of (critical) visual function development, which could increase the opportunity for effective treatment, are under 5 years of age (Siu and Murphy, 2018).

MATERIALS AND METHODS

Participants

193 children with CP were referred to our Neuro-ophthalmological Tertiary Center of Child Neurology and Psychiatry Unit, Civil Hospital of Brescia, between July 2017 and July 2020, by medical specialists, as pediatricians and child neurologists and psychiatrists, because of a visual impairment screening. Of these, 13 children (infants 6 months–2 years: 5 cases; pre-school age 3–5 years: 3 cases; school age > 6 years: 5 cases) were excluded from the study because they did not show any visual signs. The remaining 180 (104 males, 76 females) met the inclusion criteria and were selected for this study. Inclusion criteria were: diagnosis of CP, confirmed by neurological examination and brain Magnetic Resonance Imaging (MRI); age between 6 months and 18 years; presence of CVI according to Sakki et al. (2018, 2021). We made a CVI diagnosis according to the European definition "a verifiable visual dysfunction, which cannot be attributed to disorders of the anterior visual pathways or any potentially co-occurring ocular impairment." We enrolled all the CP subjects with a variable association of: oculomotor dysfunctions (abnormalities in fixation and/or smooth pursuit and/or saccades and/or abnormal ocular movements); basic visual function deficits (reduced visual acuity and/or visual field and/or altered contrast sensitivity); CVDs and larger optic disc cupping associated with optic nerve hypoplasia due to mechanism of trans-synaptic degeneration (Jacobson et al., 1997). These visual signs were not primarily caused by disorders of the anterior visual pathways (globe, retina, or anterior optic nerve).

The sample did not include any children presenting severe visual deficits due to abnormalities of the anterior segment or sequelae of retinopathy of prematurity in order to exclude subjects affected by mainly ocular visual impairment.

The study was conducted in accordance with the ethical guidelines established by the Declaration of Helsinki and was approved by the Ethics Committee of Brescia (NP 3070). Written informed consent was obtained by all participants and/or their parents before data collection.

Procedure

A demographic and clinical data collection, a neurological examination with gross and fine motor evaluation, a developmental or cognitive assessment and a video-recorded visual function examination was carried out in the children affected by CP and CVI. Data on neuroradiological findings (Conventional Brain MRI) of all CP children were also collected.

We classified CP based on criteria outlined in the Surveillance of CP in Europe algorithm Surveillance of Cerebral Palsy in Europe (2000), into four subtypes: Spastic bilateral CP, Spastic unilateral CP, Dyskinetic CP, Ataxic CP. The Gross and Fine motor function was assessed using the Gross Motor Function Classification System (GMFCS) (Palisano et al., 1997) and the Manual Ability Classification System (MACS) (Eliasson et al., 2006), respectively. To assess developmental or cognitive skills, the Griffiths Mental Developmental Scales-III (Green et al., 2017), Wechsler Preschool and Primary Scale of Intelligence III edition (WPPSI-III) (Wechsler, 2002) or the Wechsler Scales of Intelligence for Children IV edition (WISC-IV) (Wechsler, 2003) were used according to the age of the children. The developmental/intelligence quotients (IQ) were measured in standard scores and defined normal (≥ 85 standard score), mildly/moderately impaired (<85 standard score).

We carried out the visual assessment according to Fazzi and colleagues (Fazzi et al., 2012; Iodice et al., 2018) and included the evaluation of: (1) ophthalmological characteristics, detecting possible refractive errors (assessed in cycloplegia), anterior segment and ocular fundus abnormalities; dynamic retinoscopy was not carried out; (2) oculomotor functions (fixation, smooth pursuit, and saccades and orthoptic evaluation to detect strabismus, ocular motility deficit and abnormal eye movements); (3) basic visual functions (visual acuity, contrast sensitivity, visual field); (4) cognitive-visual profile, carried out in children at school-age (subgroup 3) with normal IQ or mild cognitive impairment (full-scale IQ > 50 and verbal IQ > 70 standard scores) and visual acuity not less than three-tenths in binocular vision. As regards oculomotor functions, we defined fixation as present (stable for more than 3 s) or impaired (unstable or absent); we defined smooth pursuit as present (continuous) or impaired (discontinuous or difficult to elicit/absent); we defined saccadic eye movements as present (both latency and amplitude

of saccade were normal) or impaired (dysmetric and/or with increased latency or absent). Visual acuity was evaluated under maximum refractive correction with test suitable for patient's age and cooperation using Teller Acuity Cards (Teller et al., 1986), Lea Symbols or letter optotypes (Hyvärinen et al., 1980): children belonging to subgroup 1 were evaluated using Teller Acuity Cards while children belonging to subgroup 2 and 3 using Teller Acuity Card, Lea Symbols or letter optotypes. We defined visual acuity score as normal or reduced: for children belonging to subgroup 1 we used normative data according to Teller acuity cards Handbook (Teller et al., 1986); for children belonging to subgroup 2 we applied age-specific norms according to the Current American Academy of Pediatrics guidelines updated in 2016 (Donahue et al., 2016) (normal visual acuity $>$ 4 tenths for 36–47 months, $>$ 5 tenths for 48–59 months and $>$ 6 tenths for $\geq$ 60 months of age); for the children belonging to subgroup 3 we referred to the WHO International Classification of Disease-10 definition of visual impairment (World Health Organization [WHO], 2004) (normal vision $>$ 8 tenths; deficient $<$ 8 tenths). We evaluated contrast sensitivity using the Hiding Heidi Low Contrast "Face" Test (HH). Since Leat and Wegmann (2004) reported that most children aged between 1 and 8 years old correctly responded to the lowest contrast at the HH, we considered the ability to identify targets as "normal" at 1.25% contrast level and as "altered" when $\geq$ 2.5%. We evaluated the ability to locate targets presented in different areas of the visual field binocularly using kinetic perimetry (van Hof-van Duin et al., 1992), based on child's behavioral reactions (e.g., movements of the head, eyes, or a limb toward the target) and we classified it as normal or reduced, according to age-specific normative data reported in the literature (Heersma et al., 1989; Wilson et al., 1991; van Hof-van Duin et al., 1992); we considered normal a result within 2 standard deviation.

We performed the cognitive-visual assessment using a battery of tests referring to visual motor and visual perceptual skills. Visual motor skills were analyzed using the Developmental Test of Visual-Motor Integration -VMI- (Beery and Buktenica, 2000), a paper-and-pencil test for visual motor integration abilities, and the Block Construction -BC- task, a subtest of NEPSY battery (Korkman et al., 2011), for constructional praxia. Visual perceptual skills, in children $<$ 11 years old, were assessed using the Bova et al. (2007) battery that includes the evaluation of: (1) The perceptual categorization, that means the ability to recognize the structural identity of an object when its projection on the retina is altered (using the Street Completion Test (Street, 1931) - SCT-, colored photographs of objects viewed from unusual perspectives - UP-, photographs illuminated in unusual ways -UI-), (2) The constancy of internal representation of objects (using a series of Imaginary Figures -IF-), and (3) The Semantic categorization, which is the capacity of recognizing semantic and functional attributes of stimuli (using Matching Tasks respectively -MC- and -MF-). We used the Street Completion Test on children $>$ 11 years old to evaluate visual perceptual skills. Visual motor and visual perceptual functions were considered impaired if z score derived from normal controls was under -2 on at least one of the tasks evaluated. A CVD was considered present in case of visual motor and/or visual perceptual dysfunction.

A multidisciplinary team carried out the visual function evaluation: a child neuropsychiatrist performed the oculomotor/basic visual functions assessment supported by a child therapist who conducted the video-recording; an ophthalmologist performed the ophthalmology evaluation, an orthoptist detected the presence of strabismus, ocular motility deficit and abnormal eye movements and a neuropsychologist assessed the cognitive visual functions. The video-recorded examination allows the teams to observe and judge the child performance (especially the qualitative functions as fixation, smooth pursuit and saccadic movements).

We classified Brain MRIs according to the MRI Classification System proposed by the Surveillance of Cerebral Palsy in Europe (Himmelmann et al., 2017), that consists of five main groups: (A) maldevelopments, (B) predominant white matter injury, (C) predominant gray matter injury, (D) miscellaneous, and (E) normal finding.

Statistical Analysis

Demographic data, clinical features (subtype of cerebral palsy, level of gross and fine motor impairment, IQ) and the neuroimaging findings of the entire sample and of the three subgroups were described using means, standard deviation, and range for quantitative variables (gestational age, birth weight) and counts and percentage for qualitative variables (subtype of cerebral palsy, level of gross and fine motor impairment, IQ and brain MRI classification). Comparison between age subgroups and these variables were performed using Kruskal-Wallis test for quantitative variables and Chi squared test for qualitative variables.

For the first aim, data on neurovisual profile according to the three different age subgroups were described using means, standard deviation, and range for quantitative variables (visual acuity and contrast sensitivity) and counts and percentage of impaired qualitative variables (ophthalmological, oculomotor functions and basic visual functions). For the second aim, we compared the evolution of neurovisual profiles between the different age subgroups using a logistic regression model for all visual variables (ophthalmological, oculomotor and basic visual functions), results were reported as odds ratio (OR) and 95% Confidence Interval (CI). We carried out a multiple correspondence analysis (MCA) to investigate the relationships between categorical variables: refractive errors, fundus oculi abnormalities, strabismus, nystagmus, fixation, smooth pursuit and saccadic alterations, abnormal visual acuity, altered contrast sensitivity and visual field deficit (visual motor and visual perceptual disorders were not included in the analysis because assessed only in the subgroup 3). The 10 visual items were dichotomized ("yes/no" when the visual disorder was present/absent). The MCA approach provides coordinate plots that can be graphically interpreted as follow: (1) variable categories with a similar profile are grouped together; (2) negatively correlated variable categories are positioned on opposite sides of the plot origin (opposed quadrants); (3) the distance between category points and the origin measures the quality of the variable category on the factor map; (4) category points that are away from the origin are well represented on the

factor map. The quality of the representation of each variable is called the squared cosine (cos2), which measures the degree of association between variable categories and a particular axis. We added age (categorized) as a supplementary variable, that is, it was not used to generate the principal dimensions but rather the category coordinates were projected on the coordinate plot defined by the active variables (10 visual items). Multiple comparisons' *p*-values were adjusted using Tukey algorithm.

For the third aim, data on cognitive visual functions in the oldest age group were described using counts and percentage of the impaired visual motor and visual perceptual variables. The relationship between the presence of cognitive visual disorder and IQ values (FIQ, VIQ, and PIQ) was evaluated using logistic regression model; results were reported as OR and 95% CI.

All analyses were performed using R statistical package (version 4.0.3) assuming a significance threshold of 5%.

RESULTS

Of the 180 children selected for this study, 62 belonged to subgroup 1, 50 to subgroup 2 and 68 to subgroup 3. **Table 1** summarizes the demographic data, the clinical features and the neuroimaging findings of the entire sample and of the three subgroups; these characteristics were comparable between each of the three subgroups. Data on neurovisual profiles (ophthalmological, oculomotor and basic visual functions) of the three subgroups are summarized in **Table 2** and **Figures 1**–**3**.

Comparison of the Neurovisual Profiles Between the Three Subgroups

Comparing the neurovisual profiles between subgroup 1 and subgroup 2, we observed that CVI signs (refractive errors, fundus oculi abnormalities, strabismus, ocular motility deficits, nystagmus, altered smooth pursuit and saccades, and visual field deficits) did not significantly differ, except for fixation ($p = 0.02$), visual acuity ($p = 0.03$) and contrast sensitivity ($p < 0.01$) that were more frequently impaired in younger children (subgroup 1). From the comparison of the neurovisual profiles between subgroup 2 and subgroup 3, we found no differences in refractive errors (although myopia was more frequent, $p = 0.02$, and hypermetropia less frequent, $p = 0.052$ in the subgroup 3), fundus oculi abnormalities and nystagmus. The two subgroups

TABLE 1 | Demographic, anamnestic, clinical, and neuroradiological characteristics of the sample and of the age subgroups.

	Total sample	Subgroup 1 (6 mo-2 yr)	Subgroup 2 (3–5 yr)	Subgroup 3 (> 6 yr)	*P*-value
N subjects	180	62	50	68	
Mean age (mo) ± SD (range)	66 ± 42 (6–192)	21 ± 8.3 (6–35)	58 ± 9.9 (36–71)	111 ± 25.8 (75–192)	
Male/Female distribution N (%)	104(58)/76(42)	37(60)/25(40)	31(62)/19(38)	36(53)/32(47)	0.576
Mean GA (wks) ± SD (range)	34.9 ± 5 (24–42)	35 ± 5 (24–41)	35 ± 5.2 (25–41)	34.7 ± 5 (24–42)	0.838
Preterm birth N (%)	105(59.0)	33(53.2)	28(57.1)	44(65.7)	0.280
Mean birth weight (g) ± SD (range)	2289 ± 968 (380–4860)	2265 ± 936 (620–3700)	2343 ± 1,068 (380–4630)	2270 ± 932 (800–4860)	0.935
Type of cerebral palsy:					0.722
Spastic unilateral, N (%)	63 (35)	17 (27)	18 (36)	29 (43)	
Spastic bilateral, N (%)	94 (52)	37 (60)	27 (54)	29 (43)	
Dyskinetic, N (%)	20 (11)	8 (13)	4 (8)	8 (12)	
Ataxic, N (%)	3 (2)	0	1 (2)	2 (3)	
Gross motor involvement:					0.613
Mild (GMFCS level 1 or 2), N (%)	90 (50)	28 (45)	25 (50)	37 (54)	
Moderate (GMFCS level 3), N (%)	7 (4)	2 (3)	1 (2)	4 (6)	
Severe (GMFCS level 4 or 5), N (%)	83 (46)	32 (52)	24 (48)	27 (40)	
Fine motor involvement:					0.769
Mild (MACS level 1 or 2), N (%)	102 (57)	32 (52)	29 (58)	41 (60)	
Moderate (MACS level 3), N (%)	25 (14)	9 (14)	7 (14)	9 (13)	
Severe (MACS level 4 or 5), N (%)	53 (29)	21 (34)	14 (28)	18 (27)	
Developmental/Cognitive quotient:					0.623
Normal, N (%)	55 (31)	17 (27)	18 (36)	20 (29)	
Mild/moderate impaired, N (%)	125 (69)	45 (73)	32 (64)	48 (71)	
Brain MRICS:					0.649
MRICS type A, N (%)	7 (4)	2 (3)	3 (6)	2 (3)	
MRICS type B, N (%)	106 (59)	38 (61)	28 (56)	40 (59)	
MRICS type C, N (%)	49 (27)	18 (29)	11 (22)	20 (29)	
MRICS type D, N (%)	18 (10)	4 (7)	8 (16)	6 (9)	

N, number; mo, months; yr, years; SD, Standard deviation; GA, gestational age; wks, weeks; g, grams; GMFCS, gross motor function classification system; MACS, manual ability classification system; MRICS, magnetic resonance imaging classification system.

TABLE 2 | Neurovisual profiles between the three subgroups.

	Subgroup 1 (*N* = 62)	Subgroup 2 (*N* = 50)	Subgroup 3 (*N* = 68)	Comparison between subgroups, OR (CI 95%); *p*-value			
				1 vs. 2	2 vs. 3	1 vs. 3	
Refractive errors N	**58**	**47**	**63**	*1.08 (0.1; 6.2); p = 0.98*	0.80 (0.1; 4.0); *p = 0.93)*	0.87 (0.1; 4.0); *p = 0.96*	1 = 2 = 3
Mixed refractive errrors	42	35	44	1.1 (0.4; 2.7); *p = 0.94*	0.7 (0.3; 1.8); *p = 0.76*	0.8 (0.3; 1.9); *p = 0.89*	1 = 2 = 3
Astigmatism (isolated/mixed)	52	41	54	0.88 (0.2; 2.6); *p = 0.93*	0.85 (0.3; 2.4); *p = 0.91*	0.74 (0.2; 2.0); *p = 0.72*	1 = 2 = 3
Hypermetropia (isolated/mixed)	37	33	31	1.31 (0.5; 3.1); *p = 0.70*	0.43 (0.1; 1.0); ***p = 0.052***	0.57 (0.2; 1.2); *p = 0.19*	1 = 2 > 3
Myopia (isolated/mixed)	13	8	25	0.72 (0.2; 2.1); *p = 0.71*	3.05 (1.1; 8.3); ***p = 0.02***	2.19 (0.9; 5.3); *p = 0.09*	1 = 2 < 3
Anterior segment Ab N	**4**	**1**	**4**	0.3 (0.02; 3.6); *p = 0.45*	3.06 (0.2; 35.2); *p = 0.44*	0.9 (0.1; 4.5); *p = 0.98*	1 = 2 = 3
Fundus oculi Ab N	**38**	**30**	**45**	0.95 (0.4; 2.2); *p = 0.97*	1.30 (0.5; 3.0); *p = 0.70*	1.24 (0.5; 2.7); *p = 0.77*	1 = 2 = 3
Disc pallor	18	16	27	1.15 (0.4; 2.8); *p = 0.9*	1.4 (0.5; 3.3); *p = 0.58*	1.61 (0.7; 3.6); *p = 0.34*	1 = 2 = 3
Disc cupping	9	3	6	0.38 (0.08; 1.7); *p = 0.27*	1.52 (0.3; 7.5); *p = 0.76*	0.57 (0.1; 1.9); *p = 0.5*	1 = 2 = 3
Disc pallor, cupping, nerve hy	11	11	12	1.31 (0.4; 3.7); *p = 0.78*	0.76 (0.2; 2.1); *p = 0.77*	0.99 (0.3; 2.7); *p = 1.00*	1 = 2 = 3
Strabismus N	**47**	**38**	**43**	1.01 (0.3; 2.7); *p = 0.99*	0.54 (0.2; 1.3); *p = 0.23*	0.55 (0.2; 1.3); *p = 0.21*	1 = 2 = 3
Esotropia	30	26	20	1.16 (0.5; 2.6); *p = 0.88*	0.38 (0.1; 0.9); ***p = 0.02***	0.44 (0.2; 1.0); ***p = 0.052***	1 = 2 > 3
Exotropia	17	12	23	0.86 (0.3; 2.2); *p = 0.89*	1.45 (0.5; 3.6); *p = 0.54*	1.25 (0.5; 2.9); *p = 0.77*	1 = 2 = 3
EOM deficit N	**33**	**25**	**26**	0.88(0.3; 2.0); *p = 0.9*	0.62 (0.2; 1.4); *p = 0.33*	0.54 (0.2; 1.2); *p* = 0.15	1 = 2 = 3
Abduction deficit	25	19	20	0.91 (0.3; 2.1); *p = 0.94*	0.68 (0.2; 1.6); *p = 0.5*	0.62 (0.2; 1.4); *p = 0.32*	1 = 2 = 3
Upshoot in adduction	3	2	3	0.82 (0.1; 6.5); *p = 0.95*	1.1 (0.1; 8.6); *p = 0.99*	0.91 (0.1; 5.8); *p = 0.98*	1 = 2 = 3
Upshoot in abduction	5	4	3	0.99(0.2; 4.6); *p = 1.00*	0.53 (0.09; 3.0); *p = 0.63*	0.53 (0.1; 2.8); *p = 0.59*	1 = 2 = 3
Nystagmus N	**27**	**19**	**31**	0.79 (0.3; 1.8); *p = 0.76*	1.37 (0.5; 3.1); *p = 0.60*	1.09 (0.5; 2.3); *p = 0.95*	1 = 2 = 3
Fixation Ab N	**41**	**21**	**27**	0.37 (0.1; 0.8); ***p = 0.02***	0.91 (0.3; 2.1); *p = 0.95*	0.34 (0.1; 0.7); ***p < 0.01***	1 > 2 = 3
Smooth pursuit Ab N	**58**	**45**	**49**	0.62 (0.1; 2.9); *p = 0.71*	0.2 (0.09; 0.9); ***p = 0.03***	0.1 (0.05; 0.6); ***p < 0.01***	1 = 2 > 3
Saccadic Ab N	**51**	**47**	**49**	3.38 (0.7; 15.3); *p = 0.13*	0.16 (0.04; 0.6); ***p < 0.01***	0.56 (0.2; 1.4); *p = 0.29*	1 = 2 > 3
Visual acuity deficit	**54**	**34**	**35**	-1.1 (-2.2; -0.08); ***p = 0.03***	-0.69 (-1.5; 0.1); *p = 0.13*	-1.85 (-2.8; -0.8); ***p < 0.01***	1 > 2 = 3
N of sbj: Teller Acuity Cards	62	20	14				
Mean value in cy/cm ± SD	3.4 ± 2.5	3.9 ± 4.1	3.1 ± 3.3				
Range	0.23–19	0.32–13	0.43–13				
N of sbj: Lea Sy; letter O	/	30: 22; 8	54: 4; 50				
Mean value in tenths ± SD		5.9 ± 2.9	7.2 ± 3				
Range		1–10	1–10				
Contrast sensitivity Ab N	**36**	**13**	**12**	0.25 (0.1; 0.6); ***p < 0.01***	0.61 (0.2; 1.6); *p = 0.43*	0.1 (0.06; 0.3); ***p < 0.01***	1 > 2 = 3
Mean value in % ± SD	38.6 ± 44.7	23.6 ± 41.1	8.8 ± 23.9				
Range in %	1.25–100	1.25–100	1.25–100				
Visual field deficit N	**36**	**25**	**21**	0.72 (0.3; 1.6); *p = 0.6*	0.45 (0.1; 1.0); *p = 0.06*	0.32 (0.1; 0.7); ***p < 0.01***	1 = 2 > 3
Right or left field defect	16	12	12	0.91 (0.3; 2.4); *p = 0.95*	0.68 (0.2; 1.8); *p = 0.6*	0.62 (0.2; 1.6); *p = 0.42*	1 = 2 = 3
Upper or inferior field defect	2	1	1	0.61 (0.04; 9.6); *p = 0.87*	0.7 (0.03; 16.9); *p = 0.96*	0.45 (0.03; 7); *p = 0.73*	1 = 2 = 3
Generalized field loss	18	12	8	0.77 (0.2; 2.0); *p = 0.76*	0.42 (0.1; 1.2); *p = 0.15*	0.33 (0.1; 0.9); ***p = 0.03***	1 = 2 > 3

N, number; Ab, abnormalities; hy, hypoplasia; EOM, extrinsic ocular motility; Lea Sy, Lea symbols, letter O, letter optotype. Bold and italic values represent significant findings.

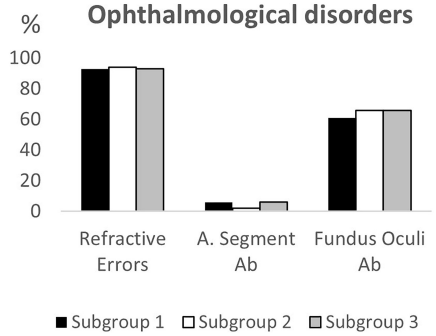


FIGURE 1 | Ophthalmological disorders according to age subgroups. A. Segment Ab, Anterior Segment abnormalities; Fundus Oculi Ab, Fundus Oculi abnormalities.

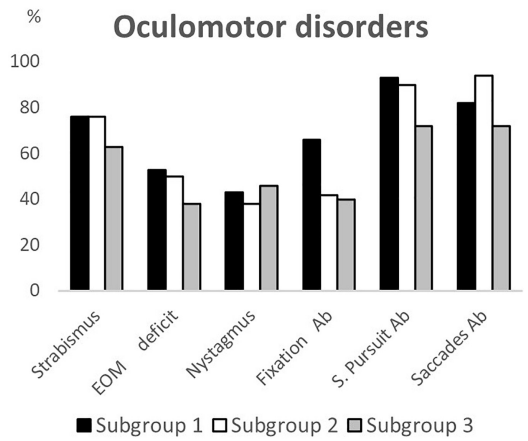


FIGURE 2 | Oculomotor disorders according to age subgroups. EOM deficit, extrinsic ocular motility deficit; Ab, abnormalities; S. Pursuit, smooth pursuit.

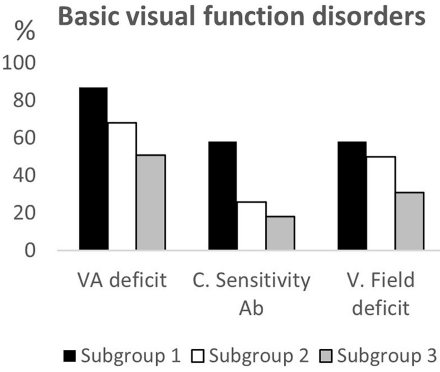


FIGURE 3 | Basic visual function disorders according to age subgroups. VA deficit, visual acuity deficit; C. Sensitivity Ab, Contrast Sensitivity abnormalities; V. field deficit, visual field deficit.

significantly differed for esotropia ($p = 0.02$), and alteration of smooth pursuit ($p = 0.03$) and saccades ($p < 0.01$), more frequently present in subgroup 2.

Moreover, neurovisual profile was significantly different between subgroup 1 and 3 for fixation, smooth pursuit, visual acuity, contrast sensitivity and visual filed ($p < 0.01$) being less frequently impaired in the older children (subgroup 3). Findings are summarized in **Table 2** and in **Figures 4–6**.

MAC Analysis

MCA (**Figure 7**) was able to explain 46% of the total variation using the two main dimensions (**Supplementary Figure 1**). The

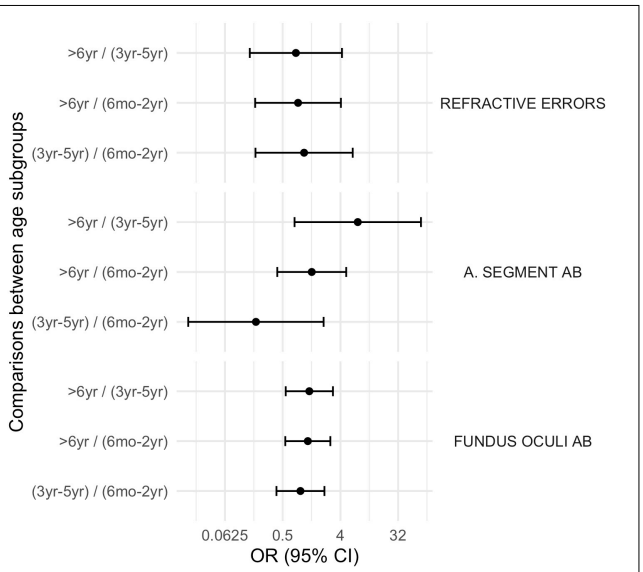


FIGURE 4 | Comparison between subgroups, OR (CI 95%): ophthalmological disorders. A. Segment Ab, Anterior Segment abnormalities; Fundus Oculi Ab, Fundus Oculi abnormalities.

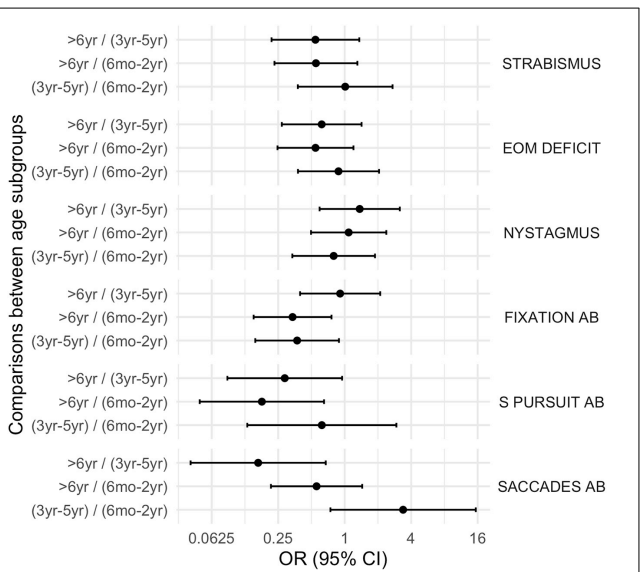


FIGURE 5 | Comparison between subgroups, OR (CI 95%): oculomotor disorders. EOM deficit, extrinsic ocular motility deficit, Ab, abnormalities, S. Pursuit, smooth pursuit.

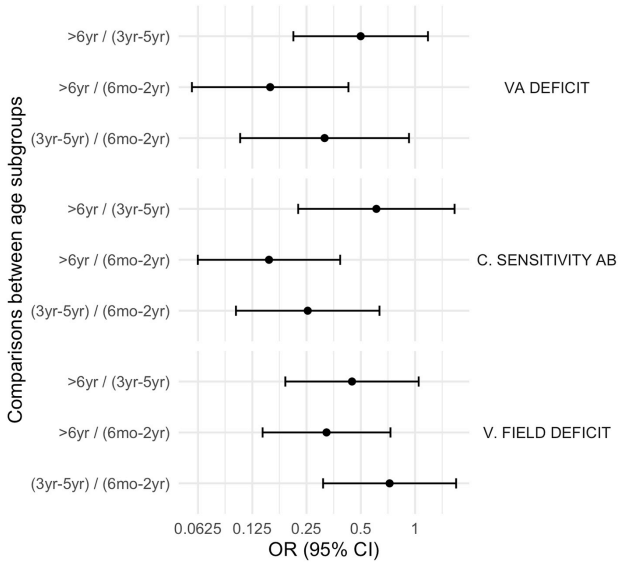


FIGURE 6 | Comparison between subgroups, OR (CI 95%): basic visual function disorders. VA deficit, visual acuity deficit; C. Sensitivity Ab, Contrast Sensitivity abnormalities; V. field deficit, visual field deficit.

coordinate plot documented two possible average profiles. In the first, the 10 visual items were predominantly impaired, while the second was characterized by the absence of visual problems. We added age subgroups as a supplementary variable in order to address the interpretation of those profiles: the younger children (6 months – 2 years) fitted perfectly in the first profile, while the older ones (> 6 years) were consistent with the second profile. Only the presence/absence of refractive errors remained distant from the two profiles, probably because they were extremely frequent in all three age-subgroups and they seem basically unrelated to visual dysfunctions. The squared correlation of each variable to the first two MCA dimensions are provided in **Figure 8**.

