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Pediatric Multiple Sclerosis: an Update

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Abstract

Purpose of Review Diagnostic criteria for pediatric-onset multiple sclerosis (POMS) and related demyelinating disorders have been updated, neuroimaging studies have revealed new insights, biological assays identify patients with specific antibodies that influence both diagnosis and treatment, clinical trials are informing on treatment efficacy and safety, and longitudinal studies of neurological, cognitive and quality of life outcomes are informing on the impact of these diseases. We provide updates to assist providers caring for these children.

Recent Findings The recent 2017 McDonald Criteria for MS provide a simplified means to confirm diagnosis at onset and over time, and have been shown to be equally applicable for POMS. MRI analyses demonstrate that brain volume is reduced at onset, and that both volumetric and tissue integrity measures decline over time, indicating that POMS shares the degenerative aspects that also characterize adult-onset disease. The presence of myelin oligodendrocyte glycoprotein (MOG) antibodies at onset is detected in more than 50% of children with acute disseminated encephalomyelitis. When persistent over time, they are associated with relapsing disease. The first randomized clinical trials of disease supports superiority of fingolimod over subcutaneous interferon beta 1a, and demonstrated a favorable safety profile. Finally, while Expanded Disability Status Scale (EDSS) scores remain low in the first 10 years post-onset, POMS is associated with high rates of patient-reported fatigue and reduced engagement in exercise and carries a risk for cognitive impairment.

Summary The past 15 years have borne witness to a marked expansion in recognition and research in POMS. There are now more specific diagnostic criteria, antibodies to CNS proteins appear to define diagnostically distinct disorders, clinical trials have successfully launched and one has completed, and we are gaining increasing appreciation of the impact of MS and related disorders on the lived experience of children and adolescents.

Keywords Pediatric multiple sclerosis · 2017 McDonald Criteria · Fingolimod · MOG · Myelin oligodendrocyte glycoprotein antibody · Review

Introduction

Multiple sclerosis is one of the leading causes of disability in young adults. Two to five percent of patients with multiple sclerosis have been reported to experience their first demyelinating event prior to age 18 [1, 2]. Recent years have seen an expansion in the number of centers caring for children with MS, with over 140 members now included in the International Pediatric Multiple Sclerosis Study Group. The onset of MS in childhood, at a time when key risk factors are likely to be experienced, also provides a means to evaluate the earliest aspects of the disease.

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Epidemiology

Pediatric multiple sclerosis is rare. The incidence and prevalence of acute demyelinating syndromes in children is typically reported in the range of 0.5–1/100,000 [3–7]. However, a small number of prior studies have suggested rates of nearly

3/100,000 in certain regions [8, 9]. Although no single study has attempted to evaluate incidence across the world, there is the suggestion that pediatric incidence rates may be impacted by latitude as has been seen in adult multiple sclerosis [10]. Interestingly, a recent study using an international adult MS population-based registry including 22,162 patients found that age of MS onset was nearly 2 years earlier (from age 32 to age 30) among individual living at high latitudes (50° to 56°) compared to those in lower latitudes (between 18° and 39°) [11].

The median age at first attack in most POMS cohorts is between 11 and 13 years. While the majority of POMS patients are Caucasian, a recent study in the USA demonstrated that the proportion of Caucasian patients was lower than would be expected in an adult MS cohort [1, 12, 13].

Comorbidities/Risk Factors

Although the cause of MS remains elusive, risk factors for MS include vitamin D insufficiency, genetic haplotypes, specific single nucleotide polymorphisms, smoking (or exposure to secondhand smoke in the case of POMS), obesity (most notably during adolescence), and specific viral exposures.

