Cleveland Clinic

Mellen Center Approach: Pediatric Onset Multiple Sclerosis

Q: Do children get multiple sclerosis?

A: While rarer than adult-onset, pediatric-onset multiple sclerosis (POMS), defined as first clinical relapse before age 18 years does occur. The world-wide estimate is that about 5% of MS patients present under age 18 years. In the United States, studies estimate a yearly incidence of POMS between 0.18-0.51/100,000. However, the true incidence and prevalence of POMS is not known, and large-scale epidemiologic studies are only now emerging. Delays in diagnosis are common as MS is not always recognized as a pediatric disease. Onset prior to puberty is much rarer, though children as young as 2 years old have been diagnosed. Pre-pubertal POMS tends to affect males and females equally. After puberty POMS resembles adult populations, affecting young women more frequently than young men, about 2-3:1.

Q: What are the risk factors for POMS?

A: Beyond pubertal hormones, there are a variety of other genetic and modifiable environmental risk factors for MS in general and POMS in particular (see Table 1). In general, MS is most common in Caucasian patients. While no one gene is known to "cause" MS, approximately 50 genetic susceptibility loci have been identified. In children of European ancestry, the Human Leukocyte Antigen (HLA)-DRB1*15 allele contributes the greatest risk for MS, particularly in combination with environmental risk factors. MS can run in families, with 15 to 20% of MS patients reporting their having a family member with MS. Children with a first degree relative with MS (i.e. parent or sibling) do have a 2-4% increased risk of developing MS above the general population

Table 1. Highest Risk Factors for Pediatric-Onset MS

	Genetic	Environmental	Modifiable
Caucasian	Yes	No	No
HLA-DRB1*15	Yes	Yes	No
Obesity	Maybe	Yes	Yes
Puberty	Yes	No	Maybe
Smoking (primary or second hand)	No	Yes	Yes
Epstein-Barr Exposure	No	Yes	No
Low Vitamin D	Maybe	Yes	Yes

Like adults, modifiable environmental risk factors exist for POMS. The incidence and prevalence of POMS increases the farther from the equator one lives, an effect thought to be mediated by low vitamin D levels. Vitamin D plays an important role in immune system regulation, and low vitamin D is associated with increased risks for developing MS and MS disease activity (i.e. clinical relapses and new demyelinating lesions on MRI). Other modifiable risk factors particularly important for POMS include past exposure to Epstein-Barr Virus (EBV), exposure to second-hand (or first-hand) smoking, and obesity. Obesity may interact with and exacerbate one's genetic risk for developing MS in patients with HLA-DRB1*15 alleles.

Q: What are the symptoms of POMS?

A: Like adult-onset MS, POMS patients manifests neurologic symptoms resulting from an autoinflammatory attack by the immune system directed against components of the myelin sheath, a fatty substance that surrounds and protects neuronal

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axons in the optic nerve, brain, and spine, collectively the central nervous system (CNS). This leads to loss of the myelin, or demyelination, and subsequent injury to the nerves themselves. The symptoms of POMS depend on where this inflammatory attack occurs. Children tend to present with multifocal symptoms simultaneously. However, children may not report symptoms readily, particularly if they involve bladder or bowel dysfunction. Further, children and adolescents may not be aware of their most common symptoms including fatigue, depression/irritability, and cognitive impairment, and parents may dismiss these as being a "typical teenager".

Q: Are there clinical differences between POMS and adult-onset MS?

A: Like adults, POMS patients typically have relapsing-remitting MS (RRMS), defined as discrete episodes of clinical symptom onset or exacerbation with complete or partial recovery and no progression of disability between relapses. Whereas primary progressive MS occurs in about 15-20% of adults, and is defined by progressive accumulation of disability without clinical relapses, it is extremely rare in pediatric patients. Children and adolescents tend to have more frequent relapses early in their course, with more than twice as many relapses per year as adults over the first six years after diagnosis.

Despite increased clinical disease, many POMS patients continue to have normal exams, and may not accumulate noticeable disability early on. Children also tend to recover from relapses more quickly than do adults, with mean symptom duration of 4 weeks compared to 6-8 weeks, respectively. However, due to the early onset of their disease, POMS patients do accumulate disability earlier in life than adult-onset MS patients. POMS patients are also more likely to have neurocognitive symptoms out of proportion to motor and sensory symptoms early in their course.

