Diagnostic Modalities in Multiple Sclerosis: Perspectives in Children

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Pediatric multiple sclerosis (MS) represents only 2-5% of the MS population, but children with MS have a higher relapse rate and reach permanent disability at a younger age than adult-onset MS. Early and accurate diagnosis of pediatric MS is vital for prompt treatment to mitigate ongoing neuroinflammation and irreversible neurodegeneration. However, it is difficult to differentiate MS from acute disseminated encephalomyelitis (ADEM) and neuromyelitis optica (NMO) in pediatric patients, even considering the clinical, magnetic resonance imaging (MRI), and paraclinical findings, because the first presentation of inflammatory demyelination in children is often atypical. The purpose of this review is to summarize the clinical, neuroimaging, and paraclinical key differences between pediatric patients with MS, ADEM, and NMO and to discuss novel biomarkers, such as antibodies to aquaporin-4 (AQP4) and myelin oligodendrocyte glycoprotein (MOG), which may help in making a diagnosis. *(Biomed J 2014;37:50-59)*

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Multiple sclerosis (MS) is a chronic debilitating disease with a pathological hallmark of inflammatory demyelination in the white matter and cortex, implying a disturbance of the symbiotic relationship of the axon and myelin sheath.[1] It is an immune-mediated disease involving the brain, spinal cord, and the optic nerves. The onset of MS generally occurs at the age of 30, but approximately 2-5% of MS patients have disease onset at an age younger than 16 years.[2-4] More than 85% of adult-onset patients experience a relapsing-remitting multiple sclerosis (RRMS) course and 10% have a primary progressive onset with no or only a single acute event.[5] In contrast, the RRMS course comprises more than 98% of pediatric-onset MS.[2-4,6]

The overall prognosis of pediatric-onset MS tends to be worse than adult-onset MS, with a higher relapse rate[7] and a higher magnetic resonance imaging (MRI) lesion burden.[8] Pediatric-onset MS patients often develop fixed disability on average two decades after diagnosis, and their median age at evolution to secondary progression and reaching the fixed disability milestone is about 10 years younger than that of adult-onset patients.[2,3] In addition, the social and individual impact and cost of the disease in pediatric MS patients is significantly higher. For example, cognitive dysfunction is found in about 30% of pediatric MS children and adolescents, and more than half of them have at least one psychiatric diagnosis.[9,10] These complications impair learning and the chance of sustained employment. Pediatric MS, therefore, comprises a small but important subgroup of MS, in whom the diagnosis must be differentiated from clinical mimics such as acute dis-

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seminated encephalomyelitis (ADEM) and neuromyelitis optica (NMO).

The distinction of MS, ADEM, and NMO is important for considerations of prognosis and treatment. The long-term treatments differ for MS (immunomodulation: First-line with interferon-β or glatiramer acetate[11] and second-line with natalizumab[11-15] or rarely cyclophosphamide[11,16]) and NMO (immunosuppression with azathioprine[17-20] or mycophenolate[20,21] or B-cell depletion therapy with rituximab[20-24]). In addition, immunomodulatory agents such as interferon-β may cause exacerbation in patients with NMO.[25,26] Patients with ADEM do not need long-term treatments because it is typically a single acute event;[27] however, they sometimes need prolonged steroid treatment.

In this review, we summarize the clinical, neuroimaging, and paraclinical key differences between pediatric patients with MS, ADEM, and NMO, and review the biomarkers that facilitate diagnosis and may aid decision making of management.

