Case Report

Blurred Vision, Clear Clue: The Cascade Sign in a Child with Recurrent Optic Neuritis

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ABSTRACT

Neuro-Behçet's disease (NBD) refers to a constellation of neurological signs and symptoms occurring in patients with Behçet's disease (BD). Pediatric NBD (PNBD) is extremely rare and can present with headache, meningitis, stroke, cerebral venous sinus thrombosis (CVST), psychiatric symptoms, and recurrent fever. Optic nerve involvement in BD has been reported. However, it almost always occurs alongside other features of BD or NBD, which either precede or follow ocular symptoms. Isolated ocular manifestations of PNBD are extremely rare. NBD can be associated with characteristic abnormalities in neuroimaging.

We present an unusual PNBD case with recurrent unilateral (left) optic neuritis (ON) without any systemic features or neurological manifestations. The diagnosis was made based on the Cascade sign visualized on Brain Magnetic Resonance Imaging (MRI), highlighting the importance of recognizing neuroimaging patterns. A differential diagnosis of PNBD should be considered in such unusual cases in which other causes of ON have been ruled out, and there are supporting diagnostic markers, such as human leukocyte antigen B51 (HLA-B51) positivity, with or without neuroimaging features of NBD. Early diagnosis ensures disease remission and prevents PNBD-associated morbidity.

Key words: Behcet Syndrome, Optic Neuritis, HLA-B51, Magnetic Resonance Imaging

Turkish dermatologist Hulusi Behçet first described Behçet's disease (BD) in 1937, and the term "Neuro-Behçet's disease" (NBD) was later coined by Cavara and D'Ermo [1]. Pediatric BD (PBD) is a systemic inflammatory disorder characterized by autoinflammation and systemic vasculitis [2]. The classic clinical triad of BD includes recurrent oral and genital ulcers with uveitis. BD can affect multiple body systems, including joints, skin, gastrointestinal tract, cardiovascular system, and nervous system. A strong association between BD and human leukocyte antigen B51 (HLA-B51) has been demonstrated, as genital ulcers, ocular involvement, and skin findings are common in patients with HLA B51 positivity. Most cases present before the age of 16 (average onset at 12 years) with a distinct male predominance [3]. About 9% of BD patients develop NBD (range between 3% and 30%) [4]. Diagnosing PBD is challenging due to its incomplete clinical presentation [5]. The Pediatric Behçet's Disease Study (PEDBD) group proposed and recently validated consensus diagnostic criteria. These include ophthalmological, neurological, and vascular involvement, but oral aphthous ulcers are not mandatory for diagnosis [6].

NBD affects the Central Nervous System (CNS) more commonly. Two major forms of CNS-NBD are recognized: parenchymal and vascular forms [7]. Vascular PNBD has a better prognosis and is more common in the pediatric age group [8]. Compared to adults, children with BD frequently exhibit neurological, as well as gastrointestinal involvement, arthralgia, and a positive family history [4]. Cerebral Venous Sinus Thrombosis (CSVT) is the most common neurological manifestation in PNBD [8]. Ocular manifestations include anterior and posterior uveitis, as well as pan-uveitis, iridocyclitis, keratitis, episcleritis, vitreous hemorrhage, cataracts, glaucoma, optic neuritis, retinal vasculitis, and retinal detachment [8, 9]. Papilledema has also been reported

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in PNBD [9]. Optic Neuritis (ON) as the sole manifestation of PNBD or PBD is unusual and rare.

A case of PNBD is reported here, presenting with recurrent unilateral, left-sided ON in the absence of the appearance of any other features of BD or PNBD at 5 years follow-up.

CASE PRESENTATION

A previously well, 11-year-old male patient, with no significant neurological or medical family history, was referred for evaluation of recurrent left-sided ON. The initial onset was one year ago with left periorbital pain and visual blurring. Magnetic Resonance Imaging (MRI) brain and spine during the first episode was normal. He was treated with oral steroids in tapering dose administered over 4 weeks with a good symptomatic improvement in vision and resolution of ON.