Q: Are there differences between MRI findings in POMS and adult MS?

A: POMS patients tend to demonstrate more disease activity on MRI early in their disease compared to adults. At the time of disease onset, pediatric patients have a greater number of T2 bright lesions, more large (>1 cm) T2 bright lesions, and more gadolinium-enhancing, or active lesions than their adult counterparts. In addition, they accumulate new T2 bright and gadolinium-enhancing lesions more quickly on second MRIs compared to adults; paradoxically, POMS patients are more likely than adult MS patients to show spontaneous reduction in size of existing lesions on serial scans. POMS patients also tend to have more posterior fossa lesion burden, though other anatomical distributions of lesions are similar.

Q: Are there neurodevelopmental consequences to POMS?

A: Yes. While MS is considered both a neuroinflammatory and neurodegenerative disease in adults, children and adolescents have brains that are still developing. Thus there may be neurodevelopmental consequences in addition to neuroinflammatory and neurodegenerative sequelae in POMS patients. In fact, studies have demonstrated reduced age-expected brain growth in POMS patients. Recent longitudinal studies demonstrated disproportionate cognitive impairments in POMS patients compared to their physical disability. These early deficits may have significant impacts on academic and career performance, yet be subtle enough to be missed without dedicated neuropsychological testing. In addition, adolescence is an important period of physical maturation encompassing vertical growth, sexual maturation, bone mineralization, and continued maturation of the immune system. While POMS does not appear to disrupt other organ systems (beyond neurogenic symptoms and their sequelae), treatment of POMS with immunosuppressive and immune modulating medications may have long term side effects impacting general health and other organ systems.

Q: What is the differential diagnosis for POMS?

A: Since MS is rare in pediatric populations, when considering an MS diagnosis, other MS mimicking diseases that manifest in pediatric and adolescent populations must be considered and ruled out. Other conditions to consider include: infection; other neuroinflammatory diseases such as neuromyelitis optica spectrum disease (NMOSD), and systemic inflammatory or rheumatologic diseases such as lupus or sarcoidosis; nutritional and vitamin deficiencies; and vascular disease. Genetic and metabolic diseases that present in childhood can mimic acquired demyelinating disease, and should

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be considered in any child with developmental delays or intellectual disability, or who present with radiographic abnormalities or symptoms atypical for MS (Full POMS differential is detailed in appendix, Table 4). Acute disseminated encephalomyelitis (ADEM) is a typically monophasic acute or subacute demyelinating syndrome associated with altered mental status. It is more common in childhood than adulthood, particularly in school aged children age 3-8 years of age. ADEM is often preceded by an illness or vaccination, though for many patients there is no apparent causal infectious or inflammatory event.

Q: Is POMS diagnosed differently than adult MS?

A: In 2013, the International Pediatric MS Study Group (IPMSSG) published its diagnostic criteria for POMS. Like adult MS, POMS is a clinical diagnosis, though magnetic resonance imaging (MRI) helps to sensitively identify patients with inflammatory demyelinating disease and aids diagnosis. Regardless of age at onset, MS is a dynamic disease described as being disseminated in space (DIS) and disseminated in time (DIT). Contrasted with a monophasic pediatric neurologic disease (i.e. perinatal hypoxic ischemic encephalopathy resulting in clinical sequelae), DIT refers to new clinical symptoms or radiographic lesions that occur independently at different times. DIS, on the other hand, refers to neuroinflammatory injury affecting multiple CNS regions, with or without corresponding clinical symptoms. Both pediatric and adult patients must satisfy criteria for DIS and DIT to be diagnosed with MS (see below), though adult diagnoses are based on the 2010 McDonald criteria. These criteria have not been validated in children <12 years of age.

The IPMSSG 2013 diagnostic criteria for POMS diagnosis include:

- >2 non-encephalopathic clinical relapses with presumed neuroinflammatory etiology, more than 30 days apart, and involving more than one area of the CNS
- One non-encephalopathic clinical relapse typical of MS with MRI findings satisfying the 2010 revised McDonald criteria for DIS, and a subsequent MRI with at least one new enhancing or non-enhancing lesion satisfying DIT
- ADEM followed by a non-encephalopathic clinical relapse typical of MS at least 3 months after **initial symptom onset**, and associated with new MRI lesions, satisfying the 2010 revised McDonald DIS criteria
- Children older than 12 years experiencing an acute, non-encephalopathic clinical relapse typical of MS with an MRI satisfying the 2010 Revised McDonald criteria for DIS and DIT.

