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International Pediatric Multiple Sclerosis Study Group criteria for pediatric multiple sclerosis and immune-mediated central nervous system demyelinating disorders: revisions to the 2007 definitions

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Abstract

Background: There has been tremendous growth in research in pediatric multiple sclerosis (MS) and immune mediated central nervous system demyelinating disorders since operational definitions for these conditions were first proposed in 2007. Further, the International Pediatric Multiple Sclerosis Study Group (IPMSSG), which proposed the criteria, has expanded substantially in membership and in its international scope.

Objective: The purpose of this review is to revise the 2007 definitions in order to incorporate advances in delineating the clinical and neuroradiologic features of these disorders.

Methods: Through a consensus process, in which input was sought from the 150 members of the Study Group, criteria were drafted, revised and finalized. Final approval was sought through a web survey.

Results: Revised criteria are proposed for pediatric acute disseminated encephalomyelitis, pediatric clinically isolated syndrome, pediatric neuromyelitis optica and pediatric MS. These criteria were approved by 93% or more of the 56 Study Group members who responded to the final survey.

Conclusions: These definitions are proposed for clinical and research purposes. Their utility will depend on the outcomes of their application in prospective research.

Keywords

Multiple sclerosis, pediatric multiple sclerosis, childhood multiple sclerosis, acute disseminated encephalomyelitis, neuromyelitis optica, clinically isolated syndrome

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Overview

In 2007, the initial International Pediatric Multiple Sclerosis Study Group (IPMSSG) proposed provisional definitions for pediatric acquired demyelinating disorders of the central nervous system (CNS). These definitions addressed pediatric multiple sclerosis (MS), acute disseminated encephalomyelitis (ADEM), neuromyelitis optica (NMO) and clinically isolated syndrome (CIS).[1] The definitions were designed to improve consistency in terminology, foster clinical research and facilitate epidemiological studies in pediatric demyelination. The concept of pediatric CIS was introduced and the 2001 McDonald criteria were expanded to include children of all ages. Subsequent research has illustrated the strengths and limitations of the 2007 IPMSSG definitions.[2,3]

Following the dissemination of the 2007 IPMSSG definitions, the body of knowledge regarding pediatric MS and other immune mediated CNS demyelinating disorders of childhood has grown substantially. We have also learned from studies that have applied the 2010 Revised McDonald criteria for adult MS[4] to pediatric patients.[5–7] Appendix 1 summarizes advances in pediatric demyelinating disorder research relevant to revision of the 2007 IPMSSG definitions.

There has also been a major expansion of the IPMSSG to include a more global membership with a wider scope of experience. Therefore, it is timely to review and update the original definitions with new criteria. In particular, updates reflecting the most recent advances may facilitate clinical decision-making concerning the initiation of disease modifying therapy (DMT) in pediatric MS.

The proposed criteria were submitted to the 150 IPMSSG members for feedback via a web based survey. Requested modifications were incorporated into the final definitions. Of the 56 IPMSSG members who responded to the final set of definitions and are clinically active, 93% or more approved the revised criteria.

Proposed 2012 IPMSSG criteria

Appendix 2 summarizes the contrasts between the 2007 and 2012 revised IPMSSG criteria for pediatric cases of CIS, ADEM, MS and NMO. These definitions all presuppose that the differential diagnosis for each disorder has been carefully evaluated and alternative diagnoses excluded.

Pediatric CIS (all are required)

- A monofocal or polyfocal, clinical CNS event with presumed inflammatory demyelinating cause
- Absence of a prior clinical history of CNS demyelinating disease (e.g. absence of past optic neuritis (ON), transverse myelitis (TM) and hemispheric or brain-stem related syndromes)
- No encephalopathy (i.e. no alteration in consciousness or behavior) that cannot be explained by fever
- The diagnosis of MS based on baseline magnetic resonance imaging (MRI) features (as recently defined)[4] are not met

