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ADVANCES IN PEDIATRICS

# Pediatric Multiple Sclerosis
## A Review

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**Keywords**

• Pediatric multiple sclerosis • McDonald criteria • Disease-modifying treatment

**Key points**

- Risk factors, including diet, genetics, body mass index, microbiome, and infections, are actively being explored.
- Cognitive issues can be a prominent part of multiple sclerosis (MS) in children and deserve special attention.
- Diagnostic criteria for adults with MS have changed in 2017; some evidence shows these changes are valid for pediatric-onset multiple sclerosis.
- Treatment options and paradigms are expanding for patients with MS, and this has implications on pediatric MS treatment.

Multiple sclerosis (MS) is a chronic, inflammatory condition that affects the central nervous system (CNS). Study of pediatric-onset multiple sclerosis (POMS) is relevant to adult-onset multiple sclerosis (AOMS) because children are temporally closer to the exposure of environmental influences and risk factors.

## DEMOGRAPHICS

Between 3% and 10% of MS cases are diagnosed before the age of 18 years [1–6]. MS in prepubertal children is rare and makes up less than 1% of cases [3,7]. Age at first attack is 11 to 13 years in most POMS studies [8]. Sex ratios are

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equal in prepubertal children. As children age, the distribution shows clear female predominance, similar to AOMS. The skew toward female sex distribution with age suggests a possible connection between sex hormones and disease expression [7].

As seen in adults, there is a correlation with higher latitude and increased risk for MS in pediatric cohorts [9–11]. Studies show that when people emigrate from an area of low MS risk to an area of high MS risk during childhood (up to age 15 years), they assume the risk of their new home [12–14]. Several studies report higher rates of non-Caucasian patients in POMS cohorts in the United States compared with adult cohorts, which are primarily Caucasian with Northern European ancestry. The cause for this is unknown; it could reflect changing population trends in the United States, or the increased migration of people from lower-incident MS areas to the relatively higher incident area of North America [4,5,15].

## OTHER DEMYELINATING CONDITIONS OF CHILDHOOD

### Acute disseminated encephalomyelitis

Acute disseminated encephalomyelitis (ADEM) is typically a monophasic demyelinating condition characterized by multifocal neurologic deficits and some degree of encephalopathy. Although ADEM can occur at any age, it is more common in young children, and the mean age of presentation is 5 to 8 years [16]. Rarely, ADEM can be multiphasic with recurrence; however, this should prompt further workup to rule out other diagnoses. Historically, the definition of ADEM varied widely both in research and in clinical use. In 2007, the International Pediatric Multiple Sclerosis Study Group proposed a consensus definition for ADEM, and criteria were updated in 2013 (Box 1). Examples of MRI in ADEM are shown in Fig. 1 and Table 1.

Multiphasic ADEM is defined as 2 episodes consistent with ADEM separated by 3 months but not followed by any further events. Relapses beyond a second event are not consistent with ADEM and indicate a chronic, relapsing disorder. The initial ADEM event can be considered the first attack of a chronic disease if it is followed by attacks without encephalopathy [17].

### Radiologically isolated syndrome

Radiologically isolated syndrome (RIS) has only been reported in the last 10 years and describes people who are asymptomatic and have a brain MRI (due to car crash, headache, and such) with CNS demyelination as seen in

**Box 1: Acute disseminated encephalomyelitis criteria based on International Pediatric Multiple Sclerosis Study Group 2013 revision**

- A first demyelinating, multifocal clinical attack of the CNS with inflammatory cause
- Encephalopathy not explained by fever
- Brain MRI with demyelinating findings during acute illness
- Absence of new clinical and MRI findings on follow-up

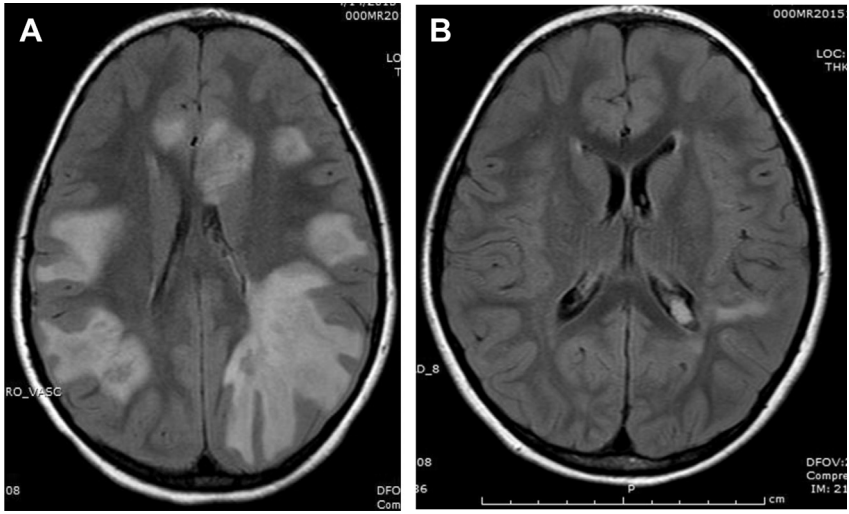


**Fig. 1.** ADEM MRI T2 fluid-attenuated inversion recovery (MS Flare). A 5-year-old girl with ADEM. (*A*) MRI from presentation shows large, confluent areas of T2-FLAIR signal abnormality predominantly in the subcortical and periventricular white matter in the bilateral parietal, frontal, temporal, and left occipital lobes. (*B*) Follow-up scan 3 months later with resolution of most of the abnormal signal.

