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Non-invasive assessment of intracranial pressure through the eyes: current developments, limitations, and future directions

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Detecting and monitoring elevated intracranial pressure (ICP) is crucial in managing various neurologic and neuro-ophthalmic conditions, where early detection is essential to prevent complications such as seizures and stroke. Although traditional methods such as lumbar puncture, intraparenchymal and intraventricular cannulation, and external ventricular drainage are effective, they are invasive and carry risks of infection and brain hemorrhage. This has prompted the development of non-invasive techniques. Given that direct, non-invasive access to the brain is limited, a significant portion of research has focused on utilizing the eyes, which uniquely provide direct access to their internal structure and offer a cost-effective tool for non-invasive ICP assessment. This review explores the existing non-invasive ocular techniques for assessing chronically elevated ICP. Additionally, to provide a comprehensive perspective on the current landscape, invasive techniques are also examined. The discussion extends to the limitations inherent to each technique and the prospective pathways for future advancements in the field.

KEYWORDS

optic nerve sheath diameter, idiopathic intracranial hypertension, spontaneous venous pulsation, vessel analysis, non-invasive and invasive, intracranial pressure, cerebrospinal fluid

1 Introduction

A range of neurological and neuro-ophthalmic conditions, including hydrocephalus, space-occupying lesions, and idiopathic intracranial hypertension (IIH), can lead to a chronic rise in the cerebrospinal fluid pressure (CSFp). IIH is characterized by the presence of pathological signs of chronic raised ICP in the absence of any identified dilated ventricles, cranial tumors, or lesions evident on a brain scan with a normal ICP composition (1–4). We use the term CSFp interchangeably with intracranial pressure (ICP) where the latter is in the context of neurological or neuro-ophthalmic disease. Elevated ICP is a critical concern in these conditions, as it can lead to significant morbidity and mortality (5, 6). Rapid detection and management of raised ICP are crucial in preventing further damage to the central nervous system and reducing adverse outcomes. The conventional methods for measuring ICP, such as lumbar puncture (LP) and external ventricular drainage (EVD), are invasive and require trained clinicians to perform (5). These procedures, while effective, are associated with potential complications such as infection, hemorrhage and equipment failure (5, 6).

Headache, nausea, pulsatile tinnitus, and transient vision obscuration have been reported by patients who have elevated ICP (7–9). However, a correlation between the severity of symptoms and the level of elevated ICP has not been found (7, 10). More than 90% of patients complain of

throbbing or bursting headaches that can be worsened by sneezing and coughing (2, 7, 11, 12). Loss of consciousness can also occur, which can be due to the displacement of the midbrain and diencephalon (e.g., because of head trauma) or reduction in cerebral perfusion pressure (CPP), leading to decreased cerebral blood flow (13, 14). Other possible clinical signs reported include pupillary dilation, impaired upgaze, and bilateral droopy eyelid (7). Blood pressure and respiratory changes are also often noticed in the late stages of raised ICP, often caused by brain stem distortion and ischemia (7).

In response to the clinical need for safer and more accessible monitoring techniques, non-invasive methods such as transcranial Doppler (TCD), Computed tomography (CT) and Magnetic Resonance imaging (MRI), and non-invasive ophthalmic methods such as the ultrasound assessment of optic nerve sheath diameter (ONSD) have been explored. The TCD methods assesses cerebral blood flow dynamics, which can be altered in the context of raised ICP, while ONSD method is based on the premise that the optic nerve sheath expands in response to elevated ICP. However, studies investigating these non-invasive methods have reported varying degrees of accuracy, suggesting that they may not yet be suitable to replace conventional invasive techniques entirely. Instead, they are often used as complementary tools or to assist in deciding whether to proceed with invasive monitoring (5, 6, 15–18).

2 Invasive techniques

Clinical guidelines recommend immediate ICP measurement in patients suspected of elevated ICP (19). However, there is debate concerning the type of pressure being monitored and the optimal location for measuring CSF pressure (20). Currently, raised ICP can be detected invasively at various anatomical locations, including intraventricular, intraparenchymal, epidural, subdural, and subarachnoid sites. LPs are the most commonly used invasive technique to measure and detect raised ICP in acute and chronic conditions (21, 22).

2.1 Lumbar puncture

LP is a widely used invasive method for measuring and monitoring chronic and acute raised ICP, such as hydrocephalus and IIH (23). It provides opening and closing CSFp values. Despite its broad use, LP can be a painful procedure and carries risks of infection and brain herniation, however the risks can be reduced by improving skills and techniques (24, 25). Headache is the most common complication reported post lumbar puncture, with up to 32% of the patients reporting some degree of headache (26). Despite the risks associated, LP remains the gold standard technique in measuring and detecting elevated CSFp in acute and chronic raised ICP (27, 28).

