

# Guideline for the diagnosis and management of multiple sclerosis in children

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Paediatric multiple sclerosis (MS) represents a particular MS subgroup with unique diagnostic challenges. Due to the narrow window of environmental exposures and clinical disease expression, children with MS may represent an important study population for gaining a better understanding of the pathogenesis of the disease. The International Paediatric MS Study Group (IPMSSG) was formulated to clarify the diagnostic and therapeutic dilemmas in this population. This guideline was adapted from the International Paediatric Multiple Sclerosis Study Group guideline and endorsed by PANDA, South Africa.

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Paediatric multiple sclerosis (MS) represents a particular MS subgroup with unique diagnostic challenges. Due to the narrow window of environmental exposures and clinical disease expression, children with MS may represent an important study population for gaining a better understanding of the pathogenesis of the disease.<sup>[1]</sup> The International Paediatric MS Study Group (IPMSSG) was formulated to clarify the diagnostic and therapeutic dilemmas in this population.

An estimated 2 - 5% of patients with MS have onset of symptoms of MS before 16 years of age.<sup>[2,3]</sup> Similar to adult studies, a female preponderance is reported for MS in adolescence.<sup>[4,5]</sup> However, there is no gender predilection in children presenting with MS under 13 years of age.<sup>[6]</sup>

## 1. Clinical presentation

Children present with a wide variety of clinical symptomatology including motor, sensory, visual, cerebellar and brainstem dysfunction.<sup>[3-5,7-10]</sup> Motor manifestations are described as the most common clinical presentation.<sup>[2,7,11]</sup> Polysymptomatic presentation is reported to be more frequent in childhood-onset MS (10 - 67%) compared with adults.<sup>[3,8,9]</sup> Encephalopathy and seizures also occur in MS.<sup>[11]</sup> Eye involvement is described in up to 50% of children with MS,<sup>[11]</sup> but is probably under-recognised especially in the young, non-verbal child. Fatigue in children is more frequent compared with adults with MS.<sup>[11]</sup> Cognitive decline is reported in 30 - 66% of children with MS and is reported to be more rapid than the cognitive decline associated with adult MS.<sup>[6,12]</sup>

## 2. Diagnostic criteria

Important caveats in the definition of paediatric MS put forward by the IPMSSG include:<sup>[13]</sup>

- The combination of an abnormal cerebrospinal fluid (CSF) (presence of oligoclonal bands (OCBs) or an elevated immunoglobulin (Ig) G index) and 2 lesions on the magnetic resonance imaging (MRI), of which 1 must be in the brain, can also meet dissemination in space (DIS) criteria.
- The MRI can meet the DIS criteria if it shows 3 of the following 4 criteria:  $\geq 9$  white matter lesions or 1 gadolinium (Gd)-enhancing lesion;  $\geq 3$  periventricular lesions; 1 juxtacortical lesion, and an infratentorial lesion.

- MRI can be used to satisfy criteria for dissemination in time (DIT) following the initial clinical event, presence of stable and active lesions on the same scan.
- A second non-acute disseminated encephalomyelitis (ADEM) event in a patient is insufficient to make the diagnosis of paediatric MS if the first event meets the criteria for ADEM. MS can only be diagnosed if there is further evidence of DIT on the MRI (new T2 lesions  $>3$  months since the second event) or a new clinical event ( $>3$  months since the second event).

## 3. Diagnostic testing

- **Neuro-imaging.** Some children lack typical MRI findings of MS and have either large tumefactive lesions with perilesional oedema<sup>[14]</sup> or deep grey matter involvement. Basal ganglia affectation in MS, though described, is uncommon. Younger children with MS may also have more diffuse, bilateral ill-defined lesions.<sup>[15]</sup> The IPMSSG strongly recommends additional imaging of the entire spinal cord to identify other sites of demyelination. The cervical spinal cord is the most common region involved in MS.
- **Other investigations.** CSF studies should include cell count, protein, cytospin, lactate, and pyruvate ratio and OCBs.

## 4. Differential diagnosis

The diagnosis of MS requires the exclusion of other possible causes of white matter disease. The complete differential diagnosis is vast and dependent on the clinical presentation and specific imaging characteristics, e.g. acute encephalopathy following hyponatraemia, with a pontine lesion would suggest pontine myelinolysis (refer to Table 1).