Q: What diagnostic testing do you recommend when considering a POMS diagnosis?

A: Diagnosing MS in pediatric patients requires both clinical and paraclinical evaluations (summarized in Table 2). In addition to a detailed history (prenatal, birth, and neurodevelopmental/school histories), and neurologic exam, paraclinical studies are also important, particularly MRI of the brain (including orbits if there is suspected optic neuritis), and cervical spine; if symptoms localize distal to the cervical cord, then a thoracic spine MRI should be included as well. While concerns have been raised about repeated gadolinium administration, the use of contrast enhanced MRI is needed both to help diagnose MS and gauge disease activity. Thus, at this time, we continue to recommend MRIs with and without gadolinium enhancement in POMS diagnosis and management.

In cases where the clinical or radiographic data are suggestive of MS, some pediatric patients may require further paraclinical studies to aid an MS diagnosis. Routine blood work should exclude the above mentioned MS mimicking diseases including NMOSD and other inflammatory diseases, infection, and metabolic abnormalities or vitamin deficiencies. In pre-pubertal children lumbar puncture for cerebrospinal fluid (CSF) analysis is warranted to rule out MS mimicking diseases, and to look for inflammatory markers consistent with MS. CSF studies in non-encephalopathic pediatric patients that satisfy the above diagnostic criteria are not mandatory, but may be considered on an individual basis, depending on clinician preference and clinical context. CSF analysis is warranted in all encephalopathic pediatric patients with demyelinating lesions, with or without fever. Other potentially useful testing in the diagnosis or monitoring of POMS may include optical coherence tomography (OCT), and evoked potentials (visual, brainstem

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Table 2. Diagnostic Testing for POMS

Recommended Diagnostic Testing

Neuroimaging

MRI brain (and orbits if needed) with and without gadolinium

MRI cervical spine with and without gadolinium

MRI thoracic spine with and without gadolinium (if symptoms localize distal to cervical spine)

Serum

CBC
CMP
NMO-IgG (cell-based assay)
ANA (with reflex to dsDNA and anti-ENA panels)
TSH
B12
MMA
Folate
VZV IgG
JCV IgG and Index
Vitamin D-25-OH
beta-HCG (in post-pubertal young women)

Other Testing to Consider

Lumbar Puncture	**Findings Suggestive of MS**
Opening Pressure	Normal or slightly elevated
CSF Cell Count	WBC < 50 (Lymphocytic predominance); Pre-pubertal children may have neutrophilic predominance
CSF Protein	Normal or slightly elevated
CSF Glucose	Normal or slightly elevated
CSF Oligoclonal Bands	>4 unique bands not found in serum
CSF IgG Synthesis Rate	Elevated
CSF IgG Index	Elevated

Dilated ophthalmology exam
OCT
Visual field testing
Visual Evoked Potentials
Brainstem Auditory Evoked Potentials
Somatosensory Evoked Potentials (Upper and lower extremity)
Neuropsychology Battery Testing

Not clinically useful:

CSF Myelin Basic Protein
CSF Kappa Lite Chains
CSF NMO-IgG

auditory, and/or upper and lower limb somatosensory). We advocate baseline neurocognitive testing for all newly diagnosed POMS patients, and subsequent testing as needed if neurocognitive symptoms manifest. A dilated funduscopic exam by a pediatric or neuro-ophthalmologist can help assess acute optic neuritis, optic atrophy, and other MS-related visual or ophthalmic abnormalities, as well as screen for other inflammatory, infectious, genetic or metabolic diseases.

Q: How do you monitor children following a first demyelinating event?

