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Myelin Oligodendrocyte Glycoprotein Optic Neuritis in Children

***Abstract*—**Introduction: Optic neuritis is a common presenting feature of paediatric central nervous system demyelinating disease. Pediatric optic neuritis (PON) can present as a unilateral or bilateral acute onset visual loss in children. It occurs in isolation or can be associated with systemic diseases. It has an incidence of two per million children per year and is considered as a different clinical entity compared to adult optic neuritis (AON). This article highlights myelin oligodendrocyte glycoprotein optic neuritis in children and the differences in the course of these two cases. Method: Case report. Results: The first case is a 14-year-old girl who presented to us at the age of 10 with left subacute painless blurring of vision. Funduscopic examination revealed left swollen optic disc with no macula star and right eye optic disc pallor. MRI scans showed demyelinating lesions. The second case was a nine-year-old boy who presented with right painless loss of vision for 1 week with a visual acuity of perception loss. Funduscopic examination showed a blurred margin of the right optic disc with no macula star. MRI brain and spinal cord were suggestive of demyelinating disease. Both cases received high dose intravenous corticosteroid and had good visual recovery. Conclusion: PON often leads to significant visual impairment but typically shows good recovery. An abnormal MRI brain scan at onset or recurring episodes of optic neuritis should prompt clinicians to consider a diagnosis of multiple sclerosis (MS) or neuromyelitis optica (NMO).

Keywords*—pediatric optic neuritis, acquired demyelinating syndromes*

1 INTRODUCTION

PON is fundamentally different from AON. It is usually bilateral with a late presentation and is associated with optic disc swelling. Clinical manifestations include acute or subacute visual loss which may be unilateral or bilateral, visual field defects, painful eye movements, dyschromatopsia and a relative afferent pupillary defect (1–4). The incidence rate of PON is 0.15–0.57 per 100,000 person-years, which is less than the AON which is estimated at approximately 1–2 per 100,000 person-years (1–4). Majority of PON cases showed female predominance in post pubertal cases while in prepubertal individuals, there is equal incidence in both genders (2–5).

Optic neuritis (ON) can stem from various causes including idiopathic origin, demyelination, or infections (1,4,6,7). The most frequent cause of AON is demyelinating disorder, whereas in PON, it derives frequently from post infective or post vaccination autoimmune process (6,8). ON in myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) however is often atypical and may be markedly steroid responsive, bilateral rather than unilateral, and may be associated with optic disc edema rather than a retrobulbar optic neuritis (8).

2 CASE ONE

A 14-year-old girl presented to us at the age of 10 with left subacute painless blurring of vision. She had a history of reduced vision over the right eye which was left untreated. She gave symptoms of urinary incontinence 3 months prior to presentation. On examination, right vision measured 2/60 and left vision was hand movement (HM). Right relative afferent pupillary defect (RAPD) was positive. Anterior segment of both eyes was unremarkable. Funduscopic examination revealed left swollen optic disc with no macula star and right eye optic disc pallor (Figure 1). Systemic and neurological examinations were normal.

Her blood analysis for inflammatory markers and infectious pathology were normal. Visual field showed right temporal hemianopia whereas the left was normal. MRI had right frontal subcortical white matter lesion which was suggestive of tumefactive multiple sclerosis (Figure 2).

She received intravenous methylprednisolone 10mg/kg/dose QID, followed by oral prednisolone 1mg/kg/day tapered within 16 weeks, with a complete recovery of visual acuity in both eyes. During follow-up, she had an episode of focal seizure associated with febrile illness with blurring of vision. A diagnosis of Acute disseminated encephalomyelitis (ADEM) was made at this point. Five months later, MRI scans showed a new demyelinating lesion. Despite treatment with subcutaneous interferon, she had multiple admissions for recurrent optic neuritis. Revised diagnosis of MOGAD was made based on seropositive myelin oligodendrocyte antibody (MOG-IgG), negative serum aquaporin 4 (AQP-4) and a borderline CSF oligoclonal band. Further discussion with the radiology team came to a conclusion that the MRI features were more suggestive of MOGAD. Throughout 4 years, she had eleven episodes of recurrent ON with an attack free period of two years from 2018 until 2020. During her last follow-up in September 2022, her best corrected vision was 6/9 over right eye and 6/18 over left eye.

