PEDIATRIC MULTIPLE SCLEROSIS
Sourcebook for MS Care Professionals

December 2018

- Pathophysiology and Diagnosis in Pediatric MS
- Disease-Modifying Treatment for Pediatric MS
- Comprehensive Care of Pediatric and Adolescent MS

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Continuing Education Supplement to the *International Journal of MS Care*
This activity is supported by an educational grant from Novartis Pharmaceuticals Corporation.

THE CONSORTIUM OF MULTIPLE SCLEROSIS CENTERS

Pediatric Multiple Sclerosis: Sourcebook for MS Care Professionals

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Neurologists, primary care physicians, physician assistants (PAs), nursing professionals, and other members of the care team who manage pediatric patients with demyelinating diseases.

Learning Objectives

1. Apply currently recommended criteria for the differential diagnosis of MS in pediatric patients.
2. Interpret recent evidence for disease-modifying treatment in patients with pediatric MS, including treatment selection, dosage, frequency, and need for monitoring.
3. Plan and implement a comprehensive care plan for the patient with pediatric MS that emphasizes partnership with the patient and family.

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Pediatric Multiple Sclerosis: Sourcebook for MS Care Professionals

Multiple sclerosis (MS) is often considered to be an adult disease. Approximately 3% to 5% of all cases of MS affect pediatric patients, most of whom are teenagers age 13 and over.[1-3] Diagnosis of MS in children under age 10 occurs in less than 1% (0.2% to 0.7%) of all cases of MS.[4,5] Currently pediatric MS affects an estimated 8,000 to 10,000 children in the U.S. and as many as 1,500 to 2,000 in Canada.[6,7]

Management of MS in a pediatric patient—especially in a younger child—requires a careful approach that differs in many respects from that of adults with MS. There is a need to consider the impact of treatment on the developing immune system and brain and over a longer-term disease course.[2] Family involvement is central to management but should shift toward increasing autonomy for the patient as the child matures.

Ideally, pediatric MS should be managed at a specialized center or by a pediatric neurologist with expertise in this area. However, due to geographic limitations and other access issues, some patients may be managed in a general neurology or pediatric practice in consultation with a pediatric MS center. **Appendix A** provides a listing of specialized pediatric MS centers in the U.S. and Canada.

This guidebook for MS care practitioners was developed in conjunction with two neurologists and a clinical nurse specialist who specialize in pediatric MS, based on a roundtable discussion, current research, and recent consensus statements.[8-11]

Part 1. Pathophysiology and Diagnosis of MS: Distinguishing Between Children and Adults

Characteristics of Pediatric MS

The International Pediatric MS Study Group has defined criteria for pediatric MS and other demyelinating diseases, shown in **Table 1**.[8] Careful differential diagnosis is especially important in a child with a suspected demyelinating disease. Children are more likely than adults to present with acute disseminated encephalomyelitis (ADEM), a demyelinating disorder that is usually an isolated event.[12] Other conditions that mimic pediatric MS include neuromyelitis optica spectrum disorder (NMOSD), CNS vasculitis, some neoplasms, and leukodystrophies.[2,13,14]

Definition of Pediatric MS

Pediatric MS is defined as central nervous system (CNS) demyelination in a person under age 18 with the following characteristics:[11,14]

- 2 or more episodes of CNS demyelination separated by more than 30 days and involving more than one area of the CNS.
- > 2 **non-encephalopathic** inflammatory CNS events, >30 days apart, in > 1 CNS area

OR

- 1 non-encephalopathic episode typical of MS
  - MRI, 2010 Revised McDonald Criteria for dissemination in space (DIS)
  - On follow-up MRI, ≥1 new lesion (dissemination in time; DIT)

OR

- One encephalopathic attack plus one non-encephalopathic attack > 3 months later
  - Lesions on MRI satisfying 2010 DIS criteria

OR

- Non-ADEM* event with MRI satisfying McDonald criteria for DIS/DIT (in patients >12 years of age)

