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Can early-onset acquired demyelinating syndrome (ADS) hide pediatric Behcet's disease? A case report

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Behcet's disease (BD) is a rare vasculitis characterized by multisystemic inflammation. Central nervous system (CNS) involvement is rare and heterogeneous, particularly in the pediatric population. A diagnosis of neuro-Behcet could be highly challenging, especially if neurological manifestations precede other systemic features; however, its timely definition is crucial to prevent long-term sequelae. In this study, we describe the case of a girl who, at 13 months of age, presented with a first episode of encephalopathy compatible with acute disseminated encephalomyelitis, followed, after 6 months, by a neurological relapse characterized by ophthalmoparesis and gait ataxia, in association with new inflammatory lesions in the brain and spinal cord, suggesting a neuromyelitis optica spectrum disorder. The neurological manifestations were successfully treated with high-dose steroids and intravenous immunoglobulins. In the following months, the patient developed a multisystemic involvement suggestive of Behcet's disease, characterized by polyarthritis and uveitis, associated with HLA-B51 positivity. The challenge presented by this unique case required a multidisciplinary approach involving pediatric neurologists, neuro-radiologists, and pediatric rheumatologists, with all of these specialists creating awareness about early-onset acquired demyelinating syndromes (ADSs). Given the rarity of this presentation, we performed a review of the literature focusing on neurological manifestations in BD and differential diagnosis of patients with early-onset ADS.

KEYWORDS

Behcet's disease, magnetic resonance imaging, children, early onset, acquired demyelinating syndromes (ADSs)

Introduction

Behcet's disease (BD) is an inflammatory vasculitis affecting the arteries or veins of all sizes and is characterized by cutaneous, ocular, articular, gastrointestinal, and/or central nervous

system involvement. The first symptoms and signs of the disease commonly appear between the second and the fourth decade of life, but it can rarely develop in childhood and even in infancy (1).

Neurological involvement in pediatric BD is rare, but its early diagnosis is essential to prevent unfavorable outcomes. Central nervous system (CNS) manifestations can be attributed to two major pathways: first, and most commonly, through the development of an immune-mediated meningoencephalitis, which predominantly involves the brainstem, but can also involve the basal ganglia, thalamus, cortex, white matter, spinal cord, or cranial nerves; and second, as a consequence of thrombosis within the dural venous sinuses (2).

In this study, we describe the case of a very young girl who, at 13 months of age, presented the first neurological manifestation with radiologic features of acute disseminated encephalomyelitis (ADEM) and who subsequently developed a multisystemic involvement characterized by polyarthritis and uveitis suspicious for BD.

Case report

A 13-month-old girl presented with an asymmetric weakness and hypertonia in the four limbs (both arms and legs), which appeared more severe on the right side than on the left side, with right head deviation. She could only perform some abnormal dystonic movements with the right limbs because her left limbs were almost plegic. She also presented with an altered state of consciousness, alternating periods of sleepiness with severe psychomotor agitation. Notably, 4 days before her neurological symptoms occurred, she presented with fever and cough, and 1 month prior to this, the patient had received vaccination against

diphtheria, tetanus, pertussis, poliomyelitis, haemophilus B, hepatitis B, and pneumococcus. A cerebrospinal fluid (CSF) analysis revealed that the level was within the normal range, and a broad screening for infectious agents showed a negative result. The patient was also tested for the presence of oligoclonal bands, anti-AQP4, and anti-MOG antibodies. Brain magnetic resonance imaging (MRI) showed symmetrical thalamic lesions, with extension to the hemispheric white matter and to the right optic tract, without contrast enhancement (Figure 1A). A diagnosis of acute disseminated encephalomyelitis (ADEM) was made, and endovenous high-dose methylprednisolone therapy was started for 7 days, which involved a cycle of high-dose intravenous immunoglobulins (IVIg), leading to rapid clinical recovery and radiological response at the 3-month control brain MRI, without any radiological progression (Figure 1B). Due to the unusual coexistence of extrapyramidal dystonic manifestations at onset, thiamine-responsive basal ganglia disease (BTBGD) was excluded by sequencing the SLC19A3 gene; likewise, inherited inborn errors of metabolism, including mitochondrial diseases, were excluded.