## 5. Risk of MS after a first demyelinating event

Predicting the risk of a first episode of demyelination progressing to MS is important as new immunomodulating therapies become available. Early initiation of disease-modifying therapy (DMT) reduces the risk of relapse and long-term disability.<sup>[16]</sup> Patients with ADEM progressing to MS vary from 0% to 29%.<sup>[17]</sup> Multiple historical, clinical, laboratory and radiological criteria are used to predict the risk of recurrence/progression to MS. A seasonal pattern, a history of a precipitant, seizures, bilateral optic neuritis and encephalopathy are considered more likely in ADEM compared with

**Table 1. Differential diagnosis of MS in children**

Disorder	Clinical/laboratory	Radiological
<b>Infections</b>		
HIV encephalopathy	Developmental delay, pyramidal tract signs, microcephaly	Confluent bilateral symmetrical WM changes Cerebral atrophy Basal ganglia calcification
Progressive multi-focal leukoencephalopathy (JCV)	Immunocompromised	Multi-focal, ↑T2 WI lesions Propensity for frontal/parieto-occipital areas Subcortical U-fibres involved
Other examples	Sub-acute sclerosing panencephalitis, Lyme disease, neurosyphilis, HTLV-1	
<b>Auto-immune/vasculitides</b>		
SLE	Multi-system autoimmune disorder Anti-nuclear factor positive	Multi-focal, ↓T2WI/FLAIR Infarcts Contrast enhancement of active lesions
Other examples	Isolated CNS angiitis, CADASIL (adult disorder – rare in children)	
<b>Tumour</b>		
CNS lymphoma	Insidious onset, CSF, cytospin-malignant cells	↓T1WI ↑T2WI GM more frequently involved MRS may help
<b>Leukodystrophies</b>		
Adrenoleukodystrophy	Boys with hyperpigmentation of the skin; behaviour and learning problems; abnormal, very long-chain fatty acids	Symmetrical, confluent Predominantly posterior involvement Splenum and corticospinal tracts involved Leading edge enhancement in peritrigonal area
Other examples	Metachromatic leukodystrophy, Krabbe's disease, Alexander's disease	
<b>Mitochondrial</b>		
Leigh's disease	Neuro-regression with dystonia/ophthalmoplegia Hyperlactataemia	Bilateral symmetrical ↑T2WI/FLAIR of putamen and caudate nuclei Can have diffuse cortical WM hyperintensities
<b>Toxins/drugs</b>		
Radiation	History of exposure	Diffuse, bilateral periventricular and central WM involved ↓T1WI, ↑T2WI Sparing of sub-cortical U-fibres
<b>Infiltrative</b>		
Sarcoidosis	Cranial neuropathies, aseptic meningitis, visual disturbances	Discrete periventricular lesions May have hypothalamic/meningeal enhancement
ODS	Rapid correction of hypo- or hypernatraemia	Symmetrical changes in BG/cerebral cortical WM T1WI ↓FLAIR or ↑T2WI Pontine: usual central with sparing of corticospinal tracts

MS = multiple sclerosis; WM = white matter; JCV = John Cunningham virus; WI = weighted image; HTLV-1 = human T-lymphotropic virus type I; SLE = systemic lupus erythematosus; CNS = central nervous system; CADASIL = cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy; FLAIR = fluid attenuated inversion recovery; CSF = cerebrospinal fluid; GM = granulocyte macrophage; MRS = magnetic resonance spectroscopy; ODS = osmotic demyelination syndrome; BG = basal ganglia.

MS.<sup>[18]</sup> Inflammatory markers, a high CSF protein and leukocytosis are also more common in ADEM.<sup>[19]</sup>

The KIDMUS study identified optic neuritis in patients >10 years of age at presentation and well-defined periventricular or sub-cortical lesions as predictive factors for a second attack. MRI characteristics that are predictive of evolution to MS include: well-defined lesions that are periaqueductal or perpendicular to the corpus callosum,<sup>[9]</sup> deep grey matter involvement and lesions that enhance post-contrast.

## 6. Management

MS is a chronic condition with significant impact on all aspects of the family's life. Most drug trials of MS therapies excluded patients <18 years of age as the drugs are not licensed for use in this age group. The long-term effects of these treatments on growth and puberty are also unknown. Management should be transdisciplinary involving psychologists, physiotherapists, occupational therapists and school teachers.

### 6.1 Management of relapses

There are no therapeutic trials for treatment of relapses in the paediatric population. Management is extrapolated from the adult MS population. The mainstay of managing relapses is high-dose corticosteroids.

Relapses associated with significant morbidity warrant high-dose corticosteroid therapy. High-dose IV corticosteroids (10 - 30 mg/kg/day) for 3 - 5 days is usually used with an optional oral tapering dose. High-dose oral steroids were found to be efficacious in adults.<sup>[20]</sup> Long-term steroid use in children is associated with growth impairment.