*Acute disseminated encephalomyelitis

In about 5% to 15% of children evaluated, an acute attack that resembles ADEM is the clinical event. For a diagnosis of MS in these cases, there

Table 1. Differential Diagnosis of Pediatric MS and other CNS Demyelinating Conditions

Based on International Pediatric Multiple Sclerosis Study Group Definitions, 2012 and 2016 revisions

Pediatric clinically isolated syndrome (CIS) (all are required)

- Clinical CNS event with presumed inflammatory demyelinating cause
- Absence of clinical history of CNS demyelinating disease (if any, see pediatric MS)
- No encephalopathy except as readily explained by fever
- Criteria for MS diagnosis on baseline MRI are not met

Pediatric acute disseminated encephalomyelitis (ADEM) (all are required)

- First polyfocal, clinical CNS event with presumed inflammatory demyelinating cause
- Encephalopathy not explained by fever
- No new clinical or MRI findings 3 months or more after onset
- Abnormal brain MRI during acute (3 months) phase with typically diffuse, poorly demarcated large lesions involving predominantly the cerebral white matter

Pediatric MS (any of the following)

- 2 or more CIS separated by > 30 days involving more >1 area of CNS
- 1 CIS associated with MRI findings consistent with dissemination in space (DIS) criteria ***and*** follow-up MRI showing at ≥1 new lesion consistent with dissemination in time (DIT) criteria
- 1 ADEM attack followed by 1 CIS, 3 or more months after symptom onset associated with new MRI findings consistent with criteria for DIS
- A CIS whose MRI findings are consistent with criteria for DIS and DIT (at least 1 T2 lesion in at least 2 of 4 areas: spinal cord, infratentorial, juxtacortical, and periventricular [DIS] associated with a simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions [DIT] if the patient is ≥12 years old

Pediatric neuromyelitis optica spectrum disorder (NMOSD)

NMOSD with AQP4-IgG

1. At least 1 core clinical characteristic (see below)
2. Positive test for AQP4-IgG (cell-based assay strongly recommended)
3. Exclusion of alternative diagnoses

Core clinical characteristics

- Optic neuritis
- Acute myelitis
- Area postrema syndrome: episode of otherwise unexplained hiccups or nausea and vomiting
- Acute brainstem syndrome
- Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions
- Symptomatic cerebral syndrome with NMOSD-typical brain lesions

NMOSD without AQP4-IgG or unknown AQP4-IgG status

1. At least 2 core clinical characteristics occurring as a result of one or more clinical attacks and meeting all of the following:
   a. At least 1 core clinical characteristic must be optic neuritis, acute myelitis with LETM, or area postrema syndrome
   b. Dissemination in space (2 or more different core clinical characteristics)
   c. Fulfillment of additional MRI requirements, as applicable
2. Negative tests for AQP4-IgG using best available detection method, or testing unavailable
3. Exclusion of alternative diagnoses

AQP4=aquaporin-4
LETM= longitudinal extensive transverse myelitis
Source: Krupp LB, Tardieu M, Amato MP, et al. International Pediatric Multiple Sclerosis Study Group criteria for pediatric multiple sclerosis and immune-mediated central nervous system demyelinating disorders: revisions to the 2007 definitions. *Mult Scler.* 2013;19(10):1261-1267.

must be a second, *non-ADEM* attack as well as either further MRI findings of clinically silent new lesions, or a third attack also not meeting criteria for ADEM.[12] See **Table 2** for a description of ADEM characteristics.[15-18]

Diagnostic Workup and Differential Diagnosis

High-quality imaging of the brain, orbits, and spinal cord are key to the diagnosis of pediatric MS. Due to frequent involvement of the optic nerve, structural and functional evaluations of the

Table 2. Distinguishing ADEM from MS[15-18]

Initial signs of acute disseminated encephalomyelitis (ADEM):

- Abrupt onset encephalopathy (alteration in consciousness or behavioral change unexplained by fever, systemic illness or postictal symptoms)
- Rapidly progressive clinical course, typically developing over hours and progressing to maximum deficit within days (mean of 4.5 days)
- Some cases show continued deterioration of function for periods as long as 4 weeks
- Rapid-onset encephalopathy is typically associated with multifocal neurologic symptoms
- Encephalopathy, unexplained by fever, should be present for a diagnosis of ADEM, though it may not be the presenting sign.

