# Pediatric-Onset Multiple Sclerosis

**Information from clinical trials in children with MS is furthering understanding and improving treatment options for this rare presentation.**

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### Introduction

Multiple sclerosis (MS) most commonly presents in adulthood; however, in 3% to 5% of patients with MS, the first clinical attack occurs prior to age 18 years.[1] The first demyelinating attack in childhood is termed an *acquired demyelinating syndrome* (ADS), which may be a monophasic illness or a first attack of a relapsing demyelinating disorder, such as MS. The proportion of children with ADS who have MS ranges from 15% to 45%.[2] Pediatric-onset MS (POMS) follows a relapsing-remitting course at onset, with fewer than 2% of pediatric patients presenting with a primary progressive form of MS.[1,3] More frequent relapses in early disease stages compared with adults is characteristic of POMS.[4] Children tend to have more complete recovery after attacks, and disability accumulation is slower compared with adult-onset MS. Secondary progressive disability usually does not occur until approximately 20 years after onset.[1,3] Treatment is largely based on data obtained from clinical trials in adult patients; however, there are 2 recent randomized clinical trials performed in children that provide high-quality efficacy and safety data. In this review, we discuss the clinical features, neuroimaging, disease course, and available treatments for children with MS.

### Epidemiology

Incidence of POMS is 0.07 to 2.9 per 100,000 children, several times lower than in adults.[3,5] Incidence rises during adolescence with a median age of first attack between 11 and 13 years.[6] Onset prior to age 10 years accounts for less than 1% of all cases. There is a female-to-male ratio as high as 4.5 to 1 in those age 12 years and up. In POMS with onset under age 12 years, the ratio appears to be more even.[1,3]

### Immunologic Features

Most immunopathologic studies have been completed in adults with MS. In a study comparing 10 children with POMS with 10 adults with MS and 10 healthy control subjects of all ages, patients with POMS had increased numbers of circulating memory T cells producing interleukin (IL)-17 and a higher proliferative response to myelin peptides.[7] (See also Immunopathogenesis of Multiple Sclerosis in this Issue)

### Risk Factors

Risk factors for POMS and adult-onset MS include having 1 or more HLA-DRB*15 alleles, Epstein-Barr virus (EBV) exposure, low serum vitamin D levels, obesity, and second-hand smoke exposure. HLA-DRB1*15 is the strongest genetic risk factor for MS. In a study of 266 children presenting with ADS, those with HLA-DRB*15 were more likely to be diagnosed with MS than controls (odds ratio [OR] = 2.7).[8] A multinational study found that 86% of patients with POMS (108/125) were seropositive for remote EBV infection compared with 64% of matched controls, irrespective of geographic residence.[9]

Meta-analysis utilizing Mendelian randomization to estimate the causal association between low vitamin D and POMS found increasing vitamin D levels in serum decreased odds of POMS (OR = 0.72, 95% CI: 0.55-0.94; $P$ = .02) after controlling for sex, genetic ancestry, HLA-DRB1*15, and more than 100 MS-risk variants.[10] Vitamin D status may also influence disease activity. In a retrospective study of 110 people with POMS, every 10 ng/mL increase in adjusted 25-hydroxyvitamin $D_3$ level was associated with a 34% decrease in relapse rate, highlighting the role of vitamin D supplementaion in routine care of those with POMS.[11]

Elevated body mass index (BMI) has also been associated with a higher risk of developing POMS. Obesity is believed to induce the Th17 response via an IL-6–dependent process eliciting an inflammatory response. Increased adiposity also leads to increased risk of vitamin D deficiency and decreased response to vitamin D supplementation.[10]

Finally, secondhand smoke exposure in a study of 81 patients with POMS compared with 216 children with mono-ADS showed that secondhand smoke exposure did not independently increase risk for MS, but when both sec-

ondhand smoke exposure and HLA-DRB*15:01 were combined, the odds of MS were significantly increased (OR = 3.7, 95% CI: 1.17-11.9).[12]

## Clinical Features and Disease Course

The initial clinical presentation of POMS relates to the site of active demyelination and includes visual loss (acute optic neuritis), paresthesias, focal weakness, urinary symptoms, diplopia, or ataxia. Onset prior to age 10 years is more likely to manifest with brainstem involvement, polyfocal deficits, and encephalopathy.[1,3] When encephalopathy is present, the diagnosis of acute disseminated encephalomyelitis (ADEM) is also considered and serial clinical and MRI observation is essential to determining whether a diagnosis of MS is appropriate. Seizures have also been reported as an initial presentation of POMS.[1]