Oral prednisone was tapered in 2 months. Four months later, the child reached the gait milestone, and a limping on the right leg was noticed, with an attitude in extra rotation of the right lower limb. One month later, and 17 days after the vaccination against measles, parotitis, and rubella, the patient presented with a second neurological episode characterized by the acute onset of gaze paralysis, left eye esophoria, vertical nystagmus, and inability to walk due to severe gait ataxia. The patient again underwent a brain and spinal cord MRI, which showed new lesions in the supra- and infratentorial white matter, optic nerves, some of which with gadolinium enhancement, and longitudinally extensive transverse myelitis (LTEM) lesion at the C2–C4 level, suggestive of
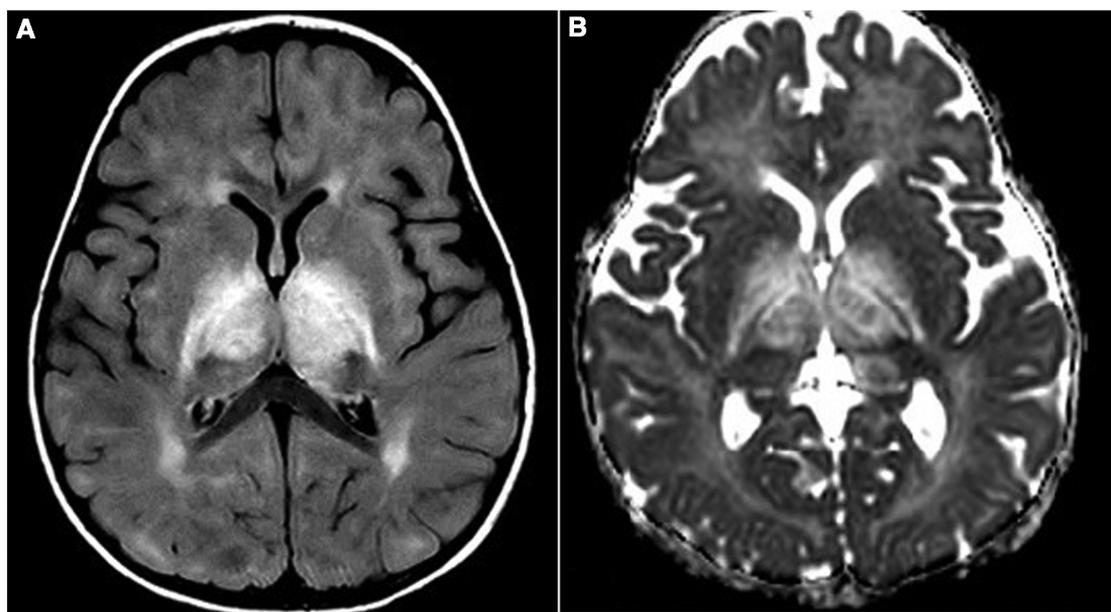

FIGURE 1
(A,B) First MRI study: FLAIR (A) and ADC (B) images show diffuse thalamic and internal capsule bilateral involvement with increased diffusion as for vasogenic edema.
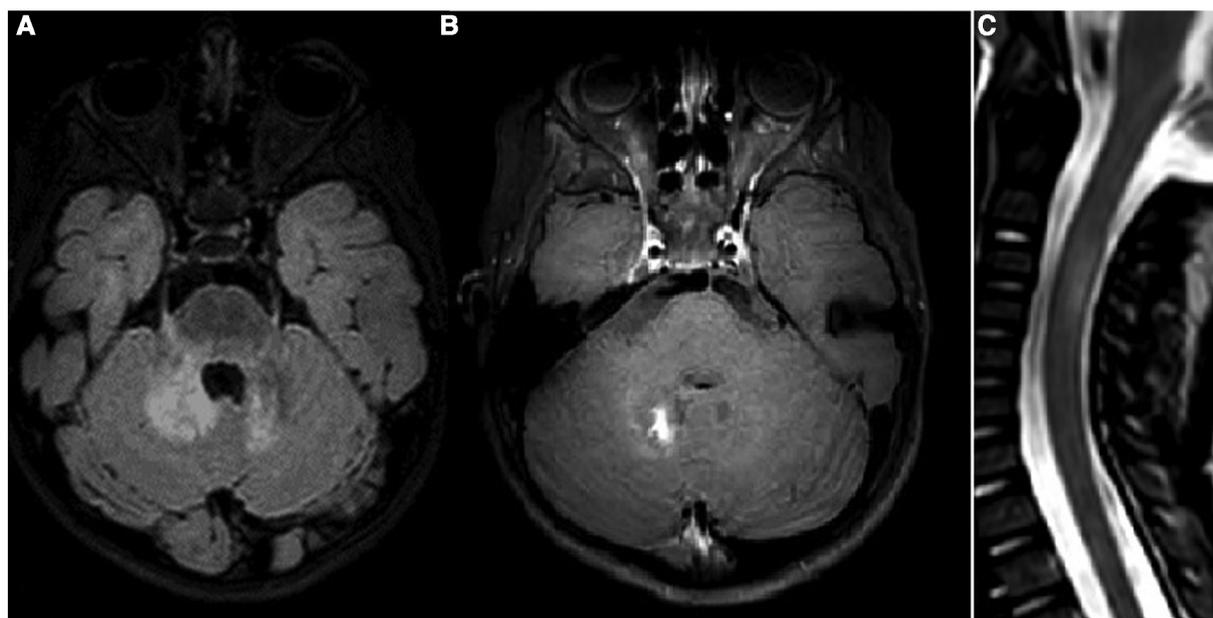
FIGURE 2
(A−C) Third MRI study: FLAIR (A) and postcontrast T1WI (B) of the cerebellum and a STIR midsagittal image of the cervical spine (C). New lesions on deep cerebellar white matter and V cranial nerves origin are visible, with a postcontrast enhancement of the right lesion. A new lesion in the cervical spine is also visible at the C3−C4 level.

