Update on pediatric optic neuritis

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Abstract

\textbf{Purpose of review—}To summarize recent developments in the classification, investigation and management of pediatric optic neuritis (PON).

\textbf{Recent findings—}A recent surge in interest surrounding antibodies to myelin oligodendrocyte glycoprotein (MOG-Ab) has instigated a paradigm shift in our assessment of children with PON. This serological marker is associated with a broad spectrum of demyelinating syndromes that are clinically and radiologically distinct from multiple sclerosis (MS) and aquaporin-4 antibody positive neuromyelitis optica spectrum disorder (AQP4+NMOSD). Optic neuritis is the most common presenting phenotype of MOG-Ab positive associated disease (MOG+AD). MOG-Ab seropositivity is much more common in the pediatric population and it predicts a better prognosis than MS or AQP4+NMOSD, except in the subset that exhibit a recurrent phenotype.

\textbf{Summary}

A better grasp of MOG+AD features and its natural history has facilitated more accurate risk stratification of children after a presenting episode of PON. Consequently, the initial investigation of PON has broadened to include serology, along with neuro-imaging and cerebrospinal fluid analysis. Acute treatment of PON and chronic immunotherapy is also becoming better tailored to the suspected or confirmed diagnoses of MS, AQP4+NMOSD and MOG+AD.

\textbf{Keywords}

Pediatric optic neuritis; myelin oligodendrocyte glycoprotein; multiple sclerosis; neuromyelitis optica spectrum disease; aquaporin-4 antibody

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CONFLICTS OF INTEREST

There are no conflicts of interest.
INTRODUCTION

Optic neuritis (ON) is an inflammatory condition of the optic nerve, that causes visual impairment and may herald demyelinating disease. While our understanding of adult optic neuritis (AON) is considerable, we have a weaker grasp of pediatric optic neuritis (PON), owing to its relative rarity.

Recently, there has been a substantial increase in studies of PON that can be attributed to an expanding interest in myelin oligodendrocyte glycoprotein antibody (MOG-Ab). When this biomarker first emerged, it was most frequently associated with acute disseminated encephalomyelitis (ADEM) in young children; however, recent studies have found ON to be its predominant phenotype. Seropositivity for MOG-Ab (MOG+) was previously thought to designate a benign subset of multiple sclerosis (MS), but is now understood to prognosticate a non-MS disease course. It has also been identified in many patients with neuromyelitis optica spectrum disorder who lack serological evidence of aquaporin-4 antibodies (AQP4-Ab). Now that MOG-Ab positive associated disease (MOG+AD) is recognized as a nosological entity, our categorization of ON and associated demyelinating syndromes is changing.

This review article compares PON with AON and summarizes recent data regarding clinico-radiological features, natural history and management of PON due to MS, AQP4-Ab and MOG-Ab.

PEDIATRIC vs ADULT OPTIC NEURITIS

Pediatric optic neuritis is rare with an annual incidence rate of 0.15–0.57 per 100,000 person-years [1–4], compared with 5.1 per 100,000 person-years in adults [5]. The incidence of PON is substantially higher among adolescents compared with younger children [1–4]. Most studies observe a female predilection resembling that in adults, with a female to male ratio ranging from 1.42:1 to 2.7:1 [1–3, 6, 7]. A racial disparity may also exist, with higher incidence of ON seen in non-white children, than non-white adults [2, 4, 8].

Considerable clinical differences exist between childhood and adult ON. Bilateral involvement is rare in adults, but reported in 32–50% of children in recent studies [6, 7, 9, 10*, 11]. Optic disc edema is more commonly observed in PON (50–74%) (Figure 1A) [6, 7, 9], compared with AON (35%) [12]; and orbital pain is less frequent in children (43–49%) [6, 7, 10*], compared with adults (92%) [12]. Vision loss is more pronounced in PON, with more than 50% of children presenting with visual acuity (VA) poorer than 20/200 [6, 9, 10*], compared to 36% of adults [12]. However, better recovery is seen in children, with 71–81% regaining VA of 20/20, in comparison to 50% of adults, a year after ON [6, 10*, 13].

