

# Consensus definitions proposed for pediatric multiple sclerosis and related disorders

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**Abstract—Background:** The CNS inflammatory demyelinating disorders of childhood include both self-limited and life-long conditions, which can be indistinguishable at the time of initial presentation. Clinical, biologic, and radiographic delineation of the various monophasic and chronic childhood demyelinating disorders requires an operational classification system to facilitate prospective research studies. **Methods:** The National Multiple Sclerosis Society (NMSS) organized an International Pediatric MS Study Group (Study Group) composed of adult and pediatric neurologists and experts in genetics, epidemiology, neuropsychology, nursing, and immunology. The group met several times to develop consensus definitions regarding the major CNS inflammatory demyelinating disorders of children and adolescents. **Results:** Clinical definitions are proposed for pediatric multiple sclerosis (MS), acute disseminated encephalomyelitis (ADEM), recurrent ADEM, multiphasic ADEM, neuromyelitis optica, and clinically isolated syndrome. These definitions are considered operational and need to be tested in future research and modified accordingly. **Conclusion:** CNS inflammatory demyelinating disorders presenting in children and adolescents can be defined and distinguished. However, prospective research is necessary to determine the validity and utility of the proposed diagnostic categories.

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To expand our understanding of pediatric multiple sclerosis (MS) and other demyelinating conditions in children and adolescents, a series of workshops was organized by the National Multiple Sclerosis Society (NMSS) and included an international panel of adult and pediatric neurologists, researchers from the fields of genetics, epidemiology, neuropsychology, and nursing, and representatives from the NMSS and the MS Society of Canada. The main objectives of these meetings were as follows:

1. To advance our understanding of pediatric MS and related inflammatory demyelinating disorders of childhood
2. To establish a platform for future research on the clinical features, causes, prognosis, and treatment of pediatric MS by agreeing to uniform terminology and by identifying research priorities
3. To identify the major clinical and neuroimaging findings typically associated with each disorder; this included a review of similarities and differences between adult and pediatric MS

The panel agreed that a major priority was to distinguish transient demyelinating syndromes from the lifelong disease, MS. This issue was addressed by establishing criteria for monophasic acute disseminated

encephalomyelitis (ADEM), variants of ADEM associated with a repeat episode, neuromyelitis optica (NMO), clinically isolated syndrome (CIS), and pediatric MS. Criteria were finalized only after full consensus had been reached. It was agreed that a prerequisite for each definition was that a comprehensive evaluation, as delineated elsewhere in this supplement, revealed no alternative diagnosis. The term “pediatric” in this classification applies to children defined according to the World Health Organization’s terminology as younger than 10 years of age. For the purposes of the proposed operational definitions, pediatric MS refers to “children” (under the age of 10) and “adolescents” (aged 10 and above but prior to the 18th birthday).

Criteria for each disorder were selected by reviewing the literature and shared clinical experience. The Study Group was in uniform agreement that the proposed definitions were starting points and that prospective research is needed to test their clinical utility and biologic validity.

## **Results. Definitions.**

### **ADEM (monophasic).**

- A first clinical event with a presumed inflammatory or demyelinating cause, with acute or subacute onset that affects multifocal areas of the

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CNS. The clinical presentation must be polysymptomatic and must include encephalopathy, which is defined as one or more of the following:

- Behavioral change, e.g., confusion, excessive irritability
- Alteration in consciousness, e.g., lethargy, coma
- Event should be followed by improvement, either clinically, on MRI, or both, but there may be residual deficits
- No history of a clinical episode with features of a prior demyelinating event
- No other etiologies can explain the event
- New or fluctuating symptoms, signs, or MRI findings occurring within 3 months of the inciting ADEM event are considered part of the acute event
- Neuroimaging shows focal or multifocal lesion(s), predominantly involving white matter, without radiologic evidence of previous destructive white matter changes:
  - Brain MRI, with FLAIR or T2-weighted images, reveals large (>1 to 2 cm in size) lesions that are multifocal, hyperintense, and located in the supratentorial or infratentorial white matter regions; gray matter, especially basal ganglia and thalamus, is frequently involved
  - In rare cases, brain MR images show a large single lesion ( $\geq 1$  to 2 cm), predominantly affecting white matter
  - Spinal cord MRI may show confluent intramedullary lesion(s) with variable enhancement, in addition to abnormal brain MRI findings above specified