Pathogenesis

The pathogenesis of pediatric MS is complex. Current evidence suggests that the disease might arise from interactions between immune systems and environmental factors (e.g. Epstein-Barr virus infection, smoking) and partly depends on the individual susceptibility [e.g. human leukocyte antigen (HLA) gene, vitamin D deficiency].[28-31] These complex interactions are supported by a cohort study comprising 302 children with a first inflammatory demyelinating episode, which found that children with all three risk factors (remote Epstein-Barr virus infection, low serum 25-hydroxyvitamin D concentrations, presence of HLA-DRB1*15 alleles) were more likely to have a diagnosis of MS eventually than those with no or only one risk factor.[32]

Epidemiology

The incidence of acquired inflammatory demyelinating syndromes of the central nervous system (CNS) has been estimated to be 0.6-1.66/100,000 children per year,[33-36] and a quarter to a third of them eventually are diagnosed with MS.[32,34,37] About 80% of pediatric-onset MS patients had a first acquired inflammatory demyelinating syndrome onset at over 10 years of age.[38] The initial presentation of pediatric-onset MS can be with polyfocal clinically isolated syndrome (CIS) (26-66%), optic neuritis (ON; 10-23%; more commonly bilateral involvement), isolated acute transverse myelitis (TM; 2-14%), or ADEM (8-18%).[39,40] Bilateral sequential or recurrent ON with an abnormal brain MRI is associated with an increased risk of MS in children.[41] In addition, an inter-attack interval shorter than 1 year, multiple relapses in the first 2 years of the disease, or a higher number of relapses increased the risk of developing a secondary progressive MS.[42]

Diagnostic consensus

The diagnosis of MS in both adults and children is evolving, but the early diagnosis in children is still a challenge because the initial presentation of acute CNS inflammatory demyelination is usually atypical. Two other major mimics of MS are ADEM and NMO; both are more common in pediatric populations than in adults and have different treatment strategies. The first consensus definition for pediatric MS and related disorders for patients younger than 18 years of age was published in 2007[43] and later revised in 2013[27] by the International Pediatric Multiple Sclerosis Study Group (IPMSSG). Table 1 shows the main criteria used currently for diagnosing CIS, ADEM, and NMO. Table 2 summarizes the diagnostic requirements for pediatric MS; each row constitutes a separate case definition for MS. The MRI criteria for pediatric MS diagnosis should apply the updated 2010 revised McDonald criteria[44] and are detailed in Table 3.

The clinical CNS event

The first event of acquired inflammatory demyelinating syndromes is defined as a single acute-onset CNS event caused by presumed inflammatory demyelination in a previously healthy and developmentally intact child without any clinical history of symptoms of CNS demyelination. The symptom must last at least 24 h and the diagnosis must have "no better explanation" than inflammatory demyelination. For instance, leptomeningeal enhancement suggests a vasculitic or malignant process[45] and any previous insidious or progressive pattern of onset suggests an inheritable white matter disease.[46] After the first attack, the second or MS-defining event is typically within 2 years.[47] If the first event is bilateral ON, 36% of pediatric cases develop MS within 2 years.[48,49]

Clinically isolated syndrome

The term "clinically isolated syndrome" is used to define the first CNS event suggestive of inflammatory demyelination, but which does not fulfil the diagnosis of ADEM, NMO, or MS.[50,51] The CIS can be either monofocal or polyfocal without encephalopathy. The presentation is heterogeneous involving optic nerve, spinal cord, brain stem, cerebellum, and any parts of the supratentorial brain.

Acute disseminated encephalomyelitis

ADEM presents with a polyfocal clinical index event with encephalopathy and an abnormal brain MRI within 3 months of the onset. Typically, the MRI shows diffuse, poorly demarcated, bilateral but usually asymmetrical T2-hyperintense lesions lager than 1-2 cm. T1-weighted

Table 1: Diagnostic consensus for pediatric clinically isolated syndrome, acute disseminated encephalomyelitis, and neuromyelitis optica[27]