Pediatric CIS needs further study. CIS in adults and in children share the same criteria: CIS is a very heterogeneous syndrome with respect to its clinical manifestations (ON, TM, brain stem syndromes and consequences of supratentorial lesions). To meet the criteria for CIS, symptoms must last at least 24 h. Conceptually, the term CIS would be better applied to patients with a truly 'isolated', monophasic, demyelinating event (although the clinical features at onset may be mono- or polyfocal in localization). The proposed criteria are supported by studies showing that the absence of encephalopathy increases the risk of MS,[2,8] however one study did not find encephalopathy to be a negative predictor of MS among children with a polyfocal initial demyelinating event.[3] Longitudinal studies clearly demonstrate that the likelihood of an MS diagnosis following a first attack is extremely low in children with a normal brain MRI.[9,10] For example, in a series of 35 children with ON, none with normal brain MRIs developed MS over a mean of 2.4 years.[9] Similarly, when the clinical and neuroimaging findings in children with TM are limited to the spinal cord, the likelihood of subsequent events leading to a diagnosis of MS is also low.[11] However, the period of follow-up of these studies is relatively short compared to adults with CIS. For example, among adults with CIS and a normal baseline brain MRI, as many as 21% can develop a second clinical event leading to an MS diagnosis, over a 20-year follow-up period.[12] It needs to be determined whether similar results will be found in studies with longer longitudinal follow-up of children.

Pediatric ADEM (all are required)

- A first polyfocal, clinical CNS event with presumed inflammatory demyelinating cause
- Encephalopathy that cannot be explained by fever
- No new clinical and MRI findings emerge three months or more after the onset
- Brain MRI is abnormal during the acute (three-month) phase.
- Typically on brain MRI:
  - Diffuse, poorly demarcated, large (>1–2 cm) lesions involving predominantly the cerebral white matter
  - T1 hypointense lesions in the white matter are rare
  - Deep grey matter lesions (e.g. thalamus or basal ganglia) can be present

Clarification of terminology. ADEM is a heterogeneous entity and is best viewed as a 'syndrome' rather than a specific disorder.

The term 'encephalopathy' was defined by consensus and refers to an alteration in consciousness (e.g. stupor, lethargy) or behavioral change unexplained by fever, systemic illness or postictal symptoms. The clinical features subsumed under the term ADEM typically follow a monophasic disease course, although confirmation of monophasic ADEM is retrospective and requires prolonged observation.

The clinical symptoms and radiologic findings of ADEM can fluctuate in severity and evolve in the first three months following disease onset. A 'second event' is defined as the development of new symptoms at least three months after the incident illness irrespective of steroid use. More data to support the biological rationale for the three month requirement are needed.

ADEM followed by subsequent clinical event(s). **Multiphasic ADEM:** In the discussions that framed the 2007 IPMSSG definitions, it was noted that as many as 10% of children with an initial diagnosis of ADEM experienced another ADEM attack (with encephalopathy), typically occurring in the first 2–8 years after the initial illness.[13] However, in subsequent follow up studies of children with an initial, acute demyelinating event, much lower frequencies of multiphasic ADEM have been observed. In one series, multiphasic ADEM was diagnosed in only two of 117 (1.7%) children[3] and in another series it was diagnosed in five of 132 (3.8%) children.[14] Due to its very low frequency, the category of 'recurrent ADEM' has been eliminated. The definition of multiphasic ADEM is revised and is now defined as two episodes consistent with ADEM separated by three months but not followed by any further events. The second ADEM event can involve either new or a re-emergence of prior neurologic symptoms, signs and MRI findings.

Relapsing disease following ADEM that occurs beyond a second encephalopathic event is no longer consistent with multiphasic ADEM but rather indicates a chronic disorder, most often leading to the diagnosis of MS[14] or NMO.[15–18]

Pediatric ADEM as the first manifestation of pediatric MS: When pediatric ADEM is followed by subsequent events leading to a diagnosis of MS, the MS onset is considered at the time of the ADEM event. Such cases have been observed in several large pediatric series with variable frequency.[2,10,14,19] A prospective study of children with ADEM (defined by the 2007 IPMSSG criteria) showed that 18% had a second attack suggesting MS.[14] However, other studies applying the 2007 IPMSSG definitions of ADEM have shown lower frequencies ranging from 2–10%.[2,10,19] Among the subset of individuals presenting with ADEM who later relapse, in 80% of individuals the second event occurs within two years of the initial episode.[2,14,20] Less commonly, relapses following ADEM occur many years later.[8,13]

At what point after pediatric ADEM should ongoing disease activity lead to an MS diagnosis? We propose that criteria for MS are met if after the initial ADEM a second clinical event meets the following three requirements: (a) is nonencephalopathic: (b) occurs three or more months after the incident neurologic illness: and (c) is associated with new MRI findings consistent with revised radiologic criteria for dissemination in space (DIS).[4] These criteria need to be tested in prospective studies.