*Comment.* Historically, the term ADEM has been applied inconsistently. The inclusion criteria have varied as to whether events required 1) a monofocal or multifocal onset, 2) a specific duration, 3) the possibility of recurrence, 4) a change in mental status, and 5) documentation of a prior infection. The proposed definition requires both encephalopathy and multifocal involvement. A single clinical event of ADEM can evolve over a period of 3 months, with fluctuations in clinical symptoms and severity. In contrast, MS is characterized by discrete demyelinating events separated by at least 4 weeks. The Study Group specifically stipulated that encephalopathy (defined as mental status changes and/or behavioral alterations such as marked irritability) be a requisite feature of ADEM. Encephalopathy is typically not associated with MS. While the requisite inclusion of encephalopathy for ADEM may be overly restrictive, the Study Group required this feature for specificity purposes. The rationale for the specific clinical features critical to the diagnosis, the possibility of a prolonged course for one discrete event, and the typical MRI features were determined by a systematic review of published clinical series,<sup>1-6</sup> and are further discussed elsewhere in this conference report.

The definition requires MRI features of large lesions that typically involve the white matter but can also involve gray matter, which are relatively uncommon in MS. Nonetheless MRI findings alone are insufficient for the diagnosis of ADEM.<sup>7</sup> Critically important is the fact that the diagnosis of ADEM must rest on clinical features first. For example, a child with isolated optic neuritis (but no mental status changes) and large multifocal MRI changes would be classified as CIS, not ADEM.

Viral infection more often precedes symptoms of ADEM than in MS. However, documentation of a prior infection and isolation of an infectious agent are not required for diagnosis since whether an infection is documented varies by the extent of the prior workup and whether the patient was seen by medical personnel at the time of the infection.

As reviewed elsewhere in this conference report, typical laboratory findings in ADEM include elevations in the CSF protein and white blood cell count (WBC). Elevations of the WBC of >50 cells/mm can be seen in ADEM, whereas this is a highly atypical finding in MS.<sup>3</sup> Oligoclonal bands are less frequently observed in ADEM compared to MS, but occasionally can be present.<sup>8</sup>

#### Recurrent ADEM.

- New event of ADEM with a recurrence of the initial symptoms and signs, 3 or more months after the first ADEM event, without involvement of new clinical areas by history, examination, or neuroimaging
- Event does not occur while on steroids, and occurs at least 1 month after completing therapy
- MRI shows no new lesions; original lesions may have enlarged
- No better explanation exists

#### Multiphasic ADEM.

- ADEM followed by a new clinical event also meeting criteria for ADEM, but involving new anatomic areas of the CNS as confirmed by history, neurologic examination, and neuroimaging
- The subsequent event must occur 1) at least 3 months after the onset of the initial ADEM event and 2) at least 1 month after completing steroid therapy
- The subsequent event must include a polysymptomatic presentation including encephalopathy, with neurologic symptoms or signs that differ from the initial event (mental status changes may not differ from the initial event)
- The brain MRI must show new areas of involvement but also demonstrate complete or partial resolution of those lesions associated with the first ADEM event

*Comment.* Criteria for recurrent ADEM and multiphasic ADEM were established to describe children who experience a subsequent event after an initial ADEM illness. While recurrent demyelinating events are characteristic of MS, the Study Group agreed that in some children a self-limited and transient multiphasic demyelinating phase occurs but is

not associated with a lifelong disorder characterized by an ongoing demyelinating process.<sup>3</sup> The distinction between multiphasic and recurrent rests on whether the second ADEM illness involves new brain regions—multiphasic—or whether the second event is a recapitulation of the prior illness—recurrent. In both, the new event must meet clinical criteria for ADEM, including the presence of encephalopathy. Serial MRIs of patients with multiphasic ADEM, obtained following resolution of the second demyelinating event, should ultimately show a complete or partial resolution in the MRI lesions, in contrast to serial MRI findings in patients with MS that typically demonstrate ongoing accrual of asymptomatic lesions. There was no consensus as to whether multiphasic ADEM could encompass more than two ADEM episodes. Cases with more than two events were considered extremely suspicious for MS. To avoid excessive complexity, the terms biphasic or relapsing ADEM have been abandoned.