MS, including ovoid and well-circumscribed lesions [18,19]. RIS is described in adults, but recently Makhani and colleagues [20] reported on a pediatric cohort with RIS followed with serial scans [18,19,21]. Forty-two percent developed a clinical attack consistent with CNS demyelination within a median of 2 years after the first MRI scan. Evolution of the MRI findings was seen in 61%, in line with findings in adults. Increased risk of developing a clinical event was seen in those with spinal cord lesions on MRI and positive oligoclonal bands in the cerebrospinal fluid (CSF) [21].

## Neuromyelitis optica spectrum disorder

Neuromyelitis optica spectrum disorder (NMOSD) is a chronic, relapsing, autoimmune demyelinating disease that affects the CNS and, in particular,

**Table 1**
MRI findings in multiple sclerosis versus acute disseminated encephalomyelitis

| POMS | AOMS | ADEM |
|---|---|---|
| • Can have larger and more diffuse lesions than in adults, especially younger children<br>• More likely to have infratentorial lesions | • Periventricular lesions<br>• Black holes<br>• Well-circumscribed lesions<br>• Asymmetric lesions | • Diffuse, fluffy, or ill-defined lesions<br>• Can be symmetric<br>• Can involve the basal ganglia or thalamus<br>• Tend to spare PV areas |

*Abbreviation:* PV, periventricular.

the optic nerves and spinal cord. In 2004, a highly specific autoimmune antibody for neuromyelitis optica (NMO) targeted against the aquaporin-IV water channel was described. Pediatric onset makes up just 3% to 5% of all NMOSD cases [22]. Pediatric patients can present with bilateral or unilateral optic neuritis, longitudinally extensive transverse myelitis, or brainstem symptoms (Fig. 2). Rarely, children can exhibit multifocal deficits and encephalopathy, which can be confused with ADEM [23]. Prompt identification of NMOSD is important because treatment differs from MS, and attacks are often severe with poor recovery.

### Myelin oligodendrocyte glycoprotein antibody

Anti–myelin oligodendrocyte glycoprotein (MOG) antibodies are present in some patients with acquired demyelinating syndrome (ADS) (this has not been defined anywhere), including young children with monophasic ADEM and older children with recurrent optic neuritis, transverse myelitis, and antibody-negative NMOSD. MOG is a glycoprotein with a role in myelination of the nerves of the CNS [24,25]. Children are more likely to be positive than adults with the same diagnosis [26–28]. There has been debate about whether the presence of anti-MOG antibodies constitutes a separate demyelinating condition or is seen as part of other conditions. Recent investigations helped clarify clinical characteristics of relapsing anti-MOG$^{+}$ patients. In children who are positive, a substantial amount, one-third, experienced a relapse within 2 years of initial presentation [29].

However, many children with monophasic ADEM are anti-MOG$^{+}$. Following MOG titer may be helpful in guiding management. Risk of recurrent

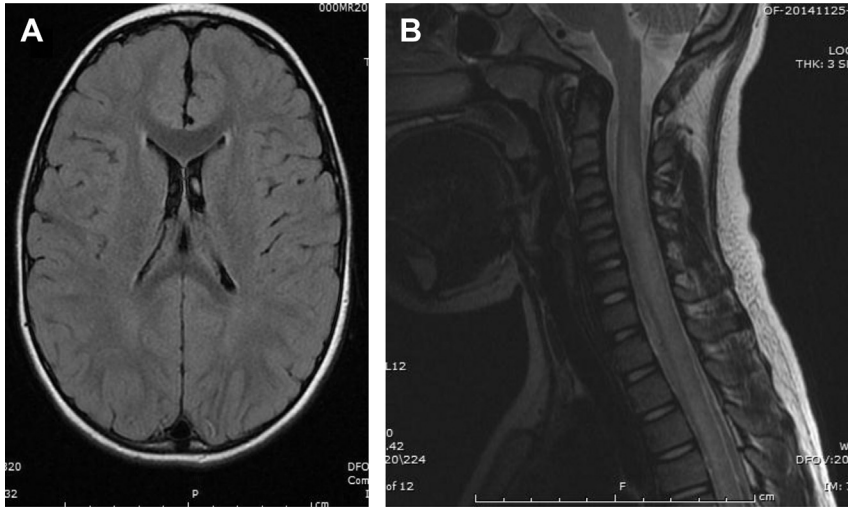


**Fig. 2.** Pediatric NMO case. (*A*) Note normal brain MRI. (*B*) Longitudinally extensive cord lesion.

demyelinating disease is very low if the anti-MOG antibody titer decreases over time [30,31]. Thus, a persistently high titer could serve as a marker for relapsing disease. Persistence of high titer has been described in children with recurrent optic neuritis and NMOSD. It is rare to find anti-MOG antibodies in children with MS [30,31]. In 1 study, 3 patients with MS had anti-MOG$^+$ antibodies at disease onset but had undetectable levels over time [31].