neuromyelitis optica spectrum disorder (NMOSD) (**Figure 2**). Visual evoked potentials (EPs) showed an increase in P100 latency in both eyes, while brainstem auditory and somatosensory EP demonstrated an increased central conduction velocity. CSF analysis again showed that the level was within normal range, and no oligoclonal bands nor anti-AQP4 or anti-MOG antibodies were detected. However, a CSF cytokine panel assay showed multiple increases in proinflammatory cytokines, such as IL-6, IL-1Ra, MCP-1, and IP-10/CXCL10 (**Supplementary Table S1**). Blood tests showed antinuclear antibody (ANA) positivity (>1:640 titer) and the presence of HLA-B51. The patient was re-treated with high-dose steroids and monthly high-dose IVIg, which resulted in good neurological recovery, despite the persistence of a fluctuating limp in the right leg with a limited range of motion.

An MRI performed at 29 months of age did not show any new brain or spinal cord lesion but highlighted the presence of active arthritis of the right temporomandibular joint (**Supplementary Figure S1**). A complete joint assessment performed at that time by pediatric rheumatologists revealed swelling, pain, and limitation in the motion of the right knee and ankle. The presence of active arthritis was confirmed by an ultrasound assessment.

The very early onset of neurological manifestations and the subsequent development of polyarthritis led us to consider the wide spectrum of inherited diseases characterized by neuroinflammation. Type I interferon signature was negative. Whole-exome sequencing was then performed, with a particular focus on the genes involved in neuroinflammatory pathways (3) without any evidence of pathogenic variants.

Given the broad differential diagnosis performed, the presence of CNS parenchymal lesions located in the brain and spinal cord

with a relapsing-remitting course, the good clinical recovery with immunomodulating treatment, and the evidence of polyarthritis associated with HLA-B51 positivity suggested a possible diagnosis of Bechet's disease with neurological involvement.

Intra-articular steroid injections were administered on the right knee and ankle, and therapy with colchicine (0.5 mg/daily) and methotrexate (7.5 mg/weekly) was started, with a stabilization of the neurological picture both clinically and radiologically. Due to the occurrence of tibiotarsal arthritis relapses, two more intraarticular steroid injections with the addition of biologic therapy with anti-IL6 (tocilizumab) were required for the girl at the age of 3 years and 3 months, which resulted in a very good clinical response and complete articular remission.

However, 3 years and 6 months from the disease onset, the patient developed bilateral uveitis despite ongoing treatment with tocilizumab and was, therefore, switched to adalimumab as part of anti-TNFα treatment, following which she showed a positive clinical and ophthalmological response. At the last follow-up, performed at the age of 5 years, 6 months after the start of adalimumab, the patient appeared fine with the disease and uveitis in remission.

Discussion

Early-onset neurological manifestations are often a diagnostic challenge, especially when they are the first and isolated clinical features. In children, systemic symptoms may develop over the years and differential diagnosis covers a broad range of conditions, including systemic autoinflammatory/autoimmune

disorders, acquired demyelinating syndromes (ADSs), and inherited autoinflammatory, neurological, and metabolic disorders. The case herein presented highlights this diagnostic dilemma.