Many of the commonplace PON signs and symptoms are unusual in AON and mimic the “atypical features” that trigger exhaustive investigations in adults. It is important to consider alternative diagnoses such as sarcoidosis, infectious neuroretinitis, papilledema, leukemia, systemic lupus erythematosus and viral or vaccination induced PON. However, this review will concentrate primarily on isolated PON or that associated with demyelinating disease.
CATEGORIZATION OF PEDIATRIC OPTIC NEURITIS

Optic neuritis can occur as an isolated, monophasic condition or may be recurrent without any other manifestations. Alternatively, it may represent a sentinel attack or relapse of a chronic demyelinating disorder such as MS, NMOSD or MOG+AD.

Multiple Sclerosis—Multiple sclerosis is an inflammatory demyelinating disease of the central nervous system (CNS), for which the precise immune-mediated pathophysiology remains uncertain. Predicting progression from PON to pediatric-onset MS (POMS) remains challenging. A quarter of children presenting with PON are subsequently diagnosed with MS, and this risk increases with age [10*, 11]. Overall, the likelihood of conversion to MS is lower in children than adults, with 22–29% over varied follow-up periods [10*, 11] compared with 50% over 15 years, respectively [14].

Clinical Features and Investigations: Certain presenting features of PON raise suspicion for MS. The absence of optic disc swelling is more commonly seen in MS related ON (MS-ON) [10*], as is the presence of cerebrospinal fluid (CSF) oligoclonal bands (OCB) [10*, 15–18], and characteristic periventricular white matter lesions on initial brain magnetic resonance imaging (MRI) [10*, 11, 17–19]. A study of 357 children with isolated PON found a 27-fold higher hazard ratio of developing MS when OCB and MRI lesions were present, compared with absence of both markers [17].

Diagnostic Criteria: The updated 2017 McDonald diagnostic criteria for MS [20] has been found to perform well in children [21, 22]. It differs from the 2010 version by re-introducing OCB as evidence of dissemination in time, and eliminates the requirement for MRI lesions to be clinically silent [23]. These changes facilitate earlier diagnosis of MS and hence earlier treatment. However, optic nerve lesions are still excluded as evidence of dissemination in space, as their common occurrence in other demyelinating syndromes reduces specificity [23, 24].

Visual Prognosis and Clinical Course of MS-ON: The diagnosis of MS-ON imparts a poorer visual prognosis in children. A recent multi-center study of 102 children found that only 27% of children with MS-ON experience complete visual recovery after a year, compared with 90% of isolated PON [10*]. Furthermore, 68% of children with MS-ON had persistent visual field deficits, compared with 22% of isolated PON cases [10*].

Pediatric onset MS is associated with higher relapse rates [25, 26] and greater accrual of MRI lesions [27] when compared with adults; in addition to failure of age-expected brain growth [28] and prominent cognitive impairment [29]. Younger children exhibit a slower pace of MS progression [30]; however, irreversible disability occurs approximately 10 years earlier than in adult MS, due to earlier onset of disease [31]. After the initial demyelinating episode, the risk of relapse is highest within the first 2 years [26, 29], and remains elevated for 5 years [25]. Early exposure to disease modifying drugs (DMDs) is a protective factor against relapses and worsening of disability [30].

Acute Treatment: In the absence of controlled studies assessing treatment of PON, a widely accepted protocol has been derived from the optic neuritis treatment trial (ONTT) [12].
that also concurs with the international consensus for treatment of other demyelinating attacks seen in POMS [32]. It consists of IV methylprednisolone (IVMP) 20–30mg/kg/day (maximum 1g daily) for 3–5 days. If there is incomplete symptom resolution, oral prednisolone can be used at a starting dose of 1mg/kg/day, tapered over 1–4 weeks [32].

Although there is evidence that superdoses of oral prednisolone are equivalent to IVMP in adults [33], dosing is uncertain in children, hence it is rarely used [32]. The ONTT reported that steroid therapy hastened visual recovery, but did not affect final visual or neurological outcomes [12, 14, 34]. It is unknown whether these findings are applicable to the pediatric population.