Children with monophasic disease and anti-MOG$^+$ antibodies generally respond acutely to high-dose pulse steroids. Ideal treatment strategies for children with relapsing anti-MOG are still under investigation; some studies report success with immunosuppressant medications.

## DIAGNOSIS

The diagnosis of MS rests on at least one clinical episode and objective findings on examination or imaging reflecting a CNS inflammatory demyelinating event lasting at least 24 hours in the absence of fever or infection. The McDonald criteria allow diagnosis based on clinical grounds alone, but also propose that MRI, and now CSF, can serve as markers for dissemination in space (DIS) and/or time (DIT). McDonald criteria have been revised over time (2001, 2005, 2010, and 2017); the changes generally allow earlier diagnosis so patients can start on treatment more quickly than in the past.

The 2010 McDonald criteria have been evaluated in POMS patients and found to have high sensitivity, specificity, and positive predictive value (PPV, 76%) for children older than 11 [32]. In young children with a non-ADEM-like presentation, the PPV was only 55%. The low PPV in younger children suggest caution must be used when employing the criteria in this group. Also, the criteria are not suitable for application in patients with ADEM-like presentations because although no child with ADEM met clinical criteria for MS, 10 did meet the 2010 MRI criteria.

In 2017, the International Panel on Diagnosis of Multiple Sclerosis made revisions to the 2010 McDonald criteria [33,34]. Changes include accepting both symptomatic and asymptomatic lesions for DIS/DIT. The caveat to this, MRI lesions in the optic nerve of a patient with optic neuritis, is excluded. Cortical lesions on MRI can be used to establish DIS. CSF-specific oligoclonal bands can fulfill DIT, which previously required enhancing and nonenhancing MRI lesions, or an additional clinical attack of a different CNS site. The criteria require testing with MRI or CSF-specific oligoclonal bands, depending on the number of clinical attacks with objective clinical evidence [32]. For example, if someone has 1 clinical event, criteria for DIS and DIT must be met. DIS could be met by either an additional clinical attack implicating a different CNS site or by MRI showing 1 lesion in 2 or more of the areas typically affected in MS; DIT could be met by CSF-specific oligoclonal bands or another attack. Tables 2 and 3 provide the McDonald criteria for DIS/DIT and highlight 2017 revisions.

A study was conducted on 324 pediatric patients with ADS to evaluate the 2017 McDonald criteria and compare it with the 2010 McDonald criteria

**Table 2**
McDonald criteria

| DIS | DIT |
|---|---|
| One T2 lesion in at least 2 of the areas commonly affected by MS:<br>Periventricular<br>Infratentorial<br>Spinal cord<br>Juxtacortical<br>**Cortical** | • Asymptomatic *or* **symptomatic**[a] lesions, contrast-enhancing lesions, and nonenhancing lesions *OR*<br>• A new T2- or contrast-enhancing lesion on follow-up scan done at any time *OR*<br>• **CSF-specific oligoclonal bands OR**<br>• Wait for additional attack |

DIS and DIT 2017 revisions are set in bold type.
[a]Excludes lesions in optic nerve in symptomatic optic neuritis patients.

**Table 3**
McDonald criteria for diagnosis[a]

| Clinical presentation | Additional evidence for MS diagnosis |
|---|---|
| • ≥2 clinical attacks and objective clinical evidence >2 lesions<br>• ≥2 attacks, objective clinical evidence of 1 lesion with historical evidence of a prior attack in a different location | None. *DIS and DIT are met* |
| ≥2 attacks and objective clinical evidence of 1 lesion | Fulfills DIT<br>DIS needed<br>• ≥1 **symptomatic** or asymptomatic lesion in PV, juxtacortical, infratentorial, spinal cord, or **cortical location** *OR*<br>• Await second attack |
| One attack and objective clinical evidence of >2 lesions | Fulfills DIS<br>DIT needed<br>• Enhancing and nonenhancing **symptomatic** or asymptomatic typical MS lesions *OR*<br>• New T2 or enhancing lesion on follow scan *OR*<br>• **CSF-specific oligoclonal bands *OR***<br>• Await further clinical attack |
| One attack and objective clinical evidence of 1 lesion | DIT needed<br>• Enhancing and nonenhancing **symptomatic** or asymptomatic typical MS lesions *OR*<br>• New T2 or enhancing lesion on follow scan OR<br>• **CSF-specific oligoclonal bands** *OR*<br>• Await further clinical attack<br>DIS needed<br>• ≥1 **symptomatic** or asymptomatic lesion in PV, juxtacortical, infratentorial, spinal cord, or **cortical location** *OR*<br>• Await second attack in different location |

2017 revisions are set in bold type.
[a]Assumes patient has typical MS symptoms at onset.