All are required	Variants
CIS	
A first monofocal or polyfocal CNS event with presumed inflammatory demyelinating cause	
Absence of a prior clinical history of CNS demyelinating disease (e.g. absence of past ON, TM, hemispheric or brain-stem syndromes)	
No encephalopathy that cannot be explained by fever	
The baseline MRI does not meet the diagnostic criteria for MS	
ADEM	Multiphasic ADEM
A first polyfocal clinical CNS event with presumed inflammatory demyelinating cause	Two events consistent with ADEM attacks separated by ≥3 months
Encephalopathy that cannot be explained by fever	
No new clinical and MRI findings emerge ≥3 months after the onset	
Brain MRI is abnormal during the acute phase (<3 months)	
Typical brain MRI findings:	
Diffuse, poorly demarcated, >1-2 cm lesions involving mainly the cerebral white matter	
"Rare" T1-hypointense lesions in the white matter	
Deep gray matter lesions can be present	
NMO[27,54]	NMO spectrum disease
ON	Relapsing ON with positive serum anti-AQP4-IgG
Acute TM	Relapsing TM with positive serum anti-AQP4-IgG
≥2 of three supportive criteria	
Contiguous long extended spinal cord lesion ≥3 vertebral segments	
Brain MRI does not meet the diagnostic criteria for MS	
Positive serum anti-AQP4-IgG	

Abbreviations: CNS: Central nervous system; ON: Optic neuritis; TM: Transverse myelitis; MRI: Magnetic resonance imaging; IgG: Immunoglobulin G; ADEM: Acute disseminated encephalomyelitis; NMO: Neuromyelitis optica; MS: Multiple sclerosis

Table 2: Diagnostic consensus for pediatric multiple sclerosis (each row constitutes a separate case definition for MS)[27]

Number of clinical CNS events with presumed inflammatory demyelinating cause	Patient age (years)	No. of MRI scans	1st clinical CNS event	Time gap	2nd clinical CNS event	MRI requirements		
						Dissemination in space*	Dissemination in time*	Note
≥1	≥12	≥1	Non-encephalopathic episode			Yes	Yes	
≥1	<12	≥2				Yes	Yes	2nd MRI scan showed ≥1 new lesion
≥2	<18	≥1		>30 days	Non-encephalopathic episode			Involving ≥2 areas of the CNS
≥2	<18	≥2	ADEM	≥3 months	Non-encephalopathic episode	Yes		MRI scan of event 2 showed new lesions fulfilled DIS

Abbreviations: *: DIS and DIT should apply the updated 2010 revised McDonald criteria[44]; MS: Multiple sclerosis; CNS: Central nervous system; MRI: Magnetic resonance imaging; DIS: Dissemination in space; DIT: Dissemination in time; ADEM: Acute disseminated encephalomyelitis

Table 3: McDonald MRI criteria for multiple sclerosis[44]

Dissemination in space	Dissemination in time			
	No. of MRI scans	Time point of scans	Contrast agents requirement	MRI findings
Asymptomatic lesions* found in the following ≥2 of 4	1	At any time point	Yes	Simultaneous presence of asymptomatic gadolinium-enhancing† and non-enhancing lesions
≥1 Periventricular ≥1 Juxtacortical ≥1 Infratentorial ≥1 Spinal cord	2	At any time point	No	Scan 2 compared to scan 1 showed ≥1 new T2 lesion
			Yes	Scan 2 compared to scan 1 showed ≥1 gadolinium-enhancing lesion

Abbreviations: *: In cases of brain stem and spinal cord syndromes, all lesions within the symptomatic region were excluded[53];
†: Gadolinium-enhancing lesion should be reliably determined not due to non-MS pathology; DIS: Dissemination in space; DIT: Dissemination in time; MRI: Magnetic resonance imaging

hypointense lesion in the white matter is rare. Patients are designated as having multiphasic ADEM if they have a second episode consistent with ADEM occurring more than 3 months after the index event. If the third episode occurs, with or without encephalopathy, it is no longer "ADEM" but should be considered another clinical entity with chronicity, such as MS or NMO.[27] ADEM was classified as monophasic, recurrent, and multiphasic types in previous consensus,[43] but the current version eliminates the term "recurrent ADEM".[27]

Multiple sclerosis

The diagnosis of clinical definite MS requires two clinical events separated by at least 1 month: Evidence of dissemination in time (DIT) and clinical and paraclinical (neurophysiology or neuroimaging) evidence for the lesions exhibiting dissemination in space (DIS), and exclusion of alternative diagnoses.[52] MRI is the most powerful paraclinical method to demonstrate both DIT and DIS, even with only one baseline MRI at the first event.[44] It is of note that MRI evidence of both DIS and DIT is specific for MS, especially for young adults with typical CIS presentations (unilateral ON, myelitis, and brainstem syndromes).[53]