The distinctions made between monophasic ADEM, recurrent ADEM, and multiphasic ADEM were based on an analysis of prior clinical series,<sup>2,3,6,9</sup> which are more extensively reviewed elsewhere in the conference report. While the Study Group's shared clinical experience was in alignment with the proposed definitions, there was universal agreement that prospective longitudinal research with preferably long (1 to 2 decades) follow-up is needed to test the utility of these definitions.

Neuromyelitis optica (modified criteria from 2005).<sup>10</sup>

- Must have optic neuritis and acute myelitis as major criteria
- Must have either a spinal MRI lesion extending over three or more segments or be NMO positive on antibody testing

*Comment.* NMO is another recurrent demyelinating disorder of the CNS affecting optic nerves and spinal cord that affects adults as well as children.<sup>11</sup> Frequent clinical features of NMO include severe optic neuropathy with fixed visual loss of 20/200 or greater, and moderate to severe weakness following an acute event. CSF can show a pleocytosis greater than or equal to 50 WBCs.<sup>7</sup>

In 2005, revisions to the definition of NMO were proposed. The modifications incorporate the inclusion of patients with brain lesions, and also include the NMO-IgG antibody as a confirmatory test.<sup>10,12</sup> The modified criteria are also applicable to the pediatric age group. Brain lesions, located in the hypothalamus, brainstem, or diffuse cerebral white matter, have been described in children who have typical features of NMO.<sup>12</sup>

CIS. A CIS is a first acute-clinical episode of CNS symptoms with a presumed inflammatory demyelinating cause for which there is no prior history of a demyelinating event. This clinical event may either be monofocal or multifocal, but usually does not include encephalopathy (except in cases of brainstem syndromes).

Examples include but are not limited to the following:

- Optic neuritis (unilateral or bilateral)
- Transverse myelitis (typically partial)
- Brainstem, cerebellar, and/or hemispheric dysfunction

*Comment.* The term CIS is applied to the first clinical demyelinating event (i.e., isolated in time). In contrast to ADEM, there is no encephalopathy or fever. Some adult series have restricted CIS to describe only those patients who have a single clinical phenotype referable to a single CNS lesion. The Study Group elected to define CIS as multifocal if the clinical features could be attributed to more than one CNS site and monofocal if the clinical symptoms could be attributed to a single CNS lesion. These distinctions are based solely on clinical findings. The term multifocal cannot be applied to a clinically monofocal presentation in which the MRI shows multiple asymptomatic lesions. MRI evidence of multiple clinically silent lesions may be associated with an increased risk of MS. Nonetheless, it is difficult to determine a more specific diagnosis for many individuals in this patient group. Hopefully, biologic markers will be further developed to allow for more accurate estimates of prognosis.

Pediatric MS.

- Pediatric MS requires multiple episodes of CNS demyelination separated in time and space as specified for adults,<sup>13,14</sup> however, eliminating any lower age limit (e.g., includes those under age 10)
- The MRI can be used to meet the dissemination in space requirement if the McDonald criteria<sup>15</sup> for a “positive MRI” are applied; the MRI must show three of the following four features: 1) nine or more white matter lesions or one gadolinium enhancing lesion, 2) three or more periventricular lesions, 3) one juxtacortical lesion, 4) an infratentorial lesion
- The combination of an abnormal CSF and two lesions on the MRI, of which one must be in the brain, can also meet dissemination in space criteria; the CSF must show either oligoclonal bands or an elevated IgG index
- MRI can be used to satisfy criteria for dissemination in time following the initial clinical event, even in the absence of a new clinical demyelinating event; new T2 or gadolinium enhancing lesions must develop 3 months following the initial clinical event
- An episode consistent with the clinical features of ADEM cannot be considered as the first event of MS, unless the clinical disease course meets the caveats described in the comment section.

*Comment.* Just as in adults, children with two discrete demyelinating events separated in time and space meet criteria for MS.<sup>13,14</sup> In children, these events must not meet ADEM criteria. The dissemination in space criteria can be satisfied in the neurologic evaluation if the history and findings are consistent with multifocal disease. Failure to meet MRI criteria of dissemination in space does not pre-

