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Diagnostic Criteria for Pediatric Multiple Sclerosis

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Abstract An estimated 2 % to 5 % of all persons with multiple sclerosis (MS) have onset of symptoms before 16 years of age Krupp and Hertz (Neurology 68(Suppl 2), 2007). As in adults, the diagnosis of pediatric MS is a clinical one, requiring recurrent episodes of CNS demyelination with supportive paraclinical data (MRI findings, CSF characteristics) in the absence of another plausible diagnosis. The differential diagnosis is broad and, the more atypical the case and the younger the child, the more consideration is necessary before making a diagnosis of MS. MS must be differentiated from acute disseminated encephalomyelitis (ADEM) or neuromyelitis optica (NMO). After initial presentation with a CNS demyelinating event or clinically isolated syndrome (CIS), children can meet the diagnostic criteria for MS if serial changes are noted on MRI and other disorders are excluded. Accurate diagnosis of pediatric MS is critical because of the implications of the diagnosis, including the need for long-term disease modifying therapy.

Keywords Pediatric · Children · Multiple sclerosis (MS) · Demyelinating · Diagnosis · Diagnostic criteria · MRI · CSF · NMO · ADEM

Introduction

Multiple sclerosis (MS) is an autoimmune disease characterized by recurrent episodes of CNS demyelination which typically occurs in young adults. Although the precise prevalence is unknown, an estimated 2 % to 5 % of all persons with MS have onset of symptoms before 16 years of age [1]. MS onset prior to 10 years of age occurs in about 20 % of pediatric cases [2]. In contrast to adults, over 95 % of pediatric MS patients have a relapsing-remitting course (RRMS), so a primary-progressive time course should prompt consideration of a different diagnosis [3••].

As in adults, the diagnosis of pediatric MS is a clinical one, requiring recurrent episodes of CNS demyelination with supportive paraclinical data (MRI findings, CSF characteristics) in the absence of another plausible diagnosis. Various criteria for the diagnosis of MS in adults have been evaluated in children and adolescents. Diagnosis can, therefore, be made after an initial demyelinating event and a changing MRI scan. The major challenge to diagnosing MS in the pediatric population is to distinguish transient demyelinating events from life-long MS, and to differentiate MS from other inflammatory or infectious conditions.

Initial Demyelinating Event or Clinically Isolated Syndrome

The term clinically isolated syndrome (CIS) refers to a first acute clinical episode of CNS demyelination which can be monofocal or multifocal but which does not typically include encephalopathy [4]. Examples of CIS in children and adolescents are similar to those occurring in adults and can include optic neuritis, transverse myelitis, and brainstem, cerebellar, or hemispheric dysfunction [4]. Children with CIS should undergo additional diagnostic testing to define the disease burden, evaluate for supportive laboratory data, and consider other conditions in the differential diagnosis of multiple sclerosis including infections, metabolic disease, and other inflammatory/autoimmune conditions.

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Hahn et al. [5] recommend that minimal diagnostic testing in children and adolescents after an initial demyelinating event include:

(1) MRI brain and cervical spine, with and without contrast,
(2) CSF studies: cell count with differential, total protein, IgG index, oligoclonal bands (compared with paired serum sample with isoelectric focusing and immunodetection), and cytology, if possible,
(3) Complete blood count with differential, erythrocyte sedimentation rate (ESR) and antinuclear antibody (ANA).

Imaging the thoracic cord can be useful as well, as asymptomatic lesions can be missed with cervical spine imaging alone [6••]. Need for additional evaluation depends upon the age of the child, the symptoms at presentation, and MRI findings.

Differential Diagnosis of Pediatric MS

Clinical and paraclinical findings that suggest an alternative diagnosis to initial presentation of MS include: fever, encephalopathy, progressive clinical course lacking discrete attacks, involvement of the peripheral nervous system or other organs, elevated ESR or leukocyte count, markedly elevated CSF white blood cells or protein, and the absence of CSF oligoclonal IgG [5]. The differential diagnosis of CNS demyelination is broad. The more atypical the case and the younger the child, the more consideration is necessary before making a diagnosis of MS. Table 1 summarizes inflammatory, infectious, vascular, and metabolic diseases in the differential diagnosis of pediatric multiple sclerosis. The list is not exhaustive but highlights key conditions that mimic MS.