If steroids are contraindicated, or there is little improvement with IVMP, then treatment options include plasma exchange (PLEX), 5–7 exchanges over 10–14 days, or intravenous immunoglobulin (IVIG), 2g/kg divided over 2–5 days [32].

**Chronic Immunomodulation:** Historically, a second demyelinating episode would transpire before the diagnosis of MS was made. However, the current trend is towards earlier diagnosis so that DMDs can be promptly initiated, with the aim of minimizing long-term disability.

In 2018, the first randomized controlled trial (RCT) investigating DMDs in POMS reported superiority of fingolimod over intramuscular interferon β−1a in reducing annualized relapse rates [35]. Ongoing RCTs are assessing the efficacy of peginterferon β−1a [36, 37], dimethyl fumarate [36, 38, 39], teriflunomide [40] and alemtuzumab in children [41]. Observational studies have also shown promising results for natalizumab [42, 43] and rituximab [44, 45].

**Neuromyelitis Optica Spectrum Disease**—Neuromyelitis Optica (NMO) is typified by acute, severe episodes of ON and transverse myelitis. It is most often associated with antibodies against aquaporin-4, a water channel protein that is highly concentrated on astrocyte endfeet [46]. There is growing evidence that AQP4-Ab causes direct astrocytopathy and neuronal necrosis with secondary oligodendrocyte loss and demyelination [47, 48]. This mechanism is thought to explain the severity of NMOSD attacks in comparison to those seen in MS and MOG+AD.

**Clinical Features and Investigations:** Roughly 60% of children with NMOSD initially present with PON [49, 50]. Poor visual recovery despite high dose steroids should raise suspicion of NMOSD. Other red flags include bilateral optic nerve involvement, MRI enhancement of the posterior optic nerve, optic chiasm or optic tract, or lesion extension beyond half the optic nerve length; especially in the absence of brain lesions [19, 51**]. MRI Brain and full spine with contrast is recommended in all patients presenting with suspected NMOSD [52].

Recent optical coherence tomography (OCT) studies have observed that thinning of the peripapillary retinal nerve fibre layer (pRNFL) is more pronounced and diffuse in NMOSD related ON, compared with MS-ON [53, 54]. The utility of ganglion cell layer (GCL) OCT when disc edema precludes reliable pRNFL measurements has yet to be assessed. Optical...
coherence tomography can be a useful objective measure of severity in younger children who cannot reliably perform visual acuity, visual field or color vision testing.

In clinically suspicious cases of PON, obtaining AQP4-Ab serology is critical as seropositivity portends a poorer prognosis and is predictive of a relapsing course. Newer cell-based assays for AQP4-Ab have specificities approaching 100%, but sensitivities range from 70–100% [55, 56]. Hence re-testing should be considered in typical cases that are initially seronegative. Circulating AQP4-Ab increases just before an attack and can decrease during remission or after treatment with steroids or PLEX, but AQP4-Ab titers do not currently appear to be a reliable indicator of disease activity or prognosis [57].

**Diagnostic Criteria:** In 2007, the term NMO was broadened to NMOSD, which is inclusive of patients with limited forms of the disease who are at risk of future relapses, e.g. recurrent or bilateral ON [58]. In 2015, the international criteria were stratified into NMOSD with AQP4-Ab (AQP4+NMOSD) and NMOSD without AQP4-Ab, permitting inclusion of newer biomarkers such as MOG-Ab, and seronegative patients who otherwise meet clinical diagnostic criteria [58]. As most clinical, radiological and laboratory characteristics of pediatric NMOSD are similar to adult disease, these diagnostic criteria are considered to be applicable in children [50, 58].