Cognitive-Visual Evaluation in Subgroup 3 (>6 Years)

Thirty-four out of 68 children (50%) met the criteria for the cognitive-visual evaluation. The mean age was 112.9 months (SD 28, range 72–192 months), 17 (50%) were females and 17 males (50%). The mean gestational age was 35.5 weeks (SD 5.2, range 24–42 weeks), 14 (41%) were born preterm and 20 (59%) at term; the mean birth weight was 2,408 g (SD 921.1, range 860–3,810 g). 20 children (59%) presented a spastic unilateral CP and 14 (41%) a spastic bilateral CP; the level of gross motor impairment at GMFCS evaluation was mild in 27 cases (79%), moderate in 2 (6%) and severe in 5 subjects (15%), while the level of manual ability impairment at MACS was mild in 29 children (85%) and moderate in 5 (15%). The mean full IQ was 82.1 standard scores -s.s.- (SD 17.2, range 50–114 s.s.), the mean Verbal IQ was 93.2 s.s. (SD 14.9, range 70–139 s.s.) and the mean Performance IQ was 77.5 s.s. (SD 22, range 43–127 s.s.). Brain MRIs lesion were classified as predominant white matter injury in 22 subjects (65%), predominant gray matter injury in 10 (29%) and miscellaneous in 2 cases (6%).

30 children aged < 11 years underwent all the 8 tasks for cognitive visual assessment while 4 aged > 11 years completed

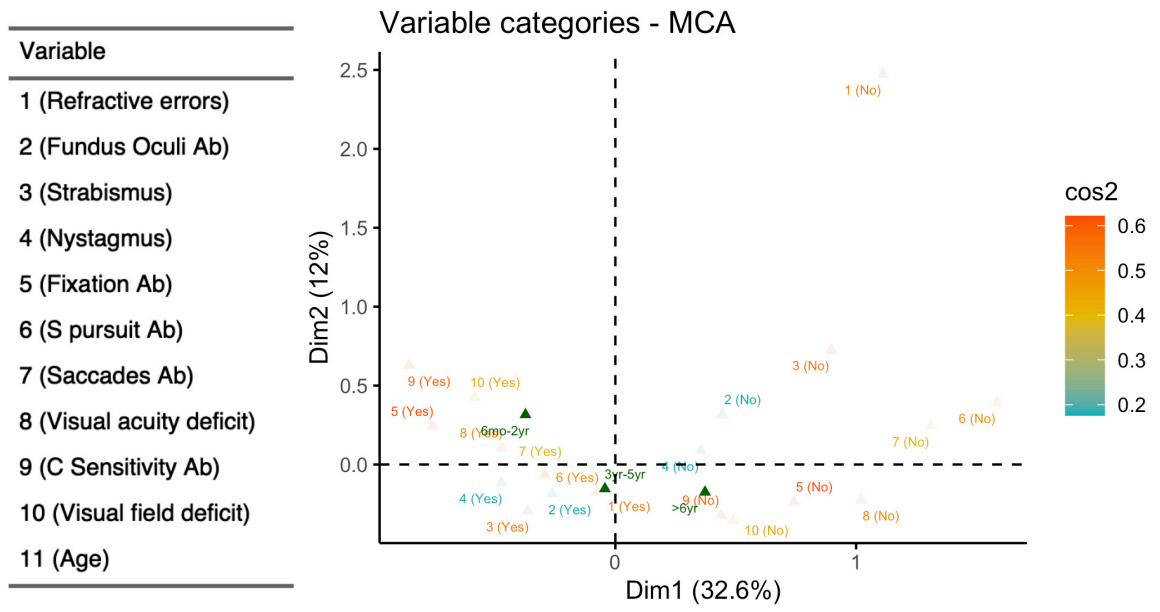
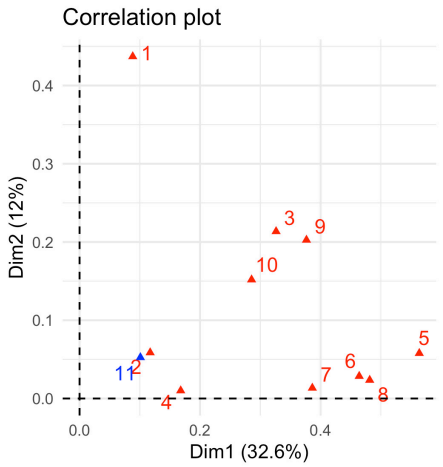


FIGURE 7 | Multiple correspondence analyses (dichotomized items). Coordinate plot: MCA of 10 visual items after dichotomization; supplementary variables: age subgroup, defined as 6 months-2 years, 3–5 years, > 6 years. Explained variability: 1st dimension (horizontal axis) 32.6%; 2nd dimension (vertical axis) 11.9%. Yes (presence of visual deficit); No (absence of visual deficit); Ab (abnormalities).



Squared correlations between variables and dimensions

Variable	Dim 1	Dim 2
1 (Refractive errors)	0.09	0.44
2 (Fundus Oculi Ab)	0.12	0.06
3 (Strabismus)	0.33	0.21
4 (Nystagmus)	0.17	0.01
5 (Fixation Ab)	0.56	0.06
6 (S pursuit Ab)	0.46	0.03
7 (Saccades Ab)	0.39	0.01
8 (Visual acuity deficit)	0.48	0.02
9 (C Sensitivity Ab)	0.38	0.20
10 (Visual field deficit)	0.29	0.15
11 (Age)	0.10	0.05

FIGURE 8 | Squared Correlations (r^2) between each variable and the first two main Dimensions 1 and 2. The r^2-values related to the two dimensions determined by the MCA for 10 variables, identified from the neurovisual evaluation carried out in 180 children belonging to the three different age subgroups. Dimension 1 accounts for 32.6% of the variance in this analysis, while Dimension 2 accounts for 12%.

the VMI, BC and SCT. An impairment of cognitive visual skills was detected in 21 out 34 subjects (18 aged < 11 years; 62%). See **Table 3** for details on impaired cognitive visual performances of the 21 children. BC, VMI, UP and UL seemed to be the most frequently impaired tasks as detailed in **Figure 9**. The statistical analysis performed to evaluate the impact of IQ on cognitive visual disorders, revealed positive associations between FIQ and CVDs (OR 0.92; CI 95%: 0.85, 0.97; $p = 0.008$), PIQ and CVDs

TABLE 3 | Details on cognitive visual tasks of children with a CVD (belonging to subgroup 3).

Sbj	Age (yr, mo)	FIQ/VIQ/PIQ	VA	Cognitive-visual disorders (z-scores)							
				Visual motor tasks		Visual perceptual tasks					
				BC	VMI	SCT	UP	UL	IF	MC	MF
1	6	114/139/77	0.7	–2	–3.2	–1.3	–1.4	–4.9	0	–9.6	–6.6
2	6,7	78/114/50	0.5	–1.6	–3.1	–1.3	–1.7	–2.5	–0.7	–3.6	–0.6
3	7,2	73/97/45	0.4	–3	–4	–1.9	–3.2	–2.1	–1.4	–1.6	–1.4
4	7,3	87/90/87	0.5	–2.8	–2	0.4	–0.5	–0.8	0.8	0.3	0.8
5	7,4	70/88/43	0.5	–8.1	–2.7	–3.6	–2.2	–2	–1	0	0
6	7,5	76/81/76	0.9	–2.3	–1.5	0.6	–0.5	0.6	–0.6	0	0
7	7,6	53/88/63	0.3	–6.4	–6.4	–2.7	–4.6	–7.3	–5.2	0	0.7
8	8,1	85/92/82	1	–2	–1.6	0.6	–0.2	1.1	0.5	0	0.7
9	8,1	55/70/48	0.8	–2.6	–2.2	–0.4	–1.4	–3.9	0.4	0	–2.8
10	8,5	87/99/77	0.9	–3	–2	–2.3	–2.5	–0.8	–1.8	0.3	0.7
11	9	99/92/107	0.6	–0.3	0.5	0.4	–1.6	–2.5	0	0	0.7
12	9	50/70/48	0.9	–2.6	–2.7	–1	–2.1	–2	–1.2	0	–2.1
13	9	77/92/66	0.9	–2	–1.9	–1.6	–2.7	–2	–3.5	0	0.4
14	9,5	75/102/52	1	–3	–3.7	0.4	–4.8	–6.2	–2.8	–1.8	–2.8
15	10	57/70/53	1	–2	–1.8	–2.3	–2.5	–5.4	–5.5	0	0
16	10,8	67/70/77	0.6	–1.3	–1.1	–0.2	–2.5	0	–2.4	0	0
17	11	70/70/83	1	–2	–1.7	0.6	–0.9	0	0.2	0	0
18	11	70/100/56	1	–2.7	–2.4	–0.8	–4.5	–3	–10.3	0	0
19	11,8	55/77/45	1	–3.3	–2.1	–2.3	/	/	/	/	/
20	13,6	97/110/93	1	–1.3	–0.8	–2.8	/	/	/	/	/
21	16	83/93/76	1	–3	–2.7	–2.1	/	/	/	/	/

Sbj, subject; yr, years; mo, months; FIQ, full intelligence quotient; VIQ, verbal intelligence quotient; PIQ, performance intelligence quotient; VA, visual acuity in tenths; BC, Block Construction task; VMI, Developmental Test of Visual-Motor Integration; STC, Street Completion Test; UP, colored photographs of objects viewed from unusual perspectives; UL, photographs illuminated in unusual ways; IF, Imagery Figures; MC, Matching Tasks for the ability to recognize semantic attributes of stimuli; MF, Matching Tasks for the ability to recognize functional attributes of stimuli.

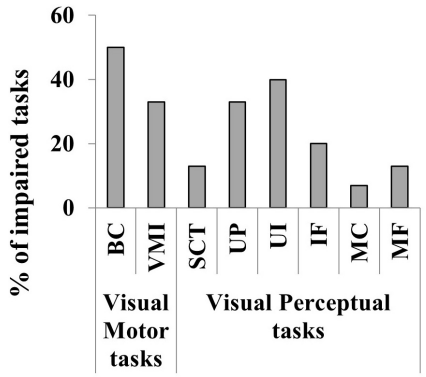


FIGURE 9 | Percentage of the impaired cognitive visual tasks in the 34 children evaluated. Visual motor skills (BC, Block Construction task; VMI, Developmental Test of Visual-Motor Integration) and Visual perceptual skills (STC, Street Completion Test; UP, colored photographs of objects viewed from unusual perspectives; UL, photographs illuminated in unusual ways; IF, Imagery Figures; MC, Matching Tasks for the ability to recognize semantic attributes of stimuli; MF, Matching Tasks for the ability to recognize functional attributes of stimuli).

(OR 0.91; CI 95%: 0.83, 0.96; $p = 0.006$); no associations emerged between VIQ and CVDs (OR 0.97; CI 95%: 0.92, 1.02; $p = 0.2$).

DISCUSSION

Cerebral Visual Impairment in children with CP is researched in current literature and considered a core symptom of CP on account of its high prevalence (Dufresne et al., 2014) and its impact on daily life (Pavlova and Krägeloh-Mann, 2013). Hence, in the present study we aimed at exploring the characteristics of CVI in a large sample of children affected by CP according to three different age groups (infants 6 months–2 years; pre-school age 3–5 years; school age > 6 years). Our hypothesis is that the clinical spectrum of CVI may vary according to age; particularly the older children may show a milder visual impairment characterized by a lower number of visual signs compared to the younger ones, due to visual system maturation and adaptive neuroplasticity that has implications in the organization of motor, somatosensory and visual functions (Fiori et al., 2019).

We found signs of CVI in a high percentage of children (180 out 193, 93%); this data confirms our previous study on children affected by CP (Fazzi et al., 2012) in which, for example, a reduced visual acuity was detected in 87% of the subjects and altered saccadic movements in 89%. We suggest that the higher percentage detected in the present study (compared to the one reported in literature, which ranges from 16 to 70%) is related to the evaluation method that involves a multidisciplinary team (comprising a child neuropsychiatrist, ophthalmologist, orthoptist, and child therapist specializing in visual function and neurological development). Furthermore, the video-recordings of the assessment allow the professionals to observe and judge the child performance at a later time (especially the qualitative functions as fixation, smooth pursuit and saccadic movements).

This study shows that refractive errors, especially astigmatism associated with hypermetropia or less frequently with myopia, are extremely common in children affected by CP. Our data were in line with literature (Jacobson and Dutton, 2000; Kozeis et al., 2007, 2015; Marasini et al., 2011; Fazzi et al., 2012; Park et al., 2016). It has been hypothesized that the preterm birth and postnatal distress or diseases can interfere with the normal emmetropisation process (Hsieh et al., 2012), especially in children with brain lesions (Sobrado et al., 1999; Saunders et al., 2010). Moreover, we observed that the high frequency of refractive errors persisted among the three age-subgroups although hypermetropia tended to decrease in contrast to the progression of myopia. These findings seem to be similar to those observed in healthy subjects. During childhood a lower percentage of hypermetropia and a higher percentage of myopia is observed due to intrinsic and extrinsic factors such as the fast progression and axial length elongation of eye as well as environment, particularly extensive near work (schooling, study, reading) that have been known to cause abnormal eye growth (Kaiti et al., 2021). The high prevalence of refractive errors in CP highlights the importance of screening for these easily treatable disorders since the first years of life. Indeed, uncorrected refractive errors can limit activities of daily living, impair the development of cognitive functions (Aghaji et al., 2013) and may increase the risk of reading difficulties (Kozeis et al., 2015).

Fundus oculi abnormalities were detected in more than half of children in each subgroup and no significant differences among the three groups were found. These abnormalities consist of optic disc pallor, isolated optic disc cupping and optic nerve hypoplasia and may be related to axonal loss due to brain damage (retrograde transynaptic degeneration) as reported by Jacobson et al. (1997) and in previous studies by our group (Ruberto et al., 2006; Fazzi et al., 2012).

We observed strabismus in almost three-quarters of children in each subgroup. Strabismus is common in children affected by CP (Fazzi et al., 2012) due to defects of afferent pathways caused by axonal interruption in the optic radiation (Jacobson and Dutton, 2000), abnormality of vergence neurons (Mays et al., 1986) or of the pathways involved in eye movements (Tychsen and Lisberger, 1986), maldevelopment/dysfunction of visual cortex (Tychsen et al., 1996). Esotropia was the most common type of strabismus in group 1 and 2 while exotropia in group 3. There are contrasting data on which type of ocular misalignment (esotropia vs. exotropia) is the most common in CP children (Collins, 2014; Park et al., 2016; Jeon et al., 2019; Duke et al., 2020). Several factors may be related to the expression of esotropia or exotropia, as the type and the severity of CP (Collins, 2014; Jeon et al., 2019), brain injury (Brodsky, 2016) or ethnicity (Duke et al., 2020). We hypothesized that another factor may be age, since data on healthy individuals report that esotropia occurs more frequently in infants and children at

preschool age (Matsuo and Matsuo, 2005; Khorrami-Nejad et al., 2018).

Nystagmus, mostly represented by continuous jerk nystagmus or transient, and extrinsic ocular motility disorders, mostly characterized by abduction deficit, was detected in about half of the sample and the presence seemed to be stable with age. Different prevalences of nystagmus have been reported in literature, ranging from 1 to 50% in children affected by CP (Marasini et al., 2011; Fazzi et al., 2012; Dufresne et al., 2014; Tinelli et al., 2020). We suspected that our data were in the higher range probably because we considered all types of nystagmus (continuous and transient forms). Our data agreed with literature for the prevalence of extrinsic ocular motility disorders (Fazzi et al., 2012).

The most frequently oculomotor function anomalies detected were discontinuous smooth pursuit and impaired saccadic movements (mainly dysmetric with increased latency). Literature reports that the prevalence rate of oculomotor disorders in CP varies from 22 to 85% (for smooth pursuit) and from 18 to 89% (for saccades) (Fazzi et al., 2012; Duke et al., 2020). The presence of altered smooth pursuit and saccadic movements prevents children affected by CP from acquiring environmental scanning strategies and exploiting their visual function (Salati et al., 2002) and it can contribute to learning difficulties such as impaired reading (Jacobson et al., 1996). Comparing the subgroups, we observed a progressive improvement of fixation (from subgroup 1 to subgroup 2 and 3), smooth pursuit (from subgroup 1 to subgroup 3 and from subgroup 2 to subgroup 3) and saccadic movements (from subgroup 2 to subgroup 3) according to age. It is widely known that oculomotor functions progressively develop with age in healthy subjects (Helo et al., 2014). If the ability to fixate a target is already acquired in the first months of life (Chandna, 1991), the accuracy of smooth pursuit improves (Ross et al., 1993) and saccadic movements stabilize (Fukushima et al., 2000; Luna and Sweeney, 2004; Irving et al., 2006; Alahyane et al., 2016) until adolescence (Aring et al., 2007; Luna et al., 2008). However, data on the maturation processes of oculomotor functions in subjects with brain lesions are poor, but they could occur even in the presence of cerebral nervous system damage. Ego et al. (2015) showed that children with CP aged from 5- to 16-year-old present an improvement of oculomotor functions with age comparable to that of healthy subjects. A possible explanation may be that the participation in daily life activities spontaneously ameliorate oculomotor functions during childhood. In the present study we revealed that fixation improved from the preschool age while smooth pursuit and saccades needed more time to ameliorate; in fact, we noted a significant improvement during school age. This could be related to the fact that the ability to fixate is necessary to realize smooth pursuit or saccades, in fact eye movements depend not only on target-related signals from the peripheral visual field but also on the ability to fixate a target at the fovea (Krauzlis et al., 2017). Moreover, fixation is controlled by neuronal mechanisms that include many of the same brain regions involved in the generation of voluntary eye movements (superior colliculi and medio-posterior cerebellum). Early and accurate evaluation of oculomotor functions is therefore an important tool used to monitor the outcomes of dedicated training programs aimed at improving fixation time, pursuit movements and saccadic efficiency.

Our results also confirm the high frequency of basic visual function disorders in children affected by CP (Fazzi et al., 2012; Tinelli et al., 2020). Reduced visual acuity was detected in three quarters of the sample, limitation in visual field in almost half and altered contrast sensitivity in one third. Comparing the three subgroups, we found a progressive improvement of visual acuity and of contrast sensitivity (both from subgroup 1 to subgroup 2 and from subgroup 1 to subgroup 3) and of visual field (from subgroup 1 to subgroup 3) according to age. Literature on physiological maturation occurring in healthy new-borns suggests that perceptual visual abilities improve with age, especially during the first years of life due to visual system maturation characterized by the development of foveal cones and refinement of retinal and cortical architecture and to environmental factors (Lewis and Maurer, 2005; Sgandurra et al., 2017; Fazzi et al., 2021). Although studies on maturation of perceptual functions in subjects with brain injury are limited, they document an improvement of these skills. In a recent study of our group (Fazzi et al., 2021) a better visual acuity and contrast sensitivity has been documented not only in infants who underwent an early visual treatment but also in the control group. We hypothesized that the developing brain would be able to "amplify" visual function through neuroplastic changes involving local and global functional connectivity networks by activating, modulating and strengthening residual visual signals (Sabel et al., 2018; Fazzi et al., 2021). As regard visual field, some authors have observed a recovery of visual field limitation in children with early brain lesions at school age, probably attributable to the maturation of the ability to shift attention rather than an enlargement of the visual field (Mercuri et al., 2003; Guzzetta et al., 2010). MCA analysis confirmed our results, underlying the differences in the expression of CVI spectrum according to age: the younger children presented a wider association of signs of visual function involvement, while the older ones had a milder CVI phenotype consisting of limited number of visual dysfunctions. Unfortunately, the cognitive visual profile could not be included in the MCA because assessed only in children over 6 years of age.

More than half of children assessed for cognitive visual functioning belonging to subgroup 3 presented signs of CVDs, with visual motor and visual perception skills often simultaneously impaired. Specifically, visual motor abilities (BC and VMI) and perceptual categorization (UP and UL) seemed to be the most affected. These difficulties seem to be related to a damage to the superior longitudinal fasciculus, connecting the occipital cortex with the parietal-frontal cortices, as documented in our previous work (Galli et al., 2018). There is no accepted prevalence of these disorders among children with CP, with the rate found to vary between 5 and 85% (Stiers et al., 2002; Fazzi et al., 2004; Atkinson and Braddick, 2007; Pagliano et al.,

2007; Ortibus et al., 2009; Ego et al., 2015) depending on the assessment tools applied, the diagnostic criteria used, and the type of CP evaluated. A positive association was found between FIQ/PIQ and CVDs, a pattern well documented in the literature (Ito et al., 1997; Fedrizzi et al., 1996; Stiers et al., 1999, 2002). However, literature data report that CVDs seem to be independent from impairment in non-verbal intelligence, reflecting the coexistence of two separate deficits (the so called, "dual deficit hypothesis") (Stiers et al., 1999). To confirm the data and/or verify alternative hypothesis, it would be useful to expand the case series and consider other possible influencing factors, as the characteristics of brain lesions (type, timing, site), the clinical pictures (such as bilateral or unilateral CP), and the neurovisual profiles. Cognitive visual function involvement can be detected at school age, even when visual functions, such as visual acuity, are normal or only mildly impaired. In children over 6 years of age, these difficulties may cause problems in academic skills as mathematics and reading (Ben Itzhak et al., 2020). In this regard, literature data report that visual motor difficulties could be related to calculation problem solving (Arp et al., 2006) and operations as borrowing or carrying (Venneri et al., 2003) and that both the visual motor and perceptual abilities were involved in different level of visual word processing (Rosazza et al., 2009; Woolnough et al., 2021). Therefore, clinicians need to be aware of this possibility in order to early recognize a CVD and suggest environmental adaptation mitigating their impact on academic skills.

The main strength of the present study is that we did not use questionnaires or registers to collect data, instead we evaluated the children with CP directly using a complete and detailed video-recorded visual function examination, based on a multidisciplinary approach that involves the participation of several health professionals (child neuropsychiatrist, ophthalmologist, orthoptist, psychologist and child therapists specializing in visual function and neurological development).

Regarding potential limitations associated with the study, we need to consider that it was not conducted using a longitudinal design but instead selecting each subject that was consecutively referred to our Center. Hence, the risk of selection bias has to be considered. For this reason, we are carrying out a longitudinal study on 50 children affected by CP belonging to the sample presented in this work: preliminary data seem to confirm our findings (oculomotor functions seem to improve with age in more than half of the sample while basic visual functions in about one third of cases). Moreover, the cross-sectional design without normal controls should also be mentioned as limitation. Maturation effects may partly be caused by group differences since they were not matched; impairment rates (especially for the oculomotor functions) should be judged carefully in the absence of normative comparison. As regards the cognitive visual evaluation, we would mention two limitation. First, we could not investigate the presence of a cognitive visual dysfunction in all the children belonging to subgroup 3 due to the nature of the tests used for the assessment; it is highly likely that the children excluded from the cognitive visual assessment will have had significant cognitive visual deficits (with or without deficits in primary visual functions). Second, we cannot analyze the effect of age on CVDs since we were able to conduct this assessment only in those children over 6 years of age; further studies on characteristic of CVDs from pre-school age to adolescence should be performed considering also a larger sample size. Due to limited number of children assessed for the cognitive visual performances, the interpretation of our results needs attention and we cannot generalize them to all the sample.

On the basis of these observations, we can conclude that younger children with CP showed more signs of CVI compared to the older ones. In this direction, we suggest an early neurovisual evaluation for all these measures because it allows to define the type of habilitative intervention, directing resources toward the weak functions that can still improve. Acting as early as possible is fundamental given that neuroplasticity is maximal within the first 2 years of age (Yin et al., 2019). In our recent work we found that, although the presence of a spontaneous recovery, an early intervention could amplify the visual functions and the developmental outcomes (Fazzi et al., 2021), especially if the exposure to the visual training happens within the first years of life (for details on visual training please see Fazzi et al. (2021)). Moreover, an early assessment may prevent the mild spectrum of CVI from being unrecognized until it impacts on child's learning, mobility, development, independence and quality of life, especially at school age (Bauer and Merabet, 2019).

We hypothesized that the improvement of visual functions could be related to the physiological maturation of the visual system and mechanisms of neuroplasticity that have induced the re-organization of visual functions after the damage (Ego et al., 2015). However, in contrast to the case of ocular blindness, literature data on morphological, structural and functional connectivity changes in subjects with CVI have been scant because highly heterogeneity across individuals in terms of location, timing, extent and cause of damage (Bennett et al., 2020). There is the need for further functional neuroimaging studies to investigate neural correlates associate with CVI and to the potential neuroplastic compensatory processes (Bennett et al., 2020).

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Comitato Etico di Brescia, ASST Spedali Civili di Brescia, Italy. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

JG, EL, and AM drafted the manuscript. AM, AR, AF, and SM collected the data. SC performed the statistical analysis. JG, EF, and FS designed the study. All authors contributed to the article, reviewed the manuscript, and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnhum.2022.750464/full#supplementary-material

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Object Recognition and Dorsal Stream Vulnerabilities in Children With Early Brain Damage

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Aim: Visual functions of the dorsal stream are considered vulnerable in children with early brain damage. Considering the recognition of objects in suboptimal representations a dorsal stream dysfunction, we examined whether children with early brain damage and impaired object recognition had either general or selective dorsal stream dysfunctions.

Method: In a group of children with early brain damage (n = 48) we evaluated the dorsal stream functioning. To determine whether these patients had an increased risk of a dorsal stream dysfunction we compared the percentage of patients with impaired object recognition, assessed with the L94, with the estimated base rate. Then we evaluated the performance levels on motion perception, visual attention and visuomotor tasks in patients with (n = 18) and without (n = 11) object recognition abnormalities. A general dorsal stream dysfunction was considered present if a patient showed at least one abnormally low score in two out of three additional dorsal stream functions.

Results: Six of the eighteen (33.3%) patients with object recognition problems scored abnormally low on at least two additional dorsal stream functions. This was significantly higher than the base rate (p = 0.01). The difference of 24.1% between the patients with and without object recognition problems was not significant. Of the patients with object recognition problems 72.2% had at least 1 dorsal weakness, whereas this was only the case in 27.3% of patients without object recognition problems. Compared to patients with normal object recognition, patients with object recognition problems scored significantly more abnormally low on motion perception and visual attention (ps = 0.03) but did not differ on visuomotor skills.

Conclusion: Children with object recognition problems seem at risk for other dorsal stream dysfunctions, but dysfunctions might be rather specific than general. Multiple functions/aspects should be evaluated in neuropsychological assessment of children at risk.

Keywords: L94, visual search, visual attention, motion perception, object recognition, dorsal stream dysfunction, visuomotor skills, early brain damage

Abbreviations: CA, chronological age; DA, development age, median age-equivalent based on PIQ outcomes; PIQ, Performance Intelligence Quotient; RDK, Random dot kinematogram.

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INTRODUCTION

Studies on visual perception in children with developmental disorders (Atkinson et al., 2003) and early brain damage (Gunn et al., 2002; Fazzi et al., 2004) suggest that the dorsal stream of the cerebral visual system is more vulnerable than the ventral stream. The dorsal stream is associated with motion perception (Braddick et al., 2001; Stiers et al., 2006), visuomotor integration (James et al., 2003), and visual attention (Pollmann et al., 2003). Different brain areas are thought to be crucial for these functions: V5/MT + for global motion, motion speed and motion-defined form perception (Ho et al., 2005; Reiss et al., 2005; Wang et al., 2007); the superior temporal sulcus (STS) area for biological motion perception (Bonda et al., 1996) and target detection (Pollmann et al., 2000); the temporoparietal junction (TPJ) for attention shift (Corbetta and Shulman, 2002), the intraparietal sulcus (IPS) for visuospatial attention (Corbetta and Shulman, 2002) and response preparation (Pollmann et al., 2000); the inferior parietal lobule (IPL) for visuomotor planning (Glover, 2004), and the superior parietal lobule (SPL) for attentional bias (Pollmann et al., 2003), action, visuomotor control (Glover, 2004). The ventral stream, which projects into the inferotemporal cortex, is associated with form perception, object recognition (Atkinson et al., 2003; James et al., 2003) and face recognition (Atkinson et al., 2003).

Although object recognition is primarily considered a ventral stream function, existing evidence indicates that it is not a ventral stream function alone: IPS (Vuilleumier et al., 2002; Konen and Kastner, 2008), IPL (Vuilleumier et al., 2002; Eger et al., 2007) and SPL (Eger et al., 2007) play a role in object recognition in suboptimal representations. Damage in the parietal lobe is associated with impaired recognition in the following suboptimal representations: incomplete pictures (Renzi and Spinnler, 1966; Warrington and James, 1967), overlapping drawings (Warrington and Taylor, 1973; Fazzi et al., 2004), objects presented from an unconventional view (Warrington and Taylor, 1973; Vaina, 1994), and drawings degraded by noise (Warrington and Taylor, 1973).