Consensus Definition of Pediatric MS

In an effort to improve diagnosis and treatment of pediatric MS, an expert panel met in 2004 and 2005, and published recommendations in 2007 [1]. The study group agreed to uniform terminology and consensus definitions for pediatric MS and other demyelinating disease, such as acute disseminated encephalomyelitis (ADEM) and neuromyelitis optica (NMO) [4]. Table 2 outlines the consensus definition for pediatric MS.

As in adults, pediatric MS can be diagnosed after 2 discrete demyelinating events separated in time and space. In children, the events must not meet criteria for acute disseminating encephalomyelitis (ADEM), namely the child or adolescent cannot have been encephalopathic during the event. In a child with ADEM as an initial demyelinating event, a second non-ADEM event is not sufficient for diagnosis of MS, but requires further dissemination in time with either another non-ADEM clinical event or a changing MRI scan at least 3 months from the second event. Of note, Waldman et al. used the Delphi technique to assess consensus amongst US neurologists with interest or expertise in pediatric MS and other CNS demyelinating conditions. Among the 42 correspondents, 54 % agreed with the current working definitions, and 35 % agreed but suggested modifications. Of those participants that suggested modifications, over 60 % questioned the need for encephalopathy in patients with ADEM. Furthermore, over half of the participants stated that a prior episode of ADEM should count as an initial event in the diagnosis of MS [7].

Differential Diagnosis of MS

Pediatric MS must be differentiated from acute disseminated encephalomyelitis (ADEM) or neuromyelitis optica (NMO), as the natural history and treatment differ considerably. MRI findings differ in each of these conditions as well (Fig. 1).

ADEM

Acute disseminated encephalomyelitis is an inflammatory disorder of the CNS commonly preceded by an infection, presenting with multifocal, mainly white matter, abnormalities of the brain, and spinal cord [8]. ADEM occurs more commonly in children than adults, is typically monophasic, and includes encephalopathy. MRI abnormalities consist of T2-weighted lesions that are large, patchy and asymmetric in white matter and subcortical regions with more symmetric lesions in the deep gray matter [8]. ADEM is typically a monophasic illness, but can recur, making the distinction between ADEM and MS more challenging.

NMO

NMO is a recurrent CNS demyelinating disorder primarily affecting optic nerves and spinal cord. The presence of serum or CSF antibodies directed against aquaporin 4 (NMO-IgG) is fairly sensitive and very specific for NMO [9].

Features that suggest NMO or an NMO-spectrum disorder include [3••]:

(1) Longitudinally extensive myelitis, cord lesions extending radiographically over 3 or more spinal segments
(2) Optic neuritis which is particularly severe or occurs bilaterally, associated with a swollen optic nerve, chiasmal lesion, or an altitudinal scotoma
(3) Intractable nausea/vomiting or hiccups with evidence of periaqueductal medullary lesion on MRI

Table 1 Differential diagnosis of pediatric MS by disease subtype (adapted from Chitnis T, et al. [22])

