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Pediatric Optic Neuritis: What Is New

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Abstract

Few diseases blur the margins between their childhood and adult-onset varieties as much as optic neuritis. This report will review our state of knowledge of pediatric optic neuritis, as well as its relationship to the latest consensus definitions of neuroinflammatory disease. Current diagnostic and treatment options will be explored, as well as our potential to uncover an understanding of pediatric optic neuritis through systematic prospective studies. The risk of evolving multiple sclerosis is probably less than in adults, but pediatric optic neuritis is more likely to be an initial manifestation of acute disseminated encephalomyelitis. Steroids may hasten visual recovery, but they do not change visual outcome except in cases because of neuromyelitis optica. The role of puberty in modifying the presentation and risk associations is unknown. Prospective studies are required to resolve these diagnostic and management issues.

It is axiomatic that children are not little adults; most diseases afflicting children are different than those affecting adults, despite assignation of identical names. Few diseases blur the margins between their childhood and adult-onset varieties as much as optic neuritis. In 1959, Hierons and Lyle (1) first described pediatric optic neuritis (PON) as completely unique in its presentation. They noted that children with PON were frequently male, often presented with painless bilateral papillitis and severe vision impairment after a prodromal illness, and rarely developed multiple sclerosis (MS). These features were clearly distinguished from typical adult-onset optic neuritis occurring as a painful unilateral, retrobulbar inflammatory optic neuropathy in young women, often associated with MS.

Subsequent decades have seen a burgeoning understanding of adult-onset optic neuritis with the recognition that, in the absence of granulomatous or infectious etiologies, it is usually a

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harbinger of MS (2,3). However, PON remains enigmatic. This is partly due to the inclusion of adolescents and young adults in most reported case series, but it is largely due to the evolution of neuroimaging and serologic tests that have redefined demyelinating diseases. Hence, shifting definitions over the periods of data collection obfuscates most case series. Furthermore, a sense of urgency has developed to understand the systemic risks of PON, as new therapies have developed to control demyelinating disease.

This report will review our state of knowledge of PON, as well as its relationship to the latest consensus definitions of neuroinflammatory disease. Current diagnostic and treatment options will be explored, as well as our potential to uncover an understanding of PON through systematic prospective studies.

IMPACT ON VISION

Between 1959 and 2009, there were at least 31 case series on PON (generally defined by patient age <18 years) in the medical literature (4). Only 2 series reported exclusively on children presumed to be prepubertal (age ≥12 years) (5,6). These included a total of 53 children, of which 62% had >3 years of follow-up (range: 1 week–20 years). Seventy percent of prepubertal cases were bilateral, and only 5 affected eyes had initial acuity better than 20/200. (By comparison, 64% of adult eyes from the Optic Neuritis Treatment Trial had initial acuity better than 20/200 [7]). Seventy-three percent of patients were treated with steroids. Recovery of vision was excellent, regardless of whether or not they received steroids. A subsequent diagnosis of MS occurred in 4 cases, 3 of which reached criteria for MS within 6 months. Thirty percent of cases less than 9 years of age were diagnosed with acute disseminated encephalomyelitis (ADEM) (5).

In most reports of PON, most patients were older than 12 years. Thus, the prevalence is felt to be greater in postpubertal children. It is important to note, however, that no studies of PON have defined puberty by anything other than age.

Recent studies have generally affirmed previously noted clinical manifestations and outcomes. A retrospective study of 59 children presenting with the first episode of PON (at ages 3.9–18.8 years) showed that 89% of patients recovered at least 20/40 visual acuity within 1 year (8). Only 2 patients had vision ≥20/200 in the worse eye at 1-year follow-up; both of these patients developed MS. Visual acuity at presentation, sex, bilateral involvement, optic disc edema, and underlying diagnoses were not associated with poor visual outcomes. All but 4 patients with unilateral optic neuritis and mild vision impairment were treated with steroids and/or intravenous immunoglobulin of plasma exchange. It is uncertain whether the visual outcome by underlying diagnosis was affected by treatment.

Because visual recovery is usually good regardless of treatment, at issue is the risk of developing neuroinflammatory or demyelinating disease, and whether or not vision loss can be minimalized in those cases that fail to recover.