There is strong research to demonstrate an association between low vitamin D levels and increased MS risk in adult patients [14]. In one recent update to this body of work, whole genome sequencing data from a large database of previously genotyped individuals was used to identify a low-frequency synonymous coding variation in CYP2R1 that had a large effect on vitamin D levels. The same group then analyzed over 5000 MS patients and controls and demonstrated increased odds of multiple sclerosis in patients with this coding variation (OR = 2.2, CI 1.78–2.78, $p = 1.26 \times 10^{-12}$) [15]. An association between vitamin D and multiple sclerosis has also been seen in POMS. In a study of 110 pediatric MS patients with an average disease duration of 1 year, multivariate regressions models demonstrated that each 10 ng/ml increase in vitamin D level was associated with a 34% lower risk of subsequent attacks [16]. A recent meta-analysis evaluated 569 cases of POMS and nearly 28,000 controls utilizing Mendelian randomization to estimate the causative association between vitamin D, BMI, and POMS. Higher vitamin D level, represented as a genetic risk score (GRS), was significantly associated with decreased rates of POMS (OR 0.72, 95% CI = 0.55–0.94; $p = 0.02$). The authors also identified a significant association between high BMI (again as a GRS) and POMS (OR 1.17 95% CI 1.05–1.30; $p = 0.01$). They interpreted their results as demonstrating "strong evidence for a causal and independent association between low serum concentrations of vitamin D and increased BMI and risk of pediatric-onset MS after adjusting for sex, ancestry, HLA-DRB1*15:01, and over 100 non-human leukocyte antigen (HLA) MS risk variants" [17].

Childhood obesity has been correlated with increased risk of future MS diagnosis [18]. Obesity has been associated with an increased risk of pediatric MS or clinically isolated syndrome in a population of 75 girls ages 11–18, but this association did not hold for boys [19]. Putative mechanisms by which this may occur have been proposed [20]. Obesity has been correlated with low-grade increased systemic inflammation [21, 22]. There are also complex interactions between vitamin D and obesity. As has recently been reviewed in detail, obesity increases the risk of vitamin D deficiency in people of all ages, possibly due to decreased bioavailability. It also leads to a decreased response to vitamin D supplementation [23].

A recent study of 81 POMS patients compared to 216 children with mono-ADS demonstrated that secondhand smoke (SHS) exposure was not an independent risk factor for MS. However, when both SHS exposure and HLA-DRB1*15:01 were included, the odds of MS were increased (OR = 3.7, 95% CI 1.17–11.9) [24].

HLA-DRB1*15:01 is a well-described genetic risk factor for MS in children and adults [25]. Specific single nucleotide polymorphisms (SNPs) have been identified as a further predictor of MS risk. In a cohort study of 188 children with ADS (53 of whom were diagnosed with POMS), 466 with adult-onset MS, and 2000 adult controls, using weight genetic risk scores, the combined effect of 57 SNPs exceeded the effect of HLA-DRB1*15:01 alone in pediatric and adult-onset patients [26]. In a separate study, 104 SNPs previously identified as risk variants in adult MS were evaluated in a POMS cohort. Twenty-eight SNPs were significantly associated with POMS risk and in these cases, effect sizes were estimated to be larger than in previously published adult MS studies [27]. Certain risk alleles such as AHI1 may also associate with relapse rates in children and adults [28].

There is a powerful interplay between the immune system and the gut microbiome. In a recent case-control study, 18 pediatric MS cases and 17 age- and sex-matched controls were evaluated. Children with POMS were found to have 2.5 times the abundance of Actinobacteria compared to children without MS (CI 1.3–4.9). This bacterial phylum has also been associated with other inflammatory conditions such as inflammatory bowel disease [29]. Similarly, in a pilot study of 17 pediatric MS patients, depletion of Fusobacteria was associated with MS at a hazard ratio of 3.2 (95% CI 1.2–9.0, $p = 0.024$) for relapse [30, 31].

Remote infection with Epstein-Barr virus has been consistently associated with increased risk for POMS and adult-onset MS [32–35]. Other herpes viruses have not been consistently associated with MS risk [33]. Cytomegalovirus exposure appears to be associated with a decreased risk of future pediatric MS in at least one study [36].

Diagnosis

The McDonald Criteria for the diagnosis of multiple sclerosis were updated in 2017 [37•]. In addition to elimination of the requirement for lesions to be clinically silent, CSF oligoclonal bands can now be utilized as evidence of dissemination in time. The new criteria have already been validated in a large pediatric cohort. As part of that analysis, the sensitivity of the 2017 criteria for POMS was found to be 0.71 (0.56–0.83), the specificity was 0.96 (0.90–0.98), the positive predictive value was 0.82 (0.67–0.92), and the negative predictive value was 0.91 (0.86–0.95). This compared favorably with the performance of prior diagnostic criteria such as the 2010 McDonald Criteria and 2016 MAGNIMS Criteria [38•].