**Acute Treatment:** Acute treatment of PON with suspected NMOSD is similar to that outlined for MS-ON. The threat of profound disability with each attack is cause for swift escalation of therapy. Hence, there is a low threshold to commence PLEX and/or IVIG, which can be administered as described for MS-ON [59**, 60]. After IVMP, PLEX is the preferred second line therapy, due to its mechanism of autoantibody clearance; followed by IVIG if PLEX is unavailable [59**, 61]. PLEX must precede IVIG administration to avoid extracting IVIG from the circulation [51**]. Only a few case reports describe successful treatment of PON with PLEX or IVIG [62–66], and this treatment algorithm is largely derived from adult studies.

In contrast to MS-ON, children with presumed NMOSD are usually subject to a slow taper of oral prednisolone over 2–6 months. Many clinicians choose to maintain doses above 20mg daily until AQP4-Ab status is known [51**]. Even a short course of glucocorticoids will cause hypothalamic-adrenal axis disruption and growth suppression, amongst other side effects; hence, early transition to steroid-sparing agents is vital.

**Clinical Course and Chronic Immunotherapy:** More than 90% of children with NMOSD experience relapses [49] and due to the severity of attacks, cumulative disability often surpasses that seen in POMS [50]. Therefore, prevention of recurrences is paramount and immunotherapy is often continued despite long periods of clinical remission, as relapses are unpredictable and can even be life-threatening. Azathioprine [67], mycophenolate mofetil [68] and rituximab [69] have all shown favourable clinical results with reduced annualized relapse rates in children [70]. Certain DMDs used in MS have been reported to exacerbate NMOSD and should be avoided, including alemtuzumab [71] interferon-β [72], fingolimod [73], and natalizumab [74].
Children with AQP4-Ab negative NMOSD should be tested for MOG-Ab as this has implications for long-term prognosis and treatment. Over 20% of AQP4-Ab negative NMOSD patients are MOG+ [75, 76], and future iterations of the NMOSD diagnostic criteria could exclude these patients, as they may be better categorized under the umbrella of MOG+AD.

Myelin Oligodendrocyte Glycoprotein Antibody Disease—Positive MOG-Ab associated disease encompasses a broad spectrum of clinical phenotypes, including monophasic ADEM, multiphasic disseminated encephalitis, isolated ON, relapsing ON and ADEM followed by recurrent ON [77*]. Optic neuritis is the predominant phenotype of all MOG+AD episodes, both in children and adults [78–80]. Pediatric ON can often occur in conjunction with ADEM or as relapses after an initial episode of ADEM; however, in depth discussion of encephalomyelitis is beyond the scope of this review article.

Myelin oligodendrocyte glycoprotein (MOG) is a transmembrane protein that forms a minor component of the CNS myelin sheath. Its functions include myelin adhesion, regulating oligodendrocyte microtubule stability and mediating the complement cascade [81]. Unlike AQP4-Ab mediated astrocytopathy, MOG-Ab is thought to cause inflammation and myelin destruction without direct astrocyte injury [82]. This mechanism may explain the less severe course of MOG+AD, in comparison to AQP4+NMOSD.

Indeed, MOG+AD was initially considered to be benign and monophasic. This assumption was disputed by growing reports of a relapsing phenotype that exhibits milder attacks, but can accrue impairment matching that of AQP4+NMOSD [83, 84].

Demographics: Amongst MOG+ children, PON is more common in teenagers (13–18 years), whereas encephalitis dominates in the younger age group (4–8 years), which suggests that regional expression of MOG is age-dependent [79, 85–87*]. The slight female preponderance of MOG-ON is in keeping with adult MOG+AD and is weaker than that seen in AQP4+NMOSD [78, 80, 87*-89].

Positive MOG-Ab have been reported in 17–57% of recent PON cohort studies [16, 90, 91]. The proportion of MOG-ON surpasses that of AQP4-Ab associated ON (AQP4-ON) in each cohort, with MOG+ children tending to be younger [16, 90, 91]. Although MOG-ON is purported to be more common in the Caucasian population [78, 83], recent studies suggest that an ethnic bias may not exist [90–92]. In contrast to AQP4+NMOSD, there is no known association between MOG+AD and other autoimmune diseases [51**].