A: Similar to adults, children with a clinically isolated syndrome (CIS) may be at increased risk for developing MS. Less than 10% of patients with ADEM go on to develop MS, whereas children and adolescents with non-encephalopathic CIS may have 30-60% risk of developing MS in 5 years, similar to adults. Pediatric patients with CIS are at higher risk for developing POMS if they present initially with: post-pubertal onset, optic neuritis, and CSF OCBs. Conversely, lower risk for POMS is associated with pre-pubertal CIS onset, multifocal symptoms with encephalopathy, and transverse myelitis. While still experimental, antibodies against myelin oligodendrocyte glycoprotein (anti-MOG), are negatively correlated with a second demyelinating. For pediatric CIS patients we advocate close clinical follow up with frequent (i.e. every 6 month) MRI of the brain, though follow up MRI as early as 3 months may be appropriate. Educating parents and children about symptoms of demyelination may help hasten their reporting a second relapse. New MS-typical T2 or gadolinium enhancing MRI lesions, even without new symptoms, would be sufficient to diagnose MS and would warrant treatment. For asymptomatic pediatric patients with incidentally found demyelinating lesions, or Radiologically Isolated Syndrome (RIS), we recommend following clinically and with MRI of the brain with and without contrast every 6 months. As in adults, there is no clear correlation between RIS and clinically definite MS in children, even if new T2 lesions develop on subsequent MRIs. **However, if there are new gadolinium-enhancing lesions, or T1 black holes found on MRI, it is our opinion that these patients are at high risk for MS and should be offered treatment.**

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Q: What treatments are available for relapses in POMS?

A: Treatment of acute relapses in POMS is similar to adult MS. First line treatment for an acute relapse utilizes high dose corticosteroids, typically methylprednisolone 30mg/kg/day (sometimes divided q6h) with a maximum dose of 1000mg daily, for 3-5 days. While not obligatory, pulse steroids are often followed by a two-week tapering dose of oral prednisone (starting dose1-2mg/kg/day, or 60mg/day, then 40mg/day, then 20 mg/day). In patients with refractory disease that respond incompletely to high dose IV steroids, or have symptom exacerbation while on oral tapering steroid, a second round of high dose steroids may be needed followed by a slower oral steroid taper over 6 weeks. All pediatric patients treated with high dose steroids need to be counseled about potential steroid side effects, and prophylactic treatment with an H2 blocking medication or proton-pump inhibitor should be provided for the duration of the treatment to prevent steroid-related gastritis. Other acute treatment considerations in refractory POMS relapse include intravenous immunoglobulin (IVIG) 2mg/kg divided over 2-4 days, or plasma exchange (PLEX). However, if a patient is either refractory to steroid treatment, or exquisitely steroid-responsive with breakthrough disease on taper, consider another diagnosis other than POMS.

Q: What treatments are available to prevent relapses in POMS?

A: Early treatment of MS with a disease modifying therapy (DMT) is essential to preventing clinical relapses, and CNS injury which leads to both cognitive and physical disability. At present there is no cure for MS, therefore POMS patients will require life-long treatment to prevent relapses and disability accumulation, and address sequelae of this chronic disease. With this in mind, the new standard by which DMTs are judged is the prevention of all disease activity and disability accumulation, or "No Evidence of Disease Activity" (NEDA). This high benchmark, which includes both clinical and radiographic evidence of disease activity, has been incorporated into clinical trials as a secondary outcome measure. However, in clinical practice, NEDA has been shown to be extremely difficult to achieve, with one prospective review demonstrating only 7% of patients achieving NEDA after 7 years. There is no data regarding NEDA in POMS. However, as a clinical principle we endorse NEDA as the goal for all MS patients, regardless of age of onset of their disease.

At this time there are 14 FDA-approved DMTs to treat adults with relapsing forms of MS, and several more in clinical trials or under regulatory review. In contrast, none have been rigorously studied in clinical trials of pediatric patients, and thus none are approved for patients less than 18 years of age. The off-label use of injectable beta-inteferon-1a or 1b or glatiramer acetate has been the standard of care for POMS patients since their introduction in the 1990s. Retrospective analyses have demonstrated these treatments to be safe, well tolerated, and to have similar efficacy as in adult MS patients. However, pharmacokinetic studies in children remain lacking, and thus dose adjustments for younger or smaller children are not available; typically adult dosing is recommended unless there is a toxicity or tolerability issue. Roughly 30% of POMS patients will have an inadequate response to their injectable DMT, and thus need to be switched to another DMT. The IPMSSG defines inadequate response as:

- Adequate trial of the DMT for at least 6 months with good compliance, and
- MRI disease activity defined as new T2 lesions or new T1 enhancing lesions, or
- 2 or more clinical or radiographic relapses in 12 months or less, or
- Increased disease activity or no reduction in disease activity compared to the pre-treatment period