[35]. At the time of the first attack, the 2017 criteria performed well in identifying children with MS. The presence of oligoclonal bands to establish DIT increased the number of diagnoses. As in 2010, the 2017 McDonald criteria had a lower PPV for children under 11 years of age, suggesting caution when applying the criteria in young children. Also, 2017 McDonald criteria should not be applied to ADEM-like presentation; the diagnosis of MS in these children requires at least 1 non-ADEM relapse and the accrual of clinically silent new lesions [35].

## RISK FACTORS FOR THE DEVELOPMENT OF PEDIATRIC

### Genetics

Epidemiologic studies have shown about 2% to 5% risk of MS in first-degree relatives and 25% to 30% in monozygotic twins [36]. Most of these genetic risk factors are associated with immune regulation genes [37]. Genome-wide association studies have identified more than 200 susceptibility genes associated with adult MS, including at least 13 major histocompatibility complex (MHC) loci [38,39]. About one-third of the adult MS genetic variants are associated with POMS, suggesting a shared genetic inheritance. The first genetic risk factor identified in Caucasians with MS is *HLA-DRB1*15:01*, in the MHC class II. Presence of the variant increases MS risk about 3-fold. A similar association is seen in POMS [37,40].

### Environmental factors

*Infection*

Prior infection with Epstein-Barr virus has consistently been associated with an increased risk for pediatric MS [41]. For individuals with prior herpes simplex (HSV)-1 infection, the contribution to POMS risk depends on *HLA-DRB1*1501* status [41,42].

*Diet and dietary micronutrients*

Several studies have assessed dietary factors associated with risk of developing MS, including average caloric intake and consumption of fats, proteins, carbohydrates, sugars, fruits, vegetables, dairy, fiber, vitamins, iron, salt, and beverages. Notably, only low levels of vitamin D and low-iron intake have shown significant associations with pediatric MS [43,44].

*Gut microbiome*

The composition of gut microbiota in pediatric MS displays some differences compared with healthy controls. A study showed differences in gut microbial taxa enrichments and depletions between cases and controls demonstrating alteration of the gut microbiota in POMS patients toward a more inflammatory environment [45].

*Obesity*

Many studies show a high percentage of POMS patients are overweight. At least 49% of 1 cohort of children with MS were overweight or obese [46]. Higher body mass indexes (BMIs) are associated with an increased risk of

developing POMS in postpubertal girls [47]. Overweight or obese girls had an earlier age of disease onset compared with those with a lower BMI [48].

*Smoking exposure*

One study showed parental smoking at home doubles the risk for first episode of MS [49]. Second-hand cigarette smoke exposure is more common in POMS (37% exposed) compared with monophasic ADS (29.5% exposed). Cigarette smoke exposure combined with *HLA-DRB1*1501*-positive status increased the odds of pediatric MS by 3.7 times compared with monophasic ADS [50].

## MRI FINDINGS IN PEDIATRIC-ONSET MULTIPLE SCLEROSIS

There are notable differences in MRI findings in POMS versus AOMS patients. Waubant and colleagues [51] examined both initial MRI scans and follow-up scans comparing pediatric and adult cohorts. They found the POMS group had an initial scan with higher total number of T2-hyperintense foci and more large (≥1 cm) foci compared with the adults. A greater portion of children had gadolinium-enhancing foci (68.4% vs 21.2%) and T2-hyperintense foci in the posterior fossa (68.3% vs 31.4%). When follow-up scans were compared, the children still had a greater number of new T2-hyperintense foci and gadolinium-enhancing foci than the adults; however, several children showed greater than 50% reduction of previously seen T2-hyperintensities compared with their adult counterparts (22.5% children vs 0% adults). Fig. 3 and Table 4 provide POMS MRI characteristics.

These findings suggest POMS patients have higher MRI disease burden at presentation and higher disease activity on follow-up scans. Pediatric patients have more frequent radiologic involvement of the infratentorial region than adults. MRI findings match the clinical findings, that is, that POMS patients have symptoms of cerebellum or brainstem involvement more often than AOMS [52]. Pediatric patients demonstrated more ill-defined and larger T2-hyperintense foci on initial scans, suggesting that the inflammatory process in children is from more edematous reactions; however, these differences could be due to the immature blood-brain barrier and microglia in children. There was resolution (>50%) of previously seen T2-hyperintense signal in a greater percentage of pediatric patients compared with adults, suggesting less destructive or more reversible lesions in children [51]. This finding could be explained by less axonal loss and demyelination or by better remyelination in children than adults. Despite the resolution of lesions, however, the fact that pediatric patients have a higher MRI disease burden, greater occurrence of new lesions early in MS onset, and higher frequency of infratentorial lesions is concerning. These same features have been associated with more rapid disability in AOMS patients.