Clinical Features and Investigations: Many patients with MOG-ON report a prodromal illness, but thus far, no specific viral link has been identified [51**, 78]. Bilateral optic nerve involvement is reported in more than 80% of patients [19, 83, 90]. While mixed adult and child studies report that optic disc edema is more prevalent in MOG-ON [19, 83], no significant difference is noted in exclusively pediatric studies [90]; suggesting that disc edema may just be more prevalent in all subsets of PON (Figure 1A). Despite equivalent presenting VA, MOG-ON demonstrates better visual recovery compared to AQP4-ON, with 89–98% versus 33% achieving VA of 20/25 or better after 6 months [90, 91].
There are mixed reports regarding OCT findings after MOG-ON. Some describe significantly less thinning of pRNFL and GCL compared with AQP4-ON [91, 93], while others report profound thinning that is comparable to AQP4-ON, but with relatively preserved vision [90, 94, 95]. A proposed explanation is that demyelination in the optic nerve is accompanied by relative sparing of ganglion cell axons, as MOG-Ab is not known to cause direct astrocytopathy [95].

In mixed adult and child studies, bilateral and longitudinally extensive lesions with perineural enhancement are commonly seen with MOG-ON (Figure 1B) [19, 88]. Although some overlap exists with AQP4-ON, MOG-ON tends to exhibit more involvement of the anterior optic pathways, with relative sparing of the chiasm and optic tracts [19, 96].

On MRI, the absence of Dawson’s fingers, absence of well-defined periventricular ovoid lesions and the presence of poorly demarcated brain or brainstem lesions is helpful in distinguishing POMS from MOG+AD [51**, 79, 97]. However, MRI distinctions may not be useful in children with isolated MOG-ON, who tend to have small, non-specific brain lesions, if any at all [78, 79]. While CSF pleocytosis is common, presence of CSF OCB is unusual in MOG+AD [15, 78, 87*].

For more reliable results, it is currently recommended that MOG-Ab testing is performed with cell-based assays, using full length human MOG as the target antigen [77*, 98, 99].

To minimize false positives and overdiagnosis of MOG+AD, international recommendations released in 2018 outline indications for MOG-Ab serology in adults and adolescents. They advocate less scrupulous adherence to the guidelines in children due to the higher prevalence of MOG-Ab in this population [77*]. When cell based assays are used, double seropositivity for MOG-Ab and AQP4-Ab almost never occurs [82]. Therefore, testing for the more likely autoantibody with reflex testing to the other, is preferred to testing for both autoantibodies simultaneously.

**Visual Prognosis and Clinical Course:** After the initial attack of MOG-ON, visual recovery in children is typically good, and significantly better than that seen in AQP4-ON [19, 83, 90, 91], and adult MOG-ON [80, 88]. A monophasic course is reported in approximately two thirds of MOG+ children [18, 79]. The remaining third develop relapsing disease, with recurrent ON being the most frequent manifestation, especially in children older than 9 years [16, 18, 78, 79]. In fact, reassessment of adults previously diagnosed with chronic relapsing inflammatory optic neuritis (CRION) has found that the vast majority are MOG+ [83, 100–102].

Currently there are no reliable predictive factors at the outset of pediatric MOG+AD to forecast a relapsing course. There is no correlation between MOG-Ab titer at the first demyelinating episode, but persistence of raised MOG-Ab titers is associated with a recurrent disease course [16, 18, 51**, 103]. Hence, some clinicians elect to repeat MOG-Ab titers at regular intervals to help predict the risk of relapse. Seroconversion to MOG-Ab negativity is not uncommon in children, after which they tend to remain relapse free [80, 104]. MOG+ at the initial PON episode has the added benefit of predicting a non-MS disease course [15, 18, 105].
**Acute Treatment:** There are no guidelines for initial management of MOG-ON, but accepted acute therapy is akin to that described for MS-ON and AQP4-ON [51**]. The pace of oral steroid taper depends on the severity of the attack and clinical suspicion of seropositivity. Once MOG+ is confirmed, children typically remain on steroids for 4–6 weeks [51**]. The majority of patients will experience rapid resolution with steroid therapy, but are more vulnerable to relapses on tapering or withdrawal. About 70% of patients relapse when oral prednisolone is weaned below 10mg daily, or within 2 months of steroid cessation [78].