The 2013 International Pediatric Multiple Sclerosis Study Group consensus diagnostic criteria for POMS incorporated the 2010 McDonald Criteria [39] and the next update will likely incorporate the 2017 criteria. In addition to formal criteria, the presence of at least one T1 hypointense lesion (black hole) and one T2 hyperintense lesion located in the periventricular white matter can be useful in clinical practice. This was originally noted by Verhey et al. in 2011 [40]. In the recent analysis discussed above, this straightforward approach was found to have a 78% predictive power for POMS diagnosis [38•].

Differential Diagnosis: Recurrent Non-MS Demyelinating Disorders

Myelin Oligodendrocyte Glycoprotein Antibody-Associated Demyelination

The presence of antibodies directed against MOG occurs in monophasic demyelinating disorders, particularly, in younger children and patients with ADEM. However, up to 1/3 of these children with MOG-abs will relapse within 2 years [41•, 42•]. Recent cohorts have suggested that a significant percentage of patients with recurrent optic neuritis, multiphasic demyelinating encephalomyelitis (MDEM), ADEM associated with optic neuritis (ADEMON) [43], and neuromyelitis optica spectrum disorders (NMOSD) have MOG-abs. For example, in a cohort of 210 children with ADS followed longitudinally, 57% of 60 ADEM patients were MOG-ab positive; 35 children had recurrent non-MS episodes (22 of whom were MOG-ab positive); 11 patients in the cohort had MDEM or ADEMON (all MOG-ab positive); 11 children had recurrent optic neuritis (8 were MOG positive); and finally, 16 children manifested with NMOSD (9 were MOG positive and 6 were aquaporin 4 antibody positive) [41•]. In another cohort, 237 patients with ADS were tested for MOG, 76 (32%) were positive. 64% of the patients with ADEM were MOG-ab positive. Twenty-four of 25 patients with "relapsing ADEM" were MOG-ab positive. Overall, 36 of 75 total MOG-ab-positive patients relapsed during the 5-year study period. Of the NMOSD patients, 13 were MOG-ab positive and 14 were aquaporin 4 positive [42•].

Younger children with MOG antibodies appear more likely to manifest with ADEM, MDEM, or ADEMON. MOG-positive older children are more likely to experience optic neuritis or myelitis, and those that relapse are more likely to do so in an NMOSD pattern [44]. Recurrent demyelination which may include MDEM, ADEMON, and NMOSD can meet the McDonald Criteria for multiple sclerosis but not respond to therapy. In such cases, alternative diagnoses should be considered early in the clinical course [39].

In the USA, testing for MOG antibodies in the clinical, rather than research setting, is now enabled by the availability of regulatory agency-approved, high-quality, cell-based assays (through CLIA, the Clinical Laboratory Improvement Amendments).

Recent papers have suggested a decreased rate of recurrence for patients with recurrent demyelination associated with MOG who were treated with immunosuppression. A study of 102 children with relapsing MOG-ab-associated disease demonstrated no decrease in annualized relapse rate (ARR) during treatment with the traditional injectable disease-modifying therapies (i.e., glatiramer acetate or interferon beta 1a). The median ARR was reduced from 1.8 to 1 with azathioprine ($n = 20$, $p < 0.001$), 1.79 to 0.52 with mycophenolate mofetil (MM) ($n = 15$, $p = 0.03$), and 2.12 to 0.67 with rituximab ($n = 9$, $p < 0.001$). An improvement in ARR from 2.16 to 0.51 ($p < 0.001$) was seen in 12 patients treated with maintenance IVIG infusions and this was the only treatment which also improved EDSS (from 2.2 to 1.2, $p = 0.01$). Five of eight patients receiving oral prednisolone alone relapsed while receiving treatment [45••]. An Australian cohort which included both children and adults evaluated ARR prior to and on immunotherapies (oral prednisone, rituximab, MM, or maintenance IVIG alone). This cohort included 33 children and 26 adults. Pre-treatment ARR vs ARR on treatment was significantly reduced by all agents in this study from 1.4–2 to 0 (or near zero for MM). Many of the patients in this study received concurrent treatment with steroids along with another agent. Interestingly, in this study, oral prednisone alone had the lowest treatment failure rate [44]. While collectively these case series provide helpful clinical guidance, they are not designed to formally evaluate treatment efficacy.