2.2 Transducer implantation

Various invasive transducer devices have been developed to detect and monitor acute and chronic elevated ICP. These devices involve implanting a catheter connected to a transducer into the brain cavity, with the procedure named after the anatomical location of the insertion site (29). While epidural, subdural, intraparenchymal, and intraventricular methods were previously used, currently only intraventricular, and parenchymal sites are commonly performed (30). The intraparenchymal method measures brain tissue pressure as the catheter is inserted directly into the brain tissue (31, 32). The intraventricular technique was first performed in 1866 by Hollingsworth et al. (30). A catheter is inserted into the ventricles, close to the Foramen of Monroe, through a hole that is drilled into the skull, and connected to an external transducer (20, 29, 30). An External Ventricular Drain (EVD) originating from the intraventricular method is considered the gold standard for measuring global ICP (20, 23, 29, 33–35). An EVD also facilitates CSF drainage to maintain normal ICP levels and allows for the administration of drugs, such as antibiotics (20, 29, 33). The surgical procedure to place an EVD is considered minor and low risk (29). EVD placement can be challenging in younger patients due to their smaller ventricular system, while in older adults, the procedure is relatively straightforward due to age-related ventricular widening (29). A review and meta-analysis reported a 5.7% post-operative risk of hemorrhage in 1790 EVD procedures (36). Infection and colonization of bacteria in the catheter are other complications, potentially leading to skin infection, ventriculitis, meningitis, and septicemia (37–39). Nosocomial infections are the most common complication of EVD, with rates ranging from 5% to over 20% (37). Factors such as catheter misplacement, defective catheters, or skin infection at the insertion site can increase the risk of EVD-related infection (29). A study of 138 patients undergoing EVD found that 12.3% of the catheters were misplaced, necessitating secondary operations (40). EVD is mainly used in acutely raised ICP, such as traumatic brain injury and neurologic intensive care (41, 42).

3 Non-invasive assessment of ICP

Due to the complications associated with invasive techniques for measuring ICP, various non-invasive methods have been developed and trialed; however, none have made it into mainstream clinical practice. Techniques such as Computed Tomography (CT), Magnetic Resonance Imaging (MRI), Transcranial Doppler Ultrasonography (TCD), and Tympanic Membrane Displacement (TMD) have been used to screen for signs of elevated ICP and assess the need for invasive monitoring in both chronic and acute raised ICP.

3.1 Neuro-imaging

3.1.1 Computed tomography

CT is a non-invasive modality that can be used to detect elevated ICP by evaluating the integrity of intracranial structures. It provides insights into the morphology of midline shifts, basal cisterns, and ventricles. CT scans are often used in combination with other clinical symptoms to evaluate elevated ICP (43, 44). In a study involving 218 patients with severe head injuries, 74% of patients without effacement of basal cisterns had an ICP of more than 30 mmHg (44). Midline shift and compression or destruction of mesencephalic cisterns as observed on CT scans are the most accurate signs of raised ICP (43, 44). In a review of non-invasive methods of measuring ICP, it was concluded that abnormal cisterns are associated with a 3-fold increased risk of

Abbreviations: ICP, Intracranial pressure; IIH, Idiopathic intracranial hypertension; ONSD, Optic nerve sheath diameter; SVP, Spontaneous venous pulsation; CSF, Cerebrospinal fluid; LP, Lumbar puncture; ONS, Optic nerve sheath.

elevated ICP (45). CT scans are valuable non-invasive tools used in chronic and acute raised ICP, but a normal CT scan does not necessarily indicate normal ICP. The major reason for performing a CT scan of the brain in IIH patients is to exclude any other underlying cause leading to raised ICP (46, 47).

3.1.2 Magnetic resonance imaging

MRI scans are used to characterize cerebral vascular circulation for non-invasive ICP assessments (48). The exponential relationship between volume and pressure was introduced by Marmarou et al. (49), demonstrating that compliance and resistance to fluid absorption are key in determining ICP levels. Intracranial elastance, which has a linear relationship with ICP, can be measured using MRI (50). Elastance is defined as the change in volume over the change in pressure (Elastance = $\Delta\nu/\Delta p$). This volume change is obtained using phase-contrast MRI measuring intracranial vein, arterial, and CSF flows during each cardiac cycle, while the pressure change is derived from CSF velocity extracted from velocity-encoded MRI images (43, 48). Studies have examined MRI's reliability and accuracy in measuring elevated ICP, with findings ranging from modest to poor repeatability to significant correlations with invasive ICP measurements (48, 51) (Table 1).

3.2 Transcranial Doppler ultrasonography

TCD utilizes the interaction between CSF and cerebral blood flow to assess ICP non-invasively. It assesses the blood flow velocity of cerebral arteries and applies mathematical models for ICP estimation, which includes the TCD-derived pulsatility index reflecting downstream vessel resistance, calculation of cerebral perfusion pressure (CPP), and other mathematical estimations. However, the accuracy of these TCD-based methods varies significantly, as noted in a systematic review (15). TCD provides critical information on the direction and velocity of blood flow within intracranial vessels, which can change due to external pressures like ICP or internal pressures such as arterial blood pressure (15).