Disease		Presentation	Diagnostic clues/ evaluation
Metabolic/mitochondrial	ALD	Half of the cases present in childhood with cerebral dysfunction.	Symmetric involvement of parieto-occipital WM with possible leading edge enhancement
• Suspect leukodystrophy if progressive course with developmental regression, MRI with symmetric white matter disease, possible peripheral neuropathy		Half present as either a cerebellar form or as an adrenomyeloneuropathy, presenting in female carriers in their 20s–40s [23]	Elevated very long chain fatty acids in plasma
	MLD	Younger children present with PNS involvement.	MRI demonstrates symmetric, diffuse WM abnormalities.
		Those presenting later can have behavioral or psychiatric changes [24]	Elevated urine sulfatides
	Childhood ataxia with diffuse CNS hypomyelination (vanishing white matter disease)	Chronic progressive disease with episodic deterioration triggered by injury or intercurrent illness [25] Children can present with spasticity and ataxia with relatively preserved cognition	MRI most often shows symmetric involvement of the cerebral hemispheric white matter. Additionally all of the WM has signal intensity similar to CSF on proton density scans
	Alexander's disease	Symptoms typically begin between 6 and 15 years of age with bulbar dysfunction and a slowly progressive ataxia and spastic diplegia [23]	MRI bilateral frontal regions are usually affected and show cystic changes [26]
• Suspect mitochondrial disease if stroke-like episodes with optic neuropathy and/or myopathy	LHON	Typically affects males and is most often due to a mtDNA mutation affecting complex I of the ETC [27] Patients present with bilateral visual loss and optic atrophy.	Genetic testing identifies most affected individuals.
	MELAS	Characterized by episodic vomiting, lactic acidosis, myopathy, seizures, stroke-like events, short stature	Genetic testing available
	Kearn–Sayre syndrome	Triad of progressive external ophthalmoplegia (PEO), pigmentary retinal degeneration, cerebellar dysfunction, and heart block	MRI findings include progressive leukocencephalopathy and basal ganglia or deep white matter calcifications [5]
			Elevated CSF protein
Systemic immunologic/ inflammatory	SLE	Multisystemic autoimmune disorder affecting the skin, joints, and kidneys. Neuropsychiatric symptoms include cerebrovascular events, psychosis, chorea and encephalopathy [28]	Elevated CSF lymphocytes, and laboratory studies indicating renal involvement or autoimmune antibodies.
• Suspect systemic inflammatory disease when other organ systems involved, including skin, kidneys, and joints.	Behçet syndrome	Form of vasculitis associated with oral and genital ulcers and uveitis	Pathergy: nodular reaction at needle site
	Sjogren's syndrome	Should be suspected when sicca symptoms (including dry eyes, dry mouth) are prominent	Schirmer's test/slit-lamp test for xeropthalmia
		Sjogren's syndrome can affect both the brain and spinal cord.	Nuclear scan of salivary gland or salivary gland biopsy for xerostomia
	Sarcoidosis	Highly variable presentation including seizures in prepubertal children, and cranial neuropathies in olderchildren	Periventricular WM lesions or meningeal enhancement noted on brain MRI scans; tissue biopsy confirmation

Table 1 (continued)

Disease		Presentation	Diagnostic clues/ evaluation
		Hypothalamic symptoms such as diabetes insipidus, headaches, motor complaints, and papilledema [29]	
	Hashimoto's encephalitis	Should be considered when children present with encephalopathy associated with a history of thyroid disorder and elevated intrathecal anti-thyroid antibodies	Elevated intrathecal anti-thyroid antibodies.
	Langerhans cell histiocytosis	Disorder due to excessive macrophages which attack multiple organs including the nervous system [30]	CNS lesions most commonly occur in the hypothalamic pituitary region
		Onset is usually in childhood and organ involvement can include skin, bone, muscles, liver, lung, spleen, bone marrow	Cerebellar syndrome associated with bilateral symmetric lesions in the dentate nucleus and/or basal ganglia may also be seen [31]
Infections and neoplasms	HIV	CNS involvement with HIV is highest in the first 2 years of life, and is frequently the first AIDS-defining illness in children [32]	In more advanced disease, CNS imaging shows cortical atrophy and basal ganglia calcifications on CT scans and white matter lesions and central atrophy on MRI of the brain.
• Suspect CNS infection or neoplasms if fever, constitutional symptoms, or enhancing lesions and/or leptomeningeal enhancement.	Herpes virus	Viral encephalitis and cerebral thrombosis can both be initiated by herpes virus infections	MRI scan demonstrates involvement of medial temporal, inferior frontal, insular and cingulate gyrus regions with possible diffusion abnormalities or hemorrhage
	Neuroborreliosis, Lyme disease	Cranial and peripheral nerve involvement is more frequent than central nervous system involvement [33]	CSF: elevated CSF white count and protein, oligoclonal bands [34]
			MRI scan with variable numbers of small, non-enhancing T1 hypointense and T2 hyperintense lesions without mass effect [35]
	Mycoplasma	Common cause of encephalopathy and transverse myelitis in children. Mycoplasma-associated acute disseminated encephalomyelitis (ADEM) rarely includes optic neuritis.	MRI demonstrates patchy, asymmetric FLAIR and T2 hyperintensities involving grey and white matter [36]
	Primary CNS lymphoma	Rare in children, but multifocal lesions can be mistaken for MS lesions. CSF cytology has high specificity, but low sensitivity [37]	Definitive diagnosis requires cytology or open biopsy
			Diagnostic evaluation should be performed prior to steroid therapy as lymphomas are steroid-responsive and diagnostic tests performed post steroids may be falsely negative [37]
Vascular disorders	CADASIL	Usually presents in middle age with migraine-like vascular episodes and MRI brain abnormalities	Genetic testing for mutations in the NOTCH-3 gene