Based on current evidence, it appears that monthly IVIG monotherapy may emerge as an effective strategy with relatively limited toxicity [45••]. Further supporting this preliminary evidence, a dose-dependent protective effect of IVIG on antibody-mediated CNS demyelination in mouse model of MOG was recently published [46].

Given the retrospective nature of current studies, it is challenging to know if treatment truly alters the natural history of

these patients. Prospective evaluations of these treatments are warranted but will be difficult given the rarity of relapsing MOG-ab-positive patients.

Inherited Disorders

While classic leukodystrophies, such as adrenoleukodystrophy, Krabbe disease, or metachromatic leukodystrophy, are rarely confused with POMS given the progressive natures of clinical disability and the largely confluent white matter changes on MRI, inflammatory features are evident in several leukodystrophies (i.e., Aicardi-Goutieres syndrome [47], leukoencephalopathy with brain stem and spinal involvement and lactate elevation associated with DARS mutations [48], etc.), and several leukodystrophies have periods of variable worsening (i.e., vanishing white matter disorder [49]). Mitochondrial diseases also remain a key differential diagnosis. Children with Leigh syndrome can manifest with an ADEM-like presentation or experience ADEM-like events triggered by inter-current illness [50, 51].

MOG-related disorders have recently been reported to present with MRI features very similar to a leukodystrophy. Patients with this presentation may have poorer cognitive outcomes and be less likely to respond to immunotherapy [52].

CNS Involvement in Systemic Inflammatory Disorders

Patients with systemic autoimmune diseases, such as systemic lupus erythematosus (SLE), can experience CNS inflammation [53]. Furthermore, patients may have comorbid poly-autoimmune diseases, such as the co-experience of SLE and NMOSD [54]. Finally, with the advent of monoclonal and targeted therapies, emergence of "treatment-propagated" CNS white matter lesions can occur, such as is seen with tumor necrosis factor therapies [55].

Immunopathology of POMS

While few pathological studies are available, a study of 19 POMS tissue samples revealed a 50% greater extent of axonal injury in acute demyelinating plaques (median 1665 APP positive axons/mm^2) compared with tissue from 12 adult MS patients (median = 1100 APP-positive axons/mm^2). The analysis found the greatest rate of acute axonal damage in prepubertal children. It also identified a positive correlation between the number of inflammatory cells per square millimeter and the extent of axonal reduction [56].

Immunological assays have demonstrated several interesting findings in POMS. Increased T cell proliferative reactivity to myelin and other tissue antigens has been noted in POMS, but also exists in children with prior CNS surgery and in children with type I diabetes [57]. Proteomic analysis comparing 8 POMS patients to 11 children with monophasic ADS did not detect differences in the CSF presence of compact myelin antigens but did detect multiple molecules that localized to the axoglial apparatus selectively in the POMS patients [58]. A cross-sectional study of 30 pediatric MS patients, 26 adult patients, and 67 age-matched controls found a similar pattern of changes in circulating T cells (including a low number of naïve T cells and an increase in memory T cells) in adult and pediatric MS patients compared to controls. Notably, these changes were attenuated by immunomodulatory treatment [59]. T cells were studied in 10 pediatric MS patients, 10 adult MS patients, and 10 pediatric and adult healthy controls. T cells with a memory phenotype producing IL-17 were found at an elevated rate in POMS compared to controls. IL-17 was elevated in culture in POMS compared to pediatric healthy controls and adult multiple sclerosis [60].

Clinical Course

POMS almost universally demonstrates a relapsing remitting disease course. The annualized relapse rate (ARR) is highest in the first 2 years after incident attack, with rates of 1.2–1.9 in some series [61, 62]. The relapse rate remains high for at least 5 years [63]. It is hoped that highly effective therapies will mitigate this rate of relapse (see the "Treatment" section below).