Despite its advantages of being cost-effective, portable, and risk-free with high temporal resolution, making it ideal for emergency departments and bedside use, TCD has limitations. It cannot detect abnormal ICP if the cause is an obstruction in CSF circulation rather than a dysfunction in the cerebral arterial system (15). Furthermore, its utility in monitoring raised ICP in patients with idiopathic intracranial hypertension (IIH) has shown conflicted results. Some studies suggest that while TCD, particularly the pulsatility index, correlates with raised ICP, it cannot replace invasive methods and is more suitable for monitoring chronically raised ICP during follow-up sessions (52–54). These complexities highlight the need for cautious application and further research into TCD's effectiveness in various clinical scenarios.

3.3 Tympanic membrane displacement

TMD, developed in 1981, is an audiological measurement device for detecting raised ICP. It measures the movement of the tympanic membrane in response to the acoustic muscle reflex (55). The stapedius muscle contracts in response to sound stimulation, leading to the movement of the stapes. The cochlear fluid pressure level determines the resting position and direction of stapes movement due to its anatomical position on the oval window. High cochlear fluid pressure results in the inward displacement of the tympanic membrane, while low pressure leads to outward movement. The CSF pressure is transmitted to cochlear fluid pressure through the cochlear aqueduct (Figure 1). Therefore, monitoring the direction of tympanic membrane displacement can indicate normal or raised ICP (39, 56) and it can be an alternative non-invasive method of monitoring raised ICP in Hydrocephalus and neurological conditions (57, 58). To our knowledge, no study in the literature has investigated this method to detect raised ICP in IIH patients.

3.4 Otoacoustic emissions

Another novel non-invasive method of detecting elevated ICP is otoacoustic emissions, which is another auditory measurement of acutely elevated ICP. Otoacoustic emissions are produced by cochlea as a response to elevated ICP (59). Distortion product otoacoustic emissions (DPOAE) are subtypes of otoacoustic emissions that are produced in response to two specific frequencies in the ear canal (59). This technique uses microphones placed in the ear canal. Previous studies have shown that as the ICP changes, the magnitude and angles of otoacoustic emissions change; however, the shortcoming of this technique is that small changes in ICP do not produce any systematic changes in DPOAE (59, 60).

3.5 Visual evoked potential

Visual stimuli cause the production of electrical waves in the occipital lobes, which measure the conduction time from the retina

TABLE 1 Pooled specificity and sensitivity of findings in neuroimaging in IIH patients.

Findings of neuroimaging in IIH	Pooled specificity (95% CI)	Pooled sensitivity (95% CI)
Empty Stella (47, 50, 129–131)	83% (76–90)	80% (71–89)
Papilledema (47, 50, 131, 132)	99% (97–100)	17% (11–13)
Increased ONSD (47, 50, 131)	89% (85–95)	58% (48–68)
Posterior flattening of the eyeball (47, 50, 131)	98% (96–100)	66% (60–72)
Transverse sinus stenosis (46, 47, 133)	93.5% (84–97)	97% (93–100)
Vertical tortuosity of the optic nerve (46, 47, 131)	90% (85–95)	43% (37–50)
Meningoencephalocele (46, 134)	NA	11% (4–18)

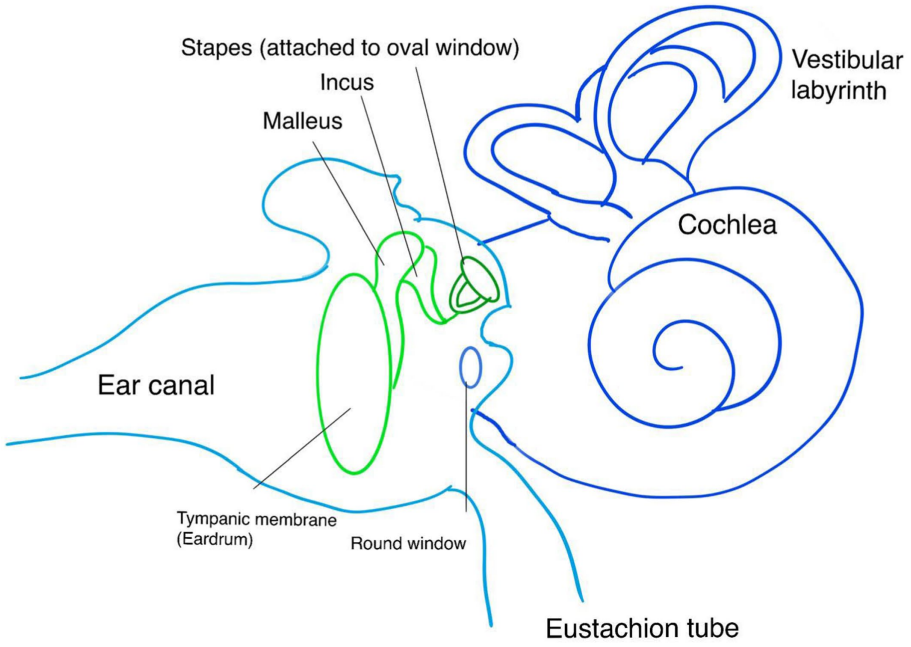

FIGURE 1
Anatomy of the ear and tympanic membrane involved in the measurement of TMD. CA, Cochlear Aqueduct; OW, Oval Window; RW, Round Window; T, Tympanic membrane; S, Sensor.