Traditionally, MS is considered a disease of the white matter, but MRI has shown gray matter involvement in both pediatric and adult patients. Relative to healthy controls, pediatric patients have lower gray matter volume, total brain

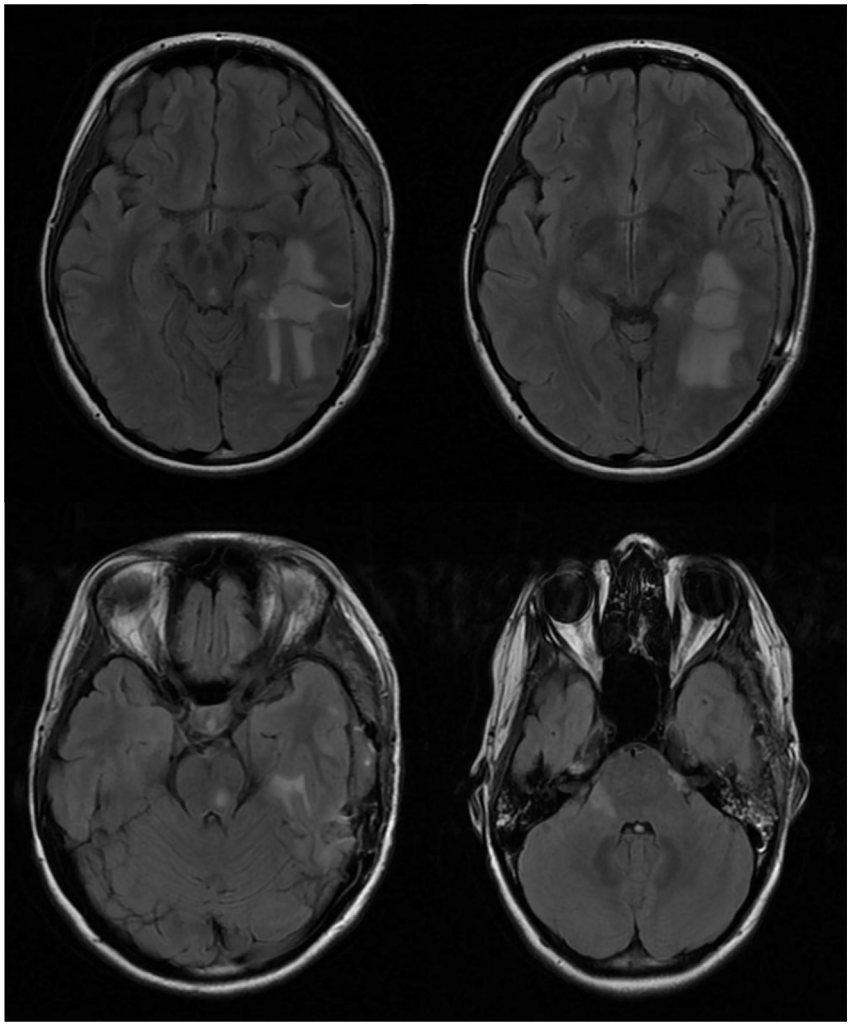

**Fig. 3.** Teen girl with MS. Note the large confluent lesions and infratentorial lesions.

volume, and thalamic volume [53,54]. One study showed that thalamic volume changes correlated with clinically identified cognitive impairment [54].

## CLINICAL COURSE AND PROGNOSIS

MS is often broken up into different subtypes; relapsing remitting MS (RRMS) is characterized by discrete neurologic attacks followed by some amount of recovery between attacks (Table 5). The overwhelming majority of POMS cases are RRMS, more than 98%. Primary progressive MS (PPMS) has gradual and progressive accumulation of disability in absence of neurologic attacks or relapses. In adults, about 15% of cases are PPMS. If a child experiences a

**Table 4**
Clinical course of pediatric-onset multiple sclerosis versus adult-onset multiple sclerosis

| | POMS | | |
|---|---|---|---|
| | Prepubertal | Postpubertal | AOMS |
| Sex | M:F | F > M | F > M |
| Clinical symptoms | Multifocal symptoms are more common, seizures, brainstem symptoms more common | Monofocal more common, brainstem symptoms more common | Examples of typical MS presentations include unilateral optic neuritis, focal supratentorial, brainstem, or cerebellar syndromes, or partial myelopathy |
| Relapses | More severe relapses<br>Increased number of relapses earlier in disease course | | Poorer recovery potential from relapse |
| Disability | Time to disability is longer, but age at disability is younger than adults | | After EDSS 4 progression is similar in POMS and AOMS |
| MS subtype | 98% RRMS | | 85% RRMS, 15% PPMS |

*Abbreviations:* F, female; M, male.

progressive course without remission, this should raise concern for alternative diagnosis and prompt further workup [7].

Studies show POMS patients suffer more frequent relapses early in their disease course compared with AOMS [55]. One study showed this increase in

**Table 5**
Multiple sclerosis subtype

| | |
|---|---|
| RRMS | • Most common disease course<br>• Clinical attacks or relapses occur and are followed by some amount of recovery and remission<br>• Over time, disability can become permanent, but no progression of disability is seen during remission periods<br>• Considered active or not active depending on whether relapses are occurring and worsening/not worsening if disability has increased |
| Secondary progressive MS (SPMS) | • People initially have RRMS, and over time most transition to SPMS<br>• Characterized by progressive worsening of disability measures<br>• Active or not active depending on whether relapses occur and MRI progresses |
| PPMS | • Very rare in children; should prompt further workup if children have progressive course<br>• Worsening disability and neurologic dysfunction from onset without early relapses<br>• Considered active if occasional relapses occur or MRI activity or not active<br>• Considered with progression or without progression depending on disability assessments |

relapse rate persisted for more than 5 years after disease onset. Also, they found that POMS patients had a shorter interval between first and second attack [56]. Another study found pediatric patients have more severe relapses compared with adults. Despite more frequent and severe relapses, pediatric patients show greater potential for complete recovery from relapses, especially early in their disease course [56–60].