Table 1 (continued)

Disease		Presentation	Diagnostic clues/ evaluation
• Suspect vascular disorder if focal neurologic symptoms and headaches		Asymptomatic children, whose parents have been diagnosed with CADASIL, have been noted to have MRI abnormalities including small T2-hyperintense lesions in periventricular and subcortical white matter [38]	
	Migraine headaches	Classical migraines are easy to recognize; however, aura sine migraine and/or atypical presentations are less easily diagnosed	MRI can demonstrate one or more small T2 hyperintensities, smaller and in fewer numbers that in pediatric [18]
	CNS vasculitis	Presents with multifocal neurologic impairments, in association with headaches, seizures, behavior changes, and TIA/stroke [5] Difficult to diagnose because of the absence of cutaneous or systemic signs or symptoms	Abnormal cerebral arteriography and brain biopsy are frequently required to make this diagnosis

AIDS acquired immunodeficiency syndrome**,** *ALD* adrenoleukodystrophy, *CADASIL* cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, *ETC* electron transport chain, *HIV* human immunodeficiency virus, *LHON* leber hereditary optic neuropathy, *MELAS* mitochondrial encephalopathy with lactic acidosis and stroke-like episodes, *MLD* metachromatic leukodystrophy, *PNS* peripheral nervous system, *SLE* systemic lupus erythematosus, *TIA* transient ischemic attack, *WM* white matter

Adult vs Pediatric MS

Increasing recognition of pediatric MS has led to more timely and accurate diagnosis. Compared to adult-onset MS where 20 %–33 % of patients have a primary progressive course, the disease course in children is greater than 90 % relapsing-remitting [10]. Although the rate of accrual of neurologic disability is lower in pediatric MS, there is typically a shorter interval between the initial and subsequent relapses, with a relapse rate higher than in adult onset MS. Symptoms in children tend to resolve more quickly than in adults. When disability is assessed in pediatric vs adult MS, studies demonstrate lower disability scores in pediatric MS vs adult MS with longer times to reach more severe neurologic deficits. Pediatric patients also have a longer time and lower probability for conversion to secondary progressive MS (SPMS) [11]. In contrast, pediatric MS patients progress to SPMS at an earlier age (30 years) than adult patients (37 years). Although pediatric patients have a more favorable outcome during the initial stages of MS compared with adults, pediatric MS patients can become disabled at a younger age, emphasizing that it is not a benign disease. Early diagnosis and treatment with disease modifying therapies is imperative.

Table 2 Consensus definition of pediatric multiple sclerosis [4]

Multiple episodes of CNS demyelination separated in time and space, without a lower age limit of diagnosis.

Dissemination in space (DIS):

- An MRI can be used to meet DIS criteria using the 2005 McDonald criteria for a "positive MRI."
- Abnormal CSF, with either oligoclonal bands or an elevated IgG index, and at least 2 lesions on the MRI can also meet DIS criteria.

Dissemination in time (DIT):

- MRI can be used to meet DIT criteria following the initial demyelinating event with new T2 or gadolinium enhancing lesions 3 months following the initial clinical event.

An episode of ADEM cannot be considered the first event of MS.

Diagnosis of MS

The timely and accurate diagnosis of pediatric MS is important to initiate appropriate treatment to reduce clinical relapses and to prevent progression of disability.

Diagnostic criteria for multiple sclerosis include clinical and paraclinical features in an effort to demonstrate CNS demyelination disseminated in space (DIS) and time (DIT) while reasonably excluding other diagnoses [3••]. Although the diagnosis can be made after 2 or more clinical events, the disease modifying therapies (DMT) for MS have been shown in adults to be useful after an initial demyelinating event and an MRI scan consistent with MS [12, 13]. Children and