to the visual cortex clinically used to examine the integrity of the visual pathway (61). VEP waveforms consist of positive (P) and negative (N) waves, the shape of these waves, the time taken to respond to these stimuli, or the latency (62). In a clinical setting, VEP is obtained by placing electrodes on the patient's head to measure the optic pathway activity from the retinal pigment epithelium to the occipital lobe (61, 62). This method uses flashes of lights or pattern stimuli; however, flashing VEP (F-VEP) has shown more variability (61). F-VEP lasts for 5 milliseconds, covering a visual field of at least 20 degrees with a recommended flash rate of 1.0 Hz ±0.1 (1 flash per second), and pattern stimuli is a checkboard pattern that reverses every half second (Figure 2A) (63). Previous studies have demonstrated a positive correlation between F-VEP and elevated ICP, mainly causing prolonged latency of N2 waves in patients with traumatic brain injuries, hydrocephalus indicating shunt dysfunction and drug-related cerebral oedema (61, 64–69). Although limited studies are available on the utility of this method in detecting raised ICP in IIH patients, available studies have presented conflicting results depending on the technique used and test time (70). During the early stages of IIH, VEP has been reported to be normal (70–73). However, other studies have shown significant delayed response to stimuli in VEP (74, 75). In conclusion, VEP is useful in monitoring the severity or the regression of the visual function of patients with raised intracranial pressure (76).

Positive (P) and negative (N) responses with different stimuli. In flash stimuli, the second negative peak (N2), with a normal latency of approximately 70–90 ms and the second positive peak (P2), with a normal latency of approximately 100–120 ms, are the most prominent waves. Pattern-reversal VEPs normally comprised of three main features: an initial negativity with a latency of approximately 70 to 80 milliseconds (N75), a larger positive part with a latency of about 90–110 ms (P100), and a large negative part with a latency of around 130–140 ms (N135) (63, 65, 77) (Figure 2B).

4 Non-invasive ophthalmic-based assessment

Given the limitations and challenges in directly accessing the brain's structure, as demonstrated above, alternative ophthalmic-based techniques have been explored due to the anatomical link between the eye and the brain's structure, vasculature, and CSF drainage pathway. These non-invasive ocular assessments aim to eliminate the need for invasive approaches as the first line of assessment in chronic raised ICP such as IIH. The most commonly studied methods are measuring the optic nerve sheath diameter (ONSD), investigating structural changes at the optic nerve head (papilledema), and examining static and dynamic retinal vessel changes.

4.1 Optic nerve sheath diameter

The optic nerve, the second cranial nerve, is responsible for transmitting visual information. It exits the globe at the optic disk, where the lamina cribrosa resides. The optic nerve is surrounded by the optic nerve sheath (ONS), an extension of the brain's meninges, with CSF running between the optic nerve and the ONS. Early studies have reported that a rise in ICP levels leads to an increase in ONSD, swelling of the optic nerve head, and deformation of the retinal pigment epithelium and Bruch's membrane in papilledema (78–81). Chronic elevated ICP leads to increased ONSD and increased retinal vein diameter (82).

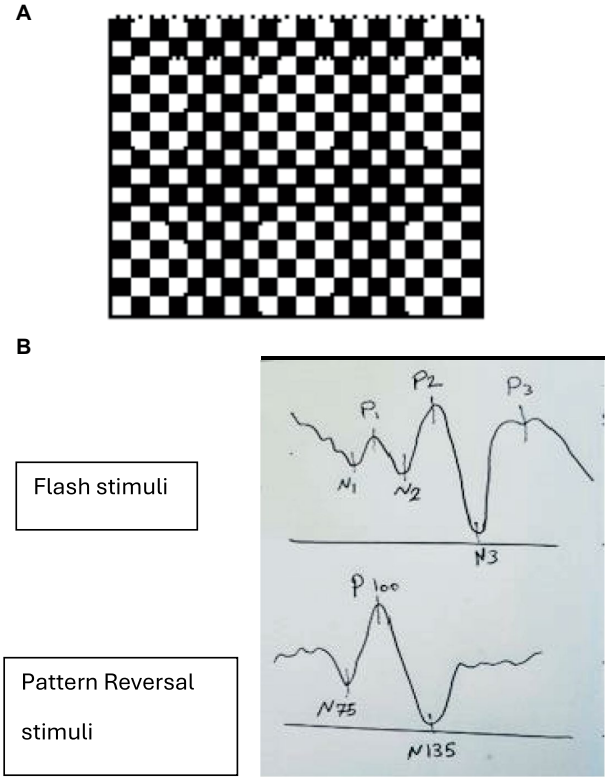

FIGURE 2
(A) Checkboard pattern with a red point fixation target in the middle. **(B)** Positive (P) and negative (N) responses to flash vs. pattern reversal stimuli.