NEUROINFLAMMATORY SYNDROMES

The current consensus spectrum of neuroinflammatory diseases that include optic neuritis is listed in Table 1. In a child with optic neuritis, the history and examination of the brain MRI and a lumbar puncture help differentiate the various conditions, especially those that are immune mediated, such as ADEM and MS. The immune-mediated disorders are further differentiated by the identification of antibodies with specific targets. The prototypical antibody-mediated central nervous system (CNS) disorder causing optic neuritis is neuromyelitis optica (NMO), which is an astrocytopathy rather than a primary disease of myelin. Currently, the identification of antibodies to other CNS targets, such as myelin oligodendrocyte glycoprotein (MOG), challenges our current diagnostic and treatment algorithms as discussed below.

Multiple Sclerosis

Similar to adults, the diagnosis of MS in children is dependent on dissemination of attacks in time and space (Table 1). The McDonald 2010 criteria are applicable to children who present with a first episode suggestive of MS and are most robust when used in children >12 years of age (9). Imaging and cerebrospinal fluid (CSF) profiles may be different in younger children, and the McDonald criteria may be less reliable. Children with optic neuritis who do not meet diagnostic criteria for MS but have typical MS lesions and/or oligoclonal bands (OCBs) in CSF are usually diagnosed with a clinically isolated syndrome (Table 1).

A meta-analysis by Waldman, et al of published cases of isolated optic neuritis from 14 case series before 2010 showed a shift in the risk associations of PON around the time of adolescence toward unilateral presentation and MS (odds ratio [OR] = 1.10/year of age, confidence interval [CI] = 1.00–1.21, $P = 0.05$) (4). Ninety-three subjects from the reviewed studies had MRI data, and these were skewed toward unilateral cases. Nonetheless, white matter lesions on MRI were strongly associated with confirmation of MS (age-adjusted OR = 27.0, CI = 6.27–125.4, $P < 0.001$).

Using the McDonald 2010 definition, a recent multicenter retrospective study (1990–2012) from Europe of 357 children (median age 13.6 years; interquartile range 10.8–15.5 years) with isolated optic neuritis and who had brain MRI, showed that 40% had MS with a median follow-up of 4 years (10). A hazard ratio (HR) for MS of 1.08/year of age (95% CI = 1.02–1.13, $P = 0.003$) supported the OR calculated by Waldman et al (4). The median age of optic neuritis for those MS was 14.7 years (IQR 12.9–16.1 years). The youngest patient confirmed to have MS presented with optic neuritis at age 4.3 years. Thus, MS occurs in patients after prepubertal optic neuritis, but it is uncommon.

Two more recent retrospective studies of PON found rates of MS conversion ranging from 7% to 39% over variable time periods (8,11). This disparity highlights the need for a prospective study of PON.

The European study confirmed MRI lesions as an independent predictor of MS (HR = 5.94, 95% CI = 3.39–10.39, $P < 0.001$) (10). The HR was even greater if there were at least 2 positive OCBs in the CSF (HR = 8.07, 95% CI = 5.38–12.11, $P < 0.001$). MRI combined

with positive OCBs markedly increased the risk of MS conversion (HR = 26.84, 95% CI = 12.26–58.74, $P < 0.001$). Neither sex nor laterality of PON influenced the risk of MS. Only 20% of patients presented with bilateral optic neuritis, consistent with the older age distribution of the cohort, yet 30% of bilateral cases developed MS.

The presence of OCBs in the CSF supports the immune-mediated pathology in MS. However, antibodies against aquaporin 4 (AQP4) or MOG predict a non-MS course. In 65 children with the first attack of demyelination (including 24 with optic neuritis), 2 of 23 (9%) patients positive for anti-MOG IgG had MS at 1 year compared with 16 of 42 (38%) children who did not have anti-MOG IgG (12). Together, negative OCBs and positive MOG antibodies were predictive in 15 of 15 (100%) with a non-MS course. In comparison, 11 of 14 (79%) children with positive OCBs but negative MOG antibodies developed MS. Only 1 child, who had a non-MS course, was positive for both MOG and OCBs. Of the 21 children with neither anti-MOG antibodies nor OCBs, 14% had MS and 86% followed a non-MS course.