Studies on dorsal stream functions in children with early brain damage or developmental disorders indicate that different aspects of object recognition in suboptimal representations (Stiers et al., 2001; Ortibus et al., 2009) and motion perception can be selectively impaired (Gunn et al., 2002; Ho et al., 2005; MacKay et al., 2005; Mendes et al., 2005; Reiss et al., 2005; Jakobson et al., 2006; Wang et al., 2007). In most studies single functions or aspects were studied, therefore it is unknown how often multiple dorsal stream functions are affected. One study in prematurely born children with complications such as periventricular white matter disease and retinopathy of prematurity, showed that 20–55% of the patients had clinically significant impairments in different dorsal stream functions (Jakobson et al., 2006). However, it was not reported whether individual patients were impaired on multiple tasks, and object recognition in suboptimal representations was not addressed in this study.

The aim of the present study was to determine whether other dorsal stream dysfunctions are commonly present in children with an identified dorsal stream dysfunction. In this study, the L94 was used to detect children with a dorsal stream dysfunction in a group of children with (indications of) early brain damage. The L94 is a valid diagnostic test battery for object recognition in suboptimal representations. Abnormally low scores on the L94 are associated with parietal lobe damage (Ortibus et al., 2009). We hypothesized that patients with object recognition abnormalities show significantly more often abnormally low scores on other dorsal stream aspects, i.e., motion perception, visual attention, and visuomotor skills, than children with normal object recognition. We also examined how often a general dorsal stream dysfunction was present, i.e., how often at least 2 out of three additional dorsal stream functions were weak.

MATERIALS AND METHODS

Participants

The patient group consisted of 48 children at risk for object recognition problems, because of brain damage, indications of brain damage, and/or reports of suspicion of visual perceptual impairments mentioned in their medical records. Patients were recruited through rehabilitation centers in the Rotterdam area (Rijndam Rehabilitation Center and Royal Dutch Visio, Center of Expertise for blind and partially sighted people, n = 19) and through the Laboratory of Neuropsychology at the University Hospital in Leuven, Belgium (n = 29). Their chronological age ranged from 4 y1m to 14y7m (M = 7y3m, SD = 2y4m).

Studies were approved by the Ethics Committees of the Erasmus Medical Center MEC-2006-056) and the Catholic University of Leuven. Informed consent was obtained for all participants through their parents or guardians.

Procedures

Medical History and Orthoptic Assessment

Data on etiology of the brain damage and imaging results (CT and/or MRI), gestational age and recent orthoptic assessments were gathered from available medical records. The participant was invited for an orthoptic assessment, if no recent orthoptic assessment was done. Eye movements, visual acuity with up-to-date refractive corrections (lenses or glasses), visual field, and binocular vision were assessed by trained professionals (orthoptists) using (developmental) age-appropriate tests. Visual field was mainly assessed with the confrontation visual field exam (Donder's test).

Participants wore their prescribed glasses or lenses during the developmental age and dorsal stream assessment.

Developmental Age Estimation

To control for cognitive impairments in the patient group, we estimated the participant's developmental age (DA). The developmental age was defined as the median age-equivalent of multiple subtests measuring performance IQ (PIQ) (Stiers et al., 2001): the patient's raw scores on non-verbal subtest were converted to age-equivalents, then the median was calculated, resulting in the developmental age at the time of IQ-assessment (DA_{IQ}). We corrected for a time-lag between IQ assessment and dorsal stream function assessment using the following

formula: $DA_{dorsal} = (DA_{IQ}/CA_{IQ})^{*}CA_{dorsal}$, where CA stands for chronological age.

To minimize the burden on the patients we decided to use recent intelligence results when available. If not available, we only studied non-verbal intelligence, because only non-verbal cognitive ability, and not verbal cognitive skill, is predictive of perceptual performance (Ito et al., 1996, 1997; Stiers et al., 1999). Although the use of a single intelligence test is preferable, the cognitive consequences of the brain damage and the broad age range in the patient group made this impossible. Because of the strong correlations (0.79–0.93) between the Performance IQs of different intelligence tests (SON-R IQ, WPSSI-R, WISC-R, WISC-III) (Moore et al., 1998; Oosterbaan et al., 2006), we considered these tests interchangeable for the DA_{IQ} estimation.

Dorsal Stream Function Assessment

The following dorsal stream functions were studied in arbitrary order: object recognition in suboptimal representations; motion perception; visual attention; visuomotor skills. Published or preliminary reference data was used to classify performance levels. We used DA, instead of CA, as entry to the reference tables. In case PIQ $\geq$ 100, DA exceeded CA, we used the patient's CA as entry to the reference tables.

If DA was out of range of the norm tables, we used the nearest age group. An object recognition score below the 5th percentile were defined as an abnormal performance. For other function tasks, a score below the 10th percentile was defined as abnormally low.

Testing was done by trained senior psychology students and neuropsychologists. All computerized tasks were run on a laptop connected to a 15-inch CRT monitor. Participants with refractive errors wore their prescribed glasses and were placed in front of the screen at approximately 40 cm.

L94: Object Recognition

To assess object recognition in suboptimal representations we used five computerized subtasks of the L94 (Stiers et al., 1998, 2001) that require recognition of line drawings of everyday objects: Visual matching (VISM); drawings occluded by noise (NOISE); overlapping line drawings (OVERL); unconventional object views (VIEW); De Vos (DE VOS).

Visual Matching

This task consists of 1 example and 10 items: line drawings of everyday objects in prototypical view. Each item is presented for 1 s, followed by a screen with a semantically identical object and three distracters. The participant must point out the target object. Items scores are 1 (correct) or 0 (incorrect).

Drawings Occluded by Noise

This task consists of 1 example and 6 items. Each object is presented for 2 s and is partly occluded by noise. Participants must name or describe the presented object. Noise level decreases until the object is recognized correctly. There are 7 noise levels (60, 50, 42, 36, 29, 24, and 0%). 0% noise level is considered the control condition. Item score is (7-j)/(7-1), where j is the number of noise levels presented before the participant recognized the object.

Overlapping Line Drawings

This task consists of 1 example and 6 items. Items are presented for 6 s and consist of two, three of four overlapping objects, followed by the target objects and two distracters, all presented separately. Participants must point out the target objects. The level of overlap decreases until all target objects are indicated correctly. There are four levels of overlap: full overlap, partially overlap, touching, and separate presentation. The last condition is considered the control condition. Item score is (4-j)/(4-1), where j is the number of overlap levels presented before a correct response is given.

Unconventional Object Views

This task consists of 20 items. Items are presented for 3 s. Half of the items are presented in three conditions: Unconventional view, less unconventional view, and conventional view. For the other half of the pictures, the level of unconventional view decreases to the conventional view in four conditions. The level of conventional view decreases until the participants named or described the object correctly. The conventional view is considered the control condition. Items scores is (k—j)/(k—1), where k is the total number of conditions and j is the number of conditions presented before the participant recognized the object.

De Vos

This task consists of 43 items. There is no time constraint. Items are presented in a target condition and a control condition. In the target condition objects are less easy to recognize because they are embedded in context, they are partial drawn, only contours are presented, a typical part of the object is omitted, or they are presented in an unconventional view. Participants must name or describe the target object. Item score is 1 (recognized) or 0 (not recognized in target condition).

Performance was expressed in a subtask score. The subtask score was the average item score, with exclusion of items not recognized in the control condition. Items with an incorrect response in the control condition were indicated as inconclusive and excluded, because an incorrect response could not only be the result of a recognition problem, but also of other problems (language etc.).

We excluded the items rifle, bench, and alarm clock from the analysis of VIEW, because Dutch controls tended to name these objects differently, for example by their general category and often did not change their answer with changing views. This was considered no problem, because inconclusive items, items that are not named correctly in the control condition of the task, are excluded in the scoring procedure of the L94.

To classify the scores we used the reference data published in a manual (Stiers et al., 2000).

Motion Perception

Motion perception was assessed with three different computerized motion perception tasks: global motion, motion-defined form, and motion speed. The preliminary cut-off values for the 10th percentile (Van der Zee et al., 2019), as presented in **Table 1**, are used to classify the participant's performance.

All stimuli consisted of white dots on a black background, with a resolution of 640 $\times$ 480 and refresh rate 25 frames/s. In

TABLE 1 | Tenth percentile scores for global motion, motion speed and motion defined-form task in different age groups.

	Global motion (GM)		Motion-defined form (MDF)		Motion speed (MS)	
	n	Coherence level	*n*	Proportion correct	*n*	Speed difference (deg/s)
4y3m–4y7m	31	0.78	31	0.45	25	23.80
4y9m–5y8m	39	0.69	43	0.63	34	20.00
5y10m–7y4m	45	0.46	43	0.74	31	12.49

the global motion task and the motion speed task psychophysical thresholds were estimated by calculating the mean of the values of the last 4 of 8 reversals, using a 2 up-1 down staircase procedure. In these tasks, a correct answer was followed by a beep. Before each task, example stimuli were used to familiarize participants with task elements and verify that they understood the task.

Global Motion

The global motion stimulus (**Figure 1**) consisted of two random dot kinematograms (RDK size 14.7 × 22.4 deg) containing 1,103 white dots (dot size 0.07 deg, limited lifetime 130 ms), presented next to one another with a distance between them (size 3.3 deg). A variable proportion of dots (starting level 100%, scaling factor 0.33) in each RDK oscillated coherently in horizontal direction (reversal time 330 ms, velocity 6.7 deg/s). Participants had to locate a horizontal strip (size 14.7 × 7.5 deg) in the middle of one of the RDKs, where the coherent dots oscillated in the opposite direction. Participants were instructed to help a lost person to find his way in the snow (presentation = 15 s, answer time 5 s). Because the proportion of coherent dots was constant throughout the RDKs, the strip could not be located by tracing the movement of single dots. The proportion of coherently moving dots, or the coherence level determined the difficulty of the task and was used to calculate the coherence threshold.

Motion-Defined Form

The motion-defined form stimuli (**Figure 2**) consisted of objects hidden in a RDK (size 20.6 × 16.0 deg, 5,000 dots, dot size 0.13 deg, lifetime 200 ms, velocity 3.4 deg/s). Each object could be displayed in three successive conditions with decreasing level of difficulty (presentation max. 15 s). In all conditions, the dots outside the contour moved coherently in oblique direction. In the first condition, the dots in the contour of the object moved coherently downwards. In the second condition, the dots in the contour were standing still, and in the third condition there were no dots in the contour. After an object was correctly identified the trial was aborted and the next trial, with a new object, was started. If the object was correctly named or described in the first, second or third condition a score of 1, 0.5, or 0 was noted. If the object was not correctly identified in the third condition the response was marked as inconclusive, and the item was not used in the computation of the visual motion perception score. Three subtasks, increasing in difficulty, with six objects were presented. Objects in task 1 were: circle, star, bear, banana, heart, and fish; task 2: Arrow, kangaroo, boat, guitar, ostrich, and bag; task 3: beetle, seat, airplane, seahorse, car, and shoe.

Motion Speed

The motion speed stimulus (**Figure 3**) consisted of two identical contours of a car (car length approx. 17 deg) filled with leftwards moving dots (dot density 11 dots/deg^2, dot size 0.07 deg, lifetime 120 ms). Participants were asked to indicate the location of the fastest car (presentation time 10 s). A decrease in the speed difference of the dots in the cars made the task more difficult (starting speed difference 17.0 deg/s, scaling factor 0.33, 0.25

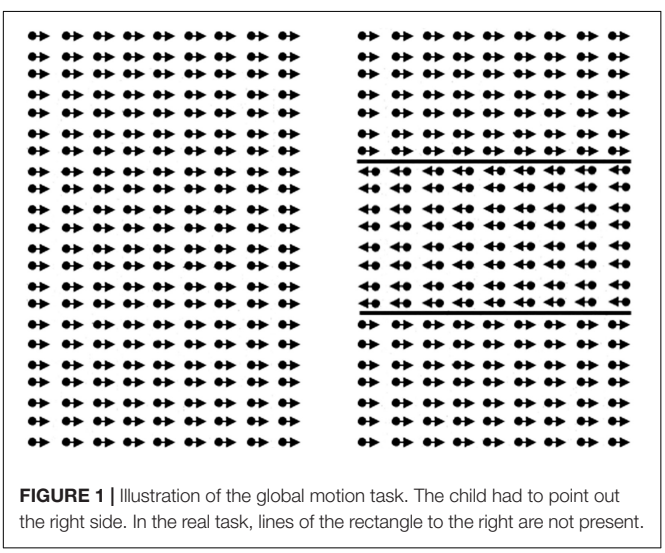

FIGURE 1 | Illustration of the global motion task. The child had to point out the right side. In the real task, lines of the rectangle to the right are not present.

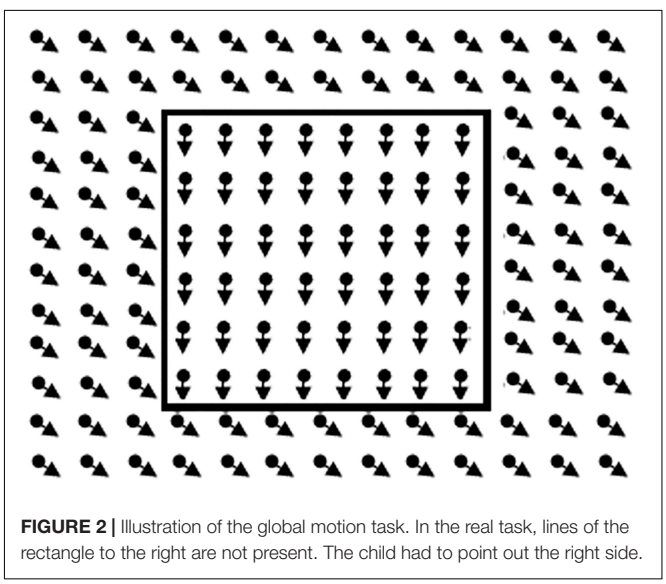

FIGURE 2 | Illustration of the global motion task. In the real task, lines of the rectangle to the right are not present. The child had to point out the right side.

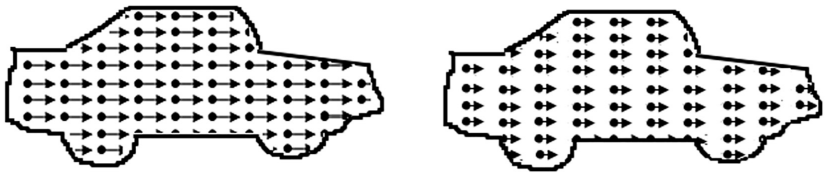

FIGURE 3 | Illustration of the motion speed task: dots in the left car move faster. In the real task, the contour of the car is not present.

from fifth reversal) and the critical speed difference was the score for this task.

Visual Attention

Visual attention was assessed by a computerized visual search task, developed at the department of Psychologic and Pedagogic Sciences of Leuven Catholic University. It consists of greyscale pictures (size 5 × 5 degrees at 40 cm distance) on a gray background (area size approximately 37 × 29 degrees, see example in **Figure 4**).

Before testing was started, all pictures were presented on the screen to familiarize the participants with the pictures. The participants were asked to name the individual pictures, after which the red-bordered target picture in the center of the screen was introduced. The participant was instructed to point out the picture identical to the central picture as fast and accurate as possible and to put his/her hands upon the table in front of the screen before each trial. The moment the participants touched a picture on the screen, the test administrator pressed the spacebar, and the trial was ended. To verify that the participants understood the task, three practice trials with a target stimulus and two distracters were presented.

Testing was started with a simple reaction-time task with five trials. In the reaction-time task only the central picture and the target picture were presented. Because the location of the target stimulus would pop-out to the participants, the reaction time was considered identical to the motor response time. The motor response time not only included the time needed by the participants to point out the target stimulus, but also the time needed by the administrator to press the spacebar.

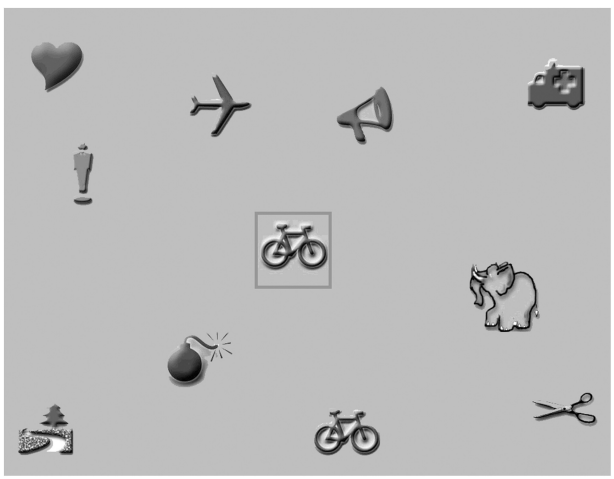

FIGURE 4 | Example of the visual search task with nine distracters and 1 target (bike).

In the next stage, three visual search tasks were presented with four, nine, and nineteen distracters. Each task consisted of 10 trials. If needed, the participant was encouraged to keep looking. To control for effects of fatigue and task experience, testing was ended with the above reaction time task.

All reaction times were saved, and the administrator noted all false alarms (mistakes: child pointed out a wrong picture). Reaction times for false alarms were excluded. Median reaction times were calculated for both reaction time tasks and for each visual search task. Because the presence of distracters in the search tasks made pop-out less likely, a serial search process (scanning individual pictures) was assumed to be needed to detect the targets. In a serial search process, the reaction time is the sum of the motor response time and the visual search time. Visual search time was our primary outcome measure, so median reaction times of the reaction time tasks were distracted from median reaction times of the search tasks.

We used the preliminary reference data of 60 typically developing children (25 boys, 35 girls) without any signs of neurological or visual impairment and with a normal visual acuity. They were recruited through primary schools in Rotterdam, The Netherlands. Their chronological age ranged from 4y3 m to 7y4m (M = 5y7m SD = 9 m). We divided the group in three age groups, equal to those for the motion perception tasks. Cut-off values for the 10th percentile can be found in **Table 2**.

Visuomotor Skills

To assess visuomotor skills, we administered the Beery-Buktenica Developmental Test of Visual-Motor Integration (Beery VMI) (Beery et al., 2004) and the subtest Mosaics of the SON-R 2 1/2–7 (Tellegen et al., 1998) as prescribed in the manuals.

Beery VMI

Each participant was asked to imitate and copy a maximum of 24 items of increasing complexity. The participant had one try per item. Tracing the pattern and erasing was not allowed. The scoring instructions in the manual were used to decide whether the copy was correct or incorrect. The test was discontinued after 3 consecutive failures (Beery et al., 2004).

Mosaics

In Mosaics the participants must copy a maximum of 15 mosaic patterns in a frame. The difficulty level was determined by

TABLE 2 | Tenth percentile scores for visual search outcomes in different age groups.

	n	5 Items Search time (s)	10 Items Search time (s)	20 Items Search time (s)	Reaction task Respon se time (s)	Overall Total number of errors
4y3m–4y7m	7	1.38	2.75	5.91	2.54	2
4y9m–5y8m	23	1.23	2.20	5.47	2.03	1
5y10m–7y4m	26	1.09	2.66	4.16	1.70	1

whether the examiner demonstrates the item, the number and color (red, yellow, and/or red/yellow) of squares the participant must use and the scale of the printed pattern. After each item feedback was given whether the solution was correct or incorrect. In case an incorrect solution was given, the participant was engaged in correcting the solution, without explaining why the solution was incorrect. The subtest was discontinued after a total of three mistakes or two consecutive mistakes at the advanced level (Tellegen et al., 1998).

Analysis

Participants were included in the analysis if at least three out of five L94 tasks had been completed.

An assessment with 5 tasks, instead of 1, increases the chance of finding at least one abnormally low score. To be confident that our patient group is at risk for object recognition problems, the percentage abnormally low scores should exceed the base rate. The base rate is the expected percentage of the healthy population that would show 1 or more abnormally low test-scores ($<5^{th}$ percentile, $z = -1.645$) on the battery of the five object recognition tasks. To estimate the base rate we used the correlations between the object recognition tasks in the reference group and then performed the Monte Carlo simulation method described by Crawford et al. (2007).

Then, we used the estimated base rate as a fixed number and used the one-sample binomial test to decide whether the observed percentage of abnormally low scores indeed exceeded the base rate. A one-sided alpha $\leq$ 0.05 was considered significant.

Next, we studied whether children with object recognition problems (score $< 5^{th}$ percentile on L94) had an increased risk of a general dorsal stream dysfunction. A dysfunction or weak function was considered present if a patient showed a score below the 10^{th} percentile ($z = -1.282$), in one of the other dorsal stream tasks. A patient was considered to have a general dorsal stream dysfunction if that patient showed at least two weak functions, i.e., had at least one abnormally low score in two out of three other dorsal stream functions: motion perception, visual attention and/or visuomotor skills. We therefore only included patients who completed at least one task per function. If only the group with object recognition problems was at risk for a general dorsal stream dysfunction, the percentage of at least 2 weak functions in this group had to be significantly higher than the base rate and the percentage of at least 2 weak functions in the patient group without object recognition problems (no score $< 5^{th}$ percentile on L94).

We used the Monte Carlo simulation method to calculate the base rate for at least 1 abnormally low score per function and then calculated the base rate for at least 2 weak functions. We used this estimated base rate as fixed numbers and performed the binomial test to decide whether the observed percentage exceeded this base rate.

To decide whether the percentages of weak functions and scores below the 10^{th} percentile in the group with object recognition problems exceeded those found in the group without object recognition problems we used the Fisher's exact test. This test was chosen, because of the smaller sample sizes, non-normal data and expected low counts (<5) (Sullivan et al., 2016). Additionally, we used the Mann-Whitney *U*-test to decide whether the performance levels in the group with object recognition problems were worse than in the group without object recognition problems. A one-sided alpha $\leq$ 0.05 was considered significant.

RESULTS

Medical History and Developmental Age

Eight patients out of 48 patients (17%) had low vision, a best corrected decimal visual acuity between 0.1 and 0.3 (US notation 20/200–20/63 or 1.0 logMAR–0.5 logMAR), but all patients should be able to perceive the detailed stimuli. Their developmental age, the median age equivalent of non-verbal intelligence subtests [as described in the procedure by Stiers et al. (1999)], ranged from 2y5 m to 7y8 m (M = 5y3 m, SD = 1y5 m). Nineteen patients (40%) had been born prematurely (gestational age $<$ 37 weeks): 6 moderately to late premature (gestational age 32–37 weeks), 12 very premature (gestational age 28–32 weeks) and 1 extremely premature (gestational age $<$ 28 weeks). In 31 patients (65%) a motor disorder was present. In another 3 patients (6%) some motor developmental problems were suspected, because a delay in motor development was mentioned in their medical record. More patient characteristics are presented in **Tables 3**, **4**.

L94: Object Recognition

At least three out of the five L94 tasks could be evaluated in 46 of 48 patients: 5 Tasks in 35, 4 in 7, and 3 in 4 patients. No tasks were systematically missing.

Based on the Monte Carlo simulation, 19.6% of the healthy population was expected to show at least 1 abnormally low score ($<5^{th}$ percentile). Two or more abnormally low scores

TABLE 3 | Presence of neurodevelopmental conditions in patients with confirmed or suspected brain damage.

Neurodevelopmental conditions	Patient group (*n* = 48)	
	n	%
Etiology		
Asphyxia	5	10
Hypoxic-ischemic encephalopathy (HIE)		
Periventricular leukomalacia (PVL)	18	38
Intraventricular hemorrhage (IVH)	3	6
PVL + IVH	1	2
Malformation	3	6
Hydrocephalus	1	2
Intracranial hemorrhage (ICH)	1	2
Intracranial hemorrhage + cytomegalovirus infection	1	2
Acquired brain damage (8 months–2.5 years)		
Tumor	1	2
Trauma	4	8
Meningitis	1	2
Genetic	3	6
Unclear	6	12
Neonatal condition		
Prematurity (Gestational age <37 weeks)	20	41
Performance IQ (PIQ)		
Normal IQ (>84)	12	25
Borderline (71–84)	11	23
Mild retardation (50–70)	12	25
Moderate retardation (<50)	6	13
Unknown	7	15
Motor disorder	**31**	**65**
Spastic cerebral palsy		
Hemiplegia	7	15
Diplegia	8	16
Quadriplegia	3	6
Undefined	1	2
Non-spastic cerebral palsy		
Athetoid	2	4
Ataxic	1	2
Mixed cerebral palsy	3	6
Bipyramidal syndrome	4	8

TABLE 4 | Presence of (neuro-) ophthalmologic conditions in patients with confirmed or suspected brain damage.

(Neuro-) ophthalmologic conditions	Patient group (*n* = 48)	
	n	%
Refractive error	**9**	**19**
Anisohyperopia (difference > 2D)	2	4
Hyperopia (>+1D and <+6D)	3	6
Hyperopia gravior (≥+6D)	2	4
Pseudophakia	2	4
Retinopathy of prematurity		
Stage I or II	2	4
Optic disc abnormality	**7**	**15**
Pale appearance	4	8
Smaller than normal	1	2
Optic nerve atrophy (posttraumatic)	2	4
Strabismus	**16**	**33**
Manifest	10	21
Intermittent	4	8
Latent	2	4
Oculomotor dysfunction	**8**	**16**
Nystagmus		
Manifest	3	6
Latent	1	2
Undefined	1	2
Saccadic dysfunction	2	4
Convergence abnormality	1	2
Horizontal oculomotor apraxia	1	2
Visual field defect	**13**	**27**
Scotoma	1	2
Mixed (hemi and altitude)	2	4
Hemianopsia	7	15
Altitude defect	1	2
Concentric, one side more affected	2	4
Other ophthalmologic conditions	**5**	**10**
Bilateral cataract	2	4
Posterior embryotoxon	1	2
Septo-optic dysplasia (SOD)	1	2
Choroidal coloboma + peripheral fundus abnormality + intact optic nerve	1	2

was expected in 4.38% and at least 3 abnormally low scores in 0.87%. The expected percentage for 4 or more abnormally low scores was near zero.

In the patient group the number of abnormally low scores ranged from 0 to 3, with a median of 1 and an interquartile range (IQR) of 1.25.

An abnormally low score on at least 1 L94 task was found in 29 out of 46 patients (63.0%). This was significantly higher than expected in the healthy population (63.0%, 95% CI:47.5–76.8% vs. 19.6%, $z = 7.18$, $p < 0.01$). At least 2 abnormally low scores were found in 11 patients (23.9%), which was significantly higher than the corresponding base rate (23.9%, 95% CI: 12.6–38.3% vs. 4.38%, $z = 6.11$, $p < 0.01$). Of these 11 patients 6 patients (13% of the total patient group) had 3 abnormally low scores, which was also significantly higher than expected (13.0%, 95% CI: 4.9–26.3% vs. 0.87%, $z = 8.10$, $p < 0.01$). These results showed that this patient group might indeed be at risk for dorsal stream dysfunctions.

Analysis on subtask level showed that only 4 out of 41 patients tested with VISM had an abnormally low score (9.8%). This was not significantly higher than was expected on a single task (9.8%, 95% CI: 2.7–23.1% vs. 5%, $z = 1.04$; $p = 0.15$, *ns*). Three of these patients scored abnormally low on at least one other task: DE VOS and/or NOISE. The percentages of abnormally low scores were significantly higher for the other four tasks: 8/45 for NOISE (17.8%, 95% CI: 8.0–32.1% vs. 5%, $z = 3.59$; $p < 0.01$); 6/45 for OVERL (13.3%, 95% CI: 5.1–26.8% vs. 5%, $z = 2.22$; $p = 0.01$); 13/44 for VIEW (29.5%, 95% CI: 16.8–45.2% vs. 5%, $z = 7.13$; $p < 0.01$); 15/40

for DE VOS (37.5%, 95% CI: 22.7–54.2% vs. 5%, $z = 9.07$; $p < 0.01$).

Dorsal Stream Functioning in Patients With and Without Object Recognition Problems

Out of the remaining 46 patients, 44 completed at least one motion perception task, 41 at least one visuomotor task, and 33 the visual attention task. This resulted in 29 patients in whom both at least three L94 tasks and all three other dorsal stream functions could be evaluated. This group only included 1 patient with an abnormally low score on VISM.

Of these patients 18 patients had object recognition problems and 11 had no object recognition problems. The median number of evaluated tasks of other dorsal stream functions was 5 out of totally 7 tasks (range 4–5, IQR 0). There was no difference between groups in the number of tasks evaluated. The group with and without object recognition problems did neither differ significantly in CA (6y2 m, range 4y1 m–8 y7m, IQR 1y5 m vs. 6y2 m, range 4y1 m–10y2 m, IQR 0y4 m; $U = 96.5$, $z = -0.11$, $p = 0.91$, *ns*) nor in PIQ (69, range 50–117, IQR 41.25 vs. 89, range 57–121, IQR 22; $U = 57.5$, $z = -1.48$, $p = 0.07$, *ns*), nor in DA (5y6 m, range 3y1 m–7y8m, IQR 2y6m vs. 4y8m, range 2y5 m–6 y8m, IQR 2y1 m; $U = 66$, $z = -1.48$, $p = 0.15$, *ns*). In the patient group with object recognition problems 5 had low vision (decimal visual acuity 0.1–0.3, US notation 20/200–20/63 or 1.0 logMAR–0.5 logMAR) and could be considered visually impaired. Five patients had a subnormal visual acuity for their age (decimal visual acuity 0.5–0.8, US notation 20/40–20/25 or 0.3–0.1 logMAR). The remaining 8 patients had a normal visual acuity. In the patient group without object recognition problems 2 had a subnormal visual acuity and the remaining 9 had a normal visual acuity.