Various studies have investigated the correlation between raised ICP and increased ONSD (83–90). Ultrasound is the most investigated non-invasive technique for detecting raised ICP by measuring ONSD, depicted in Figure 1 (91). A study measuring ONSD by ultrasound in 50 participants concluded that an increased diameter of greater than 5.5 mm has 100% specificity and sensitivity in detecting raised ICP of more than 20 cmH2O (86, 91). Previous studies have demonstrated high sensitivity of ONSD in detecting abnormal ICP (83, 85, 87–95). However, there are inconsistent reports in the literature concerning the ONSD cut-off value and the efficacy of tools used to measure ONSD distension in elevated ICP. Cut-off values ranging from 5.3 mm to 5.8 mm have been reported as indicators of raised ICP. Notably, there is considerable inter-individual variation in ONSD measurements. Studies among the Chinese population reported an ONSD threshold of 4.1 mm as a marker of elevated ICP (90), while studies in Western populations reported cut-off values over 5 mm (88–90). In Bangladeshi patients aged over 16, the upper limit of ONSD in healthy individuals is 4.75 mm (96). These variations in cut-off values across different populations lead to increased sensitivity and decreased specificity in estimating raised ICP. Some studies have reported differing findings (85, 90, 95, 96). For example, a study of 51 patients undergoing lumbar puncture showed that ONSD obtained by ultrasound is not an appropriate marker for measuring raised ICP in non-traumatic intracranial hypertension due to its low specificity and sensitivity of 44 and 75%, respectively (85). Conversely, a study examining ICP in patients with severe traumatic brain injury and measuring their ONSD with a CT scan simultaneously reported that assessing ONSD with a portable CT is a reliable method, with a specificity of 42% and sensitivity of 97% (95). Table 2 summarizes the differences in specificity, sensitivity, and cut-off values reported in meta-analyses conducted over the last 10 years (92, 97–103). The variation in findings could be attributed to differences in population ethnicity, sample size, and the modalities used to measure ONSD. Ultrasound of ONSD is highly user-dependent, and measurements can vary significantly depending on the examiner's skill (Figure 3).

4.2 OCT of the optic nerve head

Optical coherence tomography (OCT) is a widely used non-invasive technique for diagnosing papilledema, mainly in chronically raised ICP such as IIH. OCT provides cross-sectional images and quantifies retinal nerve fiber thickness (RNFL) and macular ganglion cell layer (GCL), which are key indicators for monitoring papilledema (104). There is thickening of the RNFL in papilledema. The macular GCL thickness is typically normal in patients with preserved visual function. However, in chronic, severe or untreated papilledema, irreversible damage to the retinal ganglion cells is seen as thinning of the macular GCL (105, 106). OCT of optic nerve head (Figure 4) has been instrumental in assessing peripapillary, choroidal, and retinal folds in IIH patients with papilledema, a phenomenon suggested to result from shear stress on the optic nerve head due to raised ICP (107). However, papilledema may not be an optimal marker for diagnosing and monitoring abnormal ICP, as its development and resolution can be delayed, depending on changes in ICP and axoplasmic disturbance. Additionally, optic atrophy may prevent nerve swelling in cases of raised ICP (108). Monitoring the severity of papilledema is suitable for monitoring raised ICP in chronic conditions that may guide treatment (84, 109). Previous studies denoted in Table 3 show the various findings of OCT of the optic nerve head in IIH patients with papilledema (104, 110–113). The increase in RNFL thickness and the decrease in macular GCL are correlated with the severity of papilledema and used to diagnose and monitor the progression and regression of raised ICP, mainly in chronic raised ICP (104, 105, 110, 114). Thinning of macular GCL results in visual dysfunction from neural loss.

4.3 Retinal vessel analysis

4.3.1 Static vessel analysis

Static changes in the retinal vasculature include tortuosity, arteriovenous nicking, and variations in vessel caliber. As ICP exceeds 20 cmH2O, retinal vein diameter increases, resulting in a decreased arteriole-to-venule diameter ratio (115). A study of 20 adults with papilledema observed a reduction in retinal vein and arterial diameter one-hour post-ICP lowering (82). Retinal vein diameter has been proposed as a biomarker for detecting increased retinal vein pressure due to raised ICP (116). In a randomized controlled trial involving 115 individuals with IIH, optic nerve swelling was correlated with increased retinal vein diameter, which decreased 6 months post-treatment for raised ICP (117). Retinal vessel tortuosity, associated with chronic raised ICP, is believed to result from increased vessel diameter and subsequent tortuosity (117, 118) however, no study has

TABLE 2 Specificity, sensitivity, and cut-off value of ONSD in raised ICP, measured non-invasively.

Studies (meta-analysis)	Modality	Pooled specificity (95% CI)	Pooled sensitivity (95% CI)	ONS cut off value ± mean standard deviation (SD)
Aletreby et al. (92)	Ultrasound	0.85 (0.8–0.89)	0.9 (0.85–0.94)	5.55 ± 0.5 mm
Sallam et al. (97)		0.88 (0.84–0.91)	0.9 (0.87–0.92)	Not reported
Lee et al. (98)		0.77 (0.63–0.88)	0.91 (0.87–0.94)	5.8 mm
Koziarz et al. (99)		0.86 (0.74–0.93)	0.97 (0.92–0.99)	5.0 mm
Robba et al. (100)		0.80	0.96	>4.80
Kim et al. (101)		0.73 (0.65–0.8)	0.99 (0.96–1.0)	>5.0 mm
Ohle et al. (102)		0.92 (0.78–0.98)	0.95 (0.87–0.98)	>5.0 mm
Sallam et al. (97)	CT	0.79 (0.56–0.92)	0.93 (0.90–0.96)	Not reported
Sallam et al. (97)	MRI	0.89 (0.84–0.93)	0.77 (0.64–0.87)	Not reported
Kwee et al. (103)		0.86 (0.79–0.91)	0.68 (0.55–0.80)	>2 mm