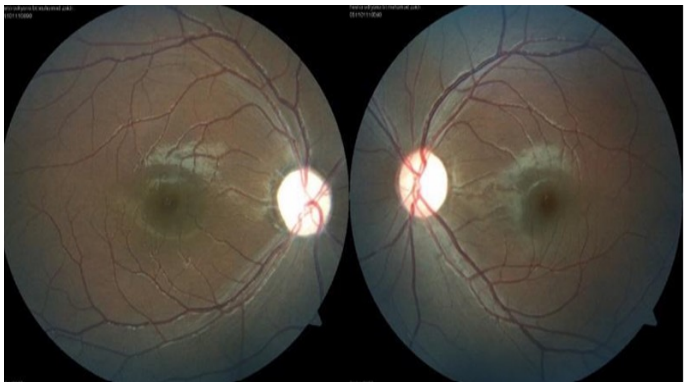

Figure 1. Pale right optic disc and swollen left optic disc

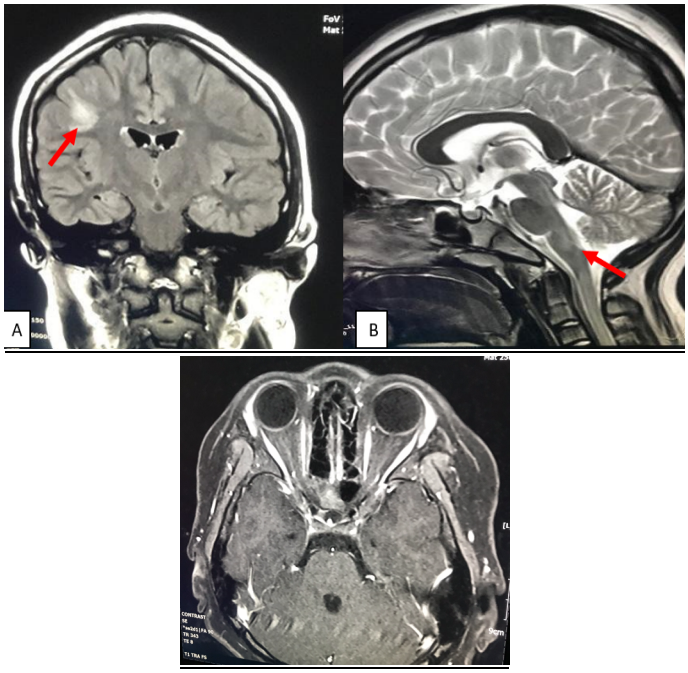

Figure 2. MRI showing (A) Multiple hyperintense white matter lesions seen at right parietal centrum semiovale. (B)Juxta cortical hyperintense lesions. (C)Minimal peripheral enhancement of the midportion of right optic nerve

3 CASE TWO

A nine-year-old boy presented with right painless loss of vision for 1 week. Preceding that, he had episodes of urinary retention with bilateral lower limb weakness.

Patient was only able to perceive light projection over the right eye and left eye visual acuity was 6/6 with a positive RAPD of the right eye. Funduscopic examination showed a blurred margin of the right optic disc with no macula star (Figure 3). Except for reduced power of 4/5 over both lower limbs, other systemic and neurological examinations were normal.

His blood inflammatory markers were normal and blood analysis was negative for any infectious pathology. His MOG-IgG was positive but AQP4-IgG was negative. MRI brain and spinal cord were suggestive of demyelinating disease (Figure 4). Prolonged P100 latency of his VEP was suggestive of optic neuritis.

He was started on three times per day intravenous Methyl prednisolone 10 mg/kg/dose QID for 5 days followed by a tapering dose of oral prednisolone 1mg/kg/day within 4 weeks. Repeated MRI brain seven months post attack showed multiple new juxta cortical inactive lesions at the brainstem and left cerebellum suggestive of multiple sclerosis. At 1 year follow up, his vision maintained at 6/6 both eyes with normal neurological examinations.