Risk of a Generalized Dorsal Stream Dysfunction

Based on the Monte Carlo simulation method 27.9% of the healthy population was expected to show at least one abnormally low score ($<10^{th}$ percentile) on the motion perception tasks, 21.1% was expected to show at least at least on abnormally low score on the visual attention task, and 16.8% was expected to show at least one abnormally low score on the visuomotor tasks. Based on these results we expected 11.8% of the population to show at least 2 weak dorsal stream functions and about 1% (0.95%) to show 3 weak dorsal stream functions.

In the group with object recognition problems 6 patients (33.3%) were considered to have at least 2 additional weak dorsal stream functions. This was significantly higher than expected in the healthy population (33.3%, 95% CI: 13.3–59.0% vs. 11.8%, $z = 2.47$; $p = 0.01$). Two patients showed 3 weak dorsal stream functions, which could be considered relatively high (11.1%, 95% CI: 1.4–34.7 vs. 1.0%, $z = 3.13$; $p = 0.01$).

In the group with normal object recognition 1 patient (9.1%) had at least 2 weak dorsal stream functions. This was as expected in the healthy population (9.1%, 95 % CI: 0.0–41.3% vs. 11.8%, $z = 0$; $p = 0.50$. *ns*).

The observed percentages of at least 2 weak dorsal stream functions in the group with and without object recognition problems did not differ significantly [difference 24.1%, $p = 0.20$ (two-sided), $p = 0.15$ (one-sided)], probably due to the small sample sizes. A *post hoc* power-analysis (power of 80%, confidence level of 95%) suggested that future samples should at least have 41 participants per group.

These results suggested that general dorsal stream dysfunctions might be more common in the group with object recognition, but our evidence is not strong enough. Additional analysis suggested that dorsal stream dysfunctions, specific and general, were more common in the patient group with object recognition problems: 13 out of 18 patients with object recognition problems (72.2%) had at least 1 weak function, while only 3 out of 11 patients without object recognition problems (27.3%) had at least 1 weak function (*Fischer's exact one-sided p-value = 0.02)*. Most of the patient group with object recognition problems had other dorsal stream problems: 6 were considered to have a general dorsal stream dysfunction and an additional 7 were considered to have a specific dorsal stream dysfunction. In the patient group without object recognition problems 1 was considered to have a general dorsal stream dysfunction and 2 were considered to have a specific dorsal stream dysfunction.

Outcomes of Different Dorsal Stream Aspects

In **Tables 5–7**, we present number of abnormally low scores per function and (sub) task and median task outcomes for both groups.

Motion Perception

The group with object recognition problems had a significantly higher percentage of abnormally low scores on motion perception (50% vs. 9.1%; $p = 0.03$) than the group without object recognition problems (see **Table 5**). Abnormally low scores were found in a single motion perception task (GM or MDF) in 6 patients with and 1 patient without object recognition problems. Another 3 patients with object recognition problems had abnormally low scores on GM and MDF.

The group with object recognition problems scored significantly more often abnormally low on GM ($p = 0.02$) and their coherence level was significantly higher than that in patients without object recognition problems (coherence level 0.53 vs. 0.42; $p = 0.04$). Although the percentage of abnormally low scores did not differ significantly on MDF, patients with object recognition problems were significantly less able to recognize the motion-defined forms (percentage correct 72% vs. 92%, $p < 0.01$). No significant differences were found for the motion speed task.

Visual Attention

The percentage of abnormally low scores on the visual attention task (see **Table 6**) was significantly higher in the group with object recognition problems ($p = 0.03$).

Abnormally low scores were mainly found on a single subtask: in 6 patients with and in 1 patient without object recognition problems. In the patient group with object recognition problems another 2 scored abnormally low on 2 subtasks and 1 on all three.

TABLE 5 | Number of abnormally low scores (<10th percentile) for motion perception subtasks and subtask outcomes for patient with normal and abnormally low scores on the L94 (<5th percentile).

	Patients with 3 additional function evaluations		Statistics			
	Normal L94	≥ 1 Abnormal L94 tasks	*U*	*z*	Two-sided *p*-value	One-sided *p*-value[a]
	n = 11	*n* = 18				
Motion perception						
# Abnormal scores (%)	1/11 (9.1)	9/18 (50.0)			0.04*	0.03*
Global motion task (GM)						
# Abnormal scores (%)	0/10 (0.0)	7/16 (43.8)			0.02*	0.02*
Median coherence level (range) (IQR)	0.42 (0.32–0.58) (0.11)	0.53 (0.12–0.83) (0.43)	47.5	–1.71	0.09	0.04*
Motion-defined form task (MDF)						
# Abnormal scores (%)	1/10 (10)	5/16 (31.3)			0.35	0.23
Median percentage correct (range) (IQR)	92 (73–1.00) (16)	71 (0– 97) (27)	25.5	–2.88	<0.01*	<0.01*
Motion speed task (MS)						
# Abnormal scores (%)	0/9 (0.0)	0/5 (0.0)			*NA*	*NA*
Median speed difference deg/s (range) (IQR)	4.83 (1.70–9.66) (5.66)	4.28 (1.27–23.24) (12.01)	22.0	–0.07	1.0	0.50

[a]*We used the one-sided p-values, because we expected the patients with object recognition problems to perform worse.*
**Significant at significance level 0.05; NA, not available, values are equal/constant.*

Although the observed percentages of abnormally low scores in the visual search subtasks did not differ significantly. the difference in the condition with four distracters was near-significant ($p = 0.09$). Additionally, patients with object recognition problems were significantly slower on each subtask and made significantly more mistakes than the group without object recognition problems ($ps < 0.01$), whereas the performance on the reaction time task seemed comparable.

Visuomotor Skills

No significant differences were found in the visuomotor skills (see **Table 7**). Abnormally low scores on both tasks were only found in 1 patient with object recognition problems. The other patients seemed to have a specific problem with one of the tasks.

DISCUSSION

In this study, we provided some evidence that children with early brain damage are at risk for dorsal stream dysfunctions. While controlling for the patient's developmental age, 29 out of 46 patients with early brain damage (63%) scored abnormally low (score < 5th percentile) on one or multiple object recognition subtasks of the L94. This was significantly higher than the base rate of 12%, the expected percentage of abnormally low scores in the healthy population.

We then studied whether general dorsal stream problems were present in children with impaired object recognition ($n = 18$) and compared their performance levels to that of children with early brain damage with unimpaired object recognition ($n = 11$). We defined a general dorsal stream dysfunction as abnormally low performance levels (score below 10th percentile) on at least 2 additional dorsal stream functions, such as motion perception, visual attention, and/or visuomotor skills. The results showed that a general dorsal stream dysfunction was present in 6 out of 18 patients with impaired object recognition (33.3%). Another 7 patients scored abnormally low on 1 additional dorsal stream function. Dorsal stream problems were uncommon in patients without object recognition problems: they were only found in 3 out of 11 patients (27.3%). Of these patients only 1 (9.1%) was considered to have a general dorsal stream dysfunction. This was as many as could we expected in the healthy population.

Although these results suggest that patients with object recognition problems are at risk for general, widespread dorsal stream dysfunctions, the difference of 24.1% between the patients with and without object recognition problems was not significant. The higher percentage of patients at least 1 dorsal weakness (72.2% vs. 27.3%, $p = 0.02$) indicates that patients with object recognition problems are at risk of other dorsal stream dysfunctions, possibly rather specific than general. Motion perception and visual attention, but no visuomotor skills, were specifically affected.

In neuropsychology the terms specific and generalized are frequently used, but the definition of generalized remains arbitrary. A specific or independent disorder is considered present if a single aspect is impaired in one patient (group), whereas another aspect is impaired in another patient (group). The term generalized is used when impairments are widespread within and/or across various aspects of functioning. Although in some of our patients the dorsal stream dysfunctions seemed widespread, the dysfunctions within

TABLE 6 | Number of abnormally low scores (<10th percentile) for the visual attention task and subtask outcomes for patient with normal and abnormally low scores on the L94 (<5th percentile).

	Patients with 3 additional function evaluations		Statistics			
	Normal L94	≥ 1 Abnormal L94 tasks	*U*	*z*	*Two-sided p*-value	*One-sided p-value*[a]
	n = 11	*n* = 18				
Visual attention						
# Abnormal scores (%)	1/11 (9.1)	9/18 (50)			0.04*	0.03*
Search task 4 distracters						
# Abnormal scores (%)	1/11 (9.1)	7/18 (38.9)			0.11	0.09
Median search time sec (range) (IQR)	0.73 (0.00–1.97) (0.41)	1.21 (0.56–3.45) (1.09)	48.00	–2.29	0.02*	0.01*
Search task 9 distracters						
# Abnormal scores (%)	0/11 (0)	3/18 (16.7)			0.27	0.22
Median search time sec (range) (IQR)	1.13 (0.72–1.71) (0.46)	1.77 (0.71–6.72) (1.59)	33.5	–2.95	<0.01*	<0.01*
Search task 19 distracters						
# Abnormal scores (%)	0/11 (0)	3/18 (16.7)			0.27	0.22
Median search time sec (range) (IQR)	2.11 (0.99–3.46) (1.55)	3.90 (1.17–11.55) (3.35)	36.00	–2.83	<0.01*	<0.01*
Mistakes						
# Abnormal scores (%)	0/11 (0)	9/18 (50)			<0.01*	<0.01*
Median number (range) (IQR)	0 (0–0) (0)	1 (0–11) (3)	27.50	–3.54	<0.01*	<0.01*
Reaction time task						
# Abnormal scores (%)	0/11 (0)	1/18 (5.6%)			1.0	0.62
Median response time sec (range) (IQR)	1.32 (0.90–2.55) (0.86)	1.49 (0.94–2.83) (0.83)	76.50	–1.01	0.32	0.16

[a]*We used the one-sided p-values because we expected the patients with object recognition problems to perform worse.*
**Significant at significance level 0.05; NA, not available, values are equal/constant.*

TABLE 7 | Number of abnormally low scores (<10th percentile) for visuomotor skills and subtask outcomes for patient with normal and abnormally low scores on the L94 (<5th percentile).

	Patients with 3 additional function evaluations		Statistics			
	Normal L94	≥1 Abnormal L94 tasks	*U*	*z*	Two-sided *p*-value	One-sided *p*-value[a]
	n = 11	*n* = 18				
Visuomotor skills						
# Abnormal scores (%)	2/11 (18.2)	3/18 (16.7)			1.0	0.64
Beery before VMI						
# Abnormal scores (%)	0/6 (0)	2/16 (12.5)			1.0	0.52
Median standard score (range) (IQR)	96.5 (83–106) (17)	96.0 (73–142) (22)	48.0	0.00	1.0	0.51
Mosaics (SON-R)						
# Abnormal scores (%)	2/11 (18.2)	2/18 (11.1)			0.62	0.49
Median standard score (range) (IQR)	10.0 (3–12) (4)	10.5 (5–15) (3.5)	72.5	–1.20	0.24	0.12

[a]*We used the one-sided p-values because we expected the patients with object recognition problems to perform worse.*
NA = not available, values are equal/constant.

a single aspect, like motion perception seemed rather specific than generalized. Our estimation of a general dysfunction within aspects might be underestimated, because of missing data. The extent of generalized dysfunctions within aspects can only be reliably estimated if all patients were assessed with all subtasks.

In current study we can only deduce that the dorsal stream is affected. We have no details on the exact locations and extent of the brain damage. Although the subtasks of the L94 are likely to activate both the ventral and the dorsal stream, the subtask profile of the L94 suggest that the ventral stream is mainly intact in our patient group. The performance level on VISM, a subtask with line drawings of everyday objects in prototypical view, probably mainly relies on the integrity of the ventral stream, as demonstrated in a fMRI study with passive object viewing (Stiers et al., 2006) and patient studies (Vaina, 1994; Stiers et al., 2001). In our patient group only 4 out of 41 patients (9.8%) scored abnormally low on this subtask. The performance levels in the other four subtasks (OVERL, NOISE, VIEW, and DEVOS), probably rely in a higher extent on the integrity of the dorsal stream due to the suboptimal representations used (Renzi and Spinnler, 1966; Warrington and James, 1967; Warrington and Taylor, 1973; Vaina, 1994; Fazzi et al., 2004; Sheth and Young, 2016). In our patient group we mainly found abnormalities on these other four tasks (range 13.3% in OVERLAP to 37.5% in DE VOS). An abnormality on VISM was almost always accompanied by an abnormality on one of the other tasks. This suggests that mainly the dorsal stream was affected in our patient group, and that in some patient the ventral stream might also be deficient.

Patients with object recognition problems performed worse on the global motion and motion-defined form task and were significantly slower on the visual search tasks. They also made more mistakes, which makes a speed-accuracy trade-off less likely. The available data are insufficient to study causal or interactional relationships between functions. One possibility is that a visual attention weakness leads to abnormally low motion and object perception scores, but performance levels on the assessed tasks could also be low because of difficulties in object discrimination, impulse control, and cognitive flexibility. Therefore, to test hierarchical models, not only a larger sample size but also assessment of additional indicators is necessary.

The presence of object recognition and motion perception problems in combination with the normal visuomotor skill on the Beery VMI support the more fundamental idea that developmental age estimations based on PIQ subtests can be used to control for effects of motor impairments in addition to intellectual impairments. Because the Beery VMI (Beery et al., 2004) can provide age equivalents, it might be suggested that the outcome of the Beery VMI could be used to estimate developmental age and control for motor impairments by using these age equivalents as entry of the norm tables. Although performance IQ and the outcome of the Beery VMI are significantly related (Beery et al., 2004), we consider the developmental age estimation based on PIQ subtests more reliable, because the estimation is based on multiple subtest results instead of a single test outcome. In current study, we found two abnormal performers on the Beery VMI. The use of the age equivalents of the Beery VMI would make this impossible.

Further, a more detailed analysis of inconclusive items, i.e., items that were not named correctly in the control conditions of the L94 and the motion-defined form task and were excluded from the calculation of perception scores, might help explain performance patterns in children at risk. Inconclusive items can indicate differences in experience or object knowledge, but also the presence of other problems such as problems in language development, naming, especially in relation to words (items) with lower word frequencies, memory and attention, or a combination of these problems. Differences in the number of inconclusive items between a group with unimpaired and impaired object recognition could provide indications for the reason why abnormal performers were unable to name or describe objects in the control items.

We conclude that in children with early brain damage, dorsal stream functions and their aspects seem specifically and not generally affected, and that more extensive research is required for a better understanding of causal relationships and underlying mechanisms. For now, we recommend that in specialized clinical practice, multiple functions and their various aspects should be assessed in a neuropsychological assessment of at-risk children, using developmental age as reference level, i.e., entry of the reference table.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committees of the Erasmus Medical Centre MEC-2006-056) and the Catholic University of Leuven. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

PS and HE conceived the study. PS and YZ designed the study design and procedures, significantly contributed to procedures and execution, and interpreted the data. YZ, PS, and HE drafted, revised, and prepared the manuscript. All authors gave final approval for the submitted manuscript.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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The Multidisciplinary Guidelines for Diagnosis and Referral in Cerebral Visual Impairment

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Introduction: Cerebral visual impairment (CVI) is an important cause of visual impairment in western countries. Perinatal hypoxic-ischemic damage is the most frequent cause of CVI but CVI can also be the result of a genetic disorder. The majority of children with CVI have cerebral palsy and/or developmental delay. Early diagnosis is crucial; however, there is a need for consensus on evidence based diagnostic tools and referral criteria. The aim of this study is to develop guidelines for diagnosis and referral in CVI according to the grade method.

Patients and Methods: We developed the guidelines according to the GRADE method 5 searches on CVI (children, developmental age $\leq$ 18 years) were performed in the databases Medline, Embase, and Psychinfo, each with a distinct topic.

Results: Based on evidence articles were selected on five topics: 1. Medical history and CVI-questionnaires 23 (out of 1,007). 2. Ophthalmological and orthoptic assessment 37 (out of 816). 3. Neuropsychological assessment 5 (out of 716). 4. Neuroradiological evaluation and magnetic resonance imaging (MRI) 9 (out of 723). 5. Genetic assessment 5 (out of 458).

Conclusion: In medical history taking, prematurity low birth weight and APGAR (Appearance, Pulse, Grimace, Activity, Respiration) Scores (<5) are important. Different questionnaires are advised for children under the age of 3 years, older children and for specific risk groups (extremely preterm). In ophthalmological examination, eye movements, specially saccades, accommodation, crowding, contrast sensitivity and visual fields should be evaluated. OCT can show objective signs of *trans*-synaptic degeneration and abnormalities in fixation and saccades can be measured with eye tracking. Screening of visual perceptive functioning is recommended and can be directive for further assessment. MRI findings in CVI in Cerebral Palsy can be structured in five groups: Brain maldevelopment, white and gray matter lesions, postnatal lesions

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and a normal MRI. In children with CVI and periventricular leukomalacia, brain lesion severity correlates with visual function impairment. A differentiation can be made between cortical and subcortical damage and related visual function impairment. Additional assessments (neurological or genetic) can be necessary to complete the diagnosis of CVI and/or to reveal the etiology.

Keywords: cerebral visual impairment, visual development, visually impaired children, perinatal damage, congenital anomaly of brain, visual behavior analysis, visual functions, MRI in VI children

INTRODUCTION

Cerebral visual impairment (CVI) has been defined as a verifiable visual dysfunction which cannot be attributed to disorders of the anterior visual pathways or any potentially co-occurring ocular impairment (Sakki et al., 2018). CVI is caused by abnormalities in the retro-geniculate system and not by pathology of the eye, however, CVI can occur together with pathology of the eye for instance in retinopathy of prematurity (ROP). CVI greatly affects development in all its aspects (Boonstra et al., 2012; Ego et al., 2015) and therefore, diagnosing CVI in early life is essential to enable early and tailor made interventions (Fazzi et al., 2009). Because there is a need for clear guidelines, to structure the diagnostic procedure in this heterogeneous group, we describe the guidelines for diagnosis and referral of CVI based on five literature searches.

Cerebral visual impairment is the most common cause of visual impairment in children in western countries. Perinatal hypoxic-ischemic damage is the most frequent cause of CVI, but the etiology is variable. Hypoxic Ischemic Injury (HII) is the most common cause of CVI 60% of the children with HII also has CVI (Cioni et al., 1996; Good et al., 2001; Fazzi et al., 2007; Solebo et al., 2017; Sakki et al., 2018). Another important cause of CVI is developmental anomaly of brain (genetic).

Problems with processing of visual information and or integration of visual information are symptoms of higher order visual functions (Good et al., 2001; Fazzi et al., 2007; Philip and Dutton, 2014). In children with these impairments, a relatively good visual acuity can be found.

In ophthalmological examination associated ocular and oculomotor deficits can be found such as strabismus, nystagmus, motility disorders of the eye, delay in saccades, pallor of the optic nerve and visual field abnormalities. In CVI retro-geniculate damage results in ganglion cell layer thinning due to retrograde *trans*-synaptic degeneration (RTSD) (Jacobson and Dutton, 2000; Hoyt, 2003; Khetpal and Donahue, 2007; Bosch et al., 2014b; Jacobson et al., 2019). In CVI these ocular and oculomotor deficits are often found in both eyes and sometimes show the same outcome in right and left eye. In addition, a clear clinical picture can be found as a result of damage or congenital abnormalities in different stages of the development of the visual system:

- Congenital abnormalities of brain and deviations in brain development.
- Perinatal damage.
- Postnatal damage.

Children with CVI are not always visually impaired, according to the WHO definition (visual acuity $< 6/18$). Children with CVI may have a better visual acuity (mildly impaired 6/12 to 6/18 or even better). CVI is often caused by HIE (Hypoxic Ischemic Encephalopathy), which is found in 6/1,000 life born infants in western countries and about 26/1,000 in non-western countries. 60% of these children have CVI (Fazzi et al., 2007; Solebo et al., 2017).

Another important cause of CVI is congenital anomaly of brain as a result of a genetic anomaly. Children with congenital anomalies of brain are not always referred to an ophthalmologist, therefore the incidence of CVI might be even higher. Children with a history of perinatal damage or congenital anomaly of brain need examinations specific for CVI because they often are not aware of their limitations and a majority has no specific ophthalmological complaints (Sakki et al., 2021). However, they can have slow eye movements (saccades), crowding (the impairment of the ability to recognize objects in clutter), and impairment of accommodation or complaints that are related to impairment of processing of visual information (Bosch et al., 2014b). Children with CVI can also show several peculiar behavioral signs; short visual attention span; markedly fluctuating visual performances; the need for time, environmental stability, and repetition of items to obtain the best response (Fazzi et al., 2007).

Demarcation of content: In the developing process of the guidelines a clear definition and description of the patient group was necessary. The group in this study contains children between 0 and 18 years with CVI caused by various diseases, manifesting with various complaints and function deficits. Often co-morbidity is found. After the decision to study five topics the authors have chosen for a practical approach; firstly, articles were selected where the abbreviation CVI was used. Articles about impairment of visual functions may therefore not always have been included and the abbreviation CVI may have been defined differently in different articles. Five topics have been selected to focus upon, following a bottleneck analysis by the involved national professional associations: The Dutch ophthalmological organization, the organization of clinical geneticist, neonatologists, neurologists, radiologists, rehabilitation physicians, physicians for multiple impaired and youth healthcare physicians, the society for child and hospital and the society for patients with visual impairment.

The five topics are also mentioned by McConnell et al. (2021) who described the assessments currently used to investigate and diagnose CVI. According to Mc Connell, there is a lack of common practice in the approaches used by clinicians to

investigate and diagnose CVI in children. At present, a "diagnosis of exclusion" remains the most common means to diagnose CVI. Therefore development of clinical guidelines for assessment and diagnosis are necessary to ensure consistency in the diagnosis of CVI and the timely implementation of support to alleviate the impact of CVI on the child's daily living. The aim of this study is to develop guidelines for diagnosis and referral in CVI according to the grade method.

The topics:

1 Medical history and CVI- questionnaires.
2 Ophthalmological and orthoptic assessments in CVI.
3 Neuropsychological assessment.
4 Neuroradiological evaluation and MRI.
5 Genetics assessment.

Medical History and Cerebral Visual Impairment-Questionnaires

In general, children with CVI enter the diagnostic circuit in three ways:

1 Parents worry about the visual functioning of their child.
2 Children with an increased risk on CVI, without a specific question of the parents. In this group, active screening is necessary using a CVI questionnaire.
3 Children with an intellectual disability or syndrome who can be screened on visual functioning.

Ophthalmological and Orthoptic Assessments in Cerebral Visual Impairment

If children with possible visual impairment or deviations of visual behavior, are referred to an ophthalmologist a series of test possibilities are available. We aimed to identify which tests are relevant for the diagnosis CVI.

Neuropsychological Assessment

If the history or the ophthalmological and orthoptic or psychological examination shows indications for disorders in visual information processing and when ophthalmological findings provide insufficient explanation neuropsychological assessment can be useful to aid the diagnosis.

Although it is recommended to perform a neuropsychological assessment in children with possible CVI (Fazzi et al., 2009; Boot et al., 2010; Ortibus E. L. et al., 2011), there is no consensus in terms of a diagnostic protocol. Therefore, professionals have no reference for the appropriate age, domains of functioning and tests to include in the assessment.

Neuroradiological Evaluation and Magnetic Resonance Imaging

Imaging is part of the diagnostic possibilities in CVI. Neuroradiological imaging in children with CVI could be applied to make an inventory of the damage of those parts of the brain that are concerned in visual processing.

In this question we can define two sub questions:

1 What is the prognostic value of MRI in children with a risk on CVI?
2 In children with deviant viewing behavior that have been referred because of suspected CVI, what is the role of MRI in the differential diagnosis of CVI.

Several anomalies of brain can be found in CVI. Such as embryological deviations (Encephalocele, holoprosencephalies) cortical developmental malformations (occipital lissencephaly, pachygyria, polymicrogyria, and schizencephaly) periventricular leukomalacia (PVL), periventricular and intraventricular hemorrhages, neonatal encephalopathy, or cerebral ischemia after the perinatal period (Hoyt and Taylor, 2017).

These congenital malformations of the brain can result in damage to the visual pathways. In preterm born babies a lack of oxygen results in white matter damage, while full term born babies are at risk for gray matter damage (cortex). Cerebral damage can result in a large range of CVIs varying from hardly noticeable visual field impairment to severe visual field impairment and even blindness. Individuals with CVI exhibit a wide range of visual deficits and, in particular, present with impairments of higher order visual spatial processing (referred to as "dorsal stream dysfunction") as well as object recognition (associated with processing along the ventral stream; Bennett et al., 2020). The value of neuroradiological imaging is not yet clearly defined in this group of patients. Guidance is warranted for the application of neuroradiological examination in this population and its role in the diagnosis CVI. Because of the radiation burden from CT-scans in childhood (Pearce et al., 2012) and the fact that ultrasound is not possible after the age of 1 year this chapter focusses on MRI (McGuirt, 2016).

Genetic Assessment

Traditionally, CVI was seen as a result of perinatal damage. Nowadays, it is clear that CVI can also be caused by several genetic disorders (Bosch et al., 2014b,a; Hoyt and Taylor, 2017). This recent knowledge, however, is not yet well known by professionals. Therefore, CVI is often still defined as a result of perinatal damage and children with CVI as a result of a genetic disorder might not receive the correct visual rehabilitation interventions. This search question aimed to investigate in which genetic disorders an investigation for CVI is warranted.

GENERAL METHODS (ALL TOPICS)

To formulate the guidelines according to the GRADE method, searches for five topics on CVI (children, developmental age $\leq$ 18 years) were performed in the databases Medline, Embase and Psych info.

AGREE and GRADE

The guidelines were formulated according to the AGREE II method (Appraisal of Guidelines for Research & Evaluation II; Brouwers et al., 2010). This is a well-structured method which commences with a bottleneck analysis: With the different disciplines involved priority was given to specific topics based

on medical and organizational arguments. This was followed by a discussion on the concepts of search questions. Together this emerges into final search questions. The searches were performed for systematic reviews, SIGN, Medline, and with specific key words for each search question in Medline, Embase, Psych info. The guideline research group selected relevant articles, based on the pre-defined selection criteria. The articles selected were used to answer the search questions for each search topic.

For quality criteria of the different studies, we used instruments to reduce the risk of bias as recommended by the Cochrane Collaboration: AMSTAR for systematic reviews, Cochrane for randomized controlled research trials, ACROBAT-NRS for observational research; QUADAS II, for diagnostic Research. The relevant results of the articles were described in evidence tables (**Supplementary Appendix**). The most important results from literature were summarized in the literature summary of each search. If sufficient studies were available, a quantitative summary (meta-analysis) was given. For the rating of diagnostic tests or etiology or prognostic value, the GRADE ranking was used (Grading Recommendations Assessment, Development and Evaluation[1]). In GRADE, four levels of evidence of scientific prove are described: High, Moderate, Low and very low, with the starting aim at high with downgrading for the risk of bias, inconsistency, indirectness, imprecision, and publication bias.

Levels of evidence referring to the amount of evidence based on the outcome of literature (Guyatt et al., 2008) are:

- Very low: the true effect is probably markedly different from the estimated effect.
- Low; the true effect might be markedly different from the estimated effect.
- Moderate; the authors believe that the true effect is probably close to the estimated effect.
- High; the authors have a lot of confidence that the true effect is similar to the estimated effect.

The outcome of the searches was assessed by two authors for each search, in a predefined procedure; Each author selected relevant articles if there was a large difference in selection, the articles were selected with the help of a third independent person.

PICO

In order to define the systematic search, the characteristics of the research questions were defined in a PICO.

Definitions were used as mentioned in the different articles. PICO stands for:

P: Patient group: The specific target group that the research question is about.
I: Intervention: The intervention or test or assessment that the research question is about.
C: Comparison: Alternative to Intervention which is applicable to the research question.
O: Outcome: The desired intervention, assessment or test for the research question.

[1]http://www.gradeworkinggroup.org/

Search, General Inclusion Criteria (All Topics)

The searches were performed in March-July 2017 and in December 2021 for publications dealing with etiology, risk factors and clinical history elements of CVI in Medline (OVID) and Embase[2] using relevant terms and in the topic on neuropsychological assessment PsychInfo was used because of the content. The searches have been carried out by a clinical librarian of the Dutch Institute for Medical Specialists and the clinical librarian of the Radboud Medical center. Inclusion criteria were:

- Systematic reviews.
- Randomized controlled trials.
- Cohort studies and case series with more than five patients, no case reports were included.
- Written in English.
- Age of the children ranging from 0 to 18 years developmental age.
- Diagnosed with CVI as defined in the introduction.
- Start of outcome population according to the definition of CVI in the introduction and published in peer reviewed Journals.
- Population start and end outcome: according to the CVI definition in the introduction. Studies with an unclear metabolic disorder or without DNA diagnosis were excluded. CVI was due to *etiological* conditions occurring between ages 2 and 12 years, because all causes of damage during development of the visual system can cause CVI. Articles dealing with acquired brain injury which was caused after the age of 12 years, which means after major development of the visual system, were *excluded* as well as those describing functional visual disturbance. Acquired brain injury studies with etiology between 3 and 12 years (during the major development of the visual system) and published in peer-reviewed journals were *included*. Studies on learning and behavioral problems were excluded in all topics but topic 3 (neuropsychological assessment).