ADEM may be distinguished from MS by certain clinical features:

- Recent history (a few days or weeks) of infectious illness or immunization, although a clear preceding event may be absent. Respiratory or GI illnesses of viral etiology are most common, although a specific virus is seldom identified.
- Fever, followed by a phase of afebrile improvement (2 days to 3 weeks) before the onset of neurologic findings. Partial or complete recovery from the prodromal illness at the time of onset of ADEM. Documentation of at least 1 fever-free day is especially suggestive of ADEM. ADEM may occur in the wake of several weeks of fever of unknown origin.
- Mental status changes or seizures
- Lack of posterior column abnormalities (more common in MS)
- Age younger than 11 in ADEM (versus > 12 in MS)
- Tendency to occur during winter months

visual pathway may be helpful, including optical coherence tomography (OCT), visual evoked potentials (VEP), low-contrast and high-contrast visual acuity, visual fields, and color testing.[2,14] Optic neuritis may be underreported, particularly in young children who are unable to report symptoms.[19]

As part of the workup, most pediatric patients will eventually need to have a lumbar puncture to evaluate white blood cell count, protein, IgG index, and oligoclonal bands (OCB). White blood cell count in the cerebrospinal fluid (CSF) may be very high in some conditions that mimic MS, such as infection, but tend to be lower in MS. White blood cell count in the CSF may be higher in very young children with relapsing demyelinating disorders.[20]

Blood tests should be used to rule out other demyelinating disorders of the CNS such as neuromyelitis optica spectrum disorder (NMOSD). This is confirmed via a positive serum test for aquaporin-4 autoantibody (AQP4).[21,22] Testing should also rule out systemic rheumatologic conditions such as systemic lupus erythematosus (SLE), particularly if there is a history of joint pain or rash. In some cases, testing may need to be repeated a few months after the first event, with MRI, a neurologic exam, serum testing and, rarely, repeat lumbar puncture.

DISCUSSION
How Do Clinical and MRI Presentation Differ in Pediatric Patients?

Ann Yeh: Most pediatric patients come to our clinic having already received MRI scans. Given the possibility of many MS mimics, our workup is actually quite extensive, particularly in a very young child. For those under age 10, we would have a high index of suspicion for entities that are not MS. We might consider a one-time monophasic episode, systemic rheumatologic disorders, or even disorders related to immunodeficiency syndrome or infection.

A lot of research has been done to evaluate the sensitivity and specificity of adult MRI criteria in children. In pediatric patients who are above 12 years of age or postpubertal, the adult MS criteria are generally applicable. Under 12 years of age, it's less clear. This is why we need to be quite careful in the younger kids.

Jennifer Graves: Prepubertal disease tends to manifest differently on MRI. Younger

children often have very numerous and much larger T2 lesions at presentation. This may look like ADEM or a monophasic illness, but it could still be MS. Also, unlike adult MS, these lesions may disappear completely. In adults there is usually a permanent abnormality on MRI associated with the lesion, but children can have very large fluffy lesions that actually reduce to the point where they're no longer visible on the MRI. We don't know if it's due to remyelination, but we presume that the immaturity of the immune system and the possible potential for repair in this age group may partly explain this phenomenon.

