How difficult is diagnosis of MS in children

Silvia N. Tenembaum

Referral Paediatric Clinic for MS and related disorders
Department of Neurology, National Paediatric Hospital Dr. J. P. Garrahan
Buenos Aires, Argentina
Why is difficult diagnosing MS in children

- Other childhood disorders with similar characteristics are more frequent
- Most symptoms of MS seen in adolescents are similar to those seen in adults
- Some symptoms seen in children are not typical in adults (seizures, mental status changes)
- Sensory and visual symptoms are difficult to identify in young children
- MRI lesions seen in children ≤ 10 years may be atypical (diffuse, ill-defined, or even tumefactive lesions)
Consensus definitions proposed for pediatric multiple sclerosis and related disorders

Lauren B. Krupp, MD; Brenda Banwell, MD; and Silvia Tenembaum, MD; for the International Pediatric MS Study Group*

Abstract—Background: The CNS inflammatory demyelinating disorders of childhood include both self-limited and lifelong 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 criteria.

NEUROLOGY 2007;68(Suppl 2):SST–S18

*Correspondence and reprint requests to: Lauren B. Krupp, MD, Massachusetts General Hospital and Children’s Hospital, Neonatal Neurology Program, Boston, Massachusetts 02114. E-mail: Krupp.Lauren@Childrens.harvard.edu
1. Two clinical episodes of CNS demyelination separated in time and space, as specified for adults (McDonald criteria), however, **eliminating any lower age limit**.

2. MRI can be used to meet the dissemination in space and time (DIS and DIT) requirement if the McDonald criteria for a positive MRI are applied.

3. The combination of an **abnormal CSF and two lesions on MRI** (one must be in the brain) can also meet DIS criteria.

4. Children with **ADEM at onset** were required to experience **2 non-ADEM attacks for MS diagnosis**.

*Krupp, Banwell, Tenembaum; Conference Report, Neurology 2007;68(Suppl 2): S7-12.*
Diagnostic Criteria for Multiple Sclerosis: 2010 Revisions to the McDonald Criteria

Chris H. Polman, MD, PhD, Stephen C. Reingold, PhD, Brenda Banwell, MD, Michel Clanet, MD, Jeffrey A. Cohen, MD, Massimo Filippi, MD, Kazuo Fujihara, MD, Eva Havrdova, MD, PhD, Michael Hutchinson, MD, Ludwig Kappos, MD, Fred D. Lublin, MD, Xavier Montalban, MD, Paul O’Connor, MD, Magnhild Sandberg-Wollheim, MD, PhD, Alan J. Thompson, MD, Emmanuelle Waubant, MD, PhD, Brian Weinshenker, MD, and Jerry S. Wolinsky, MD

New evidence and consensus has led to further revision of the McDonald Criteria for diagnosis of multiple sclerosis. The use of imaging for demonstration of dissemination of central nervous system lesions in space and time has been simplified, and in some circumstances dissemination in space and time can be established by a single scan. These revisions simplify the Criteria, preserve their diagnostic sensitivity and specificity, address their applicability across populations, and may allow earlier diagnosis and more uniform and widespread use.

ANN NEUROL 2011;69:292–302
2010 Diagnostic criteria: DIS

DIS: ≥ 1 asymptomatic T2 lesion in ≥ 2 topographies
2010 Diagnostic criteria: DIT

New T2 lesion on follow-up MRI at any time

Simultaneous presence of asymptomatic gad-enhancing and non-enhancing lesions, at any time
MRI criteria: Differentiation of paediatric MS from ADEM

MS diagnosis if:

• ≥ 2 periventricular lesions
• presence of black holes
• absence of diffuse WM lesions

Callen et al; Neurology 2009
Proposed 2012 IPMSSG criteria for paediatric MS

International Paediatric MS Study Group criteria for paediatric multiple sclerosis and immune-mediated CNS demyelinating disorders: Revisions to the 2007 definitions

Paediatric MS can be satisfied by any of the following:

1. **Two or more CNS clinical events** separated by more than 30 days, and involving more than one area of the CNS.

2. **One non-encephalopathic episode typical of MS** with MRI findings consistent with **DIS criteria** and a follow-up MRI showing at least one new enhancing or non-enhancing lesion consistent with **DIT criteria**.

3. **One ADEM attack** followed three or more months by a **non-encephalopathic clinical event** and associated with new MRI lesions that fulfill **DIS criteria**.

4. Among **children 12 years and older** an acute event that does not meet ADEM criteria and whose MRI are consistent with the 2010 Revised McDonald Diagnostic MRI criteria for DIS and DIT may be diagnosed with MS at the time of the acute event.

*Krupp L et al. Mult Scler 2013; Apr 9 [Epub ahead of print]*
Examples of red flags in paediatric patients

<table>
<thead>
<tr>
<th>Atypical neurological findings</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hearing loss</td>
<td>Susac syndrome</td>
</tr>
<tr>
<td>Headache</td>
<td>CNS vasculitis, Susac syndrome</td>
</tr>
<tr>
<td>Hypothalamic symptoms</td>
<td>NMO, neurosarcoidosis</td>
</tr>
<tr>
<td>Brainstem syndrome</td>
<td>NMO, pontine glioma</td>
</tr>
<tr>
<td>Longitudinal extensive myelopathy</td>
<td>NMO, B12 or copper deficiency, Alexander disease (juvenile)</td>
</tr>
<tr>
<td>Severe or recurrent optic neuropathy</td>
<td>NMO, LHON</td>
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</tbody>
</table>
Brain MRI changes are not disease specific.

- ANE
- POLG 1 mutation
- SLE
- CNS primary vasculitis
- MELAS
- Gliomatosis cerebri
- Posterior reversible leukoencephalopathy
- NF1: brainstem UBOs
Why early diagnosis in children is important?

- Disease occurs during key periods of age-expected brain growth, active primary myelination, and maturation of neural networks.
- Disease activity (clinical and MRI) is higher in paediatric-onset MS than in adult-onset MS.
- Acute axonal damage is more severe in paediatric MS lesions.
- There is a progressive cognitive impact of MS in childhood.
- Irreversible disability is usually reached in paediatric MS at an earlier age.

Renoux et al, 2007; Amato et al, 2008; 2010; Pfeifenbring et al, 2012
Paediatric MS: Key conclusions

- 2010 McDonald criteria are useful to identify adolescents at risk for MS relapses.
- Caution is advised when applying these criteria in younger children.
- MS diagnosis in childhood is still challenging, even using rigorous inclusion criteria and standardized definitions.
- 2010 McDonald criteria are not suited to predict MS outcome in children whose initial event is consistent with ADEM.