POMS patients take longer to reach disability levels, but because they are younger at disease onset, they reach disability 7 to 12 years younger than adults. The European Database for MS enrolled patients from 1967 to 1997 and followed them through 2003. A total of 394 patients with disease onset before age 16 were studied, and time to reach expanded disability status scale (EDSS) score of 4 (limited ability to walk 500 meters unassisted) was 20 years, whereas the time to same EDSS score for adult-onset patients was 8 years [7]. After this point, progression rates are similar between adults and POMS. Long-term follow-up data of POMS and disability status occurred before the current treatment strategies. It is hoped that modern treatment options, which include more powerful immunosuppressant medication, could help improve prognosis in the future. Risk factors for poor outcome in pediatric patients include shorter time between relapses (<1 year), incomplete recovery after first attack, and brainstem involvement in initial attack.

Cognitive effects in pediatric MS patients are significant and fairly common, seen in as many as one-third of patients [60]. Correlation of cognitive deficits and imaging findings, like brain atrophy, has been reported. Lower IQ scores have correlated with younger age at disease onset. In a longitudinal study of POMS, 25% of patients had cognitive decline from baseline at 1 year and 75% had decline after 2 years [61]. Care should be taken to monitor for these issues. School concessions and strategies can be addressed through a child's individual education plan.

## TREATMENT

Today, there are more medications for MS than ever before, which can allow more individualized management, but also increases the complexity of treatment and concern for serious side effects. The concept of NEDA, or no evidence of disease activity, measured by lack of clinical and radiologic progression is an ultimate goal of MS treatment. In studies evaluating NEDA, roughly 50% of adult patients followed for 2 years in any clinical trial were able to achieve NEDA, and only 7% remain NEDA at 7-year follow-up [62]. NEDA has not been longitudinally evaluated in POMS so it is not possible to say if it is a realistic goal for every patient [63].

Treatment of POMS patients with disease-modifying therapies (DMT) has largely been based on extrapolation of adult data and expert experience, because there has been a lack of clinical trials in pediatric patients until recently. Still, published case series support reduction in relapses with first-line injectable agents like Glatiramer acetate and interferons. These medications reduce relapses in adults by as much as 30%, and case series report similar efficacy in pediatric patients with similar safety profiles [64–66]. Dose and common side effects are listed in Table 6.

**Table 6**
Disease-modifying treatments

| Medication | Trade name | Mechanism of action | Dose and route | Side effects | Screening laboratory tests | Monitoring laboratory tests |
|---|---|---|---|---|---|---|
| Injectable immunomodulator | | | | | | |
| IFN-β-1a | Rebif | • Inhibits lymphocyte trafficking in CNS | 22 or 44 μg SC TIW | Flulike reactions, elevated transaminases, depression, injection site reactions<br>Serious AE are rare | • CBC<br>• LFT<br>• TSH | • CBC<br>• LFT<br>• TSH |
| IFN-β-1a | Avonex | • Enhances suppressor T-cell activity | 30 μg IM every week | | | |
| IFN-β-1b | Betaseron | • Reduces proinflammatory cytokine production | 250 μg SC every other day | | | |
| Pegylated IFN-β-1a | Plegridy | | 125 μg SC every 14 d | | | |
| Glatiramer acetate | Copaxone | • Promotes Th2 cell activity<br>• Shifts toward anti-inflammatory state | 20 mg SC qd<br>40 mg SC TIW | Injection site reactions<br>Serious AE are rare | None | None |
| Oral immunomodulator | | | | | | |
| Fingolimod | Gilenya | • Sphingosine 1-phosphate receptor modulator<br>• Leads to down-regulation in LN and prevents activated lymphocytes from leaving LN | 0.5 mg po qd | Bradycardia, macular edema, infection, lymphopenia, increased LFT | • CBC<br>• LFT<br>• VZV antibodies<br>• ECG<br>• OCT/ophthalmology examination<br>• ECG<br>• Vaccinate if needed | • First-dose monitoring<br>• Follow-up OCT/ophthalmology examination<br>• CBC<br>• LFT<br>• Periodic skin examination |