ADSs represent a group of clinical conditions characterized by an inflammation of the CNS and consequent damage to the myelin. ADSs can be classified as follows: (1) monophasic forms, such as ADEM or clinically isolated syndrome (CIS); (2) polyphasic or chronic forms, including relapsing ADEM, multiple sclerosis (MS), NMOSD, or CNS involvement in the context of systemic inflammatory diseases, such as neuro-lupus, neuro-sarcoidosis, neuro-Bechet's, and others (4). A distinction needs to be made between monophasic demyelinating syndrome and polyphasic demyelinating syndrome, which is relevant for clinical management. In monophasic forms, steroids and IVIg are the treatments of choice, while chronic disorders often require disease-modifying therapy in order to prevent the accumulation of disability.

The complex workup in a pediatric patient with a suspicion of ADS is presented in Supplementary Figure S2), and the most common differential diagnoses are summarized and detailed in Table 1.

Our patient had a very early-onset neurological manifestation, exceptionally described so far in BD (35). Aphthosis was never reported in our patient; however, oral aphthosis is rarely present during the first years of age, even in patients with a full-blown diagnosis of BD in older age (29, 30).

As no single pathognomonic test exists, BD still represents a clinical challenge, particularly in the pediatric population, and its diagnosis relies on clinical findings and the exclusion of mimicking conditions. In our patient, neuro systemic lupus erythematosus (SLE) was considered. However, the absence of

TABLE 1 Differential diagnosis in the context of acquired demyelinating syndromes in pediatric age with principal clinical characteristics.

	Pediatric ADEM (5–10)	Pediatric MS (11–19)	Pediatric NMO (20–28)	Pediatric Neuro-Behçet (29–34)
Clinical features	• Onset within days or weeks after a viral infection or immunization • Median age of onset 5–8 years • Typical presentation: altered mental status, multifocal neurological symptoms • Atypical presentation: stroke-like episodes, seizures, headache, emesis • 70%–90% monophasic vs. 10%–30% multiphasic • 65%–85% good functional recovery; 8% develop MS over time	• 3%–5% of all MS patients <16 years of age, <1% <10 years of age • Median age of onset 13 years • 98% RRMS (vs. 84% in adults) • More aggressive disease onset with disabling clinical symptoms and higher relapse rates • Slower disease progression (>10 years than adults) but moderate-to-severe disability reached at a younger age • Significant cognitive impairment	• 4% of all NMOSD • Median age of onset 10 years • Typical symptoms: visual and motor impairment and constitutional symptoms (vomiting, fever, intractable hiccups) • 90% relapsing-remitting • Poor outcome and higher EDSS	• 3%–30% of children with Behçet's disease • Median age of onset 11 years • Systemic manifestation: recurrent fever, oral and genital aphthosis, uveitis, venous and arterial thrombosis, skin lesions, gastrointestinal symptoms. • Neurological symptoms: chronic headaches, seizure, cranial nerve involvement, focal neurological signs, cognitive impairment • 75% neurological sequelae
MRI findings	• Multiple, bilateral, asymmetrical lesions • Poorly marginated • Involvement of the gray matter, in particular, the thalami or basal ganglia • Multiple and synchronous enhancement • Resolution in 3 months	• Periventricular lesions, perpendicular to the long axis of the corpus callosum • Ovoid lesions • Well-defined lesions • Black holes • Single and asynchronous enhancement	• Typical presentation: optic neuritis and/or longitudinally extensive transverse myelitis. • Other typical localizations: brainstem and fourth ventricle, diencephalon around the third ventricle and aqueduct, and periependymal lesions around the lateral ventricles.	• CNS non-parenchymal manifestations: cerebral venous thrombosis, cranial nerve palsy, meningeal involvement • CNS parenchymal manifestations: lesions that can affect the brainstem, basal ganglia, thalami, optic nerve, and bi-hemispheric white matter
Laboratory findings	• CSF analysis: oligoclonal bands rare • Anti-MOG antibodies with a high titer in the acute phase and a trend to decrease and normalize over time	• CSF analysis: oligoclonal bands in up to 92% of patients. • No specific antibodies	• CSF analysis: oligoclonal bands in 31% • Anti-AQP4 (70%) and anti-MOG (10%–15%) antibodies, 15%–20% double-seronegative	• Moderate elevation in acute phase reactants (ESR, CRP) • HLA-B51+ (40%–65% of patients with BD and in 10%–20% of healthy controls)
Therapies	• Steroids • IVIG • Plasma exchange	*First-line therapies* • Interferon beta • Glatiramer acetate • Dimethyl fumarate *Second-line therapies* • Natalizumab • Fingolimod • Rituximab • Cyclophosphamide	• Steroids • IVIG • Plasma exchange • Rituximab • Mycophenolate mofetil • Azathioprine	• Steroids • Colchicine • Azathioprine • Mycophenolate mofetil • TNFα inhibitors • Anti-IL1 (Anakinra) • Anti-IL6 (Tocilizumab)