Neuromyelitis Optica Spectrum Disorder

Neuromyelitis optica spectrum disorder (NMOSD) is a unifying term for the clinical features of optic neuritis, myelitis, as well as brainstem and cerebral signs and is further categorized by AQP4-IgG status (Table 1). The adult diagnostic criteria for NMOSD apply to children (13) who have a younger mean age of onset compared with MS (14). However, in children, NMO frequently presents as isolated optic neuritis without transverse myelitis (15,16). Only 5 of the 357 children with isolated optic neuritis reported by Heussinger et al (10) developed NMO. Most of these patients predated serologic testing and modern definition of this disease, so the actual prevalence is not known. AQP4-IgG was present in 24 of 37 (60%) children with NMOSD, but in no children with MS (N = 66), ADEM (N = 10), or other relapsing demy-elinating diseases (N = 21). AQP4-IgG positivity is associated with early recurrence and more profound permanent visual impairment (17).

In 83 adults with AQP4 antibodies (56 with NMO; 5 with relapsing optic neuritis; and 22 with longitudinal extensive myelitis), none had antibodies to MOG, and none of the 51 MOG-IgG positive patients (with clinical attacks of optic neuritis and/or myelitis, some of whom also had relapsing disease) had antibodies to AQP4. Despite similar clinical features, NMOSD with AQP4 positivity is a distinct entity from the MOG-associated disease.

Monophasic Optic Neuritis

Monophasic optic neuritis is a single attack of unilateral or bilateral optic neuritis without evidence of other CNS involvement or AQP4-IgG. In a retrospective study, bilateral PON occurred in 73 of 102 (72%) children younger than 10 years, whereas unilateral PON was present in 85 of 121 (70%) older children (≥10 years) (4).

Excluding patients with NMOSD in the Heussinger cohort, 115 children had optic neuritis with normal brain MRI and the absence of OCBs. During the 4-year follow-up, 9 (8%) children fulfilled criteria for MS (18). Thus, normal MRI and a CSF profile do not preclude the possibility of an MS diagnosis in the future, but the likelihood is low.

Isolated Recurrent Optic Neuritis

Isolated recurrent optic neuritis is currently defined in the absence of MS or NMOSD. AQP4 antibodies are absent, but OCBs or anti-MOG IgG may be positive (Table 1). CSF OCBs were detected in 12.5% of children with recurrent optic neuritis (10). The frequency of anti-MOG antibodies in children with recurrent optic neuritis is not known, whereas 13 of 37 (35%) adults with recurrent ON had MOG-IgG positivity (18).

Recurrent optic neuritis in the absence of NMOSD that can only be suppressed with chronic immunosuppression is known as chronic relapsing inflammatory optic neuropathy (Table 1).

Acute Disseminated Encephalomyelitis

ADEM is a polyfocal CNS disease with encephalopathy, usually occurring in young children (19). Multiple neurologic symptoms, such as optic neuritis, weakness, gait abnormalities, and paresthesias, may occur concurrently. Brain MRI usually reveals diffuse, poorly demarcated, large (>1–2 cm) lesions in the cerebral white matter or deep gray matter, including longitudinally extensive transverse myelitis similar to NMO (19,20). Baumann et al (21) found that 19 of 33 children with ADEM were positive for anti-MOG antibodies. The 19 patients had a uniform MRI pattern characterized by bilateral, large, and hazy lesions and the absence of small, well-defined lesions. Those individuals with anti-MOG antibodies had involvement of more anatomical areas, a complete resolution of lesions, and better outcome.

ADEM is usually a monophasic disease, but recurrences have been reported, including a distinct entity that is followed by relapsing optic neuritis. This uncommon adverse outcome seems to be more likely in those with anti-MOG antibodies (21,22). Thus, the effect of anti-MOG antibodies remains controversial (see below).

CLINICAL EVALUATION

Initial assessment of suspected PON should be directed toward ruling out those diseases for which delay in treatment can result in permanent vision loss or other neurologic impairment. These include infectious or neoplastic diseases, vasculitis, and NMO. All children with PON should have a thorough review of systems and neurologic examination looking for signs of polyfocal or systemic disease. The following blood tests should be performed: complete blood count (CBC), anti-neutrophil cytoplasmic antibody (ANCA), anti-nuclear antibody (ANA), angiotensin-converting enzyme (ACE), and anti-AQP4-IgG levels. If a review of systems suggests pulmonary or febrile disease, chest x-ray, and PPD or quantiferon gold tests are recommended. Currently, anti-MOG antibody testing is not commercially available (see below).