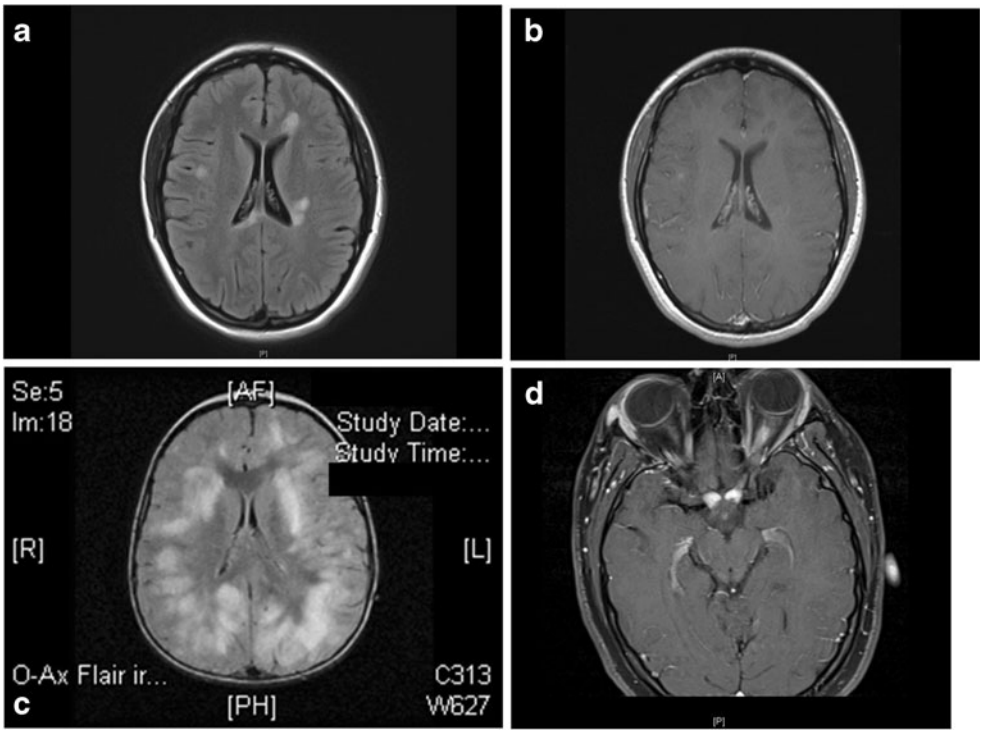

Fig. 1 **a** and **b** Pediatric MS: MRI brain with and without contrast, axial T2/FLAIR (*left*) and axial T1-post contrast (*right*). Note the periventricular and juxtacortical lesion(s), one with associated enhancement, as well as the T1 hypointense lesion. **c** ADEM: MRI brain, axial T2/FLAIR. Note the ill-defined white matter T2/FLAIR hyperintensities. **d** NMO: MRI brain and orbits, axial T1-post contrast remarkable for enhancement of the optic nerve and chiasm

adolescents, however, were not involved in these critical trials of MS therapy. Although the DMTs have been safely used in children and adolescents, they are not FDA-approved for use in the pediatric age group. Furthermore, children have a higher incident of monophasic CNS demyelinating events such as ADEM [8]. Therefore, the current consensus recommendation is to defer starting DMT in children and adolescents until after MS is diagnosed [14].

2010 McDonald Criteria

In an effort to improve early diagnosis of MS using clinical and paraclinical data, an international panel of experts created guidelines for the diagnostic criteria of MS referred to as the McDonald Criteria [15] and revised them in 2005 [16]. Since that time, it has been suggested that the Criteria be simplified to improve utility and modified to apply to different patient populations than the predominately Western Caucasian populations from which the Criteria originated. As a result, the International Panel on Diagnosis of MS (the Panel) met again in 2010 to develop the 2010 revisions to the McDonald Criteria [3••].

The McDonald Criteria should be applied to patients presenting with a typical CIS suggestive of MS because the Criteria has been validated and developed for such patients. In addition, alternative diagnoses must be considered and reasonably excluded [3••].