Intolerability and non-compliance may also require POMS patients to switch from an initial therapy. In a small 18 month retrospective study, POMS patients who switched between injectable therapies (from beta-interferon-1a to glatiramer, or vice versa), a little over 40% continued to have refractory disease on the second medication. Thus, some POMS patients will require treatment escalation from an injectable DMT to one of the higher potency oral or IV infusion medications. These second line DMTs too have not had sufficient study to be approved in patients under age 18 years. However, case series have demonstrated tolerability and efficacy of natalizumab and rituximab. While there may be clinician and parental concern about using these second-line agents in pediatric patients, the risk of any treatment should be weighed

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against the individual patient's risk of MS disease activity resulting in permanent CNS injury and disability. At the Mellen Center, we advocate using higher potency DMTs as first line agents with the goal of achieving NEDA in order to prevent MS-related neurocognitive and physical disability.

Table 3. DMTs by route of administration and Mellen Center Recommendations for POMS

DMT	Route	Efficacy/MOA	Safety/Side Effects	MC Recommendation
Interferon-beta1a	IM (once weekly) SC (twice monthly)	+ Multiple effects, promotes anti-inflammatory action of T, B, and antigen presenting cells.	+ + + + Injection reaction, LFT elevation, flu-like symptoms, worse depression, headache, and spasticity, neutralizing antibodies, not safe in pregnancy	Avonex (IM) or Plegridy (SC) as first-line for mild to moderate disease burden. Compliance is an issue.
Glatiramer Acetate	SC	+ Induces TH2 suppressor phenotype and anti-inflammatory cytokine production	+ + + + Injection rxn, liponecrosis, idiosyncratic rxn Safe to use during pregnancy if needed (Category B)	First line for mild disease activity/ burden or risk-averse family. Compliance is an issue.
Fingolimod	Oral	+ + S1P receptor modulator, Traps activated lymphocytes in peripheral lymph nodes	+ + + FDO for bradycardia, HTN, macular edema, headaches, risk for VZV/ herpes infection, remote PML risk, not safe in pregnancy	First line for mild to moderate disease activity/burden. Second line for breakthrough disease on injectable/oral DMT. Compliance is an issue.
Dimethyl fumarate	Oral	+ + Activation of NRF2 anti-oxidative stress pathway, unknown	+ + + GI upset, vasodilatory flushing, lymphopenia (may be prolonged in subset of patients), remote PML risk	First line for mild to moderate disease activity/burden. First line for mild to moderate disease activity/burden. Second line for breakthrough disease on injectable DMT. Compliance is an issue.
Teriflunimide	Oral	+ inhibits pyrimidine biosynthesis, disrupts T cell- antigen presenting cell interactions	+ + LFT elevation, alopecia, nausea, diarrhea, teratogenic (penetrates semen so caution in males too)	We do NOT recommend use of Teriflunimide in pediatric or adolescent patients.
Natalizumab	Intravenous infusion	+ + + + Monoclonal antibody against alpha-4-integrin, blocks activated lymphocyte adhesion and migration into CNS.	+ + + + (JCV negative) + (JCV Positive) Infusion reaction, fatigue, neutralizing antibodies. In JCV Positive patients, highest risk for PML associated with previous immunosuppression and >2 years Natalizumab use	First line for JCV negative patient with moderate to severe disease activity and lesion burden. Second line for JCV negative patient with breakthrough disease on other DMT. Compliance NOT an issue, directly observed therapy.

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Table 3. DMTs by route of administration and Mellen Center Recommendations for POMS (continued)

Rituximab	Intravenous infusion	+ + + + Monoclonal antibody against CD20, depletes B cells through complement-dependent and antibody mediated cellular toxicity	+ + Infusion reaction (potentially fatal), blocking antibodies, increased risk for serious infections (HBV reactivation), remote PML risk	Recommended for highly active MS patients who are JCV positive. Very expensive, and insurance coverage can be an issue. Compliance NOT an issue, directly observed therapy.
Alemtuzumab	Intravenous infusion	+ + + + Monoclonal antibody against CD52, depletion of lymphocytes, mononuclear cells, natural killer cells, some granulocytes.	+ High risk for infusion reactions, mild risk for infection, autoimmune thyroid disease, and serious autoimmune thrombocytopenia, nephropathy, and malignancy (thyroid, skin, lymphoproliferative)	Alemtuzumab should only be used in extremely refractory POMS with breakthrough disease on 2 or more higher potency DMTs, and if JCV positive. Compliance NOT an issue, directly observed therapy.
Ocrelizumab	Intravenous infusion	+ + + + Humanized monoclonal antibody against CD20, rapid depletion of B cells with more antibody-mediated cytotoxicity and less complement-mediated.	+ + + Infusion reactions, neutralizing antibodies (less risk than Rituximab), risk of serious infection (though early safety appears very promising), PML risk is unclear but likely remote	Not yet commercially available. Once available, this will be a first-line therapy for all POMS patients regardless of JCV status and disease activity. Compliance NOT an issue, directly observed therapy.