MRI

MRI of the brain and orbits with and without contrast should be performed on all children with PON to confirm optic nerve enhancement. It is important to assess the patient for sphenoid sinusitis, compressive lesions, meningeal enhancement, and inflammatory or demyelinating lesions elsewhere in the brain. In the absence of spinal cord signs, spine MRI can probably be deferred unless AQP4-IgG testing is positive.

Lumbar Puncture

Lumbar puncture is indicated in cases of PON with polyfocal white matter disease to check for OCBs in anticipation of MS. There is no benefit to checking for CSF AQP4-IgG if serum AQP4-IgG is negative (23). There is no clear indication for lumbar puncture in cases of isolated optic neuritis, although surveillance for MS might be modified by the presence of OCBs.

Bilateral PON may be confused with pseudotumor cerebri syndrome because of bilateral optic disc swelling, especially if there is vision loss of uncertain chronicity. Intracranial pressure may be elevated because of cerebral inflammation. This may be further aggravated if the lumbar puncture is performed under sedation without respiratory control of pCO_2 (24). Intracranial pressure was elevated in 15 of 53 (28%) children with ADEM, MS, or isolated optic neuritis; significantly higher than in the reference cohort from the same institution (10%) ($P = 0.0001$) (25,26). Therefore, the CSF opening pressure cannot be used to differentiate bilateral disc swelling due to pseudotumor cerebri syndrome from that due to bilateral PON.

Optical Coherence Tomography

There is a nascent role for optical coherence tomography (OCT) in the evaluation of PON, but clinical indications are uncertain. Graves et al (27) reviewed the OCT findings in pediatric patients with MS with and without a history of optic neuritis. Eyes with a history of optic neuritis showed reduced retinal nerve fiber layer (RNFL) thickness and ganglion cell layer (GCL) volumes compared with control eyes. Those without optic neuritis had lower temporal RNFL and GCL volumes than control eyes. Conflicting studies showed no RNFL and GCL thinning in MS without optic neuritis (28,29).

Implications for Anti–Myelin Oligodendrocyte Glycoprotein Antibodies

Assays for anti-MOG antibodies are not commercially available in most countries, and their specificity for disease (e.g., ADEM) is still uncertain. One should consider that the presence of anti-MOG antibodies may be due to damaged myelin, and not pathogenic. Ramanathan et al (30) reviewed the various assays and provided a diagnostic algorithm, highlighting that serum anti-MOG should be tested in cases not typical for MS, ADEM, or NMOSD, particularly when AQP4-IgG testing is negative.

Anti-MOG antibodies seem more common in pediatric disease. Anti-MOG antibodies were prevalent in younger patients with encephalopathy, whereas the older group presented almost exclusively with optic neuritis (31). This suggests that the manifestations of ADEM may be more limited with age, if anti-MOG specificity for ADEM is confirmed. It is not yet known whether MOG-related diseases should be treated differently from immune-mediated diseases or NMOSD with AQP4 antibodies. Studies have concluded that children with anti-MOG antibodies had more favorable outcomes (i.e., more rapid recovery and fewer relapses) compared with other demyelinating conditions despite the extensiveness of CNS lesions (15,20).

TREATMENT

The first-line treatment for patients with PON is intravenous methylprednisolone, although the decision to treat varies from clinician to clinician, based upon the severity of symptoms, and the associated syndromes (32). Extrapolating data from the adult Optic Neuritis Treatment Trial, IV methylprednisolone may hasten visual recovery, but most children recover visual acuity without treatment. Individual clinicians have altered their decision to treat based on age (prepubertal vs postpubertal), sex, laterality, and level of visual acuity.

As the spectrum of disorders with optic neuritis has expanded, there is a greater appreciation for the irreversible optic nerve injury associated with NMOSD. This diagnosis is not always apparent, especially when unilateral optic neuritis is the only symptom. Consequently, there has been a paradigm shift by some providers toward treatment with methylprednisolone for PON at disease onset to reduce optic nerve damage while the evaluation is ongoing.