ADEM, acute disseminated encephalomyelitis; MS, multiple sclerosis; NMO, neuromyelitis optica; RRMS, relapsing-remitting multiple sclerosis; NMOSD, neuromyelitis optica spectrum disorder; EDSS, expanded disability status scale; CNS, central nervous system; CSF, cerebrospinal fluid; MOG, myelin oligodendrocyte glycoprotein; AQP, aquaporin; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; ANA, antinuclear antibodies; ENA, extractable nuclear antigen; RF, rheumatoid factor; HLA, human leukocyte antigen; BD, Behcet disease; IVIG, intravenous immunoglobulins; TNF, tumor necrosis factor; IL, interleukin.

any cutaneous, hematological, or renal signs of the disease, the absence of specific antibodies (double-strained DNA), extractable nuclear antigen (ENA), or antiphospholipids, and the absence of complement consumption did not support this hypothesis. Furthermore, the extremely young age of the patient would have been unusual for classic SLE. Despite the intriguing monogenic SLE/interpheronopathy, the interferon gene signature was negative and the whole-exome sequencing performed excluded all genes related to those conditions. The normal level of the angiotensin-converting enzyme (ACE) and the absence of granulomatous lesions, particularly of granulomatous uveitis, made neuro-sarcoidosis unlikely.

Adult criteria for BD showed poor sensitivity and/or specificity in children (31, 32). In 2015, a consensus classification criteria set, based on a cohort of 219 children with BD, was established for pediatric BD (PEDBD) (29). The diagnosis of BD can be considered in the presence of three of the six following recurrent symptoms: oral aphthous lesions, genital ulcers, skin involvement, eye involvement, neurological findings, and vascular findings. However, clinical symptoms might develop over the years in patients with Behcet's disease, hampering the application of the classification criteria in daily clinical practice.

The term neuro-Behcet disease (NBD) is used to define the nervous system involvement in BD. The rate of pediatric NBD was variably reported in the literature from 3% to more than 30% of children (30, 33). Neurological manifestations can precede other systemic features for a long time, making the diagnostic workup challenging. Early-onset BD is often insidious, due to its proteiform presentation, and its prompt diagnosis, which is essential to prevent adverse outcomes, is difficult, particularly when a rare manifestation, such as the neurological one, is the leading or the only clinical feature.

TABLE 2 Summary of the main features and prevalence of neurological involvement in the principal international cohorts of pediatric Behcet disease.