In this study the excluded literature is not mentioned in the references. The exclusion tables for this study can be requested.

Topics

Based on evidence, articles were selected on the five topics mentioned in the introduction a control or comparison was mentioned if applicable.

The search outcome of each topic was screened and selected by two authors. In case of conflicting outcome a third independent person, with knowledge of the topic, was involved to decide on the selection.

Topic One: Medical History and Questionnaires

Questions:

1A How should screening on CVI be performed?

[2]https://www.embase.com

1B Which questionnaires should be used in case of suspected CVI? In addition, for which CVI subgroup should the questionnaires be applied?

PICO:

For question 1A: Which elements should be included in the clinical history to screen for CVI?

P: Patients: Children who possibly have CVI.
I: Investigation: Medical and perinatal history, congenital brain anomalies, developmental delay, and genetic diagnosis.
C: Comparison (control): Children with learning problems or behavioral problems and characteristics of delayed visual development.
O: Outcome: Sensitivity and specificity of medical history questions for the diagnosis of CVI.

Outcome measures were not defined *a priori*; the definitions mentioned in the studies were used.

For question 1B: Which questionnaire should be used in case the professional has a suspicion of CVI, based on the clinical history?

P: Patients with unusual visual behavior, problems with visual orientation, fixation problems, slow vision (delayed reactions on visual stimuli), predominance of sound over vision, problems with visual selection, crowding difficulties, visual field preference, visual attention, and object recognition.
I: Investigation: CVI screening questionnaires.
C: Comparison: -
O: Outcome: Sensitivity/Specificity, clinometric aspects.

Clinometric properties such as sensitivity, specificity and diagnostic value were deemed critical outcome measures.

Search and selection:

A search was performed for publications dealing with etiology, risk factors and clinical history elements of CVI in Medline (OVID) and Embase (see text footnote 2) using relevant terms. The search string is shown below (**Supplementary Appendix Figure A**).

Studies were selected based on the criteria mentioned in general methods.

The search resulted in 1,007 articles. Articles dealing with acquired brain injury after the age of 12 years were excluded as well as those describing functional visual disturbance.

Based on title and abstract review, 75 articles were selected. Of those, for Question 1A, 14 articles were withheld (**Supplementary Appendix Table 1A**). For Question 1B 9 studies were included for analysis (**Supplementary Appendix Table 1B**).

To prepare the search on clinical history and questionnaires, we first classified groups at risk for CVI by obtaining the clinical history, because based on this selection, caretakers and professionals can be alert on the risk of CVI. Secondly, the use of questionnaires is studied. Are there questionnaires that can be used as an instrument to screen on CVI? For which groups are these questionnaires applicable? Based on the outcome of a questionnaire the children could be referred selectively for an ophthalmologic and neuro-radiological and/or neuropsychological assessment.

Topic Two: Ophthalmological and Orthoptic Assessment

Questions:

Which are the ophthalmological and orthoptic assessments that are required in case of suspected CVI in a general hospital?
Which ophthalmological and orthoptic assessments can be performed in academic centers in case of suspected CVI?

The question is focused on ophthalmologists and orthoptists because these two groups of professionals often work together in case of complex neuroophthalmological pathology.

PICO:

In order to define the systematic search, the characteristics were defined in a PICO.

P: Patient: patients with unusual visual behavior who have been referred to the ophthalmologist.
I: Investigation: Ophthalmological and orthoptic investigation.
C: Comparison: -
O: Outcome: Specificity and sensitivity of tests in CVI.

Definitions were used as mentioned in the different articles.

Search and selection:

In Medline, a search was performed in April 2017 and December 2021, using relevant search terms to select studies about ophthalmological and orthoptic assessment in a peripheral hospital setting. Selected were 816 articles. Studies were selected based on the criteria mentioned in general methods.

Question 2A and B: Based on title and abstract at first 83 studies were selected of which 27 studies were excluded (other topic or small group) and after full text reading 19 studies were excluded and 37 studies remained included. Outcomes of these (A:16; B:21) searches have been included in the literature analysis. The most important study characteristics and results are represented in the evidence table (**Supplementary Appendix Tables 2A, 2B**).

Topic Three: Neuropsychological Assessment

In order to apply neuropsychological assessment in children in CVI appropriately and in a functional way it has to be clear:

1 Which aspects of visual attention and visual perceptive functions have to be examined?
2 Which neuropsychological tests are available for this assessment?
3 Which test outcome is relevant for the diagnosis CVI?
4 When abnormal test results do not support a CVI-diagnosis (i.e., differential diagnosis)?

Transparency about the content of a neuropsychological examination can add to an efficacious diagnostic procedure in CVI and appropriate and timely referral and rehabilitation.

Question 3: Which neuropsychological tests can be used in the neuropsychological assessment of children with CVI?

To define the search question a systematic literature analysis is performed for the following question.

P: Patients: Children suspected of having CVI.
I: Investigation: Neuropsychological test.
C: Comparison (control): No tests or other tests.
O: Outcome: Diagnostic value and accuracy.

Search and selection:

In the databases Medline (OVID), Psych INFO (OVID) were searched in June 2017 and December 2021 using relevant search terms for neuropsychological assessment in the context of CVI diagnostics. For this search PsychInfo was used because of the content (neuropsychological tests). The search resulted in 716 hits. The search string is shown below (**Supplementary Appendix Figure C**). Studies were selected based on the criteria mentioned in general methods. Based on title and abstract 29 studies were initially selected (**Supplementary Appendix Table 3**). After full text reading 24 studies were excluded and 5 studies were included. Studies on acquired brain injury in older children and studies on functional visual impairment (i.e., conversion disorder) were excluded. Studies on learning- or behavioral disorders were not excluded in order to include qualitative good comparison studies. The most important study characteristics and results are mentioned in the evidence table (**Supplementary Appendix Table 3**). Quality assessment of the reviews included in the topics is shown in **Supplementary Appendix Table 6** of quality assessment for systematic reviews of diagnostic studies.

Reference test: A reference tests is not yet applicable, as a result of the recent start of diagnostics in CVI in this topic.

A CVI-diagnosis is currently obtained by clinical decision making. In this search, CVI is defined the way it has been defined by the authors of the articles.

Relevant outcome measures:

Reliability, sensitivity, and specificity were used as critical outcome measures by the project group. Outcome measures were not defined *a priori*, the definitions found in the studies were used as outcome measures.

Topic Four: Neuro-Radiological Evaluation and Magnetic Resonance Imaging

Question:

Question 4A: How can neuro-radiological examination (imaging) be used to obtain the diagnosis of CVI in children?
Question 4B: Is neuro-radiological examination necessary to obtain a diagnosis of CVI?

MRI examination is chosen because it is the gold standard for children (Sie et al., 2005; Pearce et al., 2012).

To define the search question a systematic literature analysis is performed for the following question.

Two PICO's have been defined:

First PICO:

P: Patients: Children with a risk of CVI.
I: Investigation: MRI examination.
C: Comparison (control): Other ways to diagnose CVI.
O: Outcome: Prognostic value of MRI for the diagnosis CVI.

Second PICO:

P: Patient: Children with suspected CVI.
I: Investigation: MRI examination.
C: Comparison (control): Children without CVI with MRI or other imaging methods that are also used to investigate CVI.
O: Outcome: MRI findings that are compatible with the diagnosis CVI.

Search and selection:

In Medline (*via* OVID) and Embase (*via* see text footnote 2) in May 2017 and December 2021 with relevant search terms (**Supplementary Appendix Figure D**) a search has been performed on neuroradiological evaluation and MRI in CVI. The search resulted in 723 hits. Studies were selected on the criteria mentioned in general methods. Studies on acquired damage to the brain such as traumatic brain injury and stroke in children older than 12 years and studies on functional visual impairments were excluded.

Based on title and abstract 57 studies were selected. After full text reading 48 studies were excluded 9 studies were selected. The study characteristics are shown in the evidence table (**Supplementary Appendix Table 4**).

Topic Five: Genetic Assessment

Question:

Question 5A: What is the position of genetic investigations in obtaining the diagnosis in children in CVI? Is a genetic investigation necessary to obtain the diagnosis of CVI in children?

To define the search question a systematic literature analysis is performed for the following question; Does CVI co-exist in the following genetic disorder?

PICO:

Does CVI co-exist in the following genetic disorder?

P: Patients: children with a developmental age of 18 years or younger.
I: Investigation: A genetic disorder is found.
C: Comparison: Genetic disorder is not found.
O: Outcome: Children with a genetic disorder and CVI.

Search and selection:

In the databases Medline (OVID), Embase (see text footnote 2) in July 2017 a search is performed with relevant

search terms for the presence of CVI in genetic diseases. Studies were selected based on the criteria mentioned in general methods; the period for this the search (from 2000) is chosen because of the technical developments in genetics after 2000. The search resulted in 458 hits. Based on title and abstract at first 71 studies were selected of which 68 studies were excluded (case reports and small groups) two studies were selected from the search of another topic, topic two. Five studies were selected. The studies are mainly focused on CVI as part of a genetic disease. Five research outcomes were included in the literature analysis. The most important characteristics and results are mentioned in the evidence table (**Supplementary Appendix Table 5**).

Relevant outcome measure:

The authors selected the presence of CVI in children with a genetic disorder a relevant critical outcome measure for inclusion.
The authors did not define the outcome measures *a priori* but used the definitions in the studies included.

DISCUSSION AND ORGANIZATION OF CARE

A general overview of recommendations is given and an overview of the organization of the diagnostic process for a child with possibility of the diagnosis CVI is given.

This overview is based on the searches in all topics. Organizational consequences of the outcome of the different topics are discussed. Based on the results of the 5 topics, the project group made an inventory of relevant outcome measures for each search question. The project group contained ophthalmologists, a neuropsychologist, a neurologist, a geneticist and a clinical librarian of the Dutch organization of medical specialists. The authors of this study form a subgroup of the project group.

Outcome measures were rated according to their relative importance in recommendations: essential, important (but not essential) and unimportant. The project group prioritized the essential outcome measures based on clinical relevance. This relevance was based on the experience of the project group members and if necessary other specialisms were consulted (neuroradiologist, neonatologist, clinical physicist, child physiotherapist, a representative of child and hospital, a representative of patient association).

After this the project group members approached authors in European countries to make an inventory of organizational possibilities for the diagnostics and referral in CVI. Information was gathered from specialized centers in the United Kingdom, Denmark, Iceland, Norway and Finland, Ireland and Italy on the registration of risk groups (for instance CP and co-morbidity) and on epidemiology of CVI and the diagnostic approach in CVI.

RESULTS

Topic One: Medical History and Cerebral Visual Impairment

Question 1A: How should screening on CVI be performed? In this search we focused on medical history.

The studies found could be grouped into three categories (**Supplementary Appendix Table 1A**):

1 Prenatal causes; Articles dealing with Genetic causes of CVI (congenital malformation of cerebral development; Khan et al., 2007).
2 Perinatal causes and those describing the consequences of pre or perinatal damage and perinatal complications (Solebo et al., 2017), medication during pregnancy (Hamilton et al., 2010; Nadeem et al., 2015) infection during pregnancy (Coats et al., 2000) neonatal hypoglycemia (Yalnizoglu et al., 2007) and studies reporting on postnatal conditions with anoxia or anemia of brain.
3 Postnatal causes; Cranio-cerebral trauma (Poggi et al., 2000), Apparent Life Threatening Event, surgery of the heart with complications (Shen et al., 2009; Bean Jaworski et al., 2018) infections like meningitis (Chaudhary and Sharma, 2012).

Twelve studies were found mentioning risk factors for CVI (see **Supplementary Appendix Table 1A**): Drugs or medicine *in utero*, intrauterine infections (Cytomegalovirus, CMV), premature delivery/low birth weight, perinatal anoxia, LOW APGAR score, emergency cesarean section, neonatal hydrocephalus, genetic abnormalities, metabolic conditions, cerebral hemorrhages, cerebral infarctions, PVL, intracranial cysts, brain tumors, meningitis or encephalitis, diabetic coma, West syndrome, infantile spasms, and intellectual disability (Wong, 1991; Chen et al., 1992; Houliston et al., 1999; Huo et al., 1999; Shah et al., 2006; Khetpal and Donahue, 2007; Ortibus et al., 2009; van Genderen et al., 2012; Macintyre-Beon et al., 2013; Bosch et al., 2014b; Geldof et al., 2015). By Ventura et al. (2017) a cross-sectional study was performed in 32 children with Congenital Zika Syndrome (CZS). Visual impairment was detected in all 32 infants with CZS (100%). Retinal and/or optic nerve findings were observed in 14 patients (44%). There was no statistical difference between the patients with ocular findings and those without in neurological and neuroimaging abnormalities (P = 0.180). All patients (100%) demonstrated these abnormalities; 3 (9%) presented with late-onset of microcephaly. Henderson et al. (2021) characterized visual pathway abnormalities in 105 infants with CZS using Computed Tomography and Magnetic Resonance Imaging (MRI). Overall, 70 of 74 (95%) scans showed occipital volume loss, whereas 9 (12%) showed optic nerve atrophy, 3 (4%) showed chiasmal atrophy, and 1 (1%) showed an ocular calcification.

Question 1B:Which questionnaire should be used in case the professional has a suspicion of CVI, based on the clinical history?

Following the same procedure as for the first question, nine studies were selected (**Supplementary Appendix Table 1B**) Below we list the questionnaires from these nine studies.

- The PREVIAS (Preverbal Visual Assessment) for 0–24 months (**Supplementary Appendix Table 1B**) 30 questions in four domains.
- The Scottish Question inventory: Macintyre- Beon questionnaire (Macintyre-Beon et al., 2012).
- The Flemish questionnaire; 46 questions on six domains (Ortibus E. et al., 2011).
- Salavati (Salavati et al., 2017); the CVI motor questionnaire.
- The Express questionnaire: To identify CVI in children born extremely preterm (Hellgren et al., 2020).
- Gorrie (Gorrie et al., 2019): Two questionnaires: the CVI questionnaire (Zihl) and Five questions, derived from the 50 items of the Macintyre-Beon questionnaire as was the HVFQ51 (Higher Visual Function Deficits in Children With CVI) questionnaire (Chandna et al., 2021b).
- The PQCVI (Parental Questionnaire for children with CVI) for children younger than 72 months (Moon et al., 2021).
- The Structured Clinical Question Inventory (SCQI; Philip et al., 2016), based on the questionnaires of Dutton and Houliston (Houliston et al., 1999; Dutton et al., 2010).

Clinometric properties of the different questionnaires were as follows; *Specificity*: The specificity of the PREVIAS was 86,5% for visual attention, 89,5% for visual communication 81,5% for visual-motor coordination and 81,3% for visual processing (Garcia-Ormaechea et al., 2014). The Flemish CVI questionnaire showed a specificity of 70–90% depending on the items included. The motor questionnaire showed a specificity of 96% for GMFCS 1–3 and 98%for GMFCS 4 and 5.

Sensitivity: the sensitivity of the PREVIAS was 79% for visual attention, 64% for visual communication, 77,9% for visual motor coordination and 67,5% for visual processing (Garcia-Ormaechea et al., 2014). The sensitivity of the Flemish CVI questionnaire was 0,9 with a sum score of 3.

The CVI motor questionnaire had a sensitivity of 1 for the GMFCS level 1–3 and 97% for the GMFCS level 3–4.

Accuracy: The accuracy of the PREVIAS was 83% for visual attention, 77% for visual communication, 80% for visual motor coordination, and 74% for visual processing. The Flemish CVI questionnaire showed an accuracy of 79% (Ortibus E. et al., 2011) for the L94, based on a selection of seven items. The CVI motor questionnaire showed an area under the curve of 99% for GMFCS 1 and 3 and GMFCS 4 and 5.

Test –retest reliability: The test-retest reliability was performed with the PREVIAS test, and this was 97% for visual attention, 94% for visual communication, and 98% for visual motor coordination and 98% for visual processing.

For the Macintyre- Beon questionnaire, (Macintyre-Beon et al., 2012) no conclusions can be made on the sensitivity, specificity or accuracy.

The (HVFQ1) study is adapted from the Macintyre- Beon's questionnaire. One question has been modified, the intra class correlation remains the same (0.98). The reliability of the question they changed is 0.968. By Gorrie et al. (2019) two questionnaire's validities are studied five questions- sensitivity (81.7%) and specificity (87.2%; ii) CVI questionnaire- sensitivity (96.2%) and specificity-(61.5%).

Rating in levels of evidence:

Question 1A:

The studies found were all cross-sectional studies or smaller cohort studies, which were mostly based on retrospective analysis. Some studies had a comparative design.

Question 1B:

The level of evidence of the PREVIAS is lowered with one level because of limits in extrapolation of the data (bias as a result of indirectness; **Supplementary Appendix Table 1B**).

The level of evidence of the Flemish CVI questionnaire (Ortibus E. et al., 2011) has been lowered with one level as a result of limits in the design of the study, indistinctness of the independent assessment of the index-test and reference test. However, recently (Gorrie et al., 2019) published good convergent validity, internal consistency and a reliable factor structure for 5 questions, derived from the Macyntire Beon questionnaire (Macintyre-Beon et al., 2012) and the CVI questionnaire. In the list of questionnaires each article has been graded.

Rating in levels of evidence: Rating is related to each paper which has been included.

Question 1A Which elements does the clinical history need to contain to screen for CVI?

Very low GRADE	Risks for CVI have been identified from literature with the following data. Exposure to drugs or medication during pregnancy (*in utero*), infections during pregnancy (*in utero*), premature birth, very low birth weight, deficiency of oxygen during birth, low APGAR scores, emergency C-section, neonatal hypoglycemia, reanimation, congenital abnormality of brain, microcephaly, hydrocephalus, genetic abnormalities, metabolic disorders, cerebral hemorrhage, cerebral infarctions, PVL, intracranial cysts, tumors of brain, viral or bacterial infections like meningitis or encephalitis, diabetic coma, complications during operation, cerebral palsy, hypotonia, epilepsy (especially West syndrome, infantile spasm) intellectual disability (Wong, 1991; Chen et al., 1992; Houliston et al., 1999; Huo et al., 1999; Shah et al., 2006; Khetpal and Donahue, 2007; Ortibus et al., 2009; van Genderen et al., 2012; Macintyre-Beon et al., 2013; Bosch et al., 2014b; Geldof et al., 2015; Ozturk et al., 2016) .
Moderate GRADE	Cortical/ CVI may be the most common cause of blindness identified in children with CZS (Ventura et al., 2017). Cortical visual impairment related to structural abnormalities of the occipital cortex is a cause of visual impairment in children with CZS with normal eye examinations (Henderson et al., 2021)

The following items are advised in the patient history in CVI. **First** obtain the medical history:

- Structured medical history in a child that is seen because of doubts on its visual functioning (parents concern about visual functioning, or at a regular visit).

Question 1B Which questionnaire should be used in case the professional has a suspicion of CVI, based on the clinical history?

Moderate GRADE	The preverbal visual assessment (PREVIAS) has a good specificity a moderate sensitivity and accuracy for the detection of deviation of visual maturation (Lee et al., 2012; Garcia-Ormaechea et al., 2014).
Moderate GRADE	PQCVI (Moon et al., 2021; Parental Questionnaire for Children with CVI) the Cerebral visual function score and the scores corresponding to ventral-stream and dorsal-stream visual functions increased with age. The scores rapidly reached 90% of their maximum values up to the age of 36 months.
Moderate GRADE	The Express questionnaire discriminates well between children born extremely preterm and controls (Hellgren et al., 2020).
Moderate GRADE	The Flemish CVI questionnaire (Ortibus E. et al., 2011) has a moderate accuracy, a good specificity and a moderate sensitivity for the detection of (predominantly) ventral stream deficits. Five Questions and the Flemish CVI questionnaire have good convergent validity, internal consistency and a reliable factor structure (Gorrie et al., 2019).
Moderate GRADE	The SCQI and the CVI motor questionnaire have not been validated with an external reference standard. (Macintyre-Beon et al., 2012; Philip et al., 2016; Salavati et al., 2017)
Moderate GRADE	The HVFQI-51 (Higher Visual Function Deficits in Children with Visual Impairments) can detect a range of HVFDs in children with CVI with good visual acuity and clearly distinguishes these children from typically developing children (Chandna et al., 2021b).

- Pregnancy duration (<37 weeks?) and birth weight (<2,000 grams?) APGAR Appearance, Pulse, Grimace, Activity and Respiration score?
- Complications during pregnancy such as infections or medication.
- Complications after birth (such as hypoglycemia, infection) hospitalization (for example cerebral damage by complications during operation, cerebral infection).
- Severe cerebral trauma.
- Developmental milestones (for example delayed motor development or delays in speech, cognition) education (regular or special need).
- Anomalies on neuroimaging (MRI).
- Genetic diagnosis, if available.

Second, with regard to the medical history, the questioning with regard to the following items are advised when assessing for CVI:

All questionnaires show a relatively moderate or good sensitivity or specificity, however, for screening all children this is too low, because too many false positive and false negative outcomes are found. We advise to use the questionnaire only in children with a risk on CVI.

- Use the PREVIAS in children younger than 24 months.
- Use the Flemishquestionnaire (Ortibus E. et al., 2011) and the SCQI (Philip et al., 2016) in children of 3 to 5 years of age.
- Refer children that are reviewed due to complications in neonatal care, children with cerebral palsy (GMFCS 1 t/m 5) or developmental delay or traumatic brain injury <12 years to an ophthalmologist at 24 months or when the structured medical history and/or the questionnaire give rise to referral.
- Apply the CVI questionnaires (according to age category) in children that are reviewed due to complications in neonatal care, in children with cerebral palsy (GMFCS 1 t/m 5), developmental delay, traumatic brain injury or stroke <12 years.
- Refer children to an ophthalmologist when the structured medical history and/or the questionnaire warrants a referral sooner/later.

Topic Two: Ophthalmological and Orthoptic Examinations in Cerebral Visual Impairment

Questions:

Two research questions were defined after discussion with professionals and caretakers who work with children with CVI:

Question 2A: Which are the ophthalmological en orthoptic assessments that are required in case of suspected CVI by ophthalmologist and orthoptist in a general hospital?

Question 2B: Which ophthalmological and orthoptic assessments in CVI can be performed in academic centers in case of suspected CVI?

Description of literature:

Question 2A: Description of studies and results (**Supplementary Appendix Table 2A**). In a retrospective study, Dutton and Fazzi describe characteristic findings in ophthalmological and orthoptic assessments in CVI (Dutton et al., 1996; Fazzi et al., 2007, 2012) see **Supplementary Appendix Table 2A**. Fazzi describes lower visual acuity, reduction of contrast sensitivity, abnormal optokinetic nystagmus, reduction of visual field as well as abnormal fixation, reduction of smooth pursuit and saccade quality, strabismus, abnormal eye movements, fundus abnormalities, hyperopia, astigmatism, and myopia. Lowered contrast sensitivity is also found in CVI patients by Mayer et al. (2020) with the DH $\log_{10}$ CS test (a new contrast sensitivity test for pediatric patients). More information on visual field reduction was provided by Bosch et al. (2014b). In children with CVI and low visual acuity hemianopia was found in 19%, upper or lower visual field defect in 25% constriction of visual field in 56%.

Tinelli et al. (2020) found a strong correlation between brain lesions and visual function total score (global MRI score $p = 0.000$; hemispheric score $p = 0.001$; and subcortical score $p = 0.000$). Visual acuity, visual field, stereopsis and color were compromised when a cortical damage was present. Ocular motricity (and in particular fixation and saccades) were compromised in presence of subcortical brain damage. Hemispheric severity scores were significantly higher (corresponding to more severe lesions) in children with impaired visual acuity, visual field, stereopsis and color perception. Subcortical score means values were significantly higher in children with an impairment in all the visual items except for nystagmus.

Ruberto et al. (2006) studied OCT and HRT findings in CVI and describes characteristic anatomical findings of the optic nerve: the optic nerve was smaller, the cup/disk ratio larger, the rim smaller and the RNFL thinner in CVI compared to typically developing children. Van der Zee and Evenhuis (2017), see **Supplementary Appendix Table 2A**, found more crowding deficit in children with CVI compared to typically developing children.

Question 2A: Evidence from literature

For this question only observational cross-sectional studies were found, the level of evidence of these studies is low, see also **Supplementary Appendix Table 2A**. In the studies of Dutton et al. (1996); Fazzi et al. (2007, 2012), and Saidkasimova et al. (2007) there was no control group, for this reason the level of evidence is very low. Tanke et al. (2021) described the Developmental Eye Movement (DEM) test when assessing for CVI. 96 Normally sighted children, 33 visually impaired children and 30 children with CVI were compared. It was found that children with CVI or VI need significantly more time to read the DEM numbers than age-matched controls. Additionally, children with CVI needed more time than children with VI to read the horizontal DEM, but not the vertical DEM.

Rating in levels of evidence: Rating is related to each paper which has been included.

Question 2A:

Very low GRADE	Children with CVI seem to have a suboptimal visual acuity and a lower discrimination speed. (Fazzi et al., 2007; Barsingerhorn et al., 2018)
Moderate GRADE	Visual acuity, visual field, stereopsis and color were compromised when a cortical damage was present (Tinelli et al., 2020).
Low GRADE	The ratio between grating visual acuity and crowded visual acuity was significantly higher in children with pathology of the eye and/or brain damage than in typically developing children *A poorer crowding ratio is found in children with CVI compared to normally sighted (healthy) children. A higher crowding ratio was also found in nystagmus and amblyopia* (Huurneman et al., 2012; van der Zee et al., 2017).
Very low GRADE	Children with CVI as a result of cerebral palsy more often seem to have reduced contrast sensitivity (Fazzi et al., 2007, 2012).
Low GRADE	DH $\log_{10}$ CS test can be used in children diagnosed with ocular disorders or CVI, Contrast sensitivity was reduced in CVI. Inter-examiner reliability was comparable to that of adults tested previously using the same stimuli and methods (Mayer et al., 2020).
Very low GRADE	Children with CVI seem to show abnormal optokinetic nystagmus more frequently. Strabismus is found more frequently in CVI. Abnormal smooth pursuit movements are found more often in CVI (Fazzi et al., 2007).
Moderate GRADE	Ocular motricity (and in particular fixation and saccades) were compromised in presence of subcortical brain damage (Tinelli et al., 2020).
Very low GRADE	Deviation in saccades are found more often in children with CVI. *Ref* (Fazzi et al., 2012; Barsingerhorn et al., 2019). *Ophthalmological findings that are often found in CVI are strabismus (59%), optic atrophy (42%), nystagmus (12%) and significant refraction anomalies (20%). Visual functions also are deviating in CVI but in 50% of cases, these functions can develop in time* (Khetpal and Donahue, 2007).
Moderate GRADE	In children with CVI optic nerve parameters (OCT, HRT) differ from typically developing children (optic disk surface, cup/disk ratio). (Ruberto et al., 2006)
	With OCT retrograde transsynnaptic (RTSD) degeneration can be detected (Lennartsson et al., 2021) The ganglion cell thinning corresponded with the visual field defects and the extent and location of the primary brain damage. The most important sign of RTSD was asymmetry of the ganglion cell topography within the macular area (Jacobson et al., 2019).
Low GRADE	Children with CVI frequently show visual field abnormalities.; *Hemianopia, upper or lower visual field defect, and constriction of visual field. Ref* (Dutton et al., 1996; Fazzi et al., 2007; Saidkasimova et al., 2007; Luckman et al., 2020).
	In children with CVI the full field peritest (FFP) had best reliability with 44% "good" scores versus 22% for Goldmann perimetry (Portengen et al., 2020).

Question 2B: Description of studies and results (**Supplementary Appendix Table 2B**).

Cavascan et al. (2014) studied 115 children with CVI with sweep VEP. Small inter-ocular differences were found in visual acuity (grating acuity). Clarke et al. (1997) used flash VEP in 44 children, and Frank et al. (1992) studied 60 children with pattern VEP with CVI without ocular pathology, and based on observations. Good et al. (2012) studied 34 children with binocular reduced visual acuity and without ocular pathology with sweep VEP. By Chang and Borchert (2021) visual acuity was assessed clinically in 16 children with CVI using a previously published six-level scale of visual behavior. Grating acuity was assessed by eye tracking using forced-choice preferential looking, this correlated well with clinical visual acuity measurement.

In a systematic review Huurneman et al. (2012) described foveal crowding in children with CVI, two studies were included (Pike et al., 1994; Jacobson et al., 1996); larger effects of crowding were found in CVI than in healthy subjects. Pike et al. (1994) studied visual impairment in 42 children with different lesions on ultrasound examination at 35 weeks gestational age (leukomalacia, large intraventricular hemorrhages, or cerebral infarctions). Predictors of the amount of foveal crowding in children with CVI were: the type of lesions (ischemic lesions are associated with lower visual acuity than hemorrhagic lesions), oculomotor deviations (not being able to fixate), the presence of nystagmus and low visual acuity. Khetpal and Donahue (2007) described the results of ophthalmological examinations in 98 children with CVI; most important ocular findings in CVI were: Exotropia (41%), esotropia (19%), mild optic atrophy (25%), nystagmus (21%), severe optic atrophy (17%), amblyopia (12%), photophobia (4%), and retinal abnormalities (3%). In a study of Sakki et al. (2021) three subgroups of children were described with differentiated visual function characteristics on a gradient

of severity. One group showed selective visual perception and visuomotor deficits, the second group showed more severe and broader visual perception and visuomotor deficits, and variable visual acuity and a third group (B), lower-functioning group showed significant visual acuity reduction compared with the first group. Significant group differences were found according to the visual acuity and Hiding Heidi contrast sensitivity categories, with Group B having the lowest scores. The subgrouping method provides the first steps in developing a novel classification system to underpin future clinical diagnostics and profiling of early onset CVI.