Pediatric ADEM as the first manifestation of NMO: Pediatric ADEM can also lead to a subsequent diagnosis of NMO.[16] A positive anti-aquaporin-4 IgG titer during ADEM greatly facilitates this diagnosis.

MRI and laboratory findings in pediatric ADEM. The MRI in patients with ADEM shows multiple lesions, many of which are large (>1–2 cm). Gadolinium enhancement of one or more lesions occurs in 14–30% of cases.[10,13,14,21,22] Periventricular lesions are less common relative to MS but lesion number, location and size are variable.[10,23] The presence of hypointense lesions (defined as hypointense or isointense to grey matter) or persistent hypointense lesions in the white matter are infrequent in monophasic ADEM and predictive of MS.[10,23] Lesions in the thalamus and basal ganglia are more typical of ADEM than MS but less discriminating than the presence of hypointense lesions.[10] MRI characteristics noted to distinguish ADEM from MS are the absence of hypointense lesions and the absence of two or more periventricular lesions.[23] In addition to findings on brain MRI, patients with ADEM can have extensive lesions on spinal MRI.[24] Serum anti-aquaporin-4 IgG antibody should be negative, whereas serum anti-MOG (myelin oligodendrocyte glycoprotein) antibodies may be present, but are usually transient.[25] Cerebrospinal fluid (CSF) oligoclonal bands are only rarely observed.[8,26]

Pediatric MS (can be satisfied by any of the following)

- 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 one area of the CNS
- One nonencephalopathic episode typical of MS which is associated with MRI findings consistent with 2010 Revised McDonald criteria for DIS and in which a follow up MRI shows at least one new enhancing or nonenhancing lesion consistent with dissemination in time (DIT) MS criteria[4]
- One ADEM attack followed by a nonencephalopathic clinical event, three or more months after symptom onset, that is associated with new MRI lesions that fulfill 2010 Revised McDonald DIS criteria[4]
- 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)

Brain MRI criteria for pediatric MS. Appendix 3 includes different sets of MRI characteristics[4,10,23,27–29] that have been tested for their utility in establishing the diagnosis of pediatric MS[4,29] or to assess the risk of relapse after an initial event.[10,23,27,28] At the time of the first clinical presentation of a CNS demyelinating event, brain MRI findings more indicative of MS than ADEM include lesions in a periventricular location, hypointense lesions on T1 imaging and the absence of bilateral diffuse lesions.[10,23,28]

The 2010 Revised McDonald criteria were developed to facilitate an early diagnosis of MS based on studies in adult patients.[7] These criteria have been studied in children with MS and CIS;[5,6] among children 12 years and older they have a positive predictive value of 76% and a negative predictive value of 100%.[5,7] The DIS MRI criteria are more sensitive than those applied in the 2007 IPMSSG pediatric MS criteria.[6] However, they have less predictive value in younger children and are not appropriate in the context of an ADEM presentation.[5] Sensitive and specific MRI criteria for the youngest patients with MS still need to be developed.

Diagnostic considerations. Some clinical features should lead one away from the MS diagnosis, such as a history of developmental delay followed by progressive neurological decline. Such a history is unlikely to lead to an MS diagnosis as primary progressive MS is exceedingly rare in children, accounting for less than 4% of clinical presentations.[30–32]

Certain clinical scenarios do not fall into any of the proposed diagnostic categories but may represent individuals at a high risk for MS or other chronic inflammatory demyelinating disorders. An example is the patient with ADEM followed by ON with an MRI showing resolution of the initial abnormalities and no new findings. Such patients who are at risk for subsequent clinical events could have NMO, chronic relapsing inflammatory optic neuropathy or MS and require close follow-up. Patients with ADEM in whom there are no further clinical events but in whom subsequent MRI studies show new abnormalities that meet MS radiologic criteria for DIS and DIS currently do not fall into a diagnostic category. Such children require close follow-up but do not meet current criteria for pediatric MS.

Children with MS (under age 12) differ clinically from adolescents with MS. At the time of the 2007 IPMSSG definitions, it remained unclear whether the onset of MS in younger children (arbitrarily defined as aged less than 12 years) influenced clinical features, disease course, MRI findings or management. Several studies have addressed these points.[33,34] Younger children are more likely than adolescent-onset MS patients to have an ADEM-like first attack, can have large, ill-defined lesions early in the disease course, and are less likely to have CSF oligoclonal bands.[34] Nonetheless, irrespective of age at onset, MS during childhood in over 95% of individuals follows a relapsing–remitting disease course.[30–32] An international panel strongly endorsed uniform access to immunomodulatory therapies for all pediatric MS patients, regardless of age, with specific recommendations regarding safety monitoring.[35] These criteria need to be tested prospectively.