Presentation in older adolescents looks more like adult MS, commonly with sensory symptoms and optic neuritis, and is more likely to affect females. But prepubertal children tend to have more posterior compartment attacks, brainstem and cerebellar involvement, and more encephalopathy. At least, these are the attacks that bring them to medical attention. Optic neuritis and sensory relapses may be underreported in younger children who are unable to describe their symptoms.[19] In addition, there are data suggesting that oligoclonal bands are less likely to be present in the cerebrospinal fluid analysis in very young children.[20]

MOG Antibodies in Diagnosis of Pediatric MS

Recent findings related to MOG antibodies have added further complexity to classifying pediatric diseases involving the CNS (see **Sidebar**, page 12).[23,24] The importance of MOG antibodies remains unclear, including the question of whether a true isolated syndrome occurs with MOG antibody-positive patients, especially those who are prepubertal. Some young children who were initially classified as having MS may be MOG-positive, but still have lesions consistent with MS and respond to DMT.

DISCUSSION
Presenting a Diagnosis of Pediatric MS

Jennifer Graves: I deliver the diagnosis with the whole family and other representatives of our team as appropriate, and I always recommend having the child be part of the conversation. Kids are smart and they know something is going on. Some families feel that they would like to protect their children and keep the diagnosis from them. In our clinic we believe very strongly in autonomy and encouragement of self-management in older children, but that's not always what the family wants.

Ann Yeh: The complexity of the parent–caregiver relationship is an important point of care. We may see fear and anxiety among parents. Some families hold onto the hope that this diagnosis is reversible and temporary, since MS is not regarded by most people to be a childhood disease. For some families this leads to a lack of endorsement of treatment, but for others it may encourage them to want to treat more aggressively.

Jennifer Boyd: Another issue we encounter is reluctance to disclose the diagnosis, especially with increasing concerns about privacy of healthcare information. Some families don't disclose the diagnosis to school staff or to any of the children's friends. We to talk to families about the importance of sharing certain information with the school, although it doesn't need to be every single detail. But there may be areas where the child needs special accommodations—such as being closer to the front of the classroom due to visual problems—or academic support in school. Kids usually don't want to be any different from their friends, so they may resist any adaptations.

Part 2. Disease-Modifying Treatment for Pediatric MS: When, How, and Which?

There is a strong rationale for early, effective treatment of pediatric MS, considering the typically high degree of disease activity and the potential for impeding the child's long-term neurologic development.[2,9] Inflammatory activity may be particularly high in the pediatric MS population, manifesting as:[2,25,26]

- Significantly higher relapse rates (2 to 3 times higher rates than in the adult MS population)[25]
- Greater disease burden on MRI compared with adults, including significantly higher volume of enhancing lesions and T2 lesions, especially in the posterior fossa region, compared with adults.[2,26]
- Early onset or neurodegenerative signs, including atrophy, which may prevent the brain from achieving normal growth[2,27]
- Shorter time to irreversible disability, as shown in a natural history study[4]

It should be noted that relatively little is known about the long-term effects of immunomodulation in children, particularly in the prepubertal population. The impact of long-term immunoglobulin suppression and neutropenia in younger patients is unknown, but must be weighed against the need to limit permanent neurologic damage that will likely affect the child profoundly as he or she ages. For example, children with pediatric MS have been shown to have smaller overall head size, brain volume, and thalamic volume.[27-29] Early CNS injury may affect many aspects of development, including social and educational, cognitive and motor, and immune system development.[28]

DISCUSSION

Rationale for Starting DMT

Jennifer Boyd: In our area of Canada we have a high proportion of families—as many as 40%—who decline to start a DMT initially. In these cases, we discuss the rationale for recommending treatment, as well as the potential ramifications of not starting treatment.

Ann Yeh: But declining treatment doesn't mean we will not see them again. We emphasize that we are here not just to prescribe medication, but to provide care. We'll continue to follow the patient and support the family, and if at some point they are ready to start the child on treatment, they have access.

Jennifer Boyd: If the child has a serious relapse, that often serves as a wakeup call. When I first started in this field, some children would have 2 or 3 relapses, which made it easier for families to buy into the idea of treatment. Now, because we are diagnosing and introducing treatment so much earlier, families may not be not ready to make the decision because they want to believe the condition is transient.