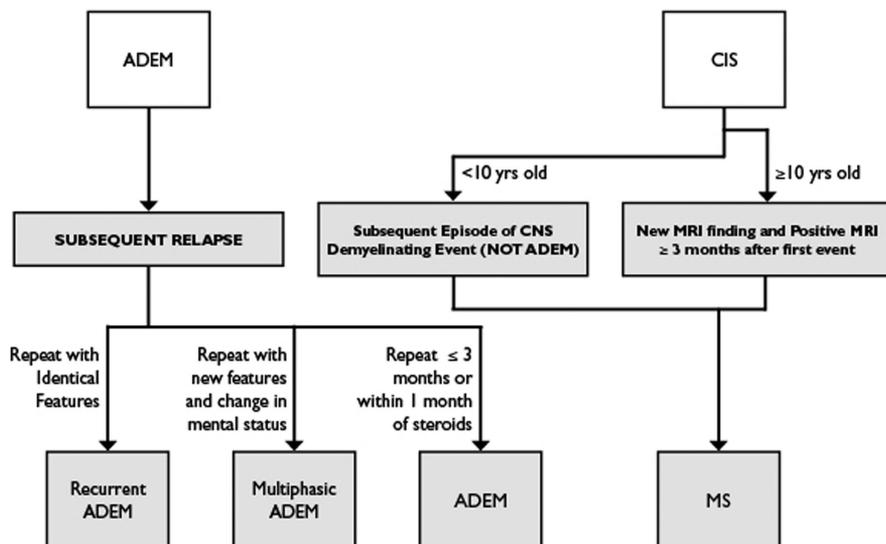


Figure. Flow chart/decision tree for the diagnosis of acute disseminated encephalomyelitis (ADEM), recurrent ADEM, multiphasic ADEM, and pediatric multiple sclerosis.

clude the subsequent diagnosis of MS, and it remains to be determined whether these MRI criteria will apply equally well in children as they do in adults.<sup>16</sup>

In the special circumstance of a child whose initial clinical demyelinating event was diagnosed as ADEM, a second non-ADEM demyelinating event alone is not sufficient for the diagnosis of MS. The Study Group believed that additional evidence of further dissemination in time, either on MRI with new T2 lesions developing at least 3 months from the second event, or a new (third) clinical event developing at least 3 months subsequent to the second event, was required. In the future, criteria may be developed such that a second event following ADEM, fulfilling certain criteria could satisfy the MS diagnosis. However, until such criteria can be supported by prospective research, the Study Group chose a more conservative approach. The rationale for this decision was based on concern that an initial ADEM event, followed by a second event not meeting ADEM criteria, might still reflect a transient demyelinating illness. It was believed that the conservative approach of requiring further evidence of a chronic disease process would be preferable to potentially incorrectly labeling a child with MS.

The Study Group elected to use the term pediatric MS to clearly define the age range of the cohort for which the definition applies, including childhood and adolescence. We chose to avoid other labels such as "early onset MS" or "childhood MS."

The figure outlines the decision-making process for determining the diagnosis of a youngster who, following an acute CNS demyelinating event, has a second episode of neurologic dysfunction. The table summarizes the typical clinical features associated with MS and ADEM. As is noted in the table and further reviewed in the case summaries, a subset of patients with ADEM presumed to have a self-limited disease course instead experience continued disease activity. Some of these patients are reclassified as

MS based on the nature of the clinical events, laboratory findings, and subsequent MRI changes.

**Selected patient histories.** Patient 1 (multiphasic ADEM). A 4-year-old boy developed a fever and pharyngitis which, 2 weeks later, was followed by ataxia, impaired swallowing, progressive weakness, and stupor. His CSF showed two WBCs, no oligoclonal bands, and his MRI showed several large (1 cm) bilateral white matter lesions with some basal ganglia involvement. He improved significantly with corticosteroids, and was discharged. Four months later (2 months after having discontinued corticosteroids) he developed new symptoms of diplopia, VII and VI nerve palsies, lethargy, confusion, and new hemiparesis. MRI showed new white matter lesions. The CSF again showed no oligoclonal bands and was otherwise similar to the first analysis. Following a course of IV steroids and a 3-month oral steroid taper, he improved. A year later only minor clinical and MRI residua were present.

**Comment.** The interval between the two events was greater than 3 months and both episodes included encephalopathy. This child therefore satisfied criteria for multiphasic ADEM.

Patient 2 (NMO). A 12-year-old girl presented with loss of vision of the left eye. At age 9 she experienced ADEM based on multifocal symptoms and coma. Her MRI showed dramatic bilateral symmetric white matter lesions. She recovered over a 3-month period, but at age 11 developed an episode of transverse myelitis followed in 8 days by bilateral optic neuritis. Following IV corticosteroids, she improved and her vision returned to normal. With the new episode of left optic neuritis she was tested and found to be positive for the NMO antibody.