Pediatric NMO[36] (all are required)

- Optic neuritis
- Acute myelitis
- At least two of three supportive criteria:
  - Contiguous spinal cord MRI lesion extending over three vertebral segments
  - Brain MRI not meeting diagnostic criteria for MS
  - Anti-aquaporin-4 IgG seropositive status

Our understanding of pediatric NMO has expanded. The criteria for adult NMO published in 2006[36] and those proposed here for pediatric NMO are the same and have changed only minimally from 2007. However, in the past several years NMO has been better delineated in children with respect to clinical and MRI characteristics.[15,16] The new points beyond the 2007 IPMSSG definition are: children can manifest NMO spectrum disorders (defined as relapsing ON or relapsing TM with a positive serum anti-aquaporin-4 IgG antibody); clinical relapses of NMO can resemble features of ADEM[15,16] and brain MRI findings can be present at the initial or subsequent events and show lesions localized to the supratentorial area, brainstem (typically around the fourth ventricle or hypothalamus[15,16] or both regions.

Summary

While the new criteria have been designed to incorporate advances in the field of pediatric acute demyelinating disorders, future research is needed to address issues pertaining areas that remain controversial or unresolved. Table 1

Table 1. Future research.

- Testing these proposed 2012 IPMSSG criteria in well characterized pediatric cohorts
- Determining the predictive validity of the 2010 revised McDonald criteria in additional data sets of pediatric MS
- Testing the proposed definition of encephalopathy and its role as a negative predictor of MS
- Testing the appropriate duration of ADEM and the necessary interval before a second clinical event is classified
- Clarifying the etiology of anti-aquaporin-4 IgG antibody negative recurrent optic neuritis
- Elucidating the spectrum of MOG-antibody associated disease
- Testing the MS diagnostic criteria proposed for those under 12 years of age

ADEM: acute disseminated encephalomyelitis; IPMSSG: International Pediatric Multiple Sclerosis Study Group; MOG: myelin oligodendrocyte glycoprotein; MS: multiple sclerosis.

summarizes several topics that require additional investigation. Future research will also need to test these criteria in prospective studies so that their utility can be fully determined.

Conflicts of interest

The authors declare that there are no conflicts of interest.

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Appendix 1. Recent advances and terminology clarifications.

- Improved understanding of pediatric ADEM[17–20, 24]
- Better delineation of the prognostic clinical and MRI features for pediatric MS following an initial clinical demyelinating event[2,3,8,10,19,23]
- Recognition that children vs adults with MS have more frequent relapses[37]
- Recognition that progressive onset is rare in children relative to adults with MS[30]
- Recognition that children with MS<12 years of age compared to older children may differ clinically and radiologically[33] in their first clinical event
- Clarification of the MRI findings specific to pediatric MS[6,10]
- Better delineation of NMO and NMO spectrum disorders in the pediatric age group[15,16]
- Greater consensus that pediatric MS should be treated with DMT soon after the diagnosis[35]
- 'Polysymptomatic' is replaced with 'polyfocal' which infers that more than one CNS location is involved

ADEM: acute disseminated encephalomyelitis; CNS: central nervous system; DMT: disease modifying therapy; MRI: magnetic resonance imaging; MS: multiple sclerosis; NMO: neuromyelitis optica.

Appendix 2. Comparison of 2007 and 2012 definitions for pediatric acute demyelinating disorders of the central nervous system (CNS).