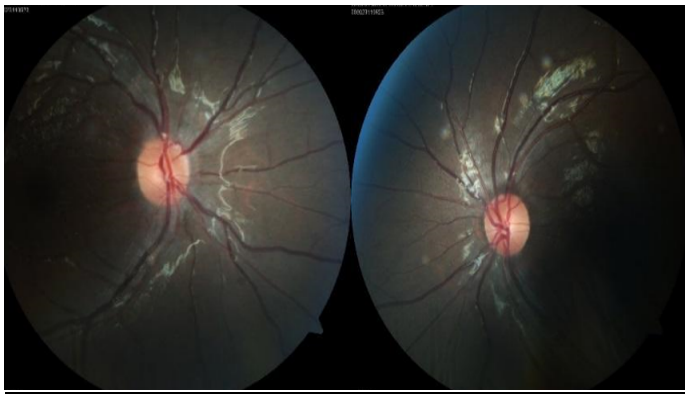

Figure 3. Blurred margin of the right optic disc with normal left optic disc

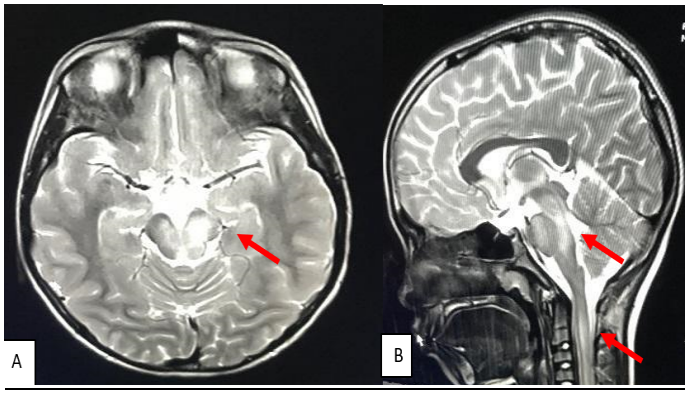

Figure 4. (A-B) MRI showing ill-defined lesions involving posterior part of pons, cerebellar peduncle and midbrain

4 DISCUSSION

ON occurs in approximately 25% of children presenting with demyelinating event (1). Although ON may occur in isolation in children, it also co-exists with multifocal inflammatory conditions of the central nervous system such as ADEM, MS, NMO or MOGAD (9). It is important to differentiate the causative mechanism as there are significant differences in treatment strategies.

Pain with eye movement is not a consistent feature of pediatric optic neuritis therefore, the absence of pain doesn't rule out optic neuritis (3). In our case report, both cases presented with profound visual loss but symptoms of eye pain were not elicited in our cases. Pain with eye movement is reported in 33%–77% of pediatric

cases (4,6). Most children with ON have a history of a fever, flu-like illness, or immunizations 1-2 weeks prior to the onset of the decreased vision and its incidence is much lower than adult ON (3,8). Some children may present with neurologic symptoms such as weakness or numbness. ON in MOGAD however is often atypical as they usually present bilaterally rather than unilateral. They may be associated with optic disc edema rather than a retrobulbar ON which is the typical ON presentation, as can be seen in both of our cases where the optic disc is swollen on presentation which thus leads us to our diagnosis.

In addition to ON associated with MS or NMO, a recent paper has identified ON related to MOG IgG (5). Both of our patients were tested positive MOG IgG with negative AQP-4. Aquaporin-4 is a major antigen in NMO, and anti AQP-4 antibodies can be detected in more than 75% of patients. This marker is highly specific for NMO and is now considered as a major diagnostic criterion for NMO. Antibodies to myelin oligodendrocyte glycoprotein have been described in patients with neuromyelitis optica spectrum disorders (NMOSD) without aquaporin-4 antibodies. Thus, patients with AQP4-Ab–negative NMO/NMOSD should be tested for MOG-Abs as shown in a study by Shahd et al where patients who were AQP4-IgG negative tested positive for MOG-Abs (10). However, double positive cases (both AQP4-IgG and MOG-IgG) are rare entities.