| | | | | | | |
|---|---|---|---|---|---|---|
| Teriflunomide | AUBAGIO | • Lymphocytopenia in T and B cells<br>• Disrupts pyridine synthesis | • 14 mg po qd<br>• 7 mg po qd | GI symptoms, alopecia, increased LFT, increase BP, peripheral neuropathy | • CBC<br>• LFT<br>• QuantiFERON gold<br>• Pregnancy test | • ALT monthly for 6 mo<br>• Then LFT periodically<br>• CBC |
| DMF | Tecfidera | • Nrf2 pathway<br>• Shift to Th2 or anti-inflammatory<br>• Cytokine profile<br>• Promotes antioxidant | 240 mg po bid | Flushing, nausea, stomach upset, UTI, lymphopenia<br>PML has been reported | • CBC<br>• LFT | • CBC<br>• LFT |
| Infusion immunosuppressant | | | | | | |
| Natalizumab | Tysabri | • mAb against alpha 4 integrin<br>• Prevents lymphocytes from crossing BBB | 300 mg IV every 4 wk (adult dose)<br>3–5 mg/kg IV every 4 wk (children) | PML, infusion reaction, hepatotoxicity | • JC virus antibody/ index<br>• CBC<br>• LFT | • JC virus antibody/ index<br>• CBC<br>• LFT |
| Ocrelizumab | Ocrevus | • mAb against CD 20 on B cells | 600 mg IV every 6 mo | Infusion reaction, UTI, URT infection<br>Malignancy | • QuantiFERON gold<br>• Hepatitis panel<br>• VZV antibodies<br>• Vaccinations if needed | • CD 19/20 counts every 3 mo<br>• Standard cancer screening |
| Rituximab | Rituxan | • mAb against CD 20 on B cells | 750 mg/m2/ dose IV (maximum 1 g) × 2 doses spaced 2 wk apart every 6 mo | Infusion reactions, PML (not in MS but has been seen in other conditions) | • QuantiFERON gold<br>• Hepatitis panel<br>• VZV<br>• Vaccinations if needed<br>• CBC, cell subsets, CMP | • CD19/20 counts every 3 mo |

(*continued on next page*)

**Table 6**
**(*continued*)**

| Medication | Trade name | Mechanism of action | Dose and route | Side effects | Screening laboratory tests | Monitoring laboratory tests |
|---|---|---|---|---|---|---|
| Alemtuzumab | LEMTRADA | • mAb against CD 52, causes long-term depletion of CD52+ lymphocytes | 12 mg IV 5 consecutive daily infusions. 1 y later 3 consecutive daily infusions | Lymphopenia, infusion reactions, risk of secondary autoimmune conditions, malignancy (thyroid cancers, melanoma) | • Skin examination baseline<br>• VZV antibodies<br>• Hepatitis panel (high-risk groups)<br>• QuantiFERON gold<br>• Vaccinations if needed | • PCP and HSV prophylaxis<br>• Thyroid studies every 3 mo<br>• CBC, creatinine, UA monthly<br>• Skin examination yearly |

*Abbreviations:* AE, adverse events; ALT, alanine aminotransferase; BBB, blood-brain barrier; CBC, complete blood count; CMP, complete metabolic panel; ECG, electrocardiogram; GI, gastrointestinal; IM, intramuscularly; LFT, liver function test; LN, lymph nodes; mAb, monoclonal antibody; OTC, optical coherence tomography; PCP, pneumocystis carinii pneumonia; SC, subcutaneous; T1W, T1 weighted; Th2, T-helper 2; TSH, thyroid stimulating hormone; UA, urinalysis; URT, upper respiratory tract; UTI, urinary tract infection; VZV, varicella-zoster virus.

## TREATMENT MODELS

Two treatment models for MS therapy are escalation and induction therapy. Induction therapy generally refers to the use of powerful cell-depleting treatments. Experimental models of MS as well as other immune-mediated diseases suggest these treatments could help ''reset'' the immune system and control inflammation from the outset [67]. A limiting factor is the potential toxicity and serious adverse events. Escalation therapy refers to sequentially advancing treatment as needed based on efficacy. There is insufficient evidence in both the adult and pediatric MS population to favor one model over the other. For an individual patient, there are many factors to consider, including personal risk tolerance and prior disease activity [63].

## INADEQUATE TREATMENT RESPONSE

Despite initiation of first-line therapies, continued relapses and/or accrued disability necessitate switching from a first-line to a second-line agent in a significant number of POMS patients [68]. In a study of more than 250 POMS patients, 28% were switched to second therapy after a mean of 1.3 years due to disease progression. However, the concept of traditional first- and second-line therapies is blurring because there is more attention paid to the individualized needs of patients [63]. A recent paper examining treatment practices in POMS has reported increased use of oral medications like DMF, Fingolimod, and infusion treatments in pediatric patients. Seventeen percent of treatment-naïve pediatric patients were started on a newer agent as first therapy [69].

In 2012, the International Pediatric MS Study Group proposed criteria for inadequate treatment of patients taking a DMT for at least 6 months: (1) no reduction in relapse rate, or new T2 lesions or contrast enhancing lesions; and/or (2) 2 or more relapses within 12 months [70].