In pediatric patients with two clinical events, the first event can be CIS followed by another non-encephalopathic attack separated by more than 30 days or ADEM followed by a non-encephalopathic event separated by at least 3 months with clinical or MRI demonstrated DIS.[27] In adolescents aged 12 years and above, a first, single, CNS non-encephalopathic event with an MRI showing evidence for both the DIS and DIT can also make the diagnosis of MS. For those aged less than 12 years, a first, single, CNS non-encephalopathic event with MRI asymptomatic lesions fulfilling DIS will need a second MRI showing at least one new lesion consistent with DIT to make the diagnosis of MS.

Neuromyelitis optica

NMO is defined as both ON and TM occurring simultaneously or sequentially with at least two of three pieces of supportive features: (1) A contiguous spinal cord MRI lesion extending over three or more vertebral segments, (2) brain MRI not meeting the diagnostic criteria for MS,[44] and (3) the presence of anti-aquaporin-4 (AQP4) IgG in serum.[27,54]

Encephalopathy

Encephalopathy is defined as an alteration in consciousness or a behavioral change unexplained by fever, systemic illness, or postictal epileptic symptoms. Encephalopathy, although still primarily a clinical diagnosis, was given a clearer definition in the current guideline than in the 2007 version.[27,43] However, change of consciousness is not very specific to distinguish ADEM from MS, and it can also occur in NMO.[55] An alteration of consciousness can also occur in adult CIS patients, initially diagnosed with ADEM.[56] As encephalopathy is crucial in the differential diagnosis of MS, especially in those aged 12 years and above, paraclinical studies such as electroencephalograph (EEG) showing an excess of background slow wave activity[57] may be used acutely to provide clearer evidence for or against the presence of encephalopathy.

Diagnostic modalities

The diagnosis of ADEM, NMO, CIS, and MS is based on the clinical presentations and paraclinical investigations. The most often deployed paraclinical tests are MRI, cerebrospinal fluid (CSF) examination, serum tests, and biopsy.

Magnetic resonance imaging

The characteristic morphological findings of brain MRI in MS are useful to help differentiate MS from ADEM and NMO in children. First, the presence of "Dawson's nger" which represents a lesion perpendicular to the long axis of the corpus callosum can predict the conversion to MS in children with high specificity.[37] It is also helpful to differentiate between NMO and MS.[58] Second, the presence of "black holes," suggesting longstanding tissue destruction, is specific for MS and is rarely visible in ADEM.[59,60] The imaging features of "black holes" are non-enhancing hypointensity on T1 and hyperintensity on T2 imaging lasting for more than 3 months. The presence of at least one black hole lesion and at least one periventricular white matter T2-hyperintense lesion abutting any portion of the lateral ventricles predicts progression to MS in children at the first acquired inflammatory demyelinating episode.[60] In addition, the MRI features of spinal cord lesions in MS patients are single or multiple focal, sharply delineated, T2-hyperintense lesions extending one vertebra (maximum two segments) in length;[61,62] however, a lesion over three or more segments can also be found in pediatric-onset MS,[63] as well as in NMO and ADEM.[64]

The specific locations of some MRI lesions, accompanied by certain clinical symptoms, are important clues suggesting NMO rather than MS. The fluid-attenuated inversion recovery (FLAIR) signal abnormality in NMO is typically contiguous throughout the periventricular and along the third or fourth ventricular periependymal tissues, and involves the hypothalamus.[65] Besides, a linear medullary or medullospinal lesion in an individual manifesting intractable hiccups and nausea lasting more than 48 h are typical for NMO and extremely rare in MS.[66]