Kooiker et al. (2014) performed eye tracking in children with mild oculomotor deviations and children with CVI. A difference in reaction time was found between children with CVI and age matched controls, children with CVI were significantly slower. Lim et al. (2005) used VEP and preferential looking for an assessment in 19 children who were born at term with a history of cerebral damage before or during birth of hypoxia and evidence on MRI for cerebral damage, in a pattern which is typical for hypoxic ischemic encephalopathy. Preferential looking (PL) acuity showed to be lower than normal for this age for nearly all children. Between the first and last measurement the mean increased with one octave; this was also found in acuity VEP. Howes et al. (2022) investigated whether pattern reversal visual evoked potentials (PRVEPs) could predict future visual acuity in infants with CVI. It was found that VEPs in young children with CVI might have prognostic value regarding future acuity.

Skoczenski and Good (2004) showed that grating acuity and Vernier acuity (the ability to discern two lines that do not fuse but run close together) was lowered in children with CVI compared to typically developing children. Graphical research showed that the Vernier acuity was more diminished than the grating acuity and therefore more sensitive in the detection of CVI.

Watson et al. (2007, 2009) investigated 39 children with CVI with sweep VEP (Watson et al., 2009), grating acuity and Vernier acuity and preferential looking. Watson and Haegerstrom-Portnoy (2010) described 33 children with CVI, who were followed for 7 years; the Vernier acuity was more comparable to the PL test than the acuity VEP. Chandna (Chandna et al., 2021a) characterized neural motion processing deficits in children with CVI by using steady-state visual evoked potentials (SSVEP′s) in 31 children with CVI and 28 age-matched healthy controls. Significant deficits in cerebral processing of relative and rotary motion was found but not of absolute motion in children with CVI compared with healthy controls. Vernier acuity, in keeping with good recognition acuity in both groups, was not different, nor were contour-related form responses.

Question 2B: Evidence from literature

One systematic review was found in which two small observational studies are described that were non-comparative in children with CVI with low level of evidence.

Observational cross-sectional studies were found with low level of evidence. In the studies of Clarke et al. (1997), Sakai et al. (2002); Salati et al. (2002), Lim et al. (2005); Khetpal and Donahue (2007), Watson et al. (2007); Watson and Haegerstrom-Portnoy (2010), and Cavascan et al. (2014) there was no control group, therefore the level of evidence was very low.

Rating in levels of evidence: Rating is related to each paper which has been included.

Question 2B:

Very low GRADE	The Flash VEP showed a sensitivity that was 85% of the normal VEP in CVI for visual acuity development. The specificity was only 35%. *Ref* (Clarke et al., 1997)
Low GRADE	In VEP stimulation in CVI an abnormal response was found often, especially at the occipital pattern VEP (more than temporo -parietal pattern VEP). *Ref* (Frank et al., 1992)
Moderate GRADE	A subset of patients with CVI have abnormal visual orienting behaviors despite a normal VEP (visuomotor dysfunction; Kelly et al., 2021)
Very low GRADE	Sweep VEP nearly always deviating from normal controls, only in 16% of children with CVI a normal (straight) eye position was found. In CVI usually strabismus is found as well as motility disorders of the eyes. *Ref* (Watson et al., 2007; Watson and Haegerstrom-Portnoy, 2010; Cavascan et al., 2014)
Low GRADE	A sweep VEP showed lower threshold values for grating acuity and contrast sensitivity in children with CVI compared to normal matched controls. *Ref* (Sakai et al., 2002; Lim et al., 2005; Good et al., 2012; Cavascan et al., 2014)
Low GRADE	The Sweep VEP test (Vernier acuity) is useful for prediction of behavioral visual acuity. *Ref* (Watson and Haegerstrom-Portnoy, 2010)
Low GRADE	Grating acuity and vernier acuity was lower in children with CVI than in healthy controls. In a graph vernier acuity was more reduced than grating acuity. Ref (Skoczenski and Good, 2004) *Difference between VEP and Preferential Looking Test is higher in CVI than in normally sighted subjects* (Raja et al., 2021).
Low Grade	With pattern reversal VEP a rough prediction can be made of future visual acuity (Howes et al., 2022).
Low Grade	In the horizontal part of the digital DEM (Developmental Eye Movement Test) children with CVI need more time than VI children of NS children (Tanke et al., 2021).
Low Grade	*Vestibular–Ocular Reflexes are commonly impaired in children with* CVI (Mansukhani et al., 2021).
Very low GRADE	Typical motility disorders of the eye in CVI are paroxysmal ocular deviations (78%), angle strabismus (86%), and reduced coordination of saccades (93%). Orientation in place (spatial; 88%) and fixation (84%) were also reduced. A deviant initiation of saccades and an abnormally preformed saccades were seen the absence of smooth pursuit, abnormal vergence, nystagmus beats and fixation instability were seen as well as problems with systematic orientation in space.*Ref* (Salati et al., 2002).

The following items are advised in an examination for CVI in an academic or diagnostic center;

In Italics the tests that are more specific for CVI;

Moderate GRADE	With Steady-state visual evoked potentials a deficit in processing on more complex relative and rotary motion was found in children with CVI compared to controls, while in processing absolute motion, vernier acuity and contour related form responses no differences were found (Chandna et al., 2021a)
Low GRADE	By the recording of eye movements with eye tracking it was shown that children with CVI reacted significantly slower on visual stimuli (cartoons and movies) than age-matched controls (Kooiker et al., 2014). Eye tracking demonstrates reliability for visual acuity assessment and high correlation with clinical assessment of visual acuity in pediatric CVI (Chang and Borchert, 2021).
Moderate GRADE	Eye tracking in children born very pre-term without apparent White and Gray matter damage on MRI: The infants in the preterm group had longer response times in detecting color patterns (red-green) and motion compared with infants in the comparison group. No impairments were detected in oculomotor functions (saccades, pursuit, and fixations; Pel et al., 2016).

1 Analyze visual behavior, observe characteristic visual behavior such as overlooking or avoiding (grasping an object while looking the other way, localizing with the periphery of the visual field) or problems with recognition, orientation, perception of movements and simultaneous perception (like overlooking while listening or feeling an object) (Porro et al., 1998).
2 Analyze *motility of the eyes* included *nystagmus*, if present, analyze eye position (strabismus, if present), fixation, *saccades*, pursuit movements and vergence. If possible, *apply eye tracking* to analyze eye movement disorders.
3 Analyze head position and torticollis.
4 Analyze *pupil and pupil reflex* and anisocoria and RAPD. A deviation in pupillary response can be a sign of optic nerve problems or pathology of chiasma (Naber et al., 2018). Pupillary responses are often normal in CVI even if mild bilateral optic atrophy is found. This part of the examination is also important in differential diagnosis.
5 Analyze binocular vision (stereopsis).
6 Measure visual acuity (matching or verbal test) near and at distance (for instance ETDRS, illiterate E, numbers, Landolt C, LH charts) and measure *the crowding ratio at near* binocular (Huurneman et al., 2012) and if possible, also monocular. A crowding ratio of 1 is found in typically developing children of about 7 years old, which means that there is no crowding deficit after 7 years. In visually impaired children and children with CVI, this reduction of crowding was not found.
7 If visual acuity measurement at distance is not found or if it is not possible, try to measure visual acuity non-verbally for each eye and for both eyes for instance with Teller Acuity Cards (TAC) or Cardiff Acuity Test.
8 Measure the *contrast sensitivity* verbally or non-verbally. For instance, with Vistech or Hiding Heidi in younger children, monocular and binocular. A reduced contrast sensitivity can be found in CVI.
9 *Measure accommodation* with dynamic skiascopy or another measurement method.
10 Investigate *visual fields* with a confrontative measurement (Donders method or behavioral method such as Stycar balls, the Behavioral Visual Field Testing (BEFIE test), the double arc perimetry or equivalent test when standard methods could not be performed (Koenraad, 2016).
11 If possible, depending on the developmental age, make a visual field with standard perimetry Goldmann and/or automatic perimetry if possible.
12 Analyze the anterior segment and media with a slit lamp (if no data are obtained before).
13 Obtain refraction in mydriasis (cycloplegia) if no data have been obtained before.
14 Analyze the optic media and *fundus by ophthalmoscopy* in mydriasis.
15 Make *OCT scan* of the optic nerve and macula with RNFL analysis and Ganglion cell layer (GCL) analysis. In CVI the optic nerve can be smaller or a larger excavation is seen (Ruberto et al., 2006; Jacobson et al., 2019).
16 If visual acuity has not been measured adequately, observe *optokinetic nystagmus*.
17 If visual acuity has not been measured adequately and OCT does not provide enough information on the optic nerve, *consider VEP*.

All items are meant to investigate CVI; deviations in fixation, saccades, accommodation, crowding ratio at near, visual field, and optic nerve are of specific importance for CVI.

Besides the ophthalmological and orthoptic examination as performed in academic centers there are two important issues for CVI.

1 Multidisciplinary cooperation is necessary. The multidisciplinary team for CVI diagnostics should minimally contain a pediatric ophthalmologist, pediatric neurologist, orthoptist or optometrist, neuropsychologist. After ophthalmological and orthoptic examination the ophthalmologist should organize multidisciplinary meetings to discuss the results and the possibilities for further assessments, if necessary. For instance, the ophthalmologist should discuss with the neurologist (or pediatrician with specialization in neurology) referral criteria if a neurological diagnosis is suspected or a neurodegenerative diagnosis is in the differential diagnosis.
2 The academic (pediatric) ophthalmologist can refer the child to a rehabilitation center or a specialized center or school for visually impaired children if there is evidence of CVI and the etiology is clear.

Topic Three: Neuropsychological Assessment

Questions:

Question 3: Which neuropsychological tests can be used in the neuropsychological examination of children with CVI?

Question 3: Description of studies and results (**Supplementary Appendix Table 3**).

A systematic review (Auld et al., 2011) describes the psychometric properties of assessment instruments for visual perception in children with hemiplegia. Because of the presence of CVI in a majority of children with cerebral palsy (CP)/hemiplegia this article is included in the literature analysis. Children with cerebral palsy (CP) often present with CVI up to 50% in an overview study by Ego et al. (2015) and more than 90% of children with CVI have multiple impairments (Khetpal and Donahue, 2007), including severe motor and language disorders. Ego described a systematic literature review to assess the frequency of visual–perceptual impairment and its relationship with patient characteristics. The systematic analysis (Auld et al., 2011) found 3 assessment instruments that met the inclusion criteria: the Motor Free Visual Perception test (MVPT), Test of Visual Perceptual skills (TVPS), and the Developmental Test of Visual Perception second edition (DTVP-2). For all tests psychometric data are available of normative studies, but not of studies with children with hemiplegia.

Vancleef et al. (2020) measured CVI related visual perception deficits with the Children's Visual Impairment Test, 3–6 years (CVIT3–6). The CVIT 3–6 is grounded in knowledge of visual perception. Reliability was assessed via test-retest correlation and intraclass correlation coefficient (ICC) in typically developing children, children with CVI, intellectual impairment, and simulated impaired vision (validation groups n = 59, mean developmental age = 4 year 10 month, 27 females, 32 males).

Ben Itzhak et al. (2021b) assessed the clinical records of 630 children (median age 77 months, interquartile range 63–98 months) referred to a CVI clinic and evaluated the diagnostic value of seven predefined dimensions of a visual perceptual schema: visual discrimination and matching, object or picture recognition, visual spatial perception, figure-ground perception, motion perception, visual short-term memory, and scene perception, using the combined results of a set of 23 subtests derived from the Beery Visual-Motor Integration test (VMI), TVPS, L94, Revised Amsterdam Children's Intelligence Test (RAKIT-2), Preschool Judgment of Line Orientation (PJLO), Neuropsychological Assessment (NEPSY-II) and several motion perception tasks.

Van der Zee et al. (2019) studied Gestalt perception using images of the Kaufman Assessment Battery for children's subtest Gestalt Closure. They analyzed gaze behavior recorded by eye tracking of 20 children with CVI.

Results

Specificity and Sensitivity for CVI were reported for the dimensions of the visual perceptive schema of Ben Itzhak et al. (2021b). For object/picture recognition, a good area under curve (AUC) was found (AUC 83%, sensitivity 82%, specificity 69%; fair AUCs were found for visual spatial perception 80%, visual discrimination and matching 78%, figure-ground perception 73%; sensitivity ranging from 75 to 78% and specificity ranging from 65 to 67%. Motion perception and visual short-term memory showed poor AUCs 63%, sensitivity 71–73% and specificity 45–49%.

Test-retest reliability is high for the complete MVPT in normally developed children and children with learning problems (ICCs = 0,63–0,79). For the TVPS, test- retest reliability is also high in children with learning problems (ICC = 0.81). No ICCs for the DTVP were reported. Internal consistency is high for the MVPT (Cronbach's coefficient α 4–10 years = 0,69–0,87 > 11 years: 0,86–0,9). For the TVPS, studies report varying internal consistency (low-excellent). The DTVP shows a high internal consistency (Cronbach's α coefficient- 0,8–0,97 concerning the subtests; 0,93 or higher for the complete test).

For the CVIT3–6, high correlations were found with tests with a strong visual perception component (L94: r = 0.74, p < 0.001; SON-R 2.5–7: r = 0.37, p = 0.01) and low correlations with other tests (Beery-VMI: r = 0.25, p = 0.09; SRS: r = 0–0.26, p = 0.09). Lowest scores were observed for children with CVI compared to the other validation groups [$F(3,44) = 5.1$, p = 0.003], supporting its validity. The tool specifically measures CVI-related visual perception deficits and is not mediated by intellectual abilities or low visual acuity. Good test-retest reliability (r = 0.82, p < 0.001, ICC = 0.80) was found (Vancleef et al., 2020).

The most discriminating dimensions between CVI and no CVI were Object/picture recognition (r = 0.56), visual spatial perception (r = 0.52), visual discrimination and matching (r = 0.47), and figure-ground perception (r = 0.39; Ben Itzhak et al., 2021b). Gestalt perception was worse in children with CVI as compared to visual impaired children with ocular disorders (Van der Zee et al., 2019). Children with CVI performed extremely weak, i.e., 60% scored below the level of the weakest 9% of healthy controls.

Given the lack of evidence for the diagnostic value of individual tests for visual perception, an assessment protocol could be composed of the neuropsychological subtests as indicated by the Delphi study reported by Ben Itzhak and derived from the tests MVPT, DTVP, TVPS, L94, Beery VMI, RAKIT-2, PJLO, and NEPSY-II.

- Dimension Object/picture recognition: L94 De Vos-task, Visual matching, Line drawings occluded by noise, Overlapping line drawings, Unconventional object views, RAKIT-2 Figure recognition, Hidden figures, Motion-defined form, and Biological motion.
- Dimension Visual spatial perception: Beery VMI Perception, Motor-coordination, visual-motor integration, TVPS-3: Visual discrimination, Visual spatial relationships, Visual memory, Visual sequential memory, Visual figure-ground, Visual closure, L94 De Vos-task, and Visual matching.
- Dimension Visual discrimination and matching: Beery VMI Perception, TVPS-3: Visual discrimination, Visual spatial relationships, Visual memory, Visual sequential memory, Visual figure-ground, Visual closure, L94 De Vos-task, Visual matching Overlapping line drawings, RAKIT-2 Hidden figures, and PJLO.
- Dimension Figure-ground perception: TVPS-3: Visual figure-ground, Form constancy, L94 Line drawings

occluded by noise, Overlapping line drawings, RAKIT-2 Hidden figures, and Motion defined form.

Given the wide variety of available subtests, the project group advises to adjust assessment protocols to the child's age-level and mental abilities.

Rating in levels of evidence: Rating is related to each paper which has been included.

Question 3A:

Low GRADE	The Motor-free Visual Perception Test and the Developmental Test for Visual Perception seem to have a high internal consistency for the complete test (Auld et al., 2011)
Low GRADE	Eyetracking for gaze fixation duration and saccades. Children with visual impairments due to cerebral damage show weaker Gestalt perception and had different looking patterns than children with ocular or without visual impairments. Children with CVI and brain damage performed significantly worse on the animate items than the group without brain damage (Van der Zee et al., 2019) To study the selectivity of visual perceptual impairment in children with early brain injury, the L94can be administered. It discriminates between congenitally disabled children with and without risk for CVI (Stiers et al., 2001)
Moderate GRADE	The CVIT specifically measures CVI-related visual perception deficits and is not mediated by intellectual abilities or low visual acuity (Vancleef et al., 2020)
Moderate GRADE	The most discriminating dimensions between CVI and no CVI were object/picture recognition (r = 0.56), visual spatial perception (r = 0.52), visual discrimination and matching (r = 0.47), and figure-ground perception (r = 0.39; Ben Itzhak et al., 2021b).

Screening and Diagnostic Assessment

If deficits in visual attention or visual perception are suspected, screening of visual perceptive functioning with the Motor-free Visual perception test is recommended and can be directive for further assessment. Refer for further assessment if test outcomes are typical for CVI. Referral can also be considered if MVPT results are normal since it does not measure all aspects of visual perceptive functioning. Refer for neuropsychological assessment for CVI to a specialized center if the neurocognitive profile shows discrepancies in disadvantage of the level of visual processing (i.e., visual selective attention, visual perception, visual memory, or visual processing speed).

Diagnostic assessment. The following assessment is advised in a child with possible CVI. Conduct neuropsychological assessment in children suspected of deficits in visual attention or visual perception using the following neuropsychological tests and principles:

- Assess visual perception with the DTVP, TVPS, L94, and CVIT 3–6. Recommendations for a fixed set of tests is not supported by evidence. The studies indicate several visual-perceptive dimensions that are sensitive to CVI, that, however, consist of the combined results of neuropsychological tests or subtests.
- It is therefore advised to select subtests from the reported set of tests and adjust the protocol to the age-level and mental abilities of the child.
- In addition the RAKIT-2, PJLO, NEPSY-II, Beery VMI, and Motion perception tasks can be used. Neuropsychological assessment of disorders in object/picture recognition, visual spatial perception, visual discrimination and matching, figure-ground perception, and visual organization or recognition in visual noise. There is no preferred test based on the literature.
- Also assess other aspects of visual information processing: Visual selective attention, visuo-spatial perception (global versus local attention).
- Discrepancies of the neurocognitive profile indicating weaknesses of visual information processing within the domains of attention, motor, and memory functions.

Furthermore the project group recommends to compare test results with normative data matched on mental developmental age. Verify whether disorders in visual attention and perception are associated with the medical history and the limitations reported in activity and participation in daily life.

Discuss symptoms of other developmental disorders and/or differential diagnostic considerations with parents and caretakers of children suspected of CVI. In very young children and in case of doubt of the validity of assessment outcome, consider temporally using a "working diagnosis" CVI to provide access to care facilities, if needed. Plan follow-up assessment is case CVI has been diagnosed or if there are doubts about the exact type of dysfunction in visual attention or perception, until a developmental age of 12 years, or at least until no change in the diagnostic outcome is expected. Discuss the outcome of neuropsychological assessment in a multidisciplinary team and incorporate the findings in diagnostic decision making and follow up trajectory.

Topic Four: Neuro-Radiological Evaluation and Magnetic Resonance Imaging

Questions:

Question 4A: How can neuro-radiological examination (imaging) be used to obtain a diagnosis of CVI in children?
Question 4B: Is neuro-radiological examination necessary to obtain a diagnosis of CVI?

Description of literature: Question 4 AB: Description of studies and results (**Supplementary Appendix Table 4**).

In 53 premature babies with PVL a correlation was found between the presence and amount of damage to the occipital white and gray matter and CVI (Sie et al., 2005). MRI images were obtained at a mean age of 20 days after birth and at 1,5 years Khetpal studied 98 children retrospectively (Khetpal and Donahue, 2007) with final diagnosis CVI, in 70% an MRI was made of which abnormalities were found in 83%. Lambert et al. (1987) included 75 children younger than 6 years with hypoxic seizure. CT scan was made in 28 children MRI in two children.

In these children (all with diagnosis CVI) global atrophy was found in 12 children, PVL in 8 children, an infarction of the occipital lobe in and mild atrophy of the optic nerve in 6 children and watershed area infarction of the parieto-occipital lobe in 2 children. The 2 children with normal scans had good visual outcome. Uggetti et al. (1996) studied 27 premature children with cerebral palsy as a result of periventricular leucomalacia, 17 were diagnosed with CVI. The MRI findings corresponded with visual acuity. There was a relation between visual functions and a reduction of the peri-trigonal white matter and calcarin atrophy contra laterally.

In a retrospective study 53 schoolchildren were described by van Genderen et al. (2012) with good binocular visual acuity but with suspected CVI. They were referred to a center for rehabilitation. The 30 children with diagnosis CVI (based on orthoptic and ophthalmological examination) had an abnormal medical history, 21 were born prematurely, 7 had perinatal asphyxia two children had trauma capitis, 20 children had cerebral palsy and 8 had epileptic seizures. In this group abnormalities on MRI were found in 86% of children. In the 27 children who were not diagnosed with CVI 6 children (25%) had an abnormal medical history; prematurity in 4 children, hydrocephalus in one child, epileptic seizures in one child.

Magnetic resonance imaging abnormalities. MRI abnormalities can also be found in genetic anomalies of brain or congenital infections like CZS (CZS) or congenital cytomegaly virus (CMV); (Bosch et al., 2014b; Henderson et al., 2021).

In a review, (Philip et al., 2020) studied the relationship between brain structure and CVI in children with Cerebral Palsy. Based on the outcome of the search they reported the brain lesion on MRI linked to CP and CVI thus grouping the subjects into the brain maldevelopment group, the white matter lesion group, the gray matter lesion group, or the postnatal lesion group and a normal MRI group.

1 Brain maldevelopment (*lesions that occurred in the 1st and 2nd trimester*) accounting for 3% of all brain lesions. In this group, spastic subtype of CP was the most common presentation (84%, $n = 103$ subjects).
2 White matter lesions (*those occurring in early 3rd trimester or preterm babies*) were the most common (83.5%, $n = 665$ subjects) classified brain lesion on MRI. Periventricular leucomalacia was the most common MRI finding reported followed by ventricular dilation, thinning of the corpus callosum and gliosis of the occipital area. CVI was reported in all the 30 studies, with dorsal stream dysfunction described in 9 studies.
3 Gray matter lesions (*occurring in the late 3rd trimester of gestation or term*) accounted for only 4% of all classified brain lesions with spastic CP seen in 103 subjects and non-spastic CP in 16 subjects.
4 The fourth and the least common pattern of brain lesions are *those that occurred in the post-natal period* and accounted for 1.0% ($n = 8$) of all the brain lesions.

In 13 of the 30 studies, CVI was further characterized into ventral or dorsal stream function or both. (i) Ventral stream (occipito-temporal pathway): also called "what" (perceptual) pathway, connecting the occipital lobe to the temporal lobe and involved with orientation, visual memory and recognition of faces, shapes, objects, and words; (ii) dorsal stream (occipito-parietal pathway): also called "where" pathway, connecting the occipital lobe to the posterior parietal lobe and is responsible for subconscious mapping of the visual scene, triggering the frontal eye fields to bring about quick eye and head movement to the object of regard subserving visual attention movement and handling of complex visual scene (Milner and Goodale, 2006) .

Tinelli et al. (2020) studied 72 children with PVL (periventricular leucomalacia), and found a significant correlation between brain lesion severity and visual function impairment in children with PVL. In a case control study (Pamir et al., 2021) compared 12 CVI children (17 years) with 18 controls (19 years). They studied activation response profiles in functionally defined early (i.e., primary visual cortex; area V1) and higher order (i.e. middle temporal cortex; area hMT+) stages of motion processing. Mean motion coherence threshold for CVI participants (44.18% $\pm$ 23.3 SD) was significantly higher (i.e., indicative of worse performance) compared to controls. Specifically, increased motion coherence was associated with an increased BOLD signal response in area hMT + for CVI, but not for the control group.

Rating in levels of evidence: Rating is related to each paper which has been included.

Question 4AB:

Very low GRADE	In children with CVI, MRI abnormalities were often found related to the visual pathways. The abnormalities are not identical. In children who have no CVI abnormalities on MRI are found less often. (Lambert et al., 1987; Uggetti et al., 1996; Sie et al., 2005; Khetpal and Donahue, 2007; van Genderen et al., 2012)
Moderate GRADE	Periventricular leucomalacia on MRI was found to have a strong association with CVI in all 30 studies. Only 13 (43%) studies described dorsal and/ventral stream dysfunction (Philip et al., 2020).
Low GRADE	MR imaging showed signs of cortical dysgenesis leading to congenital brain malformations such as polymicrogyria consistent with a prenatal timing of CNS injury (Ho et al., 2020).
Moderate GRADE	CVI participants have a significantly higher mean motion coherence threshold (determined using a random dot kinematogram pattern simulating optic flow motion) compared to controls. Using functional magnetic resonance imaging (fMRI; Pamir et al., 2021).
Moderate GRADE	Brain lesion severity strongly correlated with visual function total score. Moreover, visual acuity, visual field, stereopsis and color were compromised when a cortical damage was present, while ocular motricity (and in particular fixation and saccades) were compromised in presence of subcortical brain damage (Tinelli et al., 2020).

The following steps are advised in a child with possible CVI.

Always plan a consultation of a pediatric neurologist to organize MRI in CVI.

Discuss the implications of MRI with parents or caretakers because of the burden and risk for the child. Also, it is advised to relativize the outcome of MRI for the diagnosis CVI.

Consider MRI when there are doubts about CVI, this is necessary to exclude other causes of visual impairment. MRI can give more information on the etiology of CVI. Structural and functional neuroimaging approaches in CVI can help gain insight into abnormalities of white matter connectivity and cortical activation patterns, respectively (Merabet et al., 2017).

Discuss the results of MRI or ultrasound (in children younger than 1 year old) in CVI in a multidisciplinary team and take the considerations of different disciplines into account for diagnostic follow up. Potentially, MRI would be the best imaging modality to assess neonatal brain damage, but requires infant displacement from the neonatal intensive care unit (Sie et al., 2005), the additional value of early MRI as compared to cranial ultrasound was described previously. It was shown that early MRI can detect the precise site and extent of white matter injury at an earlier stage and allows a better differentiation of lesions than ultrasound.

In CVI ophthalmological and orthoptic examinations applied in academic centers assessment can be accompanied by pediatric, neurological, neuropsychological and neuroradiological examinations. Therefore, a multidisciplinary CVI team is necessary, this team may also function between different (specialized) centers.

Topic Five: Genetic Assessment

Questions:

Question 5 What is the role of the genetic diagnosis in the referral of a child for clinical investigation for CVI?

Description of literature:

> Question 5: Description of studies and results (**Supplementary Appendix Table 5**).

The evidence from the literature for presence of CVI in children with a genetic disease is lowered with two levels to "low" as a result of the draw backs in the study design and lack of information about the control group and the low number of patients.

Rating in levels of evidence: Rating is related to each paper which has been included.

Question 5:

Low GRADE	The following genetic disorders seem to be associated with CVI: Down syndrome (trisomie 21), 1p36 deletion syndrome, 17p13.3 deletion syndrome (Miller-Dieker syndrome), 22q13.3 deletion syndrome (Phelan-McDermid syndrome), CDG type 1a, complex I deficiency, Lissencephaly (gene DCX), Pelizaeus-Merzbacher syndrome (gene PLP1), atypical Rett syndrome (gene CDKL5), NGLY1, AHDC1, NR2F1, PGAP1and tuberous sclerosis. (Bosch et al., 2014a,b, 2016; Wan et al., 2019; Wilton et al., 2021)

In all but five studies, a possible association between CVI and a genetic cause was found in case reports or case series. In general congenital anomalies of brain can give CVI.

Research on genetic causes in a CVI population is only found in five studies (Bosch et al., 2014a,b, 2016) and only in persons with a visual acuity of $\leq$6/18. There are no studies with large populations of persons with a specific genetic disorder that have been investigated on presence or absence of CVI. Behavioral features of CVI are common in children with Down syndrome 38% of parents reported CVI symptoms (visual perception difficulties; Wilton et al., 2021). Children with Down syndrome have significantly lower visual acuity than typically developing children at distance and at near that cannot be corrected by distant refraction. They often present with accommodation deficit, crowding and strabismus (de Weger et al., 2021) and need bifocals to correct this (de Weger et al., 2019).

In several case series and reports, CVI was mentioned as one of the features. Although these reports are not of sufficient quality to include in the guidelines, a table is made of genetic diagnosis found if one of the features mentioned was CVI (**Supplementary Appendix Table 5**: Genetic cause found in case reports and case series).

The following remarks must be made:

- Cerebral visual impairment can be co-morbidity, without a causal relation, in a child with a genetic disorder.
- The table does not provide information on frequencies of CVI found in this diagnosis and if referral for further investigation on CVI is justified.
- Absence of a genetic disease in the table does not mean CVI cannot be found in this disease, because a structural examination on specific CVI items is not always performed or not mentioned in the title or abstract.

DISCUSSION

General Discussion and Organization of Care in Cerebral Visual Impairment

Based on the results of the five topics, the project group made an inventory of relevant outcome measures for each search question. Outcome measures were rated according to their relative importance in recommendations: Essential, important (but not essential), and unimportant. The project group prioritized the essential outcome measures based on clinical relevance.