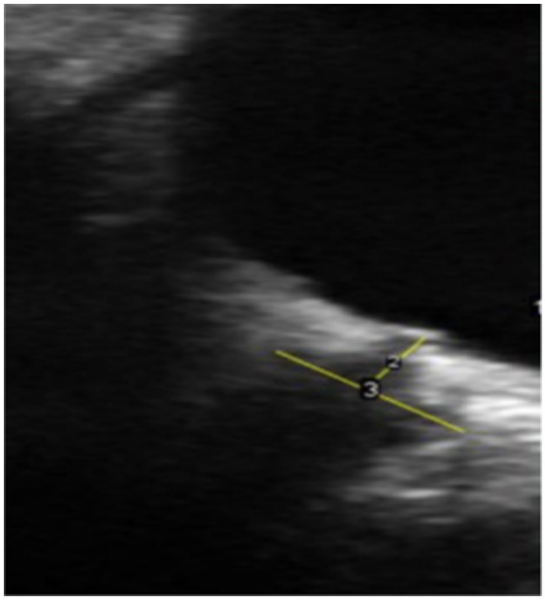

FIGURE 3
Ultrasound of optic nerve head 3 mm behind the eye socket where optic nerve exits.

systematically investigated the improvement of vessel tortuosity due to the resolution of papilledema. Investigating static vessel changes is mainly used as additional

Markers for diagnosis and monitoring chronic raised ICP.

4.3.2 Dynamic vessel analysis

Dynamic retinal vascular changes are characterized by spatial–temporal features extracted from retinal videos, including pulse wave velocity, arterial pulsatility index, and spontaneous venous pulsations (SVPs) (119–123). SVPs, observed as slight variations in retinal vein diameter at the optic nerve head, occur as a result of intra- and extra-ocular pressure compartments intersecting at the lamina cribrosa, affecting the pressure gradient (120, 122). Elevated ICP leads to increased intracranial pulse pressure and an imbalanced pressure gradient between IOP and ICP, resulting in the cessation of SVPs (122, 124). SVPs have been postulated as markers of raised ICP due to their physiological relationship with ICP and IOP (118–124). A study of 338 measurements from 9 patients showed that ICP pulse pressure controls the timing of venous pulsation (121). While earlier studies reported increased pulsation of the central retinal vein due to increased IOP (125), recent modeling studies have indicated a close relationship between SVP, IOP, and ICP, with any imbalance disrupting SVP oscillation (118, 120, 121).

4.3.2.1 Assessment of SVP

The validity and usefulness of SVPs as a predictive marker of raised ICP has been debated (122–124, 126). The presence of SVPs indicates normal ICP, but their absence does not necessarily signify raised ICP, as they can be absent in 10-20% of the population (122). A prospective study evaluating SVP and ICP in 106 patients undergoing LP concluded that SVP was not a reliable predictor of ICP, with a sensitivity of 94% to exclude raised ICP (126). However, this study assessed ICP and SVP in different positions, which could affect the results. Another study investigated the validity of smartphone-based video ophthalmoscopy for detecting SVP in 233 patients, finding a sensitivity of 82.77 and 76.82% for two observers, respectively (127) demonstrated in Table 4. However, this study faced challenges like poor video quality and camera shake. Subjective measurement of SVPs can be one of the limitations presented in previous studies however objective measurements have shown 100% detection in healthy individuals (128).

A recent study using motion-stabilized infrared videography found a significant association between SVP and ICP in 101 patients with intracranial hypertension (124). This study measured ICP and SVP in a seated position to account for postural variations in ICP (126). While further investigation is needed, there is potential for using SVP to non-invasively and reliably assess ICP (126) (Figure 5).

5 Limitations of non-invasive methods

Despite technological advances and the development of various non-invasive techniques, none have yet replaced invasive methods. This is due to limitations such as lack of portability, practicality, and availability in all clinical settings. Additionally, non-invasive methods often cannot monitor ICP continuously or measure it quantitatively, and they tend to be operator-dependent. Currently, non-invasive methods are primarily used as complementary tools in detecting raised ICP.