## MEDICATIONS

### Oral

*Fingolimod* is given as a once-daily oral medication. It sequesters lymphocytes in the lymph nodes by binding to sphingosine-1-phosphate receptors and therefore indirectly prevents activated lymphocytes from crossing into the CNS. It is the first Food and Drug Administration (FDA) -approved DMT for pediatric patients with MS aged 10 years and older. It performed well in clinical trials; when compared with interferon-β-1a, there was an 82% reduction in annualized relapse rates in the Fingolimod group as well as reduction in new lesions and brain atrophy. Serious adverse events were similar to adult studies, namely leukopenia, seizures, and allergic reactions [71,72]. Additional safety concerns include bradycardia, disseminated herpes zoster infection in absence of immunity, and progressive multifocal leukoencephalopathy (PML) risk.

*Dimethyl fumarate (DMF)* was approved by the FDA in 2013. It is administered as an oral medication given twice a day. Mechanism of action is still unclear; it has cytokine modulatory effects and is known to lower lymphocyte counts. Side effects include stomach upset and flushing, which often will abate with time. There have been rare cases of PML in persons taking DMF.

*Teriflunomide* is an oral once-daily pill. The active metabolite leflunomide has been used in rheumatoid arthritis since 1998. It reduces activation and proliferation of lymphocytes by inhibition of pyrimidine synthesis [73]. In clinical trials in adults, it was superior to placebo and comparable to interferon-β-1ba. Side effects include nausea, diarrhea, hair thinning, and elevation of transaminases. Teratogenicity potential is also of great concern [74].

### Infusion

*Natalizumab* is a humanized monoclonal antibody that targets a protein located on leukocytes causing the blood-brain barrier to block T and B lymphocytes from crossing over into the CNS. It is given as an IV infusion once a month, and the typical adult dose is 300 mg. Young children may be given a dose of 3 to 5 mg/kg per dose. Impressive reduction in both clinical relapses and MRI progression was seen in adult studies (68% reduction in annualized relapse rate and 82% reduction in new T2 lesions) [75]. Natalizumab use in POMS has been reported in retrospective series and prospective studies and generally has been well tolerated and demonstrated reduction in clinical relapses for patients with aggressive disease [76].

PML caused by reactivation of the JC virus (John Cunningham virus, a type of human polyomavirus) is a serious, potentially life-threatening complication. The TOUCH program restricts prescribing, infusing, or dispensing privileges to providers, pharmacies, and infusion centers enrolled in the program in an effort to mitigate PML risk. Overall incidence of PML in Natalizumab patients is 4.22 in 1000 patients. Risk factors for PML include positive JC virus antibody titer, prior immunosuppressant use, and duration of Natalizumab therapy [63,77].

*Rituximab* is an anti-CD20 chimeric monoclonal antibody that targets B cells and has been widely used in pediatric autoimmune diseases. There has been increasing recognition of the role of B cells in MS pathologic condition because of varied effector functions, including interactions with T cells [78]. Rituximab has been used off label for MS patients for many years. In one review of pediatric patients with various inflammatory/autoimmune conditions including MS and NMOSD, treatment with Rituximab showed benefit in 87% of patients [79]. A report of 14 MS patients with mean age of 16.5 years treated with Rituximab showed a favorable safety profile with no serious infections and no new relapses after median treatment of 2 years [80].

*Ocrelizumab* is a related B-cell suppressor therapy that has gained attention as the first FDA-approved therapy for PPMS and is also approved for

**Table 7**
Clinical trials in pediatric multiple sclerosis

| Drug | Trial name | Phase | Outcome/notes | Expected date of completion |
|---|---|---|---|---|
| DMF (Tecfidera) | CONNECT | 3 | | 2025 |
| DMF (Tecfidera) | FOCUS | 2 | • Safety date<br>• Reduction in T2 lesions during treatment period<br>• Small sample size<br>• Short treatment period | 2018 |
| Teriflunomide (AUBAGIO) | TERIKids | 3 | | 2021 |
| Alemtuzumab (LEMTRADA) | LEMKids | 3 | • Will only enroll children who had breakthrough disease on another agent | 2025 |
| Fingolimod (Gilenya) | PARADIGMS | 3 | • Reduction in relapses over comparator<br>• FDA approved for pediatric MS 10 y and older | 2017 |

RRMS. It is a fully humanized monoclonal antibody against CD20. Side effects include risk of infection and infusion reactions, and in trials, an increased risk of breast cancer was seen. It is dosed at 600 mg IV every 6 months.

*Alemtuzumab* is a humanized monoclonal antibody to $CD52^{+}$ cells that depletes certain lymphocytes. Effects are sustained for up to 1 year after treatment. By depleting T and B lymphocytes, it may help "erase" the memory cells responsible for attacking the CNS. One-third of patients experienced new-onset autoimmune diseases. These diseases may not present until several years after treatment so surveillance and monitoring must be continued for years beyond treatment [73].

## CLINICAL TRIALS

Several pediatric trials are ongoing or recently completed (Table 7).

## FINAL THOUGHTS

- As research into environmental and genetic risk factors progresses, it may broaden the understanding of MS pathophysiology.
- Evidence shows that 2017 McDonald criteria apply well to older children presenting with typical MS symptoms and could facilitate swift diagnosis and initiation of DMT
- Pediatric MS-specific clinical trials will give new information about treatment of POMS, and follow-up studies may be helpful to better understand long-term prognosis.

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