Therapeutic Selection in Pediatric MS

Fingolimod is currently the only DMT approved by the FDA for use in relapsing MS in the pediatric population (age 10 and up). Most of the pivotal clinical trials of other MS DMTs did not enroll patients under age 18. However, any of the DMTs approved for use in adult MS can be considered for off-label use in pediatric patients to limit progression of disease at the critical early stages.[30] Several retrospective observational case series have described DMT use in relatively large populations in pediatric MS. In addition, several randomized controlled trials are ongoing **(Table 3)**.[31-40]

Fingolimod

Approval of fingolimod was based on a single randomized double-blind trial of fingolimod (n=107) versus intramuscular interferon (IFN) beta-1a (n=108) in 215 children with MS aged 10 to 17 (mean age 15.3 years).[36] Both agents significantly reduced the primary endpoint of ARR, but fingolimod had superior efficacy with a 82% relative difference between the treatment groups (P<0.001). In secondary endpoint, new or newly enlarged T2 lesions on MRI, also showed significant improve-

ment for fingolimod (53% relative difference, $P<0.001$).

Safety considerations for children treated with fingolimod were generally similar to those seen in adults. There was a higher incidence of seizures in the fingolimod group compared with the group treated with IFNB-1a treated group (5.6% vs. 0.9%) (**Figure 1**).[21] Serious AEs in the IFNB group included infection (2 patients) and supraventricular tachycardia (1 patient). Based on the findings from this study, in May 2018 fingolimod became the first DMT approved for treatment of pediatric MS by the FDA, (patients aged 10 and above).[36]

The fingolimod dose for pediatric patients weighing ≤40 kg is 0.25 mg orally once daily (relative to the adult dose of 0.5 mg once daily). The labeling also recommends that when possible, pediatric patients should complete all recommended immunizations prior to initiating fingolimod therapy.[21]

Injectable Agents (Interferons and Glatiramer Acetate)

The majority of clinical experience with DMT in pediatric MS is with the injectable agents, although there are relatively few controlled clinical trials in pediatric MS. In a controlled trial based in

Table 3. Clinical Trials of MS DMTs in Pediatric Patient Populations[31-40]

DMT (Author, year)	Mean patient age, (number of patients)	Treatment duration (months)	Relapse rate reduction
IFNB-1a IM (Ghezzi, 2007)[32]	Age of MS onset, 11.7 yrs (N=52)	43	79%
INFB-1b SC (Banwell, 2006)[31]	Age at start of treatment, 13 yrs (N=43)	29	50%
	Age of MS onset, 12.4 yrs		
IFNB-1a IM	(N=38)	23.3	83%
IFNB-1a SC	(N=16)	40.7	75%
Glatiramer acetate (Ghezzi, 2005)[33]	N=9	33.3	91%
IFNB-1a SC (Tenembaum, 2006)[34]	(N=24)	44	(significant)
Glatiramer acetate (Kornek, 2003)[35]	Age of MS onset, 9–16 yrs (N=7)	24	100%
	Ages 10-18 years	24	0.12, 81.9%
Fingolimod IFNB-1a (Chitnis 2018)[38]	(N=107) (N=108)	(+ 5-year open-label extension)	0.67 (ARR)
Alemtuzumab (LemKids)[37]	0-18 years (N=50)	24	Recruiting
DMF IFNB-1a IM (CONNECT)[38]	Ages 10-17 (N=142)	24 Open label (+ extension studies)	Completion 2020
Teriflunomide vs placebo (TERIKIDS)[39]	Ages 10-17 (N=166)	96 weeks	Completion 2021
IFNB-1a SC (Tenembaum, 2013)[40] (retrospective record review)	Age under 18 (N=307)	12	ARR 1.79 before treatment 0.47 during treatment