Intravenous immunoglobulin (IVIG) (1 g/kg/day for 2 days) is an option for children with contraindications to steroid therapy. This is particularly relevant in Third-world countries where the incidence of co-morbid tuberculosis or other infections is high. Plasmapheresis is an alternative if steroids are ineffective.<sup>[21,22]</sup>

## 7. DMT

### 7.1 Indications for DMT

These therapies are known to alter the disease course and outcomes in adult MS. They reduce the frequency and severity of relapses.<sup>[23-25]</sup> The IPMSSG recommends the initiation of DMT for children with relapsing remitting disease (defined clinically or by MRI).

More than 1 exacerbation in a 1 - 2-year period and new hyperintense T2 lesions of Gd-enhancing lesions on repeat imaging over the same time period also warrants DMT.

### 7.2 Use of DMTs

First-line agents include interferon (IFN)-beta-1b, IFN-beta-1a and glatiramer acetate (GA) (Table 2).

### 7.2.1 IFN-beta-1b

Retrospective data on the use of this agent show a short-term safety profile. The dosage used varied from 4 to 8 MIU subcutaneous (SC) injection. The dose regimen also varied from every alternate day to 3 times-weekly injections to once-weekly doses.

### 7.2.2 IFN-beta-1a

The standard adult dose of IFN-beta-1a of 30 µg once per week by intramuscular (IM) injection has been used effectively in older children, but half the dose is often used for very young children (≤3 years of age). IFN-beta-1a SC injection has also been successfully administered to paediatric MS patients. Patients tolerated this drug well and reported only minor side-effects.

### 7.2.3 GA

Limited data are available on the use of GA in children 9 - 16 years of age at a dose of 20 mg daily. Available data report no serious adverse events. Case reports of second-line therapies used include azathioprine, natalizumab, cyclophosphamide and mitoxantrone.

### 7.2.4 Follow-up evaluation

Patients should be followed up to monitor safety, tolerability and efficacy. The IPMSSG recommends monthly full blood counts and liver function tests after initiation of DMT until the full dose is reached, and thereafter 3-monthly monitoring. To assess for efficacy repeat clinical assessments at 1, 3 and 6 months, followed by 6-monthly intervals, is recommended.

Follow-up MRI should be performed 6 - 12 months after the initiation of DMT. After the first year of therapy in stable patients MRI scans should be obtained annually. Treatment options in patients who demonstrate progressive disease on first-line agents include addition of monthly-pulsed methylprednisone or switching to an alternate agent such as mitoxantrone or cyclophosphamide.

## 8. Long-term complications

Most children with MS follow a relapsing, remitting course (>90%) with increasing neurodisability.<sup>[3]</sup> A slower rate of progression of disease compared with adults suggests more plasticity and potential for recovery in the developing central nervous system (CNS).<sup>[26]</sup> Children tend to have more relapses in the first 2 years of the disease.<sup>[26,27]</sup>

A primary progressive course is less common in children than adults. Patients with childhood-onset MS also take longer to reach the stage of severe disability but reach irreversible neurological disability at a younger age compared with patients with adult-onset disease.<sup>[28]</sup> More severe disease was noted in girls - when the time

**Table 2. DMTs used for childhood MS**

Study	Treatment	Outcomes	Patients N
Ghezzi <i>et al.</i> , 2007 <sup>[29]</sup>	IFN-beta-1a	Reduction in relapse rate Reduction in EDSS score	52
Tenembaum and Segura, 2006 <sup>[25]</sup>	IFN-beta-1a	Reduction in relapse rate	24
Kornek <i>et al.</i> , 2003 <sup>[24]</sup>	GA	Reduction in relapse Stable EDSS	2/7 3/7
Huppke <i>et al.</i> , 2008 <sup>[30]</sup>	Natalizumab	Induction of remission in all	3
Makhani <i>et al.</i> , 2009 <sup>[31]</sup>	Cyclophosphamide	Reduction in relapse rate Stabilisation of EDSS	17

DMT = disease-modifying therapy; MS = multiple sclerosis; IFN = interferon; EDSS = Extended Disability Status Scale; GA = glatiramer acetate.

between the first and second attacks was <1 year – for childhood-onset MS fulfilling MRI diagnostic criteria at onset, for an absence of severe mental state changes at onset, and for a progressive course.<sup>[27]</sup> In addition to the motor and sensory deficits, cognitive and emotional sequelae are also well documented.

Behaviour problems are thought to occur in up to 50% of the paediatric MS population and include depression, anxiety, oppositional defiance, and poor attention and concentration. These may manifest as risk-taking behaviour, substance abuse, school failure and family dysfunction. These problems may necessitate referral to a psychologist, social worker, or child psychiatrist and involvement of the school. Children with cognitive and/or physical deficits may need to be placed in special schools that can cater for their needs.

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