For most children with optic neuritis, a 3–5-day course of IV methylprednisolone (20–30 mg/kg/d; maximum dose of 1 g/d) is administered; thereafter, prednisone is tapered over approximately 2 weeks by some clinicians (32). In children with diffuse CNS involvement not responsive to IV methylprednisolone, intravenous immunoglobulin G (IVIg) and plasma exchange are additional options.

The treatment of neuroinflammatory syndromes includes disease-modifying therapy for MS and NMO. In pediatric MS, first-line therapies include interferon-beta and glatiramer acetate; natalizumab is used in refractory disease (32,33). Several oral therapies for adult MS are offered through pediatric clinical trials, and enrollment in such studies is recommended over their off-label use, as the effects of oral medications on the developing immune system are unknown. In NMOSD in children, rituximab is often initiated as first-line therapy, although mycophenolate mofetil and azathioprine are additional options (14,32).

POTENTIAL FOR DEFINITIVE STUDIES

The Pediatric Eye Disease Investigator Group (PEDIG) and the Neuro-Ophthalmology Research Disease Investigator Consortium (NORDIC) collaboratively launched the Pediatric Optic Neuritis Prospective Data Collection Study (34). The study involves 45 sites throughout North America, with the goal of recruiting 100 patients over 2 years. The European study retrospectively collected approximately 17 cases/year from 27 centers, excluding those with ADEM or without MRI at the time of diagnosis or <2 years of follow-up (10). Collecting 100 cases without such exclusions over 2 years from 45 sites, therefore, seems ambitious, but achievable.

Subjects will be followed prospectively with the primary aims: 1) to determine the ability to enroll patients with PON into a research protocol and 2) to estimate visual acuity outcomes 6 months after the initial presentation of PON. Other data that will be analyzed include visual acuity, low-contrast acuity, OCT, MRIs, quality of life, puberty status, and NMO antibody status. Outcomes from 5 visits over the 2-year study will be used to estimate risks of recurrence and development of MS. Treatment will be at the discretion of the site

investigator. If adequate numbers of patients are recruited for this study, consideration will be given to planning a PON treatment trial.

CONCLUSION

Optic neuritis in children presents with different clinical manifestations than in adults, and its association with neuroinflammatory diseases is likely also different. The risk of evolving MS is probably less than in adults, but PON is more likely to be an initial manifestation of ADEM. Steroids may hasten visual recovery, but they do not change visual outcome except in cases because of NMO. The role of puberty in modifying the presentation and risk associations is unknown. Prospective studies are required to resolve these diagnostic and management issues.

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TABLE 1

Neuroinflammatory syndromes with optic neuritis

Disease	Clinical Features	Laboratory Findings	Neuro-Imaging
Monophasic optic neuritis	1. Unilateral or bilateral ON (may be asymmetric), and	OCB negative	Brain MRI is normal (outside the affected optic nerves)
	2. No signs, symptoms, or examination abnormalities outside the affected eye		
Isolated recurrent optic neuritis	1. ON and at least 1 relapse, and	OCB positive or negative	Brain MRI is normal (outside the affected optic nerves)
	2. No signs, symptoms, or examination abnormalities outside the affected eye	Anti-MOG positive or negative	
Clinically isolated syndrome (CIS) (10)	1. A first monofocal or polyfocal nonencephalopathic episode typical of MS	OCB may be positive or negative if the MRI has an abnormality typical of MS.	Typically reveals at least 1 or more MS-compatible lesions (diameter >3 mm) outside the optic nerves and chiasm
	2. 2010 Revised McDonald criteria are not fulfilled.	If MRI is normal, OCB must be positive to differentiate CIS from isolated optic neuritis.	
Pediatric MS (9,19)	One of the following:	OCB positivity increases with age and is not an absolute criterion for an MS diagnosis if other clinical and radiographic features are met.	Dissemination in time:
	1. Two or more nonencephalopathic (e.g., not ADEM-like), clinical CNS events with presumed inflammatory cause, separated by more than 30 days and involving more than 1 area of the CNS		1. A new T2 and/or gadolinium- enhancing lesion(s) on follow-up MRI, with reference to a baseline scan, irrespective of the timing of the baseline MRI, or
	2. One nonencephalopathic episode typical of MS which is associated with MRI findings consistent with 2010 Revised McDonald criteria for DIS and in which follow-up MRI shows at least 1 new enhancing or nonenhancing lesion consistent with dissemination in time (DIT) MS criteria		2. Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time
	3. One ADEM attack followed by a nonencephalopathic clinical event, 3 or more months after symptom onset that is associated with new MRI lesions that fulfill 2010 Revised McDonald DIS criteria		Dissemination in space:
	A first, single, acute event that does not meet ADEM criteria and whose MRI findings are consistent with the 2010 Revised McDonald criteria for DIS and DIT (applies only to children ≥12 years old).		1. T2 Lesion in at least 2 of 4 areas of the CNS:
			Periventricular
			Juxtacortical
			Infratentorial