Next the project group members approached authors in European countries in order to make an inventory of organizational possibilities for the diagnostics and referral in CVI.

All aspects of the care in order to diagnose and refer in CVI such as coordination, communication, financial means, human resources, and infrastructure are concerned in the start of the care for CVI. Because of the diversity in CVI, the care is complex and difficult to specify. Explanation of how the diagnosis and referral of CVI is organized in different European countries, is integrated in this chapter. Organizational and financial interferences were signaled and possible solutions described (Francke et al., 2008).

Topic One: Medical History and Cerebral Visual Impairment (Search Question 1A,B)

Medical History

The structured medical history is related to the general categories which can be defined for children with risks on CVI as a result of congenital anomalies of brain or events pre-peri or postnatal that lead to brain damage during cerebral development.

None of the questionnaires offers sufficient screening in all CVI domains or for all age groups. In addition, children with behavior or emotional problems have a higher risk on false positive results with the current available questionnaires (Geldof et al., 2015).

There are two ways in which children with possible CVI can start in the diagnostic chain:

1 Parents are signaling deviant viewing behavior and are consulting a general physician, pediatrician or youth doctor or ophthalmologist. In this case a structured medical history (and if necessary a questionnaire) can be applied.
2 Identifying children by a questionnaire by healthcare professionals, this can be organized when risk groups are defined.

The use of a questionnaire is recommended, specially in high risk groups. A questionnaire provides a semi-structured interview about visual acuity and visual behavior. Some questionnaires clearly have an added value in screening when used during a first visit with a caretaker.

High risk groups for CVI:

Children with events during brain development; Prenatal; Perinatal; Postnatal (Flanagan et al., 2003; Rahi and Cable, 2003; Hellgren et al., 2016; Hellström et al., 2018; Philip et al., 2020); (group I and II) Children with congenital anomalies of brain (group II and III).

Children that are at risk for CVI on a basis of their history should have a structured history taken. If there are risk factors found, a questionnaire on CVI can be applied.

A referral at 24 months of age is always indicated for.

I Children who are included in the follow up group for Neonatal Care; prematurity < 30 weeks and/or birth weight < 1,000 gram.

II Children with Cerebral Palsy (GMFCS 1 t/m 5).

III Children with a developmental delay or TBI (traumatic brain injury).

In these groups, a CVI questionnaire is always indicated.

Group I pregnancy < 30 weeks and/or birth weight < 1,000 gram:

Based on the classification system, which was made for research goals, (Geldof et al., 2015) has found 3,8 cases of CVI compared to one in the control group, this is 24% of children in a group born after 32 weeks of pregnancy and/or with a birth weight < 1,500 grams. Based on this research it is not possible to define in how many children the diagnosis CVI was finally made. At 5 years of age, the results were evaluated, in the group of children diagnosed with CVI there was no need for rehabilitation.

In case of prematurity (Pregnancy < 37 weeks and/or Birth weight < 2,000 grams) and/or in case of clear evidence for CVI based on the structured medical history or the CVI questionnaires, it is important to refer the child to an ophthalmologist. Because of the multifactorial cause of CVI, it is not possible to formulate clear cut refer criteria based on the history or the CVI questionnaires. In Sweden 1–2% of children with ROP and prematurity (<27 weeks and/or <1,500 gram) had CVI and low visual acuity (VA < 6/18)(Larsson et al., 2005; Holmström et al., 2014). These studies were not included in the search because ROP was the primary goal of the study and CVI was not mentioned in the abstract. As a result, the search did not specifically include CVI and subnormal visual acuity is missed. Therefore, it is possible that the mentioned numbers are an underestimation. The lower the birth weight and the shorter pregnancy duration the higher the risk of CVI (Jacobson and Dutton, 2000).

Although there are just a few studies, the guideline-project group is convinced that children with severe prematurity should all be screened on CVI.

A birth weight of 1500 grams or less is classified as severe prematurity.

However, neonatologists (Federatie medisch specialisten, 2015) advise a follow up for children born after 30 weeks and/or birth weight < 1,000 gram.

Group II cerebral palsy:

Children with cerebral palsy are at risk for CVI. Visual problems are seen more often in children with spastic quadriplegia than in children with spastic diplegia. In a review Colver (Colver et al., 2014) described visual problems (ocular pathology and CVI) in 35% of the children; therefore, ophthalmological examination is advised on a regular basis in all the children with cerebral palsy. The classification system in cerebral palsy Gross Motor functioning Classification System (GMFCS) consists of five classes, from 1 (less impaired to 5 most impaired).

For children with GMFCS 1 t/m 5 screening by a questionnaire is proposed.

Children who incur a cerebral trauma after the age of 2 years (traumatic or non-traumatic) are at risk for CVI as well (Kivlin et al., 2000; Philip and Dutton, 2014). Although there are no guidelines for this group, we advise screening of visual functions by means of a questionnaire. Depending on the type of trauma and the developmental age the PREVIAS (preverbal visual assessment) CVI Questionnaire (Ortibus E. et al., 2011) or the motor questionnaire (Salavati et al., 2017) can be used.

Group III Developmental delay:

Children with developmental delay (independent of the cause) are at risk for CVI. In 5–20% of these children with intellectual disability, CVI and a low visual acuity is

found (Warburg, 2001; van Isterdael et al., 2006; Nielsen et al., 2007). For this group we advise screening with CVI screenings lists and questionnaires.

Children older than 5 years, where there were previously no doubts about visual functioning and without risk factors for CVI can still have visual problems. It is therefore important for the professional caretaker to take a structured medical history and apply the CVI questionnaire when there are doubts on visual development.

Although the Flemish CVI questionnaire shows a good AUC curve based on 7 selected items, the questionnaire has been studied in relation with a set of object recognition items with visual-spatial elements and attention specific items (dorsal stream items). In the research population, no children with only dorsal stream problems were included. The age-range of the included children was limited, only children with a developmental age between 2,75–6,5 years were included. New evidence for this questionnaire was published by Gorrie et al. (2019) and Ben Itzhak et al. (2020). None of the questionnaires offers sufficient screening in all CVI domains or for all age groups.

Topic Two: Ophthalmological and Orthoptic Assessment (Search Question 2A,B)

It is important to differentiate CVI from other diagnoses that resemble CVI, such as visual impairment by ophthalmological causes, delayed visual maturation, optic hypoplasia, congenital and acquired deviations of the optic nerve, hereditary retinal abnormalities, tumors, or other causes of compression of the optic nerve and visual pathways.

The diagnosis of children with CVI could be accomplished in academic or other specialized centers. A major problem is that diagnosing CVI is not included in the training of ophthalmologists. Another problem is that daily practice in ophthalmology is based on quick visits to the ophthalmologist. Children with CVI do not fit into this system because several assessments are needed. And the different assessments mentioned all add to the diagnosis. Priority can be given to the more specific tests in CVI in ophthalmological and orthoptic examination in this guideline (in italics) regardless of developmental age.

If an ophthalmologist has doubts about the diagnosis CVI and/or about the etiology, the child can be referred to an academic center for more specialized ophthalmological and orthoptic examinations when one of the following results is found in combination with a history that is indicative for possible CVI.

A: binocular suboptimal visual acuity, pupil and pupil reflex, insufficient accommodation and/or a crowding ratio at near that is too high for the calendar age without an explanation such as amblyopia.

B: abnormal findings of the optic nerve, such as: partial or total pallor, hypoplasia, a too large excavation, without any other explanation (such as genetic optic atrophy).

C: anomaly in saccades (delay) and or fixation (fixation area), following movements and or vergence.

D: visual field defect, reduction of contrast sensitivity.

E: If available OCT, VEP and Eye tracking are helpful.

The outcome of the ophthalmological and orthoptic examination can be:

A: Progressive cause of brain dysfunction; Referral to a pediatric neurologist or a specialized pediatrician.

B: There are doubts about the etiology and/or the diagnosis CVI. Refer the child for neurological or genetic assessment.

C: Cerebral visual impairment is diagnosed or suspected with a clear etiological factor (congenital abnormality of brain or, perinatal or postnatal brain damage); children can be referred to a center for rehabilitation of visual impaired or blind people.

A diagnostic routing should be defined with neurological, neuropsychological, and genetic examinations. After this possible additional assessments or rehabilitation can be discussed in a multidisciplinary meeting with parents and medical specialists.

The ophthalmologist can coordinate this process and is in charge of the diagnostic chain in case of CVI. The ophthalmologists can discuss the findings with the different professionals (orthoptist, child neurologist, neuropsychologist, neuroradiologist, clinical geneticist, child physiotherapist). Intensive dialog with a pediatric neurologist is recommended.

The diagnostic process of CVI is complicated and needs a follow up of at least 2 years, depending on the developmental age at referral.

Topic Three: Neuropsychological Assessment

Five neuropsychological tests were found with low to moderate evidence for diagnostic accuracy for CVI, the MVPT, DTVP, TVPS, L94 and the CVIT 3–6. Based on the psychometric properties, the MVPT is preferred for screening of visual perception and the DVTP, TVPS, L94 and CVIT 3–6 are preferred in the diagnostic assessment of CVI, because its subtests differentiate several aspects of visual perception. Also, the use of several other neuropsychological (sub)tests have been studied, but evidence for the diagnostic value of individual tests is lacking and most tests seem involved in multiple visual perceptive dimensions (Ben Itzhak et al., 2021b). Since performance differences on the DVTP were found between American and Asian children (Chan and Chow, 2005; Cheung et al., 2005), adaptation of normative data to local populations seems required. In addition, disorders in visual organization, in recognition in reduced circumstances and recognition in noise are likely typical disorders of visual processing in CVI (Stiers et al., 2001).

The project group advises to estimate the level of mental development before assessing visual perception to avoid false positive assessment outcome and over-diagnosing CVI (Stiers et al., 2001). Follow-up of the neuropsychological assessment is recommended until 12 years of age, because of continuous cerebral development and subsequent development of perceptive visual functioning (Kovacs, 2000; Klaver et al., 2011).

Despite limited evidence for the reliability and validity of neuropsychological tests for the assessment of CVI, it has been recommended to assess a wide range of visual perceptive

functions (Fazzi et al., 2009; Boot et al., 2010; Ortibus E. L. et al., 2011). This is also recommended in models for neuropsychological assessment of visual processing functions derived from clinical practice, indicating assessment of visual selective attention, visual-spatial perception, visual identification, visuomotor functions, visual (working)memory, and visual processing speed (Fazzi et al., 2009; Zuidhoek, 2015; Zuidhoek et al., 2015). Furthermore, to indicate CVI, abnormal test results should be differentiated from disorders in visual sensory and oculomotor functions, executive, attention, memory, mental or auditory functioning to indicate CVI. Hence examining the existence of such potentially co-occurring dysfunctions could be necessary. Disorders in visual organization, recognition in less optimal conditions and recognition in visual noise seem typical for CVI may guide interpretation of the neuropsychological assessment of CVI (Stiers et al., 2001).

Developmental disorders that could incorporate visual perceptive dysfunctions need to be considered during diagnostic decision-making. Visual dysfunctions found in children with developmental disorders include dysfunctions in visual attention, visual processing speed or visual memory (e.g., in ADHD and autism spectrum disorder), dysfunctions in visual identification (dyslexia) dysfunctions in visual spatial perception, visual-motor coordination (developmental coordination disorder). However, the comorbidity of CVI and developmental disorders has not been studied sufficiently (Grinter et al., 2010). Identified visual dysfunctions should therefore be evaluated in a multidisciplinary setting. Thereby, neuropsychological assessment can contribute to both accurate diagnostic decision-making as well as identifying to therapeutic possibilities.

Topic Four: Neuro-Radiological Evaluation and Magnetic Resonance Imaging

There is a relation between presence and quantity of MRI deviations (Tinelli et al., 2020) and visual functioning in children with a risk of CVI. Considerable damage, however, may be found in children with adequate visual functions.

In children with deviations in visual functions that have been referred, a relation seems to be found between MRI abnormalities (global atrophy/ischemic encephalopathy or structural malformations, agenesis of corpus callosum, porencephalic cysts, lissencephaly, Chiari malformation) and the presence of CVI.

Abnormalities of the MRI especially of the visual system can support the diagnosis CVI and can give more insight in the etiology of CVI. A normal MRI, however, does not exclude the diagnosis CVI. If making an MRI is considered this can be accompanied by a pediatric neurological examination.

Sometimes general anesthesia is necessary for successful MRI. However, this is invasive and implies an increased risk for the child. Because of these reasons the authors advise to be reluctant with indications for MRI.

Alternatives for anesthesia can be considered (McGuirt, 2016). In young children (<1 year) ultrasound of the brains can be considered.

In situations where there is a strong clinical suspicion for CVI the authors recommend to consider MRI. Other causes of CVI, where therapy it needed, such as hydrocephalus, hypoglycemic damage, intracranial pressure on chiasm or retro chiasmal, for instance by a tumor, should be excluded by MRI before rehabilitation is started.

Topic Five: Genetic Assessment

The authors suggest a case-to-case approach in which the clinical geneticist uses an actual literature search on the genetic disorder to decide whether screening on CVI in the specific patient is justified. If CVI has been described several times or even just once if only a few patients are known with the disease, we advise referral to an ophthalmologist for structural examination on CVI.

In a subset of children with CVI, there is no plausible cause (Bosch et al., 2014b). These children need to be referred to a clinical geneticist. Genetic examination of a small group of patients (n = 56) with CVI without a plausible cause resulted in an explanation in 30–50% of cases (Bosch, 2015). Therefore, the authors recommend that children with CVI without a clear explanation for the CVI in their history and/or MRI of the brain, should be referred to a clinical geneticist. Except if genetic examination was performed in the last 3–5 years.

The clinical geneticist can discuss advantages and disadvantages of genetic assessments. There can be several reasons to perform genetic testing.

- *To answer the "why" question.*
- *Is there a recurrence risk (for the child, parents, or other family member) are co-morbidities to be expected and is screening or treatment indicated?*
- *More information on the developmental possibilities and future perspectives.*
- *Parents can contact other parents with a child with the same disorder.*

Based on the recent data a genetic diagnosis alone has a limited role in the diagnosis of CVI. The genetic diagnosis is at most useful to support the diagnosis CVI.

Besides ophthalmological and orthoptic examination, performed in specialized centers other assessments can be planned. Multi-disciplinary cooperation is necessary to organize this, if necessary, between different centers.

When a genetic diagnosis is made, the geneticist can consider to refer to an ophthalmologist for examination for CVI if:

Cerebral visual impairment is described several times in literature for this diagnosis.
Cerebral visual impairment is described as least once in literature and only few persons are known with this genetic disorder.

Discuss the outcome of the genetic examinations in a multidisciplinary team and use the findings in diagnostic follow up.

CAPACITY AND WORKING LOAD

As a result of the recommendations mentioned, the availability of financial means and health care professionals as well as the applicability and necessity of measures play an important role.

It is not always possible for diagnostic centers to organize an ophthalmologist and orthoptist and neuropsychologist with specific knowledge about CVI. Further training and schooling are necessary. Furthermore in a peripheral hospital setting and academic medical center visual fields are not often measured routinely and eye tracking or OCT are not performed regularly in children either.

Neonatal encephalopathy (NE) is the clinical manifestation of disordered neonatal brain function (Kurinczuk et al., 2010). Lack of universal agreed definitions of NE and the sub-group with hypoxic Ischemic Encephalopathy (HIE) makes the estimation of incidence and the identification of risk factors problematic. NE incidence is estimated as 3.0 per 1,000 live births (95%CI 2.7 to 3.3) and for HIE is 1.5 (95% CI 1.3 to 1.7), 60% of the children with severe Hypoxic Ischaemic Injury have CVI (Good et al., 2001; Fazzi et al., 2007; Solebo et al., 2017) and a large group of children with congenital abnormalities of brain have CVI as well. This means that in the least this group has to be examined for CVI by ophthalmologists and orthoptists. In several countries the incidence of VI and CVI has been investigated (Riise et al., 1992; Rosenberg et al., 1996; Rahi and Cable, 2003).

The number of children that can actually been seen by an ophthalmologist, is dependent on the capacity of ophthalmologists. This may be different in different countries. However, this diagnostic work can be better performed by a medical specialist. It is also preferable that the whole diagnostic process is supervised by a medical specialist as there are too many factors involved that may influence the future of the child and likewise the risks of missing a progressive disease in this diagnostic process.

DATA AVAILABILITY STATEMENT

The original contributions presented in this study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work, and approved it for publication.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnhum.2022.727565/full#supplementary-material

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Longitudinal neurological analysis of moderate and severe pediatric cerebral visual impairment

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Introduction: Cerebral visual impairment (CVI) results from damage to cerebral visual processing structures. It is the most common cause of pediatric visual impairment in developed countries and rising in prevalence in developing nations. There is currently limited understanding on how neurologic, developmental, and ophthalmic factors predict outcome for pediatric CVI.

Method: A retrospective manual chart review of pediatric CVI patients seen at the tertiary pediatric hospital neurology and neuro-ophthalmology service between 2010 and 2019 was conducted. Patients were stratified into severity groups (based on a custom CVI grading score), and followed over time to identify outcome predictors. Collected baseline characteristics included perinatal, genetic, developmental, and neurologic history, along with neuroimaging and fundoscopic findings on examination. Longitudinal data collected included age, seizure control, and type of therapy received. Linear mixed-effect models were used for longitudinal CVI grade outcome analysis.

Results: A total of 249 individuals spanning 779 patient visits were identified. Mean age at diagnosis was 18.8 ± 16.8 months (2–108 months). About 64.3% were born at term age. Perinatal history revealed hypoxic ischemic encephalopathy (HIE) in 16.5%, intraventricular hemorrhage (IVH) in 11.6%, and seizures in 21.7%. At presentation, 60.3% had a diagnosis of cerebral palsy and 84.7% had developmental delay. Among all subjects, 78.6% had epilepsy; 33.8% had an epileptic encephalopathy, with spasms/hypsarrhythmia being most common. Abnormal neuroimaging was present in 93.8%. Genetic anomalies were present in 26.9%. Baseline visual examination revealed no

blink-to-light (BTL) in 24.5%; only BTL in 34.5%, fixation/tracking in 26.5%, and optokinetic drum follow in 14.4%. Longitudinal data analysis showed that perinatal history of HIE, a positive epilepsy history, using multiple (≥3) epilepsy medications, cerebral palsy, and abnormal fundoscopic findings were all negatively associated with CVI grade change over time. After controlling for significant confounders, receiving any type of therapy [early childhood intervention (ECI), physical and occupational therapy (PT/OT), refractive error correction or glasses] was significantly associated with longitudinal improvement in CVI grade compared to patients who did not receive any therapy, with glasses yielding the largest benefit.

Conclusion: This study offers extensive insights into neurologic, developmental and ophthalmologic features in patients with moderate to severe CVI. In concordance with previous findings, aspects of perinatal history and epilepsy/seizure control may help inform severity and prognosis in the general neurology or ophthalmology clinic. Conversely, these aspects, as well as genetic and specific epilepsy traits may alert vision health care providers in the clinic to pursue visual evaluation in at-risk individuals. Longitudinal follow-up of CVI patients showed that interventional therapies demonstrated vision function improvement greater than no therapy and maturational development.

KEYWORDS

cerebral vision impairment, cortical visual impairment, brain based visual impairment, epilepsy, cerebral palsy, prematurity, cortical blindness

Introduction

Cerebral visual impairment (CVI) is a result of damage or maldevelopment of the visual processing centers of the brain. Despite being the leading cause of profound pediatric vision loss in developing nations, there has been a global lack of consensus on the terminology, clinical assessment, recognition of diagnosis, as well as overall management of CVI (Sakki et al., 2018; Kran et al., 2019; Ortibus et al., 2019). This complexity primarily arises in that CVI is not a single entity, but heterogeneous in nature with multiple neurological etiologies, presentations, and severity of impairment (Good et al., 1994; Fazzi et al., 2007; Philip and Dutton, 2014).

Cerebral visual impairment can be defined as visual impairment due to injury of the retro-chiasmal or post-geniculate visual processing pathways that are not attributable to any anterior visual pathway dysfunction (Sakki et al., 2018). Underlying etiologies of CVI can be congenital or acquired, and can develop temporally during the prenatal, perinatal, and postnatal stages of human development (Dutton et al., 2006; Khetpal and Donahue, 2007). Much of the current CVI literature has been focused on terminology, screening for early recognition, and developing an algorithm and consensus of CVI clinical assessment, which commonly necessitates a multidisciplinary approach (Bennett et al., 2019; Kran et al., 2019; Ortibus et al., 2019; Ben Itzhak et al., 2020; Chandna et al., 2021).

Recently, there has been further consideration of a CVI patient's overall clinical presentation, evaluation, and optimal management (Ortibus et al., 2019; Ben Itzhak et al., 2020). A vast majority of CVI children have comorbid neurological disorders and deficits including neurodevelopmental disabilities, epilepsy/seizures, cerebral palsy, hydrocephalus, genetic changes, periventricular white matter disease, and/or anterior visual pathway diseases (Good et al., 1994; Fazzi et al., 2007; Philip and Dutton, 2014). CVI commonly co-presents with a number of ocular abnormalities of refractive error, strabismus, ocular dysmotility, and optic nerve atrophy (Huo et al., 1999; Hoyt, 2003; Good et al., 1994; Handa et al., 2018). Unrecognized moderate-to-severe anterior visual pathway disease can either mask or compound CVI visual behavior and profoundly impact the clinical approach to fully assessing CVI (Ortibus et al., 2019).

Based on the above, we hypothesized that investigating both neurologic and neuro-ophthalmic features of pediatric CVI patients at presentation and longitudinal follow-up may reveal clinical associations that would assist in subcategorizing this heterogeneous disorder and help optimize management.

The primary aim of this pediatric retrospective study was to characterize CVI vision outcomes in children presenting at both neurology and neuro-ophthalmology clinics. Data was collected via manual record review with particular focus on neurologic/neuro-ophthalmologic features of each patient with regards to vision assessment. Secondary aims included investigating longitudinal data in terms of neurologic/neuro-ophthalmologic management, vision development, and identifying common clinical and paraclinical risk factors in CVI. We intend the data in this study to help inform general pediatric, ophthalmology, and neurology practices in electing for early referral of similar patients for neuro-ophthalmic evaluation.

Materials and methods

The study was performed in compliance with all national and institutional regulations. It was reviewed and approved by the Baylor College of Medicine Institutional Review Board (H-38264). A single-center, retrospective cohort study was designed in a large referral pediatric center (Texas Children's Hospital). All children with a primary diagnosis related to disturbances of the visual pathways (ICD-10 codes H47.619, H47.9 and ICD-9 codes 369.9, 377.75) aged 0–18 years presenting to a specialized neurology and neuro-ophthalmology clinic at a large pediatric hospital between January 2010 and September 2019 were selected from the institution's electronic medical records. Subject inclusion was determined by a neuro-ophthalmologist (VS) upon chart review, to ensure an existing diagnosis of CVI. Patients were excluded if the baseline diagnosis was not consistent with CVI, or if there was insufficient clinical data available for analysis. A manual chart review was then conducted, and relevant information extracted including perinatal history, epilepsy history, developmental history (e.g., developmental delay and cerebral palsy), presence of a genetic diagnosis, baseline neuroimaging (brain MRI), and baseline fundoscopy. Patient follow-up longitudinal data was then collected and included CVI grading score (see below), presence of epilepsy (and epileptic encephalopathy), seizure control, current seizure medications, and therapy received. Ophthalmic examination including visual acuity, visual behavior, visual field preference, and fundoscopic details were also included at each time point. Neuroimaging findings were categorized by two pediatric neurologists (AJG, KF), depending on the suspected pattern(s) of injury. Ophthalmic evaluation data were categorized by two of the researchers (VSS, AJG).

Cerebral visual impairment grading score

Given the (1) lack of a standardized CVI screening and assessment method, (2) the retrospective nature of this study, and (3) integration of both neurology and neuro-ophthalmology medical record data, a custom CVI severity grading system was established. Overall visual function was graded: (0) no blink to light from a transilluminator; (1) blink to light; (2) fixate and follow; (3) objective vision, assessed via Teller Acuity Cards or optokinetic drum response (binocular testing with a manual striped drum rotated at 8–10 rpm); and (4) subjective visual acuity. Additional single points were given for positive visual field/preference noted on exam, response to kinetics/objects (other than OKN drum), light gazing, and color preference (up to 4 additional points altogether). The CVI grading score was totaled for each patient and grouped into three categories of Severe (0–2 points), Moderate (3–5 points), and Mild (6–8 points), with lower scores reflecting more impairment.

Cerebral visual impairment therapy

This study also sought to determine whether particular interventions targeted at improving visual function in patients contributed toward an improvement in our CVI grading score. A total of four interventions were assessed, which included: (1) Early Childhood Intervention (ECI) visual therapy services to help children and their families learn daily environmental adaptations that can maximize a child's functional vision; (2) physical and occupational therapy (PT/OT) which involved motor development exercises that incorporated visuospatial training; (3) refractive correction with eyeglasses prescribed by cycloplegic retinoscopy according to the preferred practice patterns by the American Academy of Ophthalmology (AAO, 2021); and (4) a combination of all therapies. Of note, subjects undergoing refractive correction followed with their preferred provider and were not monitored for compliance or changes in their refraction by this study. The treatment effect of these interventions was assessed longitudinally via the CVI grading score on a per-encounter basis.

Statistical analysis

For descriptive analysis, categorical variables were reported as count and percentage. Chi-square test or Fisher's exact test (for contingency tables with at least 20% expected frequency < 5) were used to test the associations between categorized CVI grade outcomes (mild, moderate, and severe) and categorical variables.

To assess the treatment effect of CVI interventions, a mixed-effects model was used to model the longitudinal CVI grade scores over time to account for the multiple measurements from each patient. Baseline characteristics were tested one at a time. Perinatal characteristics, history of cerebral palsy, genetic diagnosis, and abnormal fundoscopy findings were pre-specified as candidate confounders for the outcome. The confounders that were found to be significantly associated with CVI grade outcome ($p < 0.05$), and the longitudinal measured variables

at each visit (age and presence of epilepsy) were then included in a multivariable mixed-effects model. The type of treatment was the main variable of interest and was kept in the model regardless of its significance. Those that reached a significance of $p < 0.1$ were retained in the final multivariable model. The treatments being separately evaluated were: (1) Therapy documented at each visit, (2) Therapy documented in any one visit throughout the follow-up period (patient-level variable), (3) PT/OT documented at each visit, and (4) Glasses/refractive error correction documented at each visit.

No adjustments for multiple testing were made due to the exploratory nature of the study. A 2-sided p value < 0.05 was used to determine the significance of variables in all analyses. All statistical testing was performed using SAS 9.4.

Results

A total of 249 subjects spanning 779 patient visits were included for analysis from time of initial CVI diagnosis. A summary of patient age and average follow-up period is included in **Table 1**. The mean age at time-of-diagnosis was 18.8 ± 16.8 months (2–108 months). Analysis of associations between each clinical factor and CVI grade severity group at baseline are documented in **Table 2**.

TABLE 1 Summary of patient age and follow-up information.

	Summary statistics	CVI cohort
Baseline age (month)		
	N	249
	Min–Max	2.0–108.0
	Mean (SD)	18.8 (16.83)
	Median (Q1, Q3)	13.0 (7.0, 24.0)
Age at last visit (month)		
	N	249
	Min–Max	2.0–157.0
	Mean (SD)	40.0 (24.75)
	Median (Q1, Q3)	35.0 (22.0, 54.0)
Follow-up time (month)		
	N	249
	Min-Max	0.0-84.0
	Mean (SD)	21.2 (20.71)
	Median (Q1, Q3)	15.0 (3.0, 33.0)
Number of follow-up visits		
	N	249
	Min–Max	1.0–10.0
	Mean (SD)	3.2 (2.05)
	Median (Q1, Q3)	3.0 (2.0, 4.0)

SD, standard deviation; Q1, 25th percentile; Q3, 75th percentile.

Baseline characteristics

Cerebral visual impairment grade and ophthalmologic exam

According to the baseline CVI grading score of the 249 subjects, 197 (79.1%) had severe CVI with an average grade of 1.08, and 52 (20.9%) had moderate CVI with an average grade of 3.25, whereas no patients had CVI grades that qualified for mild CVI in this cohort. Visual examination of the cohort revealed no blink-to-light (BTL) vision in 24.5% of patients, BTL vision in 34.5%, fixate and follow vision in 26.5%, and preserved objective vision in 14.4%. No patients were found to have intact subjective visual acuity. Fundus examination with dilated pupils demonstrated abnormalities in 20.4% of the cohort including optic nerve pallor (49/51) and chorioretinal scarring or lacunae (3/51). The optic nerve pallor was bilateral and moderate-severe in 49% (24/51) of these patients.

Perinatal history

About 35.7% ($n = 89$) of the study cohort had a history of preterm birth [defined by the World Health Organization as any birth before 37 completed weeks of gestation (Howson et al., 2013)]. Within this preterm group, 25.8% (23/89) had a history of interventricular hemorrhage (IVH) of any grade, followed by 23.6% (21/89) neonatal seizures, and 21.3% (19/89) hypoxic-ischemic encephalopathy (HIE). In addition, 21.3% (19/89) also had a history of retinopathy of prematurity, but only 3 of these subjects had abnormal fundus findings. Conversely, only 3.8% (6/160) of the study cohort born at term had a history of IVH, 20.6% (33/160) had neonatal seizures, and 14.4% (23/160) had a history of HIE. Neonatal seizures were found in 21.7% (54/249) of all subjects, with 94.4% (51/54) in this group eventually developing future epilepsy.