Six months later, the patient developed a recurrence of similar symptoms. Notable neurological findings on examination included a left relative afferent pupillary defect (RAPD) and fundoscopic evidence of left optic cup obliteration with intense hyperemia, suggestive of left-sided ON (Fig. 1A). Visual acuity in the left eye was limited to perception of light only and was normal on the right side. There were no other focal neurological deficits or long-tract signs. Systemic, skin, oral, genital areas, and musculoskeletal examination were unremarkable. Serum myelin oligodendrocyte glycoprotein (MOG) and neuromyelitis Optica (NMO/Aquaporin-4) antibodies were negative.

Vasculitis evaluation, acute phase reactants, routine hematological and biochemical parameters, Cerebrospinal fluid (CSF) analysis, and sepsis screening were normal. CSF oligoclonal bands were negative. Visual evoked potentials demonstrated prolonged P100 latency on the left (162 ms) and normal latency in the right visual pathway (101 ms), suggestive of a left-sided demyelinating ON. Spinal imaging was normal (Fig. 1B). Contrast-enhanced MRI brain revealed a "Cascade sign" with a left mesodiencephalic lesion extending from the thalamus to the midbrain (Fig. 1C) with no diffusion restriction or contrast enhancement. Additionally, the left optic nerve demonstrated thickening and hyperintensities consistent with left ON (Fig. 1D).

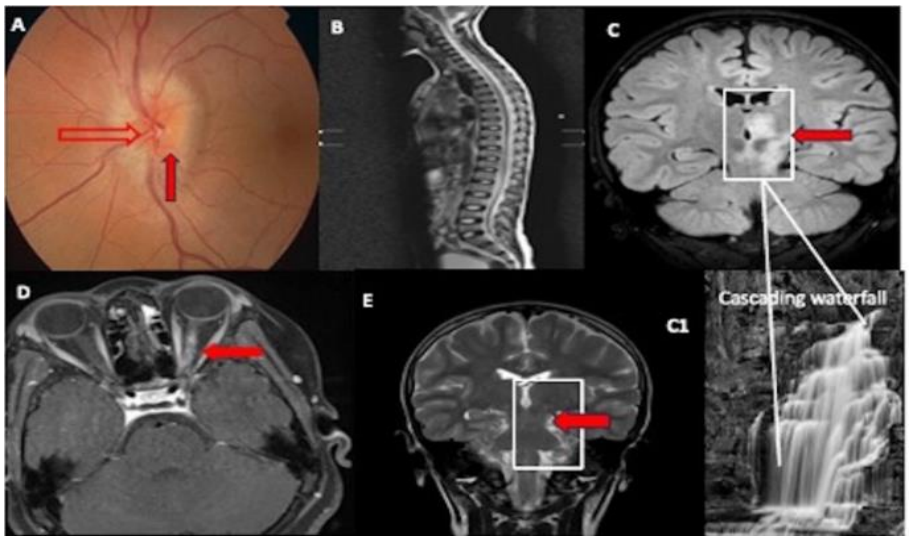

Figure 1: 1A: Fundus findings in the Left eye: Open arrow: intense hyperaemia of the optic disc. Filled arrow: obliteration of the optic cup. 1B: normal MRI Whole spine. 1C and C1: the Cascade or the waterfall sign on the T1 Weighted Coronal FLAIR (Fluid attenuated inversion recovery) MRI Brain sequence. 1D: Enlargement and hyperintensity of the left optic nerve are observed in fat suppression STIR (Short-tau inversion recovery) MRI sequence (red arrow), suggesting a left ON. 1E: T2-weighted Coronal MRI Brain sequence showing complete resolution of the parenchymal lesion (Cascade sign) at 1 year of treatment duration.