In adults presenting with 2 or more attacks of CNS demyelination with objective clinical evidence of 2 or more lesions, or objective evidence of 1 lesion with reasonable history of a prior attack, no additional data is needed for the diagnosis of MS. In this setting, paraclinical data including neuroimaging and spinal fluid analysis provide support for the diagnosis and exclude mimics. In adults presenting with an initial demyelinating event, the 2010 McDonald Criteria allows a single MRI scan of brain and spine to demonstrate DIT and DIS. This contrasts with the 2005 McDonald Criteria requirement for a baseline or reference scan at the time of the initial CIS in addition to a second scan obtained a minimum of 30 days later. According to the 2010 McDonald Criteria, DIS can be demonstrated by 1 or more T2 lesion(s) in at least 2 of the 4 following areas of the CNS: periventricular, juxtacortical, infratentorial, or spinal cord. DIT can be demonstrated by: a new T2 and/or gadolinium-enhancing lesion(s) on follow-up imaging, or simultaneous presence of asymptomatic enhancing and nonenhancing lesions at any time [3••]. In the most recent McDonald Criteria, CSF analysis was eliminated from the diagnostic criteria.

McDonald Criteria for Diagnosing Pediatric Multiple Sclerosis

The International Panel on Diagnosis of MS thought the 2010 McDonald Criteria could be applied to children and adolescents for the diagnosis of MS, but stressed the need for further validation [17••]. The Criteria, however, could not be applied to episodes of ADEM.

Sadaka et al. assessed the 2005 and 2010 McDonald Criteria in a prospective cohort of 209 pediatric subjects with clinically isolated syndromes of the central nervous system, three-fourths of who had non-ADEM presentations. Thirty-four of the 209 children in this series met historic criteria for Clinically Definite MS (CDMS) and were more likely to be female, older, and more likely to have CSF oligoclonal bands than the rest of the 209 children. The authors then applied the 2005 and 2010 McDonald Criteria to the 209 children to assess their ability to identify children with CDMS. The 2010 McDonald Criteria demonstrated better performance in children 11 years of age and older with non-ADEM presentations demonstrating high sensitivity (100 %), specificity (86 %), positive predictive value (76 %), and negative predictive value (100 %). Results were similar though less robust using the 2005 McDonald Criteria (Table 3). In this prospective cohort of pediatric subjects with non-ADEM acute demyelinating syndromes, the 2010 McDonald criteria were sensitive and specific for the diagnosis of pediatric MS.

Callen Criteria

Prior to the development of the 2010 revisions to the McDonald Criteria, Callen et al. proposed modifications to the 2005 McDonald Criteria for lesions DIS to improve accuracy of the Criteria in children with MS [18]. A retrospective analysis was completed comparing brain MRI scans from 38 children with clinically definite MS to 45 scans from children with nondemyelinating relapsing diseases with CNS involvement (migraine, systemic lupus erythematosus). MRI lesion location and size categories were analyzed between the 2 groups and the presence of at least 2 of the following features differentiated MS from nondemyelinating conditions with 85 % sensitivity and 98 % specificity:

(1) Five or more lesions
(2) Two or more periventricular lesions or
(3) One brainstem lesion

When Callen's group used the 2005 McDonald Criteria to assess their study population, the specificity was similar (100 %), but sensitivity was reduced (76 %).

The various published MRI criteria for pediatric MS were also evaluated by Komek et al. in children with a clinically isolated syndrome. They specifically compared the diagnostic efficacy of the 2010 McDonald Criteria with the Callen MS MRI criteria [18] proposed for children [6••]. Komek and colleagues were also interested in assessing whether the inclusion of spinal cord imaging provided additional significance to the 2010 McDonald Criteria. They performed retrospective analysis of MRI brain and spine scans from 52 children with CIS, comparing McDonald 2005 and 2010 Criteria with the Callen, KIDMUS [19], and the Canadian Pediatric Demyelinating Disease Network criteria [20]. In their cohort, the 2010 McDonald Criteria for DIS were more sensitive but less specific than the 2005 Criteria (Table 1). The McDonald 2010 DIS criteria were also less specific for CDMS than the DIT component. Combining DIS and DIT improved specificity. In this study, analysis of the spinal cord lesions did not dramatically improve the diagnostic efficacy of the 2010 McDonald DIS criteria. The Callen criteria were more sensitive and specific than 2010 and 2005 McDonald DIS. The KIDMUS criteria, in contrast, demonstrated high specificity, but low sensitivity and accuracy. Lastly, analysis of the Canadian Pediatric Demyelinating Disease Network criteria demonstrated less sensitivity and specificity than Callen and 2010 McDonald DIS and DIT.