Main features of neurological manifestations in pediatric neuro-Behcet disease cohorts			
	Number of cases with neurological involvement	Median age at onset, expressed in years (min–max)	Neurological manifestations
Yavuz et al. (39)	2	12 (9–15)	Midbrain stroke syndrome characterized by ipsilateral fascicular third cranial nerve palsy with contralateral hemiataxia (Claude syndrome)
Tütüncü Toker et al. (38)	5	16 (12–17)	Seizure, myopathy, transverse myelitis, polyneuropathy, venous thrombosis, and facial nerve paralysis
Uluduz (37)	26	13.5 (8–16)	Headaches (24), Epileptic seizure (3), Ataxia (2), Pyramidal findings (3), Dysarthria (1)
Metreau-Vastel et al. (40)	12	11	venous thromboses (5), recurrent meningoencephalitis (2), rhombencephalitis (2), transverse myelitis (1), peripheral neuropathy (1) or psychiatric disturbances (1)
Moraleda-Cibrián et al. (35)	1	0,5	ophthalmoplegia, followed by ataxia and dysmetria.
Koné-Paut et al. (41)	2	12 (9–15)	psychiatric disturbances, amenorrhea, massive loss of weight, frontal headaches, vomiting, and blurred vision. Headaches, nausea, and memory loss
Prevalence of neurological involvement in the principal international cohorts of pediatric Behcet disease			
	Number of cases with neurological involvement/ number of pediatric cases	Median age at onset, expressed in years (min–max)	Neurological manifestations
Ekici Tekin et al. (42)	11/72	10 (N/A)	7/11 patients had extraparenchymal disease and 4/11 patients had parenchymal disease. 6/11 patients had pseudotumor cerebri, 6/11 patients had papilledema, 4/11 patients had reversible vision loss, 2/11 patients had diplopia
Butbul Aviel et al., 2020 (43)	30/205	11 (1–15,9)	N/A
Shahram et al. (44)	9/205	10.5 (1–16)	Cerebral venous thrombosis (1), recurrent meningoencephalitis (3), parenchymal involvement (5, two of them with convulsions).
Gallizzi et al. (30)	34/110	8.3* (N/A)	Headache (27), cranial nerve palsy (5), cranial neuropathy (2), aseptic meningitis (2), optic neuritis (2), peripheral neuropathy (1). Venous thrombosis occurred in two patients.
Nanthapisal et al. (45)	13/46	4.9 (0.04–15.71)	One patient developed seizures and 11 patients reported frequent (more than once a week) headaches. One patient gradually developed neurogenic bladder dysfunction and required suprapubic catheter insertion.
Atmaca et al. (46)	4/110	11,6 (1–16)	N/A
Kone-Paut et al. (47)	10/65	8,4* (0–16)	Meningitis (6/10), benign intracranial hypertension (3/10), hemiparesis or paraparesis (3) with spastic quadriparesis in one case, seizures (2), and peripheral neuropathy including sixth nerve palsy (2). Brain computed tomography scan and magnetic resonance imaging findings included ventricular dilatation and hyperintensity signals in the pons, brainstem, putamen, and upper medulla regions. Dural sinus thrombosis was observed in three patients.

*Mean; N/A,not available.

NBD can be classified into two major forms: (1) "non-parenchymal or vascular" disease, characterized by intracranial hypertension, typically due to dural sinus thrombosis and (2) "parenchymal" disease, which may include recurrent encephalomyelitis, aseptic meningitis, cranial nerve palsy, and neuropathy. Although rare, cerebral venous thrombosis is the most common presentation of pediatric NBD (1). MRI findings, although aspecific, are essential to guide differential diagnosis (34). CSF usually reveals elevated protein levels and pleocytosis. Recent studies have suggested the involvement of proinflammatory pathways such as IL-1, IL-6, IL-33, and INFγ in the CSF of patients with NBD (36). HLA-B51 positivity is considered the most important genetic risk factor of the disease and is described in 40%–65% of patients with BD but also in 10%–20% of healthy subjects; therefore, it should not be considered a diagnostic criterium; however, its positivity during the occurrence of compatible symptoms may support the diagnosis of BD.

In a case series of 26 children with BD, 11 developed neurological abnormalities with neurologic involvement at a mean age of 13.5 years, although not all fulfilled the criteria of BD at the onset. Two patients presented with a neurologic attack prior to the systemic manifestations of BD. One had parenchymal CNS involvement as well as oral aphthae at the age of 8 and fulfilled the International Study Group for Behcet Disease (ISGBD) criteria only many years later (37). In another recent case series, five pediatric patients diagnosed with NBD were described. The mean age reported was 15 years and oral ulcers were present in all patients (38). **Table 2** summarizes the prevalence and the neurological manifestations of pediatric patients with BD and neurological involvement reported in the literature.

Conclusion

Diagnosis and treatment of pediatric NBD are challenging because of its rarity and heterogeneous presentation, particularly when neurological involvement occurs early in infancy and precedes systemic signs and symptoms. A multidisciplinary approach, involving neurologists, neuroradiologists, and rheumatologists, is crucial to define the most probable diagnosis in a timely manner and start an appropriate treatment regimen as soon as possible.

Early-onset NBD could severely affect psychomotor development, and therefore, a timely diagnosis is important to prevent the possible accumulation of disability and poor outcomes in adulthood.

Data availability statement

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

Ethics statement

Written informed consent was obtained from the minor(s)' legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

Author contributions

Funding

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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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2023.1175584/full#supplementary-material

SUPPLEMENTARY FIGURE S1 A–B
Fourth MRI study on TMJ; STIR sequence (a) and post contrast T1WI acquisition (B) show an inflammation of the right TMJ with slight bone edema on STIR (a, arrow) and periarticular enhancement after contrast (b, arrow).

SUPPLEMENTARY FIGURE S2
Flow-chart of the diagnostic approach to pediatric patients with a first neurological episode suggestive for demyelinating disease.

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