MOG-associated demyelinating disease is different from AQP4-IgG disease in terms of the underlying disease mechanisms, treatment and progress hence testing for MOG-IgG in patients with AQP4-IgG-negative NMOSD and other non-MS demyelinating disease may have significant implications to disease management (11). In Hamid et al. study, 86% of the patients who fulfilled NMOSD criteria with MOG-IgG-positive had relapsing disease (10). This result is similar to a recent study by Jarius S et al. who reported that 80% of their MOG-IgG-positive cohort followed a relapsing course (12). This explains our first case who is MOG-IgG positive and had 11 relapsing episodes.

Oligoclonal bands in the CSF are frequently seen in more than 95% of MS patients and 15-30% of patients with NMO (13). CSF oligoclonal bands were negative in our first patient who was diagnosed with MOGAD.

Although MRI is not required to diagnose ON in children, it may show focal abnormalities of the anterior visual pathway (14). Children with brain MRI abnormalities at the time of the diagnosis of optic neuritis have an increased risk of multiple sclerosis. This can be used to prognosticate recurrent attacks in the future.

Optical coherence tomography (OCT) is another tool which can be used to diagnose PON. It can provide assessments of any neuronal injury, including thickness of the retinal nerve fiber layer (RNFL) and retinal ganglion cell body and axon layers. Eyes with a history of ON in pediatric MS have been reported to have 10%–20% thinner RNFL than MS non-ON eyes (15-17). However, OCT requires a degree of patient cooperation to obtain reliable results. Young children may not be able to sit still for the duration needed to obtain accurate scans, leading to unreliable or incomplete data.

No clinical trials have been performed for PON but there is an ongoing PON prospective outcome study which will be used as a guideline. So clinical practice as for now follows evidence gleaned from the Optic Neuritis Treatment Trial. Treatment in pediatrics consists of 10-30 mg/kg per day IV methylprednisolone, maximum 1 g daily, for 3–5 days and this was the guidelines used to treat all of our 3 patients. The need for a prolonged course of oral steroids is unknown. However, one retrospective study by Himali et.al suggested no difference in outcome between a shorter (less than 2 weeks) and longer (more than 2 weeks) course of steroids in children with acute ON (18). In a study by Kishk et al, he concluded that treatment failure was higher in seropositive AQP4-IgG patients. However, it was found that there was no significant difference between seropositive and seronegative patients in terms of clinical or radiological parameters. Patients who were polysymptomatic or with older age of onset, are predicted to have higher future disability regardless of the AQP4-IgG status (19).

NORDIC is currently working to provide guidelines for pediatric ON. The results from this study are highly looked forward to.

5 CONCLUSION

In conclusion, we found that visual prognosis was favorable at final follow-up of 1 year. This information can be used to counsel patients and their families about the prognosis of the disease.

REFERENCES

[1] Banwell B, Kennedy J, Sadovnick D, Arnold DL, Magalhaes S, Wambera K, et al. Incidence of acquired demyelination of the CNS in Canadian children. Neurology. 2009 Jan 20;72(3):232–9.

[2] Pérez-Cambrodí RJ, Gómez-Hurtado Cubillana A, Merino-Suárez ML, Piñero-Llorens DP, Laria-Ochaita C. Optic neuritis in pediatric population: A review in current tendencies of diagnosis and management. J Optom. 2014 Jul;7(3):125–30.

[3] Yeh EA, Graves JS, Benson LA, Wassmer E, Waldman A. Pediatric optic neuritis. Neurology. 2016 Aug 30;87(9 Supplement 2):S53–8.

[4] Alper G, Wang L. Demyelinating Optic Neuritis in Children. J Child Neurol. 2009 Jan 1;24(1):45–8.

[5] Lana-Peixoto MA, Andrade GC de. The clinical profile of childhood optic neuritis. Arq Neuropsiquiatr. 2001 Jun;59(2B):311–7.