POMS typically presents with focal deficits such as unilateral weakness, numbness, or paresthesia. Visual loss (optic neuritis), ataxia, and transverse myelitis are also very common. Rarely, ADEM can be the first presentation of POMS. To confirm the diagnosis of MS in patients with ADEM at onset, patients must experience non-ADEM relapses and accrual of clinically silent lesions typical for MS [39].

Disability scores of POMS patients typically remain low early in their disease course. In a study of 116 POMS patients, the average disease duration prior to a confirmed EDSS score of 3.0 was 16 ± 1.17 years [1]. In another study which included 156 POMS patients, 89% had a Kurtzke Disability Status Scale less than 3 at the end of an average follow-up period of 2.9 ± 3 years [64]. In an analysis of the French database, POMS patients took an average of 10 years longer to progress to secondary progressive MS compared to disease duration-matched adult-onset MS patients. However, because of their younger age of onset, they typically accumulated disability at a younger age over all [2].

Although physical disability is not a prominent feature in POMS, cognitive deficits are measurable in approximately one third of POMS patients. As has been recently reviewed, this percentage holds across multiple different testing strategies and test batteries. Impairments are most often noted in the areas of complex attention, processing speed, fine motor speed, visual memory, and integration and more often than

in adults in linguistic abilities [65]. Several early studies reported increased rates of fatigue in POMS patients, with rates of 23–51% in parent reporting but 9–32% when reports are taken directly from patients [66–68]. A recent study correlated fatigue with decreased HRQOL in POMS patients [69]. Another recent study of 68 patients with demyelinating diseases (27 POMS, 41 monophasic acute demyelinating syndromes, and 37 healthy controls) found that children with MS were significantly less likely to participate in vigorous ($p = 0.009$) or moderate ($p = 0.048$) physical activity than either monophasic demyelination patients or controls [70]. Physical activity, sleep, and diet have been identified as potentially modifiable factors to be investigated as ways to improve fatigue and decrease obesity in POMS patients [71].

Imaging

A recent publication by Makhani et al. analyzed the clinical outcomes of children and adolescents with radiologically isolated syndromes (incidentally discovered demyelination that meet the 2010 Barkhof MRI criteria for dissemination in space). Forty-two percent (16/38) experienced a sentinel clinical attack after a median of 2 years post-initial MRI. New, clinically silent lesions were detected in 61% of the 38 children during the study period. Two or more oligoclonal band in CSF and spinal cord lesions on MRI were associated with an increased risk of first clinical event in this population [72•].

MRI also informs on MS pathobiology. In both adults and POMS, MS has a negative impact on brain tissue integrity [73]. POMS is associated with failure of age-expected brain growth in childhood and eventual progressive volume loss by adolescence [74]. Interestingly, even at the time of diagnosis, pediatric MS patients had lower brain volume than controls possibly suggesting the neurodegenerative component of MS often precedes first clinical attack [75]. Perhaps more surprisingly, brain volumes and age-expected brain growth are also impaired after even monophasic demyelination, including monophasic ADEM [76•]. The thalamus has been identified as a region of particular vulnerability to this neurodegenerative aspect of POMS [74, 77].

Diffusion tensor imaging (DTI) has shown that both lesional and normal-appearing white matter have decreased fractional anisotropy and increased mean diffusivity—consistent with loss of normal tissue alignment over time in both POMS, and interestingly, even in monophasic demyelination [78]. This further emphasizes the importance of even a single demyelinating event. 7-Tesla MRI, myelin water imaging, and magnetization transfer imaging hold great promise for providing further insights into the underlying pathophysiology of MS in the coming years.

Treatment

Treatment of POMS patients rests largely on case series, consensus, and international guidelines. None of these are sufficiently robust to inform on efficacy. However, all of the published studies of interferon and glatiramer acetate did demonstrate a reduction in relapses post-treatment, and with more rigor, also confirmed a generally favorable safety profile [79–83]. Despite receiving these treatment options, many POMS patients experience new relapses and accrue new lesions, leading to changes from first-line to second-line therapies [84, 85].