Cerebrospinal fluid

CSF is obtained for three main purposes: (1) To confirm the diagnosis of MS [e.g. presence of oligoclonal bands (OCBs)]; (2) to identify other treatable dis-

eases (e.g. infection, systemic inflammatory disease, or tumors); and (3) to detect biomarkers, for prognosis. CSF findings supporting CNS inflammatory demyelination include an elevated immunoglobulin G (IgG) index, or at least two OCBs in the CSF but not in the corresponding serum samples[44] on isoelectric focusing (IEF).[67,68] Although new diagnostic criteria for RRMS no longer require routine CSF studies, complete CSF studies are still valuable in children. In particular, a negative OCB test often prompts the consideration of other diseases mimicking MS or CIS. In children with ON, the presence of OCBs, with or without abnormal brain MRI, has been shown to be associated with subsequent MS development.[69] However, OCBs do not *always* occur in MS (85-90%), and can present in ADEM (in up to 29%)[70,71] and NMO (in up to 30%).[72] In addition, if intrathecal IgG synthesis was detected, it tends to disappear in the ADEM and NMO patients while it is persistently detectable in MS patients.

Serum autoantibodies

Existing criteria are useful in everyday practice, but diagnostic uncertainty is frequent in pediatric inflammatory demyelinating diseases. For instance, diffuse, large, poorly demarcated T2-hyperintense brain white matter lesions can be found in the children with ADEM and NMO,[55,73,74] and therefore, these findings alone are not concrete evidence for a specific diagnosis. Biomarkers are clinically useful for differentiating difficult cases and for disease course prediction. They are relatively non-invasive, more accessible, and may reflect biochemical or immune mechanisms. Currently, clinically relevant biomarkers include autoantibodies against AQP4 and possibly myelin oligodendrocyte glycoprotein (MOG). They may increase the confidence of disease diagnosis and facilitate decision making for long-term treatment.

NMO-IgG and anti-AQP4-IgG antibody

Anti-AQP4-IgG is the first clinically useful antibody in human inflammatory demyelinating diseases. In 1999, Wingerchuk *et al.* defined NMO as comprising both ON and TM with a long spinal cord lesion (three or more vertebral segments).[75] From sera of 124 clinically ascertained NMO patients, NMO-IgG outlining CNS microvessels, pia, subpia, and Virchow-Robin spaces was identified.[76] It is detectable in 60-90% of patients with NMO and is specific for NMO because the seroprevalence of this antibody in other inflammatory demyelinating diseases, including MS, is very low. The main target antigen of NMO-IgG is the astrocyte water channel protein AQP4.[77] AQP4 is concentrated at the end-feet of astrocytes facing the blood-brain barrier (BBB), forming an integral part of the BBB and the blood-CSF barrier.[78-80] The presence of NMO-IgG or anti-AQP4 antibody has been proposed as one of the diagnostic criteria for NMO.[54,81]

The pathological hallmark of NMO lesions is loss of the immunostaining for AQP4 and glial fibrillary acidic protein (GFAP); both are not lost in MS lesions unless there is a chronic inactive lesion or cavity.[82-84] The pathogenic potential of anti-AQP4 antibody was demonstrated by animal models showing that transfer of human anti-AQP4 antibody into mice or rats could induce lesions typical for NMO[85-87] with complement-dependent cytotoxicity or antibody-dependent cellular cytotoxicity as the major mechanism in the formation the NMO lesions. Currently, the presence of NMO-IgG or anti-AQP4 antibody has been one of the NMO diagnostic criteria since 2006. A spectrum of NMO disorders (NMOSD) has been formulated comprising conditions characterized by the presence of the antibody and recurrent or simultaneous bilateral ON, and idiopathic long extensive transverse myelitis.[88,89]

There have been a variety of immunoassays used to detect anti-AQP4 antibody with high diagnostic specificity for NMO (85-100%), although the sensitivity is moderate (33-91%).[90,91] Current immunoassays include cell-, tissue-, and protein-based assays.[90,92] Of these three immunoassays, the cell-based assay, using cell lines that have been transfected with AQP4 protein, has been shown to be the most sensitive.[77,91] There are two isoforms of AQP4 used for immunoassays: M1 isoform [protein generated by mRNA translation initiated at methionine (Met)-1] and M23 isoform (translation initiated at Met-23).[93] Anti-NMO-IgG generally binds with greater affinity to M23-AQP4 than to M1-AQP4,[94] and AQP4-M23 transfected cell-based assay seems to be slightly more sensitive than M1-based assay.[95-97] However, the function of M1- and M23-AQP4 and *in vivo* conformational epitopes of AQP4 in the human CNS still needs to be elucidated.[93,98-100]