Special Considerations

Despite the frequency of pediatric MS, close to 6 % of children enrolled in a study by Sadaka et al. were ultimately diagnosed with other CNS inflammatory disorders, such as NMO spectrum disorders or CNS vasculitis. One-fourth of these children with alternative diagnoses had met the 2010 McDonald Criteria for MS. This underscores the importance of remaining vigilant for clinical or paraclinical features that suggest a non-MS diagnosis [17••].

Modifications in the 2010 McDonald Criteria allow a single MRI brain with enhancing and non-enhancing lesions to meet criteria for DIS. However, given the lower specificity of these criteria in pediatric patients, it is not recommended to make a diagnosis of MS based on one MRI scan [6••].

Future Directions

ADEM is fairly common in the pediatric population (0.4/100,000/year [8]).Currently, there are no clinical, MRI or CSF findings that can definitively distinguish ADEM from ADEM-like initial CNS demyelinating events. The current clinical and radiographic criteria for diagnosis of MS are not as sensitive or specific in pediatric patients when including those with ADEM. This is certainly an area for further research. Neuroimaging features and biomarkers can hopefully be identified to distinguish among ADEM, ADEM variants, CIS, and MS [21].

As children and adolescents are being diagnosed with MS, future studies to assess improvement in outcomes with early diagnosis and treatment will be critical to improve care in pediatric MS.

Table 3 Comparison of published MRI criteria for diagnosis of pediatric multiple sclerosis

Criteria	McDonald 2005 [15]	McDonald 2010 [3••]	KIDMUS [18]	Callen [17••]	Canadian [19]
MRI findings	At least 3 of: ≥9 T2 lesions ≥3 periventricular ≥juxtacortical >1 infratentorial/spine	DIS: ≥1 T2 lesion in at least 2 of 4 areas: Periventricular Juxtacortical Infratentorial Spinal cord DIT: 1. New T2 and/or enhancing lesion(s) on follow-up MRI, compared with baseline scan, regardless of the timing of the baseline MRI 2. Simultaneous presence of asymptomatic enhancing and non-enhancing lesions at any time	All of: Lesions perpendicular to the long axis of the corpus callosum and presence of well-defined lesions	At least two of: ≥5 T2 lesions ≥2 periventricular ≥brainstem	≥1 T1 hypointense lesion and ≥1 periventricular lesion
Sensitivity, %	56 [19[b]] 74 [6] 76 [17] 91 [16, 16[a]]	63 [6[c]] 84 [6] 100 [16, 16[a]]	26 [6] 40 [19] 47 [17]	85 [17] 89 [6]	70 [6] 84 [19]
Specificity, %	72 [19[b]] 91 [16] 92 [16[a]] 100 [6, 17]	86 [16] 89 [16[a]] 100 [6]	98 [19] 100 [6,17]	90 [6] 98 [17]	90 [6] 93 [19]
Positive predictive value, %	34 [19[b]] 69 [16] 76 [16[a]] 100 [17]	59 [16] 71 [16[a]]	82 [19] 100 [17]	97 [17]	71 [19]
Negative predictive value, %	85 [17] 87 [19[b]] 97 [16[a]] 98 [16]	100 [16, 16[a]]	71 [17] 87 [19]	90 [17]	96 [19]

[a] Analysis performed excluding children with ADEM

[b] DIS criteria only

[c] Using initial MRI scan only

Conclusions

Multiple sclerosis (MS) is a disease characterized by recurrent CNS demyelination which can begin during childhood. Although the precise prevalence is unknown, an estimated 2 % to 5 % of all persons with MS have onset of symptoms before 16 years of age [1]. As in adults, the diagnosis of pediatric MS is a clinical one, requiring recurrent episodes of CNS demyelination with supportive paraclinical data (such as neuroimaging and spinal fluid analysis) in the absence of another plausible diagnosis.

Diagnosis can also be made after an initial demyelinating event and a changing MRI scan. The 2012 McDonald Criteria and Callen Criteria have very good sensitivity and specificity in children with non-ADEM presentations. The major challenge to diagnosing MS in the pediatric population is to distinguish transient demyelinating events, like ADEM, from life-long MS and to differentiate MS from other inflammatory or infectious conditions.

Conflict of Interest Jennifer P. Rubin declares that she has no conflict of interest.
Nancy L. Kuntz declares that she has no conflict of interest.

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