Diagnosis of MS rests on the concept of dissemination of disease over time and dissemination to involve multiple areas of the CNS. More than 98% of patients with POMS have a relapsing-remitting disease course. In contrast to adults, primary progressive MS is extremely rare in children. Progressive neurologic impairment from onset in a child should prompt a comprehensive evaluation for other diagnoses such as mitochondrial disease, malignancies, or neurodegenerative disease.[3] The early stage of MS in children is characterized by more frequent relapses than in adults with the annualized relapse rate (ARR) highest in the first 2 years after the initial attack. The relapse rate remains high for at least 5 years.[4]

Children with MS have lower disability scores early in the course of disease and on average do not experience significant ambulation deficits until 20 or more years after the initial attack. Patients with POMS generally take 10 years longer to convert to secondary progressive MS (SPMS) compared with adults. Due to the early age of onset, patients with POMS do reach SPMS on average 10 years earlier than those with adult-onset MS. Potential indicators for poor outcomes include a short interval (< 1 year) between the first 2 attacks, incomplete recovery after first attack, and brainstem involvement at onset.[1,3]

Although children with POMS have better physical disability outcomes compared with adults, significant cognitive impairment and fatigue are prominent features of POMS. In a study of 63 patients with POMS, approximately 31% fulfilled criteria for cognitive impairment and 73% reported fatigue.[13] Another study of 68 patients with demyelinating disease found those with POMS were less likely to participate in vigorous ($P = .009$) or moderate ($P = .048$) physical activity than either patients with monophasic demyelination or healthy controls subjects.[6] Further research is required to better identify the factors that limit engagement of those with POMS in vigorous activity.

## Diagnosis

The diagnosis of MS is based on clinical findings supported by MRI, cerebrospinal fluid (CSF) analysis, other laboratory results, and the exclusion of other diagnoses. The criteria for the diagnosis of MS were recently updated in 2017 with the following important revisions to the 2010 McDonald criteria.[14]

1. Presence of 2 or more oligoclonal bands in CSF that are not present in serum can be used as evidence of dissemination in time;
2. Symptomatic and asymptomatic MRI lesions can be included to provide evidence for dissemination in space (DIS) or dissemination in time (DIT); and
3. Cortical lesions can be used to fulfill MRI criteria for DIS.

The 2017 McDonald criteria have been validated in a large pediatric cohort and shown to be comparable to the 2010 McDonald criteria.[15] The ability to use CSF oligoclonal band findings to substitute for DIT in the 2017 criteria improved the diagnostic performance of the McDonald criteria in children.[15]
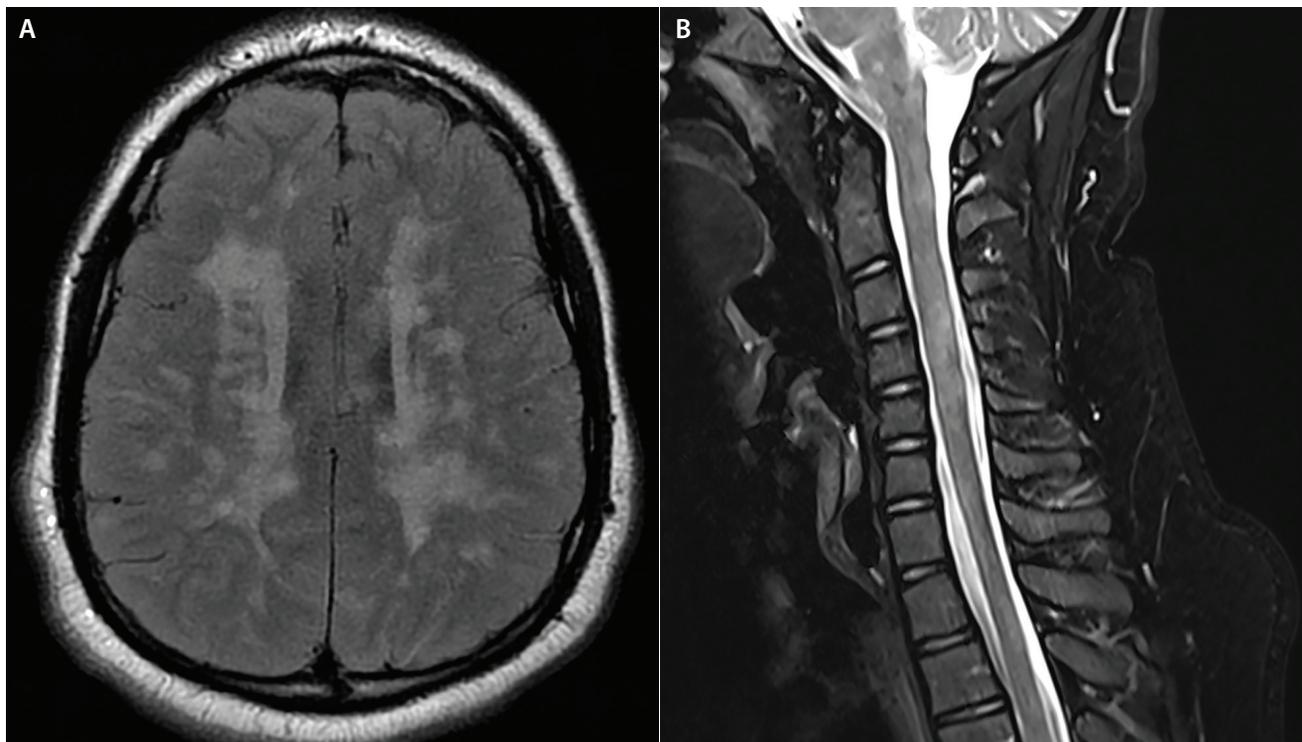
## Imaging