Despite the absence of systemic or neurological features, the Cascade sign on brain MRI aroused suspicion for PNBD. HLA-B51 genotyping was positive, supporting a diagnosis of PNBD. Treatment with five doses of intravenous methylprednisolone was initiated. This was followed by a tapering course of oral steroids over four weeks. Azathioprine was initiated during the steroid taper and continued for one year (Table 1).

Table 1. Treatment Regimen

Treatment administered during the 1st episode of ON	Dosage	Duration
IV Methylprednisolone (IVMP) 1 gram	30mg/kg/day (max 1 gram)	5 days
Oral prednisolone (following 5 doses	1.5mg/kg/day	Tapered and stopped for over 4 weeks

of IVMP)		
Treatment administered during the 2nd episode of ON		
IV Methylprednisolone (IVMP) 1 gram	30mg/kg/day (max 1 gram)	5 days
Oral Prednisolone (following 5 doses of IVMP)	1.5mg/kg/day	Tapered and stopped over 4 weeks
Tab Azathioprine	2mg/kg/day	Initiated at the 2nd week of oral steroid and continued for 1 year *

*Azathioprine was stopped after 1 year as the patient improved clinically, with resolution of the left ON, non-progression of symptoms, and no further recurrence of symptoms.

There was an excellent clinical response to immunotherapy, with normalization of fundus findings. Visual acuity improved, and there was a complete resolution of brain parenchymal changes on MRI at 12-month follow-up (Fig. 1E). The patient remained asymptomatic at five-year follow-up and is closely monitored for the appearance of new PBD symptoms.

DISCUSSION

This case had an unusual clinical presentation of a parenchymal form of PNBD with an isolated unilateral recurrent ON. In this case, the diagnosis of PNBD with ON was confirmed with the neuroimaging pattern demonstrating the **Cascade sign**. Although HLA- B51 is not diagnostic for PBD, positivity supports the diagnosis of PNBD.

The previous case reports and case series of ON in BD and NBD had at least one or more features of BD/NBD, and most cases tended to be bilateral. In a case series by Mora et al, all PNBD patients who had ocular involvement also had other BD/PNBD features; none had isolated ocular involvement [10]. More recently, a case of bilateral ON alone as an atypical presentation of juvenile BD was reported, in association with aphthous ulcers, although other features of BD were not present [11]. Another case report described a 15-year-old girl presenting initially with isolated bilateral ON but subsequently manifesting other systemic BD features five months after the ON episode [12]. Spinal involvement may present neuroradiologically as longitudinally extensive transverse myelitis, Bagel sign, and motor neuron sign, which our case did not have [4,13].

The present case was unassociated with any systemic or neurological features, even at five years of follow-up, the longest time interval reported in the literature. Continued immunotherapy is warranted in cases of PNBD [14]. Recommended steroid-sparing oral immune agents include Azathioprine or Mycophenolate Mofetil, administered for a duration of one to 2 years or longer till disease remission is confirmed [1]. Although **Cyclosporin A** is an excellent agent for the treatment of ocular BD, its use is best avoided in PNBD, as there is evidence suggesting worsening of neurological symptoms with its usage [8].

Careful follow-up for evolving features of PBD/ PNBD remains essential in atypical PNBD cases, such as this case, since the development of a full-blown BD may take longer in the pediatric population, and, unlike adults, incomplete presentations are known. Important differential diagnoses include other forms of CNS vasculitides, multiple sclerosis, demyelinating disorders, IIH, secondary causes of intracranial hypertension, stroke, space-occupying lesions, neurosarcoidosis, CNS tuberculosis, and other causes of CSVT [4].

CONCLUSION

This case highlights the variability in presentations of PNBD and the importance of recognizing neuroimaging patterns. PNBD must be considered in the differential diagnosis of ON where evaluation for common causes is negative, and there are supporting clinical or diagnostic markers for BD/PNBD. Timely diagnosis and appropriate treatment reduce morbidity and prevent disability.

Consent: Parental consent was obtained for the use of radiological images and clinical data for this publication, as the patient was a minor.

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