Italy, intramuscular interferon beta-1a (IFNB-1a IM) was evaluated in 52 children under age 16 (mean onset of symptoms 11.7±2.7 years, mean disease duration 25.9±30.3 months).[32] With treatment, mean annualized relapse rates were reduced from 1.9 at baseline to 0.4 at period of 3.5 years. Adverse events included flulike symptoms (33%), headache (29%) and myalgia (21%), most were transient.[32]

Another study conducted across 15 centers in Italy evaluated 76 patients treated with either IFNB-1a IM (n=38) or IFNB-1a SC (n=16), interferon beta-1b (IFNB-1b; n=2), or glatiramer acetate (n=9) treated for periods ranging from 23 to 40 months.[33] These treatments were highly efficacious in reducing annualized relapse rates in the patients with pediatric MS: from baseline **(Figure 2**). Side effects were consistent with those expected for these agents.[33]

Safety and tolerability of IFNB-1b was reviewed retrospectively in 43 children with MS. While the mean age of the cohort was 13, there were 8 children in the study aged 10 and under. The most common AEs included flulike symptoms (35%), abnormal liver function tests (26%), and injection site reactions (21%). The authors recommended regular liver function monitoring in keeping with labeling recommendations for IFNB-1b.[31]

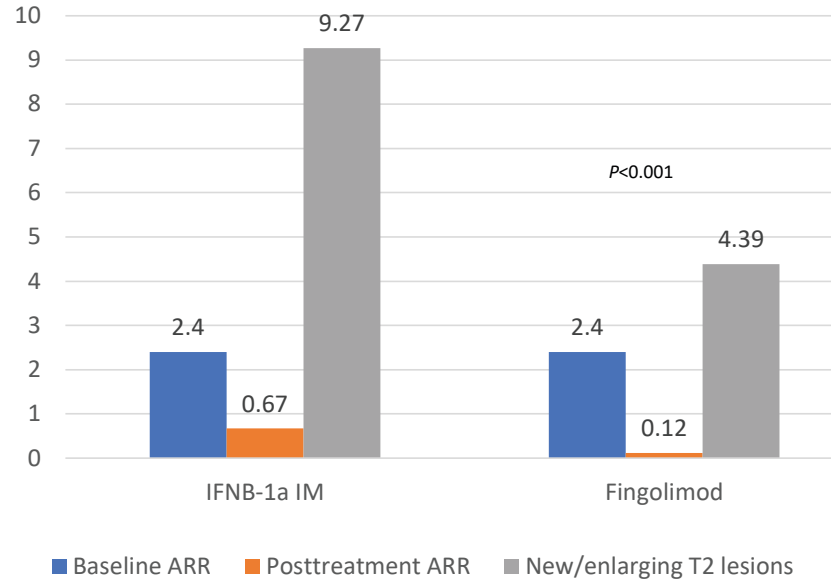

Figure 1: ARR and New Lesion Activity, Pediatric MS (Ages 10–17, Treated up to 2 years).

ARR=annualized relapse rate; IFNB-1a=interferon beta-1a

DISCUSSION

Initiating Treatment

Jennifer Boyd: I usually prefer not to discuss initial treatment selection at the same time the diagnosis is confirmed. Even if the family is prepared for it, the news of the diagnosis is so overwhelming that they just can't absorb the information or make clear decisions. There is a risk that family will leave and we won't see them again! Instead, I ask them to come back in a week or two—perhaps in conjunction with some further testing—to go through the options. I talk about mode of administration, side-effect profile and monitoring requirements (e.g., need for blood tests), but also how taking the medication fits in with the child's lifestyle, exploring what they feel they can cope with on a regular basis.

Jennifer Graves: I agree about delaying the initial decision about DMT until after the family has been able to process the information about the diagnosis. I bring patients back 2 to 4 weeks after the initial visit for a more in-depth discussion about medications. Some families may have to travel a long way to the clinic, or there is some other reason why they may not return. In those situations we try to do as much as we can in one visit. Also, many families will want to do their own research. To anticipate that, I give them basic literature about medications from a balanced source like the National MS Soci-