Neuroimaging plays an essential role in diagnosis and monitoring of POMS. The presence of 1 or more T2 hyperintense lesions characteristic of MS in 2 or more of the following areas of the CNS: periventricular, cortical or juxtacortical, infratentorial, or spinal cord demonstrates DIS. The simultaneous presence of enhancing and nonenhancing lesions at any time or new or newly enlarging T2 hyperintense or enhancing lesions on follow-up MRI demonstrates DIT.[14]

MRI is also used to monitor disease course. Compared with adults, children typically have a higher T2 lesion burden and experience a rapid accrual of new lesions in the first few years of the disease.[1,2] The International Pediatric MS Study Group (IPMSSG) recommends children with MS have MRI scans every 6 months to monitor for new lesion accrual (Figure).[16]

In addition to conventional imaging designed to detect T2 bright and T1 hypointense lesions, quantitative analyses as well as other MR sequences provide insight into nonlesional pathology. Diffusion tensor imaging (DTI) has shown nonlesional widespread tissue disruption early in the disease course of POMS and even in monophasic demyelination; however, children appear to be less affected by these findings suggesting resilience in the maturing brain.[17] These findings from DTI indicate that early demyelination that is not detected on conventional MRI might contribute to long-term outcomes and disease progression.

## Acute and Chronic Treatment

The natural history of POMS, with high relapse rates and higher volume of brain lesions early in the disease, supports a role for prompt initiation of effective disease-modifying

**Figure. Axial fluid-attenuated inversion recovery (FLAIR) MRI of the brain (A) and T2 parasagittal imaging of the cervical spine (B) from a boy, age 16 years, with multiple sclerosis. Note the high lesion burden and areas of early confluence. Children with MS are subject to more frequent relapses and typically have a higher lesion burden than adults with MS. (Images courtesy of Dr. Aaron Carlson.)**

therapy. Guidance for treatment of POMS has largely been derived from clinical trials in adult patients, small case series, international consensus guidelines, and retrospective studies in children. Recent and ongoing clinical trials in the pediatric population are beginning to provide more rigorous efficacy and safety data.

For management of acute attacks, the standard therapy has been intravenous corticosteroids (eg, 30 mg/kg methylprednisolone up to 1,000 mg/day for 3 to 5 days) as first-line treatment.[2] Intravenous corticosteroids accelerate the speed of recovery and reduce the number of actively enhancing lesions on MRI within a few days by modifying cytokine responses, reducing T-cell activation, reducing blood-brain permeability, and facilitating apoptosis of activated immune cells.[2,18]

For chronic disease management, traditional first-line therapies have included interferon β and glatiramer acetate. Both demonstrated a 29% to 34% reduction in ARR and decrease in new MRI lesion development in adult patients.[19,20] Although there have been no treatment trials of interferon β in children, safety and tolerability have been demonstrated and published in retrospective reviews.[18,21] In a study of 65 patients with POMS, the mean ARR decreased during treatment with either interferon β-1a (from 2.4 to

0.4) or glatiramer acetate (from 2.8 to 0.25).[22] The limitations of retrospective data to inform on efficacy, however, must be considered.

A recent randomized, double-blind, placebo controlled 2-year trial compared oral fingolimod with weekly intramuscular interferon β-1a.[23] Fingolimod was associated with a lower rate of relapse and less lesion accumulation on MRI, leading to approval by the Food and Drug Administration (FDA) and regulatory agencies in other countries for use of fingolimod to treat children with MS who are over age 10 years. For patients weighing less than 40 kg, a dose of 0.25 mg daily is used; the standard adult dose of 0.5 mg daily is used for those weighing more than 40 kg. Currently active clinical trials are evaluating efficacy and safety of dimethyl fumarate,[24] teriflunomide, and alemtuzumab for POMS (Table).