[6] Wilejto M, Shroff M, Buncic JR, Kennedy J, Goia C, Banwell B. The clinical features, MRI findings, and outcome of optic neuritis in children. Neurology. 2006 Jul 25;67(2):258–62.

[7] Lock JH, Newman NJ, Biousse V, Peragallo JH. Update on pediatric optic neuritis. Curr Opin Ophthalmol. 2019 Nov;30(6):418–25.

[8] El-Dairi MA, Ghasia F, Bhatti MT. Pediatric Optic Neuritis. Int Ophthalmol Clin. 2012;52(3):29–49.

[9] Kowsalya A, Ramalingam U, Chaudhary S, Kumar M. Clinical features and visual outcomes of pediatric optic neuritis in the Indian population: A prospective study. Indian J Ophthalmol. 2023;71(2):637.

[10] Hamid SHM, Whittam D, Mutch K, Linaker S, Solomon T, Das K, et al. What proportion of AQP4-IgG-negative NMO spectrum disorder patients are MOG-IgG positive.A cross sectional study of 132 patients. J Neurol. 2017 Oct 24;264(10):2088–94.

[11] Martinez-Hernandez E, Sepulveda M, Rostásy K, Höftberger R, Graus F, Harvey RJ, et al. Antibodies to Aquaporin 4, Myelin-Oligodendrocyte Glycoprotein, and the Glycine Receptor α1 Subunit in Patients With Isolated Optic Neuritis. JAMA Neurol. 2015 Feb 1;72(2):187.

[12] Jarius S, Ruprecht K, Kleiter I, Borisow N, Asgari N, Pitarokoili K, et al. MOG-IgG in NMO and related disorders: a multicenter study of 50 patients. Part 2: Epidemiology, clinical presentation, radiological and laboratory features, treatment responses, and long-term outcome. J Neuroinflammation. 2016 Dec 28;13(1):280.

[13] Bergamaschi R, Tonietti S, Franciotta D, Candeloro E, Tavazzi E, Piccolo G, et al. Oligoclonal bands in Devic's neuromyelitis optica and multiple sclerosis: differences in repeated cerebrospinal fluid examinations. Multiple Sclerosis Journal. 2004 Feb 2;10(1):2–4.

[14] Bonhomme GR, Waldman AT, Balcer LJ, Daniels AB, Tennekoon GI, Forman S, et al. Pediatric optic neuritis: Brain MRI abnormalities and risk of multiple sclerosis. Neurology. 2009 Mar 10;72(10):881–5.

[15] Yılmaz Ü, Gücüyener K, Erin DM, Yazar Z, Gürkaş E, Serdaroğlu A, et al. Reduced Retinal Nerve Fiber Layer Thickness and Macular Volume in Pediatric Multiple Sclerosis. J Child Neurol. 2012 Dec 29;27(12):1517–23.

[16] Yeh EA, Marrie RA, Reginald YA, Buncic JR, Noguera AE, O'Mahony J, et al. Functional-structural correlations in the afferent visual pathway in pediatric demyelination. Neurology. 2014 Dec 2;83(23):2147–52.

[17] Yeh E, Weinstock-Guttman B, Lincoff N, Reynolds J, Weinstock A, Madurai N, et al. Retinal nerve fiber thickness in inflammatory demyelinating diseases of childhood onset. Multiple Sclerosis Journal. 2009 Jul 22;15(7):802–10.

[18] Jayakody H, Bonthius DJ, Longmuir R, Joshi C. Pediatric Optic Neuritis: Does a Prolonged Course of Steroids Reduce Relapses? A Preliminary Study. Pediatr Neurol. 2014 Nov;51(5):721–5.

[19] Kishk NA, Abdelfattah W, Shalaby NM, Shehata HS, Hassan A, Hegazy MI, et al. The aquaporin4-IgG status and how it affects the clinical features and treatment response in NMOSD patients in Egypt. BMC Neurol. 2021 Dec 1;21(1).