Disorder	2007	2012
CIS	• A first monofocal or multifocal CNS demyelinating event; encephalopathy absent	A first monofocal or multifocal CNS demyelinating event; encephalopathy is absent, **unless due to fever**
Monophasic ADEM	• A first polysymptomatic clinical event, with presumed inflammatory cause that affects multifocal areas of the CNS • Encephalopathy is present • MRI typically shows large, ≥1–2 cm white matter lesions, grey matter involvement (thalamus or basal ganglia) is frequent • New or fluctuating symptoms, signs or MRI findings within three months of the incident ADEM are part of the acute event	• A first polyfocal clinical CNS event with presumed inflammatory cause • Encephalopathy that **cannot be explained by fever** is present • MRI typically shows **diffuse, poorly demarcated, large, >1–2 cm** lesions involving predominantly the cerebral white matter; **T1 hypointense white matter lesions are rare;** Deep grey matter lesions (e.g. thalamus or basal ganglia) can be present • No new symptoms, signs or MRI findings after three months of the incident ADEM
Recurrent ADEM	• New event of ADEM with a recurrence of the initial symptoms and signs, three or more months after the first ADEM event	• **Now subsumed under multiphasic ADEM**
Multiphasic ADEM	• New event of ADEM, but involves new anatomic areas of the CNS and must occur at least three months after the onset of the initial ADEM event and at least one month after completing steroid therapy	• New event of ADEM three months or more after the initial event that can be associated with **new or re-emergence of prior clinical and MRI findings. Timing in relation to steroids is no longer pertinent.**
MS	Any of the following: • Multiple clinical episodes of CNS demyelination separated in time and space • Single clinical event which is associated with 2001 McDonald Brain MRI criteria[a] for DIS and subsequent changes on MRI consistent with criteria for 2001 McDonald criteria for DIT[4] • An episode consistent with the clinical features of ADEM cannot be considered as the first event of MS	Any of the following: • Two or more nonencephalopathic CNS clinical events separated by more than 30 days, involving more than one area of the CNS • Single clinical event and MRI features rely on 2010 Revised McDonald criteria[b] for DIS and DIT[4] (but criteria relative for DIT for a single attack and single MRI only apply to children ≥12 years and only apply to cases without an ADEM onset) • ADEM followed three months later by a nonencephalopathic clinical event with new lesions on brain MRI consistent with MS
NMO	All are required: • Optic neuritis • Acute myelitis • At least one of two supportive criteria • Contiguous spinal cord MRI lesion ≥3 vertebral segments • Anti-aquaporin-4 IgG seropositive status	All are required: • Optic neuritis • Acute myelitis • At least two of three supportive criteria • Contiguous spinal cord MRI lesion≥3 vertebral segments • **Brain MRI not meeting diagnostic criteria for MS** • Anti-aquaporin-4 IgG seropositive status

ADEM: acute disseminated encephalomyelitis; CIS: clinically isolated syndrome; CNS: central nervous system; DIS: dissemination in space; DIT: dissemination in time; MRI: magnetic resonance imaging; MS: multiple sclerosis; NMO: neuromyelitis optica.

[a]The 2001 McDonald MRI criteria for DIS require three of the following four MRI features: ≥9 T2 lesions or 1 gadolinium enhancing lesion; ≥3 periventricular lesions; ≥1 infratentorial lesion(s); ≥1 juxtacortical lesion(s). The DIT criteria require subsequent white matter lesions whose timing depends on the temporal relation of the initial MRI with the onset of the clinical symptoms.[5]

[b]The 2010 Revised McDonald MRI criteria for DIS require the presence of at least two of the following four criteria: ≥1 lesion in each of the four locations; periventricular, juxtacortical, infratentorial and spinal cord. The 2010 Revised McDonald MRI criteria for DIT can be satisfied either by the emergence of new T2 lesions (with or without enhancement) on serial scan(s) or can be met on a single baseline scan if there exists simultaneous presence of a clinically-silent gadolinium-enhancing lesion and a nonenhancing lesion.[4]

Appendix 3. Magnetic resonance imaging (MRI) characteristics for dissemination in space (DIS) that increase the likelihood of a pediatric multiple sclerosis (MS) diagnosis.

Barkhof [27]	KIDMUS[28]	Callen MS vs ADEM[23]	Callen Diagnostic MS[29]	Verhey Differential[10]	2010 Revised McDonald[4]
3 of 4: ≥9 T2 lesions or 1 gadolinium enhancing ≥3 Periventricular ≥1 Infratentorial ≥1 Juxtacortical	1 of 2: Lesions perpendicular to long axis of the corpus callosum Sole presence of well defined lesions	2 out of 3: Absence of a diffuse bilateral lesion pattern Presence of black holes ≥2 periventricular lesions	2 out of 3: ≥5 lesions on T2 weighted images 2 periventricular lesions ≥1 brain stem lesion	2 of 2: ≥1 periventricular lesions ≥1 hypointense lesions on T1 images	2 of 4: ≥1 periventricular ≥1 juxtacortical ≥1 Infratentorial ≥1 spinal cord

ADEM: acute disseminated encephalomyelitis.