Abbreviations: GI: Gastrointestinal; IM: Intramuscular (injection); JCV: John Cunningham Virus (associated with PML); LFT: Liver Function Tests; PML: Progressive Multifocal Leukoencephalopathy; SC: Subcutaneous (injection); S1P: Sphingosine-1-phosphate; +: mild efficacy/poor safety; + + : moderate efficacy/safety; + + +: highly effective/safe; + + + +: most effect/safest.

Q: What other factors should be considered when treating POMS?

A: Other factors to consider when treating POMS patients with standard injectable DMTs or second line agents include route of administration, medication compliance, potential teratogenicity in young men and women of child bearing age, the need for safety monitoring through frequent blood work, and potential long-term effects of medication on a developing immune system and CNS. All POMS patients, but older teenagers in particular, should have a voice in treatment discussions, and while parental consent is needed to start DMT, POMS patient assent and understanding should also be sought.

Q: When should POMS patients transition to adult neurologist and other specialists?

A: Transition of care from pediatric to adult treatment teams should be planned **prior** to a patient's 18th birthday. While many pediatric neurologists can continue to care for their established patients through age 21 (or older in some cases), these discussions should include transitioning responsibility from legal guardians to the patients themselves. Most teenagers are not familiar with making and keeping appointments, taking and refilling medications, and may not be forthright in reporting new or worsening symptoms. If possible, these skills ought to be developed in the years before a POMS patient turns 18, and should continue to be emphasized by the patient's caretakers and clinical care team even after achieving the age of majority. Depending on their comfort level, some POMS patients may benefit from signing documentation permitting their parents to discuss protected health information on their behalf. The Cleveland Clinic, under the leadership of Carrie Cuomo, CPNP, will be developing pediatric to adult transitional care projects to address these issues

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(more info available at http://consultqd.clevelandclinic.org/2015/06/standardizing-best-practices-in-the-transition-from-pediatric-to-adult-care/) .

Q: Can anything else be done to improve a POMS patient's prognosis?

A: Beyond choosing a DMT, there are many factors important to maintaining one's health that can improve a POMS's patient's disease course. Vitamin D appears to play a vital role both in the pathogenesis of MS and its disease course. Vitamin D levels should be checked at clinical presentation, and if necessary oral supplementation should be initiated using a high quality Vitamin D supplement. For all POMS patients, target vitamin D levels should be in the high normal range, between 70-80 nmol/mL, and can often be achieved by oral doses of Vitamin D3 2000 to 5000 units daily (for patients >12 years or 35 kg). For younger or smaller patients, doses of 800-2000 units can be considered, depending on the baseline vitamin D level.

Like adult MS patients, disease modifying strategies are extremely important for reducing risk of MS relapses and MS-related morbidity in POMS patients. These strategies should target overall physical and emotional wellness and include:

1) Good sleep hygiene with at least 8 hours of restorative sleep per night
2) Healthy diet high in fruits, vegetables, whole grains, lean protein, polyunsaturated fats, and sparing in processed foods, refined sugars, and saturated fats from meat or dairy, with copious water consumption (1.5 to 3 L of water daily depending on size and activity level)
3) Daily cardiovascular exercise at least 30 minutes, more as tolerated
4) Stress reduction and emotional wellness, for which psychological counseling can be extremely helpful
5) Avoiding tobacco exposure, both primary and second-hand smoking, alcohol or drugs
6) Addressing and treating comorbid medical problems such as obesity, ADHD, headaches, and psychiatric conditions, and
7) Routine health maintenance screening and vaccination (inactivated vaccines preferred, particularly if on DMT) through a primary care physician.