Other treatments used to treat patients with POMS include natalizumab and rituximab. Natalizumab is a humanized monoclonal antibody against α4β1 and α4β7 integrins. Blocking these molecules prevents immune cells from crossing the blood-brain barrier.[2,25] Proven efficacious in adults,[24] the best data in pediatric patients is limited to prospective cohort studies. In a study of 55 patients with POMS using the adult dosing regimen of 300 mg intra-

| TABLE. CLINICAL TRIALS OF DISEASE-MODIFYING THERAPIES IN PEDIATRIC-ONSET MULTIPLE SCLEROSIS | | | |
|---|---|---|---|
| Study trial acronym/NCT# | POMS treatment | Proposed mechanism of action | Results of trial |
| PARADIGMS NCT01892722 | Fingolimod | -Prevents T-cell egress from peripheral lymphoid tissue to the peripheral and central circulation[2] | -Complete, with results<br>-82% reduction in primary endpoint of ARR with fingolimod compared with interferon β-1a[23] |
| FOCUS NCT02410200 | Dimethyl fumarate | -Mechanism of action of immunosuppressive effect remains to be delineated<br>-Also activates nuclear factor (erythroid-derived 2)-like 2 which upregulates antioxidative pathways | -Demonstrated safety data and efficacy for the use of dimethyl fumarate in POMS<br>-This small study showed a significant reduction in T2 hyperintense lesion burden from baseline in POMS[4,24] |
| CONNECT NCT02283853 | Dimethyl fumarate | See above | -Recruiting patients for a phase 3 randomized controlled trial comparing dimethyl fumarate with interferon β-1a<br>-Primary outcome is the proportion of participants free of new or enlarging T2 lesion on MRI brain at 96 weeks[2,6] |
| TERIKIDS NCT02201108 | Teriflunomide | Reversibly inhibits key enzyme involved in pyrimidine synthesis diminishing activation and proliferation of T and B cells[2] | -Active, recruitment complete<br>-Randomized placebo-controlled trial with a primary outcome of time to first clinical relapse |
| LemKids NCT03368664 | Alemtuzumab | Monoclonal antibody against CD52 that leads to depletion of B and T lymphocytes[2] | -Recruiting<br>-Multicenter, open-label study single arm, before and after study in pediatric patients that have experienced significant clinical and radiographic breakthrough while being treated with interferon β or glatiramer acetate<br>-Primary outcome of new or enlarging T2 lesions while on prior DMT versus alemtuzumab |

Abbreviations: ARR, annualized relapse rate; DMT, disease-modifying therapy; POMS, pediatric-onset multiple sclerosis.
Clinical trial names: Phase 3 efficacy and safety study of BG00012 in pediatric subjects with relapsing-remitting multiple sclerosis (CONNECT), Study of the effect of BG00012 on MRI lesions and pharmacokinetics in pediatric subjects with RRMS (FOCUS), A Sstudy to evaluate efficacy, safety, and tolerability of alemtuzumab in pediatric patients with RRMS with disease activity on prior DMT (LemKids), Safety and efficacy of fingolimod in pediatric patients with multiple sclerosis (PARADIGM), Efficacy, safety, and pharmacokinetics of teriflunomide in pediatric patients with relapsing forms of multiple sclerosis (TERIKIDS).

venously every 4 weeks, ARR decreased to 0.1 ± 0.2 during treatment from an ARR of 2.4 ± 1.6 in the year preceding treatment ($P < .001$).[26] Rituximab is a monoclonal antibody against CD20, a surface marker found on the majority of B cells. Rituximab has demonstrated a favorable safety profile in children[27] and appears promising for use in neuroimmunologic diseases in children, including POMS.[28]

Another monoclonal antibody directed against CD20, ocrelizumab, has shown efficacy in treatment of adults[29] with relapsing-remitting MS in 2 large clinical trials. Studies are being planned to investigate this medication for treatment of POMS.

## Conclusion and Future Directions

In children, MS has a relapsing-remitting course with frequent relapses early in the disease but with minimal disability accrual. Cognitive impairment and continued cognitive decline, however, are of major concern and have the potential to negatively impact long-term quality of life. Effective therapy reduces relapse rates, brain lesions, and brain atrophy. The long-term benefit of early therapy remains to be seen, and close monitoring for potential therapy-mediated morbidities is necessary.

Because POMS is a rare disease, it is imperative for continued recruitment of patients with POMS into research studies and clinical trials on a multinational level to better understand the implications and management of POMS. Finally, given the chronic nature of this disease, emphasis on smooth transition of care from pediatric MS providers to adult MS providers is needed to ensure excellent continuity of care. ■

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