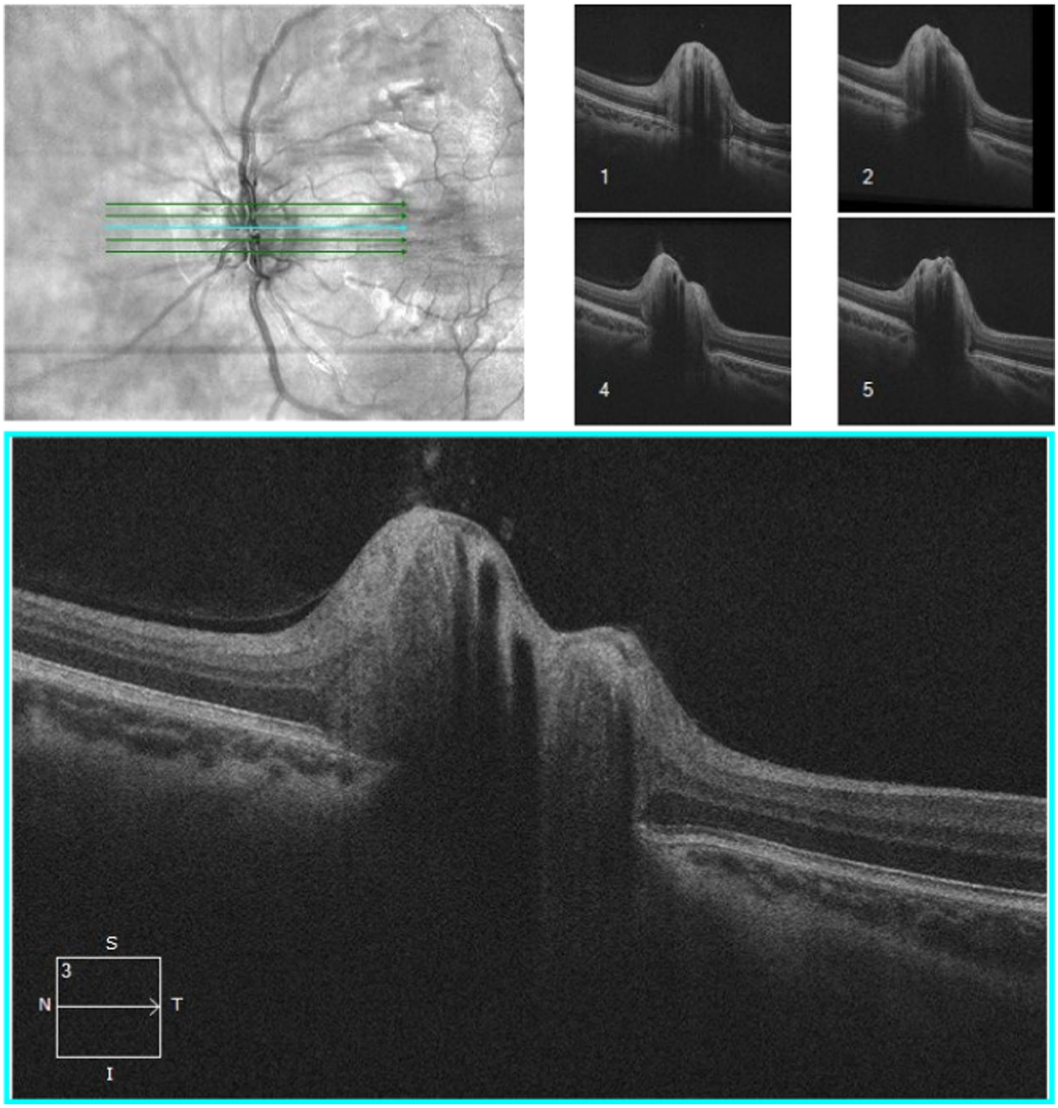

FIGURE 4
OCT of optic nerve head of an IIH patient conducted by CIRRUS SW Ver: 11.5.2.54532 Copyright 2020 Carl Zeiss Meditec.

TABLE 3 OCT findings of ONH in IIH adult patients with papilledema.

Studies	GCL volume (μm) Mean±SD	RNFL thickness (μm) Mean±SD	CSF opening pressure (cmH2O) Mean±SD
Eren et al. (110)	101.72 ± 7.46 (80.38–130.72)	127.19 ± 24.26 (94–204)	30.0 ± 0.33 (25–37)
Kaufhold et al. (113)	Not reported	99.1 ± 18.1 (58.4–155.5)	28.6 ± 0.63 (18–40)
Waisbourd et al. (111)	210 (199–220)	129.75 ± 41.34 (80–214)	32.6 ± 0.69
Rebolleda and Muñoz-Negrete (104)	Not reported	183.3 ± 74.7	Median 29 (25.5–45)
Jacobsen et al. (112)	Not reported	124.2 ± 77.8	13.4 ± 5.6 (overnight monitoring pressure)

5.1 Neuro-imaging

MRI and CT scans provide qualitative information about structural brain changes, such as midline shift, lateral ventricular compression, and dilation of the ventricular system. These neuro-imaging methods are essential for differentiating underlying conditions from secondary causes of raised ICP. However, they are not universally available. MRI and CT scans cannot measure ICP quantitatively and are not reliable for continuous ICP monitoring. MRI is time-consuming, limiting its use in emergency settings where rapid detection of raised ICP is crucial. CT scans, which use ionizing radiation, are particularly concerning in pediatric patients.

TABLE 4 Responses given by two blind observers were asked to identify SVP on Videos, compared with gold standard identification using a slit lamp (127).