The first two randomized clinical trials in POMS have recently been completed. PARADIGMS, a phase 3, 2-year randomized double-blind, double dummy study of 102 POMS patients, demonstrated an 82% reduction in ARR in the fingolimod arm compared to the interferon beta 1a arm. POMS in the fingolimod arm also demonstrated a reduction in several MRI metrics, including reduced rate of new lesions and a reduced rate of brain atrophy up to month 24 (− 0.48 versus − 0.80). More serious adverse events were seen in the fingolimod-treated group than those in interferon-treated patients. Similar to the adult population, serious adverse events included leukopenia, seizure, and hypersensitivity reactions [86••]. The FDA has recently expanded approval of fingolimod to include pediatric patients down to age 10 [87]. Publication of the full trial results is awaited.

The FOCUS trial of dimethyl fumarate was published in 2018 demonstrating safety data [88•]. This was a small phase 2 multicenter study including 22 patients. There was an initial 8-week baseline period during which T2 activity was ascertained. Twenty patients then completed the 24-week treatment period. There was a significant reduction in T2 hyperintense lesion incidence from baseline to the final 8 weeks of treatment. Adverse events were similar to those seen in adults and predominantly consisted of GI symptoms and flushing with no serious adverse events. However, the study was limited by its small size and lack of a control group. CONNECT, an ongoing phase 3 randomized controlled trial of dimethyl fumarate in POMS, is not expected to complete enrollment until 2020 with a study completion date anticipated in 2025 [89, 90].

Other planned or recruiting trials include trials of teriflunomide and alemtuzumab. TERIKIDS, a phase 3 randomized control trial of teriflunomide efficacy in POMS, is expected to have primary data collected in 2019 and study data released in 2021 [91]. LemKids, a study to evaluate efficacy, safety, and tolerability of alemtuzumab, will only enroll pediatric patients who have had disease activity on prior disease-modifying therapy. It is currently enrolling and slated for a completion date in 2025 [92].

There has been a recognition of the utility of B cell-targeted therapies in MS [93]. The mechanism is favored to be secondary to B cell interactions with T cells rather than antibody mediated [94, 95]. Rituximab is widely used in other pediatric autoimmune disorders and has been viewed as having a

favorable safety profile particularly when used in isolation rather than as a part of a combined immunotherapy regimen [96, 97]. Two large randomized clinical trials, OPERA 1 and OPERA 2, have confirmed the efficacy of ocrelizumab, a CD20-directed monoclonal antibody, in adult relapsing remitting MS [98]. Ocrelizumab is also the only FDA-approved medication for primary progressive multiple sclerosis based on positive results in a phase 3 clinical trial in adults [99].

Natalizumab (Tysabri) has been utilized off label in refractory and highly active cases of pediatric multiple sclerosis. In a large Italian registry, 101 patients with pediatric MS were treated with monthly infusions, with a total of 15 relapses in 9 patients over a mean treatment duration of 34 months noted. No serious adverse events were recorded, and no cases of PML were observed [100]. In a retrospective single-center study in Germany, 40% of their 144 patients fulfilled their criteria for highly active MS. These patients demonstrated improved relapse rates and MRI markers of disease activity on both natalizumab and fingolimod with a trend toward greater response to natalizumab [85].

While a comprehensive discussion regarding safety for all emerging new therapies is beyond the scope of this review, it is imperative that clinicians prescribing these therapies be fully versed in the relevant risks, pre-treatment assessments, drug monitoring recommendations, risks to conception, and need for birth control counseling (see Table 1 for a brief summary based on the adult literature [101–103]). All providers must also consider as yet unknown long-term risks. Of particular importance is the need to vaccinate patients (or to have written confirmation of completed vaccination schedules) prior to initiation with therapies that either lead to profound leukopenia or impair vaccine responsiveness. Administration of live, or live-attenuated vaccines is contraindicated with some therapies.