Several lines of evidence argue for a pathogenic role for anti-AQP4-IgG in NMO. First, the serum anti-AQP4-IgG was reported to be positive in blood donated 10 years before the disease onset in a 34-year-old female with NMO.[101] Second, adults with acute myelitis with less than three vertebral segments, isolated recurrent brainstem demyelination, or monophasic ON who do not fulfil the clinical criteria for NMO or NMOSD have been shown to have seropositivity of anti-AQP4-IgG at low titers.[102] Third, positive findings in repeated antibody tests do not always predict relapses.[103]

In pediatric NMO patients, the presence of NMO-IgG or anti-AQP4 antibody can help diagnose the disease, especially in those with disease onset before the age of 10 years.[55] The seropositivity seemed to be more frequent in the patients with a relapsing course than children with a monophasic disease.[21,73,104] In practice, the presence of NMO-IgG and anti-AQP4-IgG can help differentiate chil-

dren with NMO and NMOSD from ADEM, CIS, and MS. Although the role of long-term antibody titer monitoring is not known, a rising level of NMO-IgG in an individual patient may predict a new attack.[105]

Anti-MOG antibody

Another biomarker is the presence of antibodies against MOG, an autoantigen expressed exclusively in the outer sheath of CNS myelin and oligodendrocytes.[106] Although its pathogenic role is still elusive, some evidence shows that the IgG to native MOG at high titers is capable of inducing complement activation[107] and antibody-dependent cytotoxicity when natural killer cells are present *in vitro*;[108] both mechanisms contribute to CNS demyelination. The best method to detect anti-MOG antibody is a cell-based assay detecting antibodies against native MOG in natural confirmation on the cell surface and this form has been shown to be pathogenic *in vitro*.[109]

The anti-MOG antibody has been consistently detected in a substantial proportion of children with ADEM (27-47%), MS (up to 21%), CIS (up to 36%), AQP4-IgG-seronegative NMO, and in recurrent ON, but only rarely in adult MS.[107,108,110-114] Among these pediatric patients, the antibodies have been found to be transiently elevated during acute episodes. In ADEM, the level would generally decrease to an undetectable level in fully recovered patients.[110] In patients with recurrent ON or MS, the titer was persistently detectable for up to 5 years, but usually at low titers.[110,112,115] The persistent seropositivity of anti-MOG antibody may highlight the risk of ongoing inflammation, suggesting chronicity rather than an acute single episode of demyelination; so, these patients may warrant more aggressive treatment.[116]

Brain biopsy

Although rarely required, biopsies are occasionally performed to exclude other treatable diseases (most often tumors,[117] vasculitis, and encephalitis) and to establish the diagnosis of demyelinating disease.[118] The pathological study of pediatric MS and related disorders has derived mainly from atypical presentations with space-occupying lesions, fulminant illness, or fatalities. The pathology of MS is consistent with focal demyelinated plaques with various degrees of perivascular inflammation and axonal injury or loss.[119,120] In the cortex, subpial inflammatory demyelinated lesions are typical of the progressive stages of MS, although they can also be found in the early stages.[121]

Conclusion

The updated criteria simplify the diagnosis of pediatric MS, especially for those who have a first episode of acute CNS inflammatory demyelination at age 12 years and older. The formal diagnosis of MS should always take into consideration the clinical, imaging, and paraclinical evidence. When there is diagnostic uncertainty, serum biomarkers may prove very valuable in the clinical diagnosis. Currently useful biomarkers include the specific NMO marker anti-AQP4 antibody and the neuroinflammatory signature anti-MOG antibody. Both may help in clinical diagnosis and treatment decision making.

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