	SVP identified on video		SVP not identified on video	
	Observer 1	Observer 2	Observer 1	Observer 2
SVP present on slit lamp	138	116	23	35
SVP not present on slit lamp	13	38	108	83

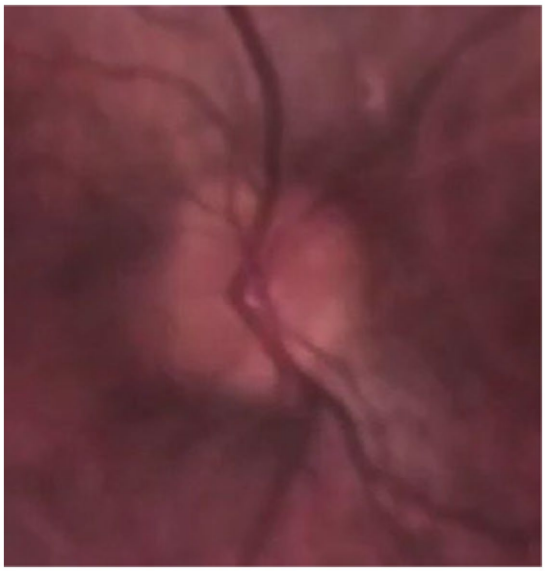

FIGURE 5
A fundus photo of retinal blood vessels as they exit the globe where SVP is detected with a smartphone-based handheld ophthalmoscope.

Collectively, neuro-imaging techniques are primarily used as screening tools where available.

5.2 Tympanic membrane displacement and otoacoustic emissions

The TMD technique requires a normal middle ear, an intact acoustic stapedial reflex, and a patent cochlear aqueduct. It is less optimal in elderly patients, as cochlear aqueduct patency often decreases with age. TMD cannot measure absolute ICP but can provide mean ICP values; however, it is not suitable for continuous ICP monitoring. Despite these limitations, TMD has proven reliable for screening patients suspected of having raised ICP. Otoacoustic emissions do not show any changes if the elevation of ICP is minor, which makes this method unreliable in acute smaller changes of ICP.

5.3 VEP

This non-invasive method is useful in detecting abnormalities in visual pathway dysfunction based on raised ICP. VEP cannot measure absolute ICP as it only detects damage to the optic nerve. If the patient is at an early stage of the disease and optic nerve damage has not happened yet, then the diagnosis can be missed or remain undetected. Another point to consider is that VEP is affected by anesthesia and cannulation and cannot be used in patients who are under anesthesia. However, it can be used as a non-invasive way of monitoring the progression of raised ICP in chronic intracranial hypertension patients.

5.4 Ophthalmic-based assessment

Ocular-based technologies and methods for non-invasive assessment of ICP have made significant advancements but have not yet achieved the clinical reliability needed to replace invasive methods. Limitations include structural variations in the eye, such as ONSD, across different ethnicities. Additionally, ocular changes may not be clinically sensitive to detect subtle, temporary ICP changes. An increase in ICP must be sustained and significant to affect retinal structures, including papilledema and blood vessel changes like the cessation of SVPs. Furthermore, none of the non-invasive ophthalmic methods developed so far can measure mean ICP; they assess abnormalities in retinal and optic nerve head structure and vasculature as surrogate biomarkers. Quantitative measurement of retinal and cranial pulse pressure also remains challenging.

6 Future directions

Developing an accurate, non-invasive method for monitoring elevated ICP could significantly impact patient quality of life. Traditional invasive methods, such as lumbar puncture, external ventricular drainage, and intraparenchymal probes, carry risks of complications like infection and brain herniation. The non-invasive techniques developed to date have their shortcomings and do not provide precise measurements of raised ICP. A holistic understanding of the link between ICP and structural and vascular changes is necessary to better comprehend the pathophysiology of raised ICP and its effects on retinal structures and blood vessels. We propose that elevated ICP could be monitored using a combination of non-invasive parameters, such as SVP, OCT of RNFL, and fundus photos, to establish a panel of biomarkers. In taking such approach a versatile panel of biomarkers can be tuned for detecting both acute and chronic elevations in ICP. For chronic conditions, more structural changes are expected, making markers such as RNFL assessments or static vascular features particularly relevant. In contrast, acute conditions, due to their dynamic nature, may show more prominent changes in dynamic vascular features (e.g., SVPs), which could more accurately reflect acute elevations in ICP. This does not imply that certain manifestations are exclusive to one condition over the other but suggests that the likelihood of

observing a change may be more pronounced in one type of feature compared to another. Collectively, this approach could enhance the specificity and sensitivity of using ophthalmic-based markers to assess raised ICP non-invasively. While this research might lead to superior non-invasive ICP assessment methods through ocular examination, it is unlikely to replace gold-standard invasive techniques but rather act as a complementary approach where access to invasive techniques is limited or not warranted. It could also be valuable for early screening and triaging, thereby improving clinical management.

Author contributions

SB: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. AA: Supervision, Validation, Visualization, Writing – review & editing, Conceptualization, Funding acquisition, Methodology, Project administration, Resources. ML: Supervision, Validation, Visualization, Writing – review & editing. CF: Supervision, Validation, Visualization, Writing – review & editing, Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Resources, Writing – original draft. MG: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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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.

Publisher's note

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