Table 1 Safety and monitoring information of oral and infusion disease-modifying therapies completed or entering trials for POMS

Potential POMS treatment	Primary safety concerns and notable side effects	Monitoring parameters
Fingolimod (Gilenya)	Transient symptomatic bradycardia, AV block, sudden death has been reportedRare elevated liver enzymes Rare macular edema Infection-deaths due to VZV, *Cryptococcus*, and HSV Teratogen Increased rate of basal cell carcinoma, rare PRES and HTN	-First dose monitoring including continuous EKG for at least 6 h or longer PRN -Ophthalmology evaluation at baseline and 3 months -Pre-test for VZV and confirm prior live vaccine administration and vaccinate if negative -Regular CBCs and transaminase screening -BP monitoring at appointments
Dimethyl fumarate (Tecfidera)	Decreased WBCs including prolonged severe lymphopenia Elevated transaminases. Single case of PML reported in MS Angioedema, Flushing, nausea, diarrhea, abdominal pain	-Routine CBC and transaminases -Discontinue if prolonged severe lymphopenia (< 500 cells per mm^3)—may be a PML risk factor
Teriflunomide (Aubagio)	Lymphopenia, flushing diarrhea, nausea, abdominal pain, elevated ALT, paresthesia, increased URI and UTI, increased BP Teratogen	-Transaminase screening, particularly the first 6 months Discontinue if > 3 times normal -Regular BP measurement -Regular CBCs—discontinue if pancytopenia -Pregnancy test prior to beginning
Alemtuzumab (Lemtrada)	Lymphopenia, Infusion reactions Secondary autoimmunity- (thyroid disorders, glomerulonephritis, cytopenias) Increased rate of HSV, CMV, and other infections Increased rate of malignancy—including thyroid cancers and melanoma	-Oral HSV and PCP prophylaxis needed -Regular monitoring labs for secondary autoimmunity with TSH, CBC diff, creatinine, UA -Baseline and monitoring skin exams -Monitor for hypersensitivity reactions during infusion -Confirm vaccinations and vaccinate if negative
Rituximab (Rituxan)	Infusion reactions Increased infection risk No cases of PML in patients treated for MS thus far	-Baseline JC virus status -CD19 monitoring for immune reconstitution and timing of re-dosing -Confirm prior live vaccine administration and vaccinate if negative
Natalizumab (Tysabri)	Elevated risks of developing PML Neutralizing antibodies in ~ 5% Rare infusion reactions Increased infection risk (HSV, hepatitis B—including fatal liver injury)	-Pre-test for JCV then monitor JC virus status at least every 6 months -Monitoring for PML—consider risk factors -Testing for neutralizing antibodies at 6 and 12 months and later for infusion related AEs or treatment failure -Vaccine confirmation and administration as above

AV atrioventricular, *VZV* Varicella zoster virus, *HSV* Herpes simplex virus, *JCV* John Cunningham virus, *PRES* posterior reversible encephalopathy syndrome, *HTN* hypertension, *CBC* complete blood count, *UA* urinalysis, *PCP Pneumocystis* pneumonia, *PML* progressive multifocal leukoencephalopathy

Conclusions and Future Directions

The continued recruitment of POMS patients and children with other demyelinating disorders into research studies and into clinical trials is required to expand knowledge and evidence-based care. Due to the rarity of POMS, recruitment of patients into trials of emerging therapies will continue to be challenging, especially when multiple trials launch concurrently. Critical will be phase 4 observation of all clinical trial participants in order to more fully inform on long-term efficacy and safety.

Models of care may evolve. We may consider transitioning from an initial approach which minimizes possible side effects to an "induction" approach with aggressive early therapy for all patients followed by a later transition to an agent with minimal side effects once excellent disease control is achieved. Ongoing studies may help us define whether this type of approach could delay or reduce the risk of secondary progressive MS, decrease the rate of brain atrophy, and prevent unnecessary morbidity.

The imperative to better provide neuroprotection and to enhance repair is shared across the MS patient age span. Failure of age-expected brain growth and progressive loss of brain integrity in POMS emphasizes this key issue.

Finally, POMS patients become adult MS patients and to date, relatively little is known about the impact of pediatric-onset disease on vocational, social, cognitive, and health-related quality of life into adulthood. Longitudinal care models, shared between pediatric and adult health care providers, are required to seamlessly follow patients over the lifespan.

Compliance with Ethical Standards

Conflict of Interest Brenda Banwell has served as a central MRI reviewer for Novartis for the PARADIGMS trial. This study is referenced in the review.

Scott Otallah declares no potential conflict of interest.

Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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- • Of importance
- •• Of major importance

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