Disease	Clinical Features	Laboratory Findings	Neuro-Imaging
			Spinal cord
			2. Gadolinium enhancement of lesions is not required for DIS. Symptomatic lesions are excluded from the criteria and do not contribute to lesion count.
Neuromyelitis optica spectrum disorder, NMO-IgG antibody positive	At least 1 core clinical characteristic	NMO-IgG antibody positive	3. Specific MRI criteria are not required to confirm diagnosis (see NMO-IgG antibody negative for typical MRI findings).
	1. Optic neuritis		
	2. Acute myelitis		
	3. Area postrema syndrome (nausea/vomiting/hiccups)		
	4. Other brainstem syndrome		
	5. Symptomatic narcolepsy or acute diencephalic syndrome with MRI lesion(s)		
	6. Symptomatic cerebral syndrome with MRI lesion(s)		
Neuromyelitis optica spectrum disorder, NMO-IgG antibody negative	1. At least 2 core clinical characteristics all satisfying: 1 of optic neuritis, myelitis, or area postrema syndrome, and	NMO-IgG antibody negative using the best available assay, or testing unavailable	Additional MRI requirements
	Dissemination in space—isolated recurrent ON or recurrent TM does not qualify.		1. Area postrema syndrome: dorsal medulla lesion
			2. Myelitis: longitudinal extensive transverse myelitis
			3. Optic neuritis: normal brain MRI, or >1/2 length of the optic nerve affected on MRI, or chiasm lesion
ADEM (19)	1. A first polyfocal, clinical CNS event with presumed inflammatory demyelinating cause	Typically OCB negative but variability occurs	Typically on brain MRI:
	2. Encephalopathy that cannot be explained by fever		1. Diffuse, poorly demarcated, large (>1–2 cm) lesions involving predominantly the cerebral white matter
			2. T1-hypointense lesions in the white matter are rare. Deep gray matter lesions (e.g., thalamus or basal ganglia) can be present.
ADEM followed by optic neuritis (22)	1. Initial presentation fulfills criteria for ADEM, and	OCBs are not detected in the CSF (a pleocytosis may be present).	1. MRI reveals typical brain or spinal cord T2 lesions consistent with ADEM initially; however, subsequent imaging shows resolution or near-complete resolution of lesions and new brain or spinal cord lesions do not appear during the ON attacks.
	2. ON diagnosed after ADEM with objective evidence of loss of visual function, and		
	3. The ON occurs after a symptom-free interval of		

Disease	Clinical Features	Laboratory Findings	Neuro-Imaging
	4 weeks and not as part of the ADEM or recurrent ADEM, and		
	4. Diagnostic criteria for pediatric MS are not fulfilled.		
Chronic relapsing inflammatory optic neuropathy (34)	1. ON and at least 1 relapse, and	NMO-IgG seronegative	MRI confirms contrast enhancement of the acutely inflamed optic nerves.
	2. Objective evidence for loss of visual function, and		
	3. Response to immunosuppressive treatment and relapse on withdrawal or dose reduction of immunosuppressive treatment		

ADEM, acute disseminated encephalomyelitis; CNS, central nervous system; CSF, cerebrospinal fluid; DIS, disseminated in space; DIT, disseminated in time; MOG, myelin oligodendrocyte glycoprotein; MS, multiple sclerosis; NMO, neuromyelitis optica; OCB, oligoclonal band; TM, tranverse myelitis.