The decision to commence maintenance immunotherapy is challenging. The high proportion of monophasic MOG+AD argues against commencing immunotherapy after the first demyelinating episode [87*]. However, this choice should also be influenced by the severity of the initial attack, response to first-line therapy and the perceived likelihood of relapse [51**] that may be suggested by persistently raised MOG-Ab titers [98]. A relapse plan involving prompt recommencement of steroids at the earliest symptoms of recurrence, is a valuable management option [78].

If chronic immunotherapy is endorsed, there are few studies to help guide drug selection. A mixed adult and child study of 59 patients with MOG+AD found that annualized relapse rates were effectively reduced by maintenance prednisolone, IVIG, rituximab and mycophenolate mofetil. Treatment failure rates were lowest with maintenance steroids (5%) in comparison to the non-steroidal immunotherapies (38%). Cyclophosphamide, azathioprine and methotrexate were poorly tolerated [78]. Another retrospective study of 102 children with MOG+AD found that IVIG was most effective in reducing annualized relapse rates, followed by rituximab, mycophenolate mofetil and finally azathioprine [87*]. These findings largely concur with a recent multicenter retrospective study of 68 adults with relapsing MOG+AD [106], that suggested a prominent role of IVIG as maintenance therapy for MOG+AD. There is no current consensus on whether cessation of immunotherapy is advisable after a long period of remission.

Distinguishing MOG+AD from MS is imperative, as conventional MS DMDs including interferon-β and glatiramer are ineffective [87*], and some agents such as alemtuzumab can cause disease worsening [107].

**CONCLUSION**

Pediatric optic neuritis is a rare condition that in general entails good visual recovery. Although isolated, monophasic forms of PON impart a good prognosis, a substantial proportion of children will subsequently develop recurrent demyelinating disease with cumulative disability. Due to substantial phenotypic overlap, distinguishing PON patients with MS, AQP4+NMOSD and MOG+AD can often be difficult, but is critical. Thorough investigation from the outset, including OCT of pRNFL and GCL, gadolinium enhanced MRI of the brain and orbits, CSF analysis for OCB, and serology for AQP4-Ab and MOG-Ab, facilitates early risk stratification. This enables timely administration of PLEX, IVIG or a prolonged steroid taper in order to prevent early relapses and facilitates appropriate choice of chronic immunotherapy if indicated.
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Curr Opin Ophthalmol. Author manuscript; available in PMC 2022 January 28.


*Expert consensus on indications for MOG-Ab testing. Although more relevant to adolescents and adults, this article provides a concise summary of clinical features that should raise suspicion of MOG+AD.


KEY POINTS

- MOG-ON is the most common antibody associated subtype of PON, of which one-third of affected patients will develop recurrent disease that is associated with severe cumulative visual disability.

- Clinico-radiological features of MOG-ON include bilateral, anterior optic nerve involvement, longitudinally extensive nerve and sheath enhancement, a paucity of brain lesions and a propensity to relapse during steroid weaning.

- Recognition of MOG+AD as a new disease entity has resulted in reclassification of many patients previously thought to have recurrent non-MS disease, AQP4 negative NMOSD or chronic relapsing inflammatory ON.

- Clinical suspicion of MS, AQP4-Ab or MOG-Ab associated PON, mandates thorough investigation with MRI, CSF analysis and serology, plus appropriate adjustment of acute therapy including consideration of PLEX, IVIG and prolonged steroid taper.

- Early and accurate diagnosis of CNS demyelinating diseases can facilitate timely immunomodulation, such that relapse-related disability is minimized.
Figure 1.
Images of a 7-year-old girl presenting with bilateral MOG-ON: (A) fundus photographs showing bilateral disc edema with multiple disc hemorrhages, (B) gadolinium enhanced MRI demonstrating bilateral, longitudinally extensive optic nerve enhancement with nerve sheath enhancement (arrow) and optic disc edema (arrowhead).