The CVI grade was most severe in the HIE group with a mean of 1.24, followed by the neonatal seizures group with a mean of 1.44. IVH had a CVI mean grade of 1.55, with 34.5% (10/29) having abnormal fundoscopic findings.

Neuroimaging

About 93.8% (198/211) of those who had neuroimaging had documented changes. Among these, 28% had a presumed genetic/structural/migrational anomaly/etiology, 28.3% had atrophic changes on MRI not inherently related to prematurity, and 23.7% had vascular changes including ischemic and/or hemorrhagic stroke and intracranial bleeding (excluding prematurity-related intraventricular hemorrhage). A total of 22.7% had presumed prematurity-related changes (e.g., IVH, periventricular leukomalacia). HIE outside of neonatal origin was observed in 22.2%. Metabolic and presumed infection related changes were present in 9.1 and 4.8%, respectively. Lastly, hydrocephalus, presumed unrelated to atrophy (i.e., not *ex-vacuo*) was observed in 11.2% of all cases. Notably, abnormal neuroimaging for presumed metabolic and genetic etiologies had a CVI mean grade of 1.06 and 1.11, respectively.

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TABLE 2 Associations between each predictor and the CVI group at diagnosis.

Baseline characteristics	YES/NO	Moderate CVI (*N* = 52)	Severe CVI (*N* = 197)	Overall (*N* = 249)	*p* Value
Abnormal perinatal history					
Prematurity	Yes	32 (61.5)	128 (65.0)	160 (64.3)	0.647
	No	20 (38.5)	69 (35.0)	89 (35.7)	
Hypoxic-ischemic encephalopathy (HIE)	Yes	45 (86.5)	163 (82.7)	208 (83.5)	0.503
	No	7 (13.5)	34 (17.3)	41 (16.5)	
Intraventricular hemorrhage	Yes	45 (86.5)	175 (88.8)	220 (88.4)	0.652
	No	7 (13.5)	22 (11.2)	29 (11.6)	
Neonatal Seizures	Yes	39 (75.0)	156 (79.2)	195 (78.3)	0.520
	No	13 (25.0)	41 (20.8)	54 (21.7)	
Retinopathy of prematurity	Yes	48 (92.3)	182 (92.4)	230 (92.4)	1.000
	No	4 (7.7)	15 (7.6)	19 (7.6)	
Epilepsy					
Epilepsy	Yes	13 (25.0)	40 (20.4)	53 (21.4)	0.479
	No	39 (75.0)	156 (79.6)	195 (78.6)	
Epileptic encephalopathy	Yes	26 (66.7)	103 (66.0)	129 (66.2)	0.940
	No	13 (33.3)	53 (34.0)	66 (33.8)	
Poor seizure control	Yes	7 (17.9)	40 (25.6)	47 (24.1)	0.303
	No	32 (82.1)	116 (74.4)	148 (75.9)	
Medications used for control	None	17 (43.6)	35 (22.4)	52 (26.7)	0.033
	1-2	18 (46.2)	101 (64.7)	119 (61.0)	
	3 or more	4 (10.3)	20 (12.8)	24 (12.3)	
Genetics					
Known Genetic diagnosis	Yes	39 (75.0)	143 (72.6)	182 (73.1)	0.726
	No	13 (25.0)	54 (27.4)	67 (26.9)	
Neurodevelopment					
Cerebral palsy	Yes	24 (46.2)	74 (37.9)	98 (39.7)	0.232
	No	28 (53.8)	121 (62.1)	149 (60.3)	
Developmental delay	Yes	6 (11.5)	32 (16.2)	38 (15.3)	0.388
	No	46 (88.5)	165 (83.8)	211 (84.7)	
Neuroimaging					
Any abnormality	Yes	2 (4.4)	11 (6.6)	13 (6.2)	0.740
	No	43 (95.6)	155 (93.4)	198 (93.8)	
Atrophy	Yes	30 (66.7)	125 (75.3)	155 (73.5)	0.253
	No	15 (33.3)	41 (24.7)	56 (26.5)	
Presumed genetic etiology	Yes	32 (71.1)	122 (73.5)	154 (73.0)	0.751
	No	13 (28.9)	44 (26.5)	57 (27.0)	
Presumed metabolic etiology	Yes	43 (95.6)	150 (90.4)	193 (91.5)	0.374
	No	2 (4.4)	16 (9.6)	18 (8.5)	
Vascular changes	Yes	34 (75.6)	130 (78.3)	164 (77.7)	0.696
	No	11 (24.4)	36 (21.7)	47 (22.3)	
Prematurity-related changes	Yes	35 (77.8)	131 (78.9)	166 (78.7)	0.869
	No	10 (22.2)	35 (21.1)	45 (21.3)	
Presumed infection-related changes	Yes	43 (95.6)	156 (94.0)	199 (94.3)	1.000
	No	2 (4.4)	10 (6.0)	12 (5.7)	
Non-neonatal HIE	Yes	36 (80.0)	131 (78.9)	167 (79.1)	0.873
	No	9 (20.0)	35 (21.1)	44 (20.9)	
Hydrocephalus (not atrophy-related)	Yes	36 (80.0)	147 (88.6)	183 (86.7)	0.150
	No	9 (20.0)	19 (11.4)	28 (13.3)	
Fundoscopic exam					
Any abnormal finding	Yes	41 (78.8)	155 (78.7)	196 (78.7)	0.979
	No	11 (21.2)	42 (21.3)	53 (21.3)	
Therapy/interventions					
Any Therapy	Yes	44 (84.6)	165 (83.8)	209 (83.9)	0.880
	No	8 (15.4)	32 (16.2)	40 (16.1)	

*Chi-square test or Fisher's exact test (for contingency tables with at least 20% expected frequency < 5) was used.

Alternatively, neuroimaging suggestive of vascular etiologies had a mean CVI grade of 1.43 with 31.9% (15/47) having abnormal retinal fundoscopic findings.

Neurodevelopment and genetics

Within this cohort, 84.7% (211/249) had a diagnosis of global developmental delay, with 59.8% (149/249) also known to have a diagnosis of cerebral palsy (CP). Among all individuals, 26.9% (67/249) had a known genetic diagnosis with a mean CVI grade of 1.54, of which 14.9% (10/67) had documented chromosomal abnormalities. Genetic testing for these individuals were originally requested for working up comorbid conditions (developmental delay, epilepsy) unrelated to CVI. A summary of identified gene and chromosomal abnormalities associated with this CVI cohort are listed in **Table 3**. 76.1% (51/67) of all subjects with known abnormal genetic testing had abnormal neuroimaging. Only 11.9% (8/67) had abnormal fundus exam findings.

Epilepsy and seizure control

A total of 78.6% (195/249) of the subjects had epilepsy, of which 75.9% (148/195) had suboptimal or poor seizure control, defined as having more than one seizure per month over at least 6 months (Chawla et al., 2002). 33.8% (66/195) had epileptic encephalopathy. The overall mean CVI grade for epilepsy was 1.46, which dropped to 1.19 with uncontrolled epilepsy. There was a statistically significant association between CVI grade and number of epilepsy medications in use at time-of-diagnosis (p = 0.033). Patients in the severe CVI group tended to be on more epilepsy medications than the moderate CVI group (64.7 vs. 46.2% on 1–2 meds; 12.8 vs. 10.3% on 3+ meds) (**Table 2**).

Longitudinal cerebral visual impairment grade outcome

To assess the effect of individual baseline characteristics on longitudinal CVI grade over time, we utilized linear mixed-effect models. Data from a combined total of 779 patient visits (including initial evaluation) from the 249 subjects were included. The contribution from individual baseline characteristics to longitudinal CVI grade is shown in **Table 4**, where a perinatal history of HIE (p = 0.043), cerebral palsy (p = 0.029), presumed metabolic etiology on neuroimaging (p = 0.049), and abnormal fundoscopy (p = 0.023) were found to be significantly associated with the longitudinally measured CVI grade outcome. Having a history of epilepsy (p = 0.051) and currently using multiple (≥3) medications for seizure control (p = 0.053) are near-significantly associated with longitudinal CVI grade. Conversely, good seizure control (p = 0.11) and hydrocephalus findings on neuroimaging that are not atrophy related (p = 0.104) demonstrate a trending association with longitudinal CVI grade improvement.

Effect of cerebral visual impairment therapy

Assessment of the effectiveness of CVI therapy was performed via multivariable mixed-effects models using longitudinal patient data from 779 patient visits. Upon including all significant baseline characteristics (Fundus abnormality, history of cerebral palsy, perinatal history of HIE) with longitudinal variables (age, presence of epilepsy, treatment received), the HIE variable lost its significance and was excluded. The final multivariate models, each focused on a particular therapy modality, are listed in **Table 5**. Overall, receiving some form of CVI therapy at each patient visit is significantly associated with an increased CVI grade outcome compared to no therapy (p = 0.043). For each patient, having at least one therapy recorded during their follow-up period is likely associated with an improved CVI grade compared to patients who never had any therapy recorded (p = 0.0646). PT/OT therapy was not significantly associated with improved CVI grade over time (p = 0.2468). However, pursuing refractive error correction with glasses and wearing them is associated with an average CVI grade increase of 0.21 units compared to those who did not wear glasses (p = 0.0363). Getting older (increased age) has a small but significant positive effect on CVI grade outcome regardless of therapy (0.01 unit increase in CVI grade for every month increase in age, or equivalently 0.12 unit increase in CVI grade for every year increase in age). Meanwhile, having active seizures, a positive history of cerebral palsy, and abnormal fundoscopic findings were all significantly associated with decreased CVI grade over time. The contribution of seizures is the largest out of the three, where patients with active seizures had on average a CVI grade of 0.4 points lower than patients who were not experiencing uncontrolled seizures.

Discussion

This study examined a large cohort of pediatric patients with a primary diagnosis of CVI with the goal of identifying

TABLE 3 List of abnormal genes and/or chromosome rearrangements identified in the CVI cohort.

Genes identified	*ASPA (2), ATP7A, ATP1A3, CACNA1A, CDKL5 (3), CDG, COXPD11, DNM-1, EIF2B5, FLAD1, FOXG1 (2), G6PD, GNAO1, GRIN2B, HECW2, KIF1A, LIS1 (5), LypopylTrans1, MCAD, MECP2, MDS, OTC, PropACID, PURA, N2, RARS, SCN2A, SDHA, SLC1A4, SLC35A2, SCN1A/SPTAN1/SYN1, SMAD4, STXBP1 (2), TBCK, TSC TREX1 (3), T18, T21 (3), TUBA1A, ZNF630*
Chromosome abnormalities	Del Xp22, del Xp11.23, Gain 15q13.2q13.3, 5q del, del 10q11.22q11.23, Gain chr13, 4p- deletion, del:1q43, 9q34del, microdup 16p11.2 loss 18p22

TABLE 4 Effect of individual baseline characteristics on longitudinal CVI grade outcome using mixed-effect models.

Baseline characteristics	Contrast	*N*	Parameter estimate (95% CI)	*p* Value
Abnormal perinatal history				
Prematurity	Yes vs. No	783	0.097 (-0.18, 0.37)	0.49
Hypoxic-ischemic encephalopathy (HIE)	Yes vs. No	783	-0.37 (-0.72, -0.012)	0.043
Intraventricular hemorrhage	Yes vs. No	783	-0.19 (-0.59, 0.21)	0.35
Neonatal Seizures	Yes vs. No	783	-0.26 (-0.58, 0.059)	0.11
Retinopathy of prematurity	Yes vs. No	783	-0.17 (-0.65, 0.32)	0.50
Epilepsy				
Epilepsy	Yes vs. No	782	-0.32 (-0.64, 0.0017)	0.051
Seizure control	Yes vs. No	606	0.29 (-0.065, 0.65)	0.11
Medications used for control	1–2 vs. zero	619	-0.33 (-0.66, 0.0037)	0.053
	>= 3 vs. zero	619	-0.57 (-1.10, -0.048)	
Genetics				
Known Genetic diagnosis	Yes vs. No	783	-0.031 (-0.33, 0.27)	0.84
Neurodevelopment				
Cerebral palsy (CP)	Yes vs. No	781	-0.30 (-0.57, -0.031)	0.029
Developmental delay	Yes vs. No	783	0.15 (-0.22, 0.51)	0.43
Neuroimaging				
Any abnormality	Yes vs. No	663	-0.024 (-0.62, 0.57)	0.94
Atrophy	Yes vs. No	663	0.0038 (-0.32, 0.33)	0.98
Presumed genetic etiology	Yes vs. No	663	0.077 (-0.24, 0.39)	0.63
Presumed metabolic etiology	Yes vs. No	663	-0.52 (-1.04, -0.002)	0.049
Vascular changes	Yes vs. No	663	-0.098 (-0.44, 0.24)	0.57
Prematurity-related changes	Yes vs. No	663	-0.27 (-0.61, 0.070)	0.12
Presumed infection-related changes	Yes vs. No	663	-0.078 (-0.70, 0.54)	0.81
Non-neonatal HIE	Yes vs. No	663	-0.24 (-0.59, 0.11)	0.18
Hydrocephalus (not atrophy-related)	Yes vs. No	663	0.34 (-0.069, 0.74)	0.104
Fundoscopy				
Any abnormal finding	Yes vs. No	783	-0.37 (-0.70, -0.053)	0.023

neurologic, developmental, genetic, and neuro-ophthalmic predictors of CVI severity and longitudinal treatment response to vision-based interventions.

Ophthalmologic exam

It is well known that CVI impacts vision on a clinical spectrum of mild visual disturbances to profound vision dysfunction. Despite devising a metric-based CVI grading system aimed at classifying mild, moderate, and severe instances of vision impairment, we found that no pediatric patients in our cohort met clinical criteria in their baseline ophthalmic examinations to be designated as having mild CVI. Rather, our cohort only describes moderate and severe cases of CVI and may reflect the fact that our larger patient population represents a tertiary referral pool with a skew toward having more severe underlying conditions and comorbidities requiring subspecialty evaluation. Conversely, pediatric patients who meet criteria for mild CVI may present with high-order visuospatial impairment that are underdiagnosed or unrecognized for appropriate workup, diagnosis, and referral (van Genderen et al., 2012; Chandna et al., 2021).

Despite not capturing the milder clinical spectrum of CVI, our scoring system helped stratify moderate from severe disease. Additionally, more than half of our cohort had severely decreased vision evident on visual function testing with 23.3% (n = 58) demonstrating an absent BTL response and 34.5% (n = 86) with only a BTL response and no further visual capability. However, CVI can also present with additional ocular comorbidities including strabismus, ocular dysmotility, and optic nerve/retinal changes. Although we did not assess for strabismus due to the variability of the documented exam, the dilated fundus exam detected optic nerve abnormalities and chorioretinal lesions (scarring or lacunae) in our cohort. Optic nerve pallor was found in 17% (51/249) of our cohort, was noted to always present bilaterally, and ranged from isolated temporal to diffuse pallor. The presence of optic nerve pallor in these CVI children could result from either co-morbid anterior visual pathway dysfunction (e.g., congenital optic

TABLE 5 Treatment effect on Longitudinal CVI grade outcome using mixed-effect models.

Longitudinal analysis

Treatment	*N*	Predictor variable	Estimate (95% CL)	*p*-Value
Therapy documented at each visit	779	Age	0.0100 (0.0066, 0.013)	<0.0001
		History of Epilepsy (Yes vs. No)	-0.38 (-0.58, -0.18)	0.0002
		Cerebral Palsy (Yes vs. No)	-0.35 (-0.61, -0.086)	0.0095
		Fundus Abnormality (Yes vs. No)	-0.32 (-0.63, -0.010)	0.0434
		Therapy At Each Visit (Yes vs. No)	0.14 (0.0044, 0.28)	0.0432
Therapy documented in any one visit throughout the follow-up period	779	Age	0.010 (0.0066, 0.013)	<0.0001
		History of Epilepsy (Yes vs. No)	-0.39 (-0.59, -0.19)	0.0001
		Cerebral Palsy (Yes vs. No)	-0.36 (-0.62, -0.096)	0.0076
		Fundus Abnormality (Yes vs. No)	-0.31 (-0.62, 0.0031)	0.0523
		Therapy At Any Visit (Yes vs. No)	0.25 (-0.015, 0.52)	0.0646
PT/OT documented at each visit	779	Age	0.010 (0.0067, 0.013)	<0.0001
		History of Epilepsy (Yes vs. No)	-0.38 (-0.58, -0.18)	0.0002
		Cerebral Palsy (Yes vs. No)	-0.35 (-0.61, -0.081)	0.0106
		Fundus Abnormality (Yes vs. No)	-0.32 (-0.63, -0.008)	0.0441
		PT/OT (Yes vs. No)	0.083 (-0.058, 0.22)	0.2468
Glasses documented at each visit	779	Age	0.0094 (0.0060, 0.013)	<0.0001
		History of Epilepsy (Yes vs. No)	-0.38 (-0.58, -0.18)	0.0002
		Cerebral Palsy (Yes vs. No)	-0.33 (-0.59, -0.069)	0.0133
		Fundus Abnormality (Yes vs. No)	-0.34 (-0.65, -0.031)	0.0311
		Glasses (Yes vs. No)	0.21 (0.013, 0.40)	0.0363

nerve abnormalities) or retrochiasmal pathology involving the optic radiation (e.g., periventricular leukomalacia) and resultant trans-synaptic degeneration (Dutton, 2003; Hoyt, 2003; Good, 2007; Lennartsson et al., 2018). Overall, our ophthalmic findings in this study are consistent with prior works that reported the prevalence of optic nerve pallor (16–42%) in CVI children (Huo et al., 1999; Hoyt, 2003; Khetpal and Donahue, 2007; Handa et al., 2018).

Perinatal and neuroimaging findings

In the 160 children of our cohort born at term, 21.3% presented with neonatal seizures, 13.1% with HIE and 3.1% with IVH. Prior studies have reported that HIE is the most common cause of CVI in preterm and term children (Good et al., 1994; Huo et al., 1999; Fazzi et al., 2007; Khetpal and Donahue, 2007). Interestingly, our cohort reported a higher prevalence of neonatal seizures than HIE in both term and preterm children as an etiology of CVI. In addition, the incidence of neonatal seizures (n = 54) in the perinatal period in both preterm and term children had a higher propensity for developing into epilepsy (n = 51/54), and to a lesser degree, epileptic encephalopathy (n = 16/54). This observation suggests that neonatal seizures may be a potential prognostic sign for a systemic disease course and raises concerns for potential development of CVI.

The distinction of prematurity, defined as a child born before 37 completed weeks of gestation, is a critical feature of characterizing CVI in children. With 35.7% (n = 89) of our cohort meeting criteria for preterm birth, neurologic clinical assessment (clinical history, APGAR score, blood gas, Sarnat staging—classification scale for HIE) and/or initial imaging demonstrated co-morbid pathologic findings consistent with IVH (25.6%; n = 23/89), neonatal seizures (23.6%; n = 21/89), and HIE (21.3%; n = 19/89). As IVH and HIE are potential contributing precursors of periventricular leukomalacia (PVL), our findings are consistent with prior studies describing an association with preterm babies presenting with PVL on neuroimaging (Banker and Larroche, 1962; Jacobson and Dutton, 2000; Dutton, 2013). Finally, retinopathy of prematurity (ROP) was found in 21.3% (n = 19/89) of our cohort. Per medical record review, these children were monitored postnatally but none experienced any vision threatening sequalae.

While neuroimaging alone cannot diagnose CVI, it does provide valuable anatomical insights into developmental

etiologies. A strength in our study was the fact that a majority of patients (211/249) had existing neuroimaging at the time of their initial ophthalmologic evaluation, and a vast majority had abnormal findings. Neuroimaging in CVI can reveal a spectrum of pathology ranging from focal to global brain involvement (Whiting et al., 1985; Eken et al., 1996; Ortibus et al., 2009). In our cohort, 93.8% presented with an abnormal finding on neuroimaging, the most common being structural anomalies suggestive of an underlying genetic etiology (e.g., migrational abnormalities) in 28.8%, followed closely by atrophy (unspecified cause, 28.2%). Outright presumed sequelae of prematurity (e.g., periventricular leukomalacia), and vascular insults in any location were also frequently reported, 22.7 and 23.7%, respectively (Bauer and Papadelis, 2019). In our study, no association was found between the type and location of identified neuroimaging findings on MRI, and the degree/severity of CVI at time-of-diagnosis, consistent with prior findings (Cioni et al., 1996; Chang and Borchert, 2020). This would suggest that, while structural neurologic injury plays a role in the pathogenesis of CVI, there may be other functional tests and characteristics of neuroimaging that better account for the severity of CVI and perhaps warrant more attention than baseline imaging (Fazzi et al., 2009; Ortibus et al., 2009). This observation is consistent with the notion that standard neuroimaging modalities are limited in their capability to correlate visual function with neuroanatomical changes in space and time. However, recent developments in novel techniques such diffusion tensor imaging and high angular resolution diffusion imaging (HARDI) will allow future investigators to closely examine white matter connectivity in the context of dysfunction and better elucidate potential pathways involved in CVI (Ortibus et al., 2009; Bauer et al., 2014; Martín et al., 2016).

Neurodevelopment and genetics

A striking majority of our CVI patients presented with either some form of developmental delay (DD) or cerebral palsy (CP) (231/249, 93.1%). We also found in our longitudinal cohort that CP at initial diagnosis was significantly associated with worsening CVI grade outcome over time. This is suspected to be due to multiple reasons. Both DD and CP are clinical diagnoses that may be comorbid, and children with CVI commonly have more than one underlying neurologic disorder (Castano et al., 2000; Fazzi et al., 2007; Handa et al., 2018). Additionally, DD and CP represent a large group of heterogeneous conditions that not only have highly variable etiologies, but in fact share many of them with CVI (e.g., prematurity, developmental and epileptic encephalopathies, and known genetic conditions).

As many as 26.1% of our patient cohort had a formal genetic diagnosis, including large chromosomal abnormalities (trisomy, deletions, duplications) and single gene pathogenic variants. The extent of our cohort's abnormal genetic findings exceeded that of prior studies (Matsuba and Jan, 2006; Bosch et al., 2014). Despite this, we still believe this underestimates the true incidence of genetic anomalies among children with CVI. Most of our genetic testing was obtained through a separate neurology clinic, where the focus was on other comorbid neurologic conditions (CP, DD, epilepsy), rather than CVI. Instead, a dedicated rigorous approach in genetic testing has the potential to uncover a larger number of etiologic targets. Our study nonetheless identified genes that have previously been implicated in CVI pathogenesis (*CDKL5, SLC35A2, LIS1*) (Bosch et al., 2014), as well as those not described elsewhere in the literature (*COXPD11, EIF2B5, FLAD1*). Despite these findings however, our study ultimately did not reveal a significant correlation between CVI severity/improvement and underlying genetic diagnosis. Instead, a rigorous and unbiased approach that examines a more homogeneous patient population (i.e., no neurological comorbidities) may be valuable.

Epilepsy

Most individuals of our cohort had a diagnosis of epilepsy at time of initial ophthalmologic evaluation (78.3%, n = 195/249). Among these, 33.8% had an identified form of epileptic encephalopathy (cerebral dysfunction related to often difficult-to-control epileptic activity), with infantile spasms/hypsarrhythmia being most common (83.3% of said group). This is likely related to the timing of initial ophthalmologic diagnosis vis-à-vis the most recent electroencephalographic studies. Nonetheless, these clinical findings are consistent with prior reports that have noted a significant seizure component in pediatric CVI patients, the majority of which were infantile spasms (Huo et al., 1999; Khetpal and Donahue, 2007; Handa et al., 2018).

With regards to seizure control, there is contradictory evidence in which earlier studies have reported improved visual development with improved seizure control, and a correspondingly poor prognosis for children with uncontrolled seizures (Wong, 1991; Good et al., 1994). However, it has also been recently reported that seizure control did not significantly improve vision, as well as evidence that seizure may not be contributory to CVI (Grant et al., 2008; Handa et al., 2018).

In the epilepsy group, 75% of patients had optimal seizure control at time-of-diagnosis of CVI. The mean CVI grade was more severe for patients with uncontrolled epilepsy (1.19) than controlled epilepsy (1.54). A trend toward mean CVI grade improvement was seen with improved seizure control. Interestingly, the use of multiple antiseizure medications (3 or more antiseizure medications) correlated with an increased baseline severity of CVI (**Table 2**). This may be indicative of the severity of the underlying epilepsy syndrome, and possibly a more reliable marker of epilepsy disease burden than subjective reporting of optimal or poor control. Additionally, the use of multiple antiseizure medications was also negatively associated with longitudinal CVI outcome, and suggests that

seizure activity reflects a cumulative burden on CVI prognosis over time. Of additional interest, a number of patients with a history of infantile spasms or other early epilepsy syndromes may have received medications known to impair visual function (e.g., vigabatrin); however, given the lack of usual related findings (e.g., visual field loss), this may not sufficiently explain the difference in CVI grade across groups. Practically, it is important for the vision care provider to consider the number of seizure medications and whether if it may be affecting the child's performance during a CVI vision assessment. This would importantly pair up with the increasing tendency toward early aggressive seizure/epilepsy management among neurologists, including offering earlier curative or palliative epilepsy surgery options and few medication trials (Prideaux et al., 2018; Roth et al., 2021; Perry et al., 2022).

Therapy/interventions

Presently, there is no standardized treatment for CVI. Given its heterogeneous nature and the broad range of visual impairment, it has been difficult to design and execute studies determining if a particular therapy or intervention is effective. Additionally, the paucity of evidence on the clinical effectiveness of CVI-based therapy makes our study unique in that our cohort was longitudinally followed for treatment effect after receiving multimodal interventions. It has been previously reported that improvements in vision in CVI patients were not associable to any unique etiology (Huo et al., 1999; Handa et al., 2018). Accordingly, our study cohort received therapies targeted at CVI visual improvement, including ECI vision therapy, visual rehabilitation (PT/OT), refractive error correction, and combination therapy.

Out of the therapy modalities that were offered to patients, we found that refractive correction with glasses was associated with the greatest improvement in CVI grade outcome over time. This is compared to ECI, PT/OT, or a combination of all therapies, which did not demonstrate significance with longitudinal CVI grade. Correcting refractive error is pursued for multiple pediatric conditions, and our study provides evidence that it is viable therapy for moderate and severe pediatric CVI as well. Prior studies have also identified treatable associated ophthalmic conditions (e.g., refractive error, accommodative insufficiency, cataract) in a significant proportion of CVI patients (Philip and Dutton, 2014; Pehere et al., 2018). Taken together, our evidence suggests that patients ought to pursue management for treatable ophthalmic conditions that co-present with CVI.

As an aggregate, having therapy documented at any visit was strongly associated with an average improvement in CVI grade of 0.14 per month, compared to no therapy. This was additionally supported at the patient level, whereby having at least one therapy recorded at any visit during a patient's follow-up period was also associated with a mean improvement in CVI grade of 0.25 per month. While refractive error correction as mentioned above may represent the majority contribution toward this improvement, the natural development of the visual system in pediatric patients may also play a role. In our multivariate model, age played a small but significant positive contribution toward CVI grade outcome, but the overall effect size is insufficiently large to explain the total improvement afforded by receiving CVI therapy during follow-up.

Limitations

Our study has multiple limitations that are common in retrospective studies. The CVI grading system described in this study was an attempt to incorporate subjective and objective clinical data, but may not have encompassed a true and robust quantification of visual function and behavior. A grading system developed after patient data collection may help better refine our CVI scale for future prospective studies. Given the retrospective nature of this study, certain aspects of data collection may be incomplete (information bias). Particularly, our data from genetic testing arose from workup targeted at separate underlying conditions (e.g., epilepsy), and may not represent the optimal context to identify causative genes associated with CVI. Due to the retrospective nature of the study, therapy modalities were not implemented in an evenly distributed manner. Additionally, our unbalanced sample sizes for our moderate vs. severe CVI groups (n = 52 vs. 197) reduces the statistical power.

Conclusion

The diagnosis and management of CVI is challenging due to its variable clinical manifestations, the presence of additional comorbidities, and the myriad associations it shares with other conditions. Herein, we present an extensive analysis of a retrospective cohort of pediatric patients with advanced CVI, showing that (1) perinatal HIE history, abnormal fundoscopic findings, and cerebral palsy are all negative predictors of CVI improvement; (2) optimizing seizure medications and epilepsy control served to benefit CVI improvement; and (3) patients who underwent longitudinal therapy, in particular refractive error correction with glasses demonstrated CVI score improvement from baseline and in comparison to an untreated cohort. This study also adds to the limited knowledge of genetics in CVI, and also provides a conceptual framework for the medical provider to screen for disease burden in the context of accessible visual function testing. Given that

our approach reveals associations consistent with previously reported comorbidities (HIE, epilepsy) that correlate with CVI, future work that evaluates the relationship between visual function development and the etiological overlap shared by these comorbidities can enhance our understanding of CVI pathogenesis, with the goal of identifying avenues of therapy and support for affected children.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Institutional Review Board Baylor College of Medicine. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

AJ-G, KF, and VS participated in study design, data collection and analysis, and manuscript draft and editing. CL and QS participated in data collection and analysis and manuscript draft and editing. KZ contributed to the statement. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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