Q: What other resources do POMS patients need?

A: Like many chronic diseases, the management of MS is complex and often requires a multidisciplinary approach. We recommend the following team:

- A pediatric or adult neurologist with experience treating MS
- A primary care physician, i.e. pediatrician or family physician to provide routine screening, vaccination, and other preventative medical practices recommended by the American Academy of Pediatrics
- Pediatric or adolescent psychologists and psychiatrists to address depression, anxiety, and other mood and stress related issues are common in POMS.
- Depending on the degree of physical disability, physiatrists, physical and occupational therapists may be needed for rehabilitation following an acute MS relapse, or for chronic symptom management.
- Neuropsychologist to document neurocognitive deficits
- School guidance counselors, psychologists, teachers, and administrators are important allies in establishing in-school supports. All parents in Ohio are permitted to request in writing a multifactored evaluation (MFE), which should be completed by the school system within 60 days, and is often needed to establish educational modifications.

Following an MS diagnosis, many children, teens, and their families feel isolated, and are in need of support beyond what is available from their healthcare team. In addition to a family's social and emotional support system, the National MS Society offers free online support through their Pediatric MS Support page. They offer free, downloadable information for parents of children and teens with MS, resources for educational and school-related issues in MS, and links to the Network of Pediatric MS Centers such as ours, where patients can find clinicians with experience in POMS.

USEFUL RESOURCES FOR POMS:

http://www.nationalmssociety.org/What-is-MS/Who-Gets-MS/Pediatric-MS/Care-for-Pediatric-MS-(Centers-of-Excellence)

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http://www.nationalmssociety.org/Resources-Support/Resources-for-Specific-Populations/Pediatric-MS-Support-Network

http://www.usnpmsc.org/

http://www.ipmssg.org/

Summary:

While rare, pediatric-onset MS (POMS) occurs in roughly 5% of all MS cases. POMS patients tend to have more frequent relapses early in their course, and appear to have disproportionate neurocognitive symptoms compared to physical disability. However, due to their early disease onset, POMS patients tend to be more disabled at earlier ages than their adult counterparts. Treatment for acute relapses in POMS is identical to adult MS patients, while no disease modifying therapy (DMT) is FDA-approved for use in patients < 18 years. However, early treatment with off-label use of DMTs is standard of care in POMS, typically beginning with a standard injectable DMT and escalating as needed (and with caution) to second-line therapies. Clinical trials of DMTs in POMS are currently recruiting patients. All POMS patients should have vitamin D testing and be supplemented aggressively to achieve blood levels between 70-80 nmol/mL. POMS patients require multidisciplinary care, and strategies that promote general emotional and physical wellness improve prognosis.

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Table 4. Differential Diagnosis of Pediatric Demyelinating Diseases (from Chitnis 2013):