**Comment.** According to recently proposed criteria for NMO in adults,<sup>10</sup> brain involvement can be included in the clinical features of NMO. Another modification has been the inclusion of a positive NMO antibody in clinically suspect cases. However, NMO antibody testing is not infallible; a false nega-

**Table** Comparison of typical features of ADEM and MS

Typical features	ADEM	MS
Demographic	More frequently younger age groups (<10 years); no gender predilection	More frequently adolescents; girls predisposed more than boys
Prior flu-like illness	Very frequent	Variable
Encephalopathy	Required in definition	Rare early in the disease
Seizures	Variable	Rare
Discrete event	A single event can fluctuate over the course of 12 weeks	Discrete events separated by at least 4 weeks
MRI shows large lesions involving gray and white matter	Frequent	Rare
MRI shows enhancement	Frequent	Frequent
Longitudinal MRI findings	Lesions typically either resolve or show only residual findings*	Typically associated with development of new lesions
CSF pleocytosis	Variable	Extremely rare, white blood cell count almost always <50
Oligoclonal bands	Variable	Frequent
Response to steroids	Appears favorable	Favorable

\* A subset of patients with acute disseminated encephalomyelitis (ADEM) fail to have a self-limited disease course and instead experience additional relapses and accumulate lesions on neuroimaging. Subsequently, these patients are reclassified as multiple sclerosis (MS).

tive result occurs in an estimated 30% of cases and the utility of the test is still unknown in pediatric cases.

**Patient 3 (MS).** A 9-year-old girl developed confusion, lethargy, and unsteady gait preceded by fever, nausea, and vomiting. MRI showed large, somewhat ill-defined, bilateral white matter lesions. A diagnosis of ADEM was made. The child clinically recovered and the MRI abnormalities completely resolved. At age 11, she developed unilateral optic neuritis and hemiparesis. Her MRI was consistent with McDonald's criteria for a positive MRI and the CSF showed oligoclonal bands. Her vision improved to normal with corticosteroid therapy. At age 12, she experienced a third event characterized by ataxia. MRI showed multiple lesions with enhancement. She met the criteria for a diagnosis of MS.

**Comment.** The second clinical episode did not include encephalopathy and therefore did not meet criteria for ADEM. Whether MS can be diagnosed in a patient with a history of ADEM who experiences a second event that does not fit criteria for recurrent or multiphasic ADEM remains controversial. We have elected not to ascribe the diagnosis of MS in this circumstance, and require a third demyelinating event. This is purely an operational decision. Clinical judgment by the treating physicians is critical to the management of patients whose diagnosis remains unclear and the proposed criteria are not meant to dictate treatment decisions in such cases.

**Discussion.** The underlying premise of the classification system is that greater consistency in terminology can help set the stage for hypothesis testing regarding the prognosis for different clinical syndromes. Until more reliable biologic markers are

identified, the major clinical and radiologic features of the demyelinating disorders of childhood are our best predictors of outcome. There is a growing number of carefully described published series of pediatric MS including patients with very early ages at onset.<sup>17</sup> Nonetheless, whether clinical event features, in the absence of biomarkers, can ultimately distinguish courses of monophasic, transiently multiphasic, or chronic demyelinating illness requires further testing.

While MS is more commonly preceded by CIS, there have been cases in which the initial presentation met criteria for ADEM. At what point a patient presenting with ADEM who has a subsequent event not associated with encephalopathy should be reclassified as MS remains unclear. Prospective research should help distinguish those presentations of MS that phenotypically resemble ADEM at the time of the first relapse from cases that remain monophasic and hence fulfill criteria for ADEM as currently defined. The flow diagram provides an overview of how one clinical event can be reclassified based on subsequent changes over time.

For each of these proposed definitions, there will be patients who are exceptions. It is also expected that, as our understanding of these disorders grows, the definitions will be revised and refined. The improved precision from the definitions and increased patient homogeneity should facilitate international research. Future prospective cooperative multicenter research should lead to revisions and improvement of the definitions as biologic, radiographic, and clinical longitudinal data are collected. It is hoped that, until we have more prospective data, these definitions will enhance clinical care by providing consistent diagnostic tools, and by providing the necessary

platform from which collaborative studies can be launched.

## Appendix

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