DIFFERENTIAL	WORK UP
Tumor	
CNS Lymphoma	MRI; MRS; PET; CSF Cytology; Cell Count
Astrocytoma/glioma	MRI; MRS; PET imaging
Metastasis	MRI; MRS; PET imaging; tumor survey
Immunologic	
Systemic lupus erythematosus	Antinuclear antibody (ANA) (extractable nuclear antibodies if ANA is positive); complement; double-stranded DNA; rheumatologic evaluation
Antiphospholipid syndrome	Antiphospholipid antibodies (anti-cardiolipin, ß-2 glycoprotein 1); lupus anticoagulant; rheumatologic evaluation
Rheumatoid arthritis	Rheumatoid factor; erythrocyte sedimentation rate; rheumatologic evaluation
Poststreptococcal syndrome	Antistreptococcal antibody
Behçet syndrome	Examination for orogenital ulcers; pathergy test
Sarcoidosis	Angiotensin-converting enzyme level serum and CSF; chest x-ray; rheumatologic evaluation
Sjogren syndrome	ANA; anti-Ro (SSA) antibody; anti-La (SSB) antibody
Wegener granulomatosis	Antineutrophil cytoplasmic antibody; rheumatologic evaluation Consider uveal biopsy
Lymphomatoid granulomatosis	CSF cytology with B-cell subsets; immunohistochemistry PCR-single-stranded conformational polymorphism analysis for heavy-chain immunoglobulin and T-cell receptor gamma
Hemophagocytic lymphohistiocytosis	Histiocytes on peripheral blood smear or bone marrow, or biopsy of lymph node or CNS lesion
Hashimoto encephalopathy	Antithyroid peroxidase; antithyroglobulin antibodies in serum; thyroid function tests
Limbic encephalitis	Anti-N-methyl-D-aspartate (NMDA) receptor and anti-voltage-gated potassium channel-complex antibodies in serum and CSF
Infection	
Lyme Disease	Lyme antibody in serum and CSF PCR in endemic areas
HIV	HIV testing; screening for opportunistic infections
Herpes simplex virus	Herpes simplex virus PCR in CSF
Human T-cell lymphotropic virus type 1	Human T-cell lymphotropic virus type 1 antibody in CSF
Progressive multifocal leukoencephalopathy	John Cunningham (JC) virus PCR in CSF
Neurosyphilis	Serum and CSF Venereal Disease Research Laboratory (VDRL) test
Catscratch disease	Serology for Bartonella henselae
Whipple disease	Histopathologic study or PCR; lymph node biopsy with Gram stain
Vascular disorders	
Stroke	MRI with diffusion-weighted imaging sequences; stroke in young workup
Arteriovenous malformation	Magnetic resonance angiogram (MRA)
Consider conventional angiogram	
Sickle cell disease	Hemoglobin electrophoresis; peripheral blood smear
Moyamoya disease	MRA; Consider conventional angiogram
Notch 3 mutation; skin biopsy	
Complicated migraine	Point mutations in the CACNA1A, ATP1A2, and SCN1A genes if history is suggestive of familial hemiplegic migraine

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DIFFERENTIAL	WORK UP
Vascular disorders (continued)	
Primary angiitis of the CNS	Serum erythrocyte sedimentation rate, C-reactive protein, von Willebrand factor antigen, MR angiogram Consider conventional angiogram and brain biopsy
Susac syndrome	Retinal fluorescein angiogram; audiometric testing
Nutritional	
Vitamin B12 deficiency	Vitamin B12 in serum; methylmalonic acid; homocysteine level; peripheral blood smear for macrocytes; mean corpuscular volume
Folate deficiency	Folic acid level in serum and CSF: Consider methylenetetrahydrofolate reductase levels
Metabolic	
Fabry disease	Low or absent alpha-galactosidase A; enzyme level in plasma, serum, leucocytes, or cultured fibroblasts; DNA analysis; skin, kidney, or conjunctival biopsy
Biotinidase deficiency	Serum biotinidase; ammonium and lactic acid levels
3-Methylglutaric acid deficiency	Urine organic acids (3-methylglutaric acid)
Neuronal ceroid lipofuscinosis	Skin biopsy; enzyme assay for CLN1 and CLN2; molecular genetic testing for CLN1, CLN2, CLN3, CLN6; electroretinogram
Adult polyglucosan disease	Glycogen branch enzyme; molecular genetic testing
Leukodystrophy	
Adrenoleukodystrophy or adrenomyeloneuropathy	Plasma very long chain fatty acids; ABCD1 genetic mutation
Metachromatic leukodystrophy	Arylsulfatase A in leukocytes and culture fibroblasts; sulfatides in urine; evoked potentials including visual evoked potentials, somatosensory evoked potentials, and brainstem auditory evoked potentials; nerve conduction study; molecular genetic testing for SUMF1
Alexander disease	Molecular genetic testing for GFAP mutation
Krabbe disease	Galactocerebroside-ß galactosidase in leukocytes or cultured fibroblasts and CSF; EMG/nerve conduction velocity; GALC genetic testing
Pelizaeus-Merzbacher disease	PLP gene mutation
Vanishing white matter disease	EIF2B1-5 genetic mutation
Mitochondrial Disease	
Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS)	Lactate and pyruvate levels in CSF and serum; mitochondrial genetic testing; muscle biopsy and histopathology
Leber hereditary optic neuropathy	Lactate and pyruvate levels in CSF and serum; mitochondrial genetic testing; muscle biopsy and histopathology study
Degenerative	
Hereditary spastic paraparesis	Hereditary spastic paraparesis genetic testing
Friedrich ataxia	Levels of vitamin E, albuminemia, cholesterol and triglyceride; ECG; nerve conduction studies; ophthalmologic testing; molecular genetic testing
Spinocerebellar atrophy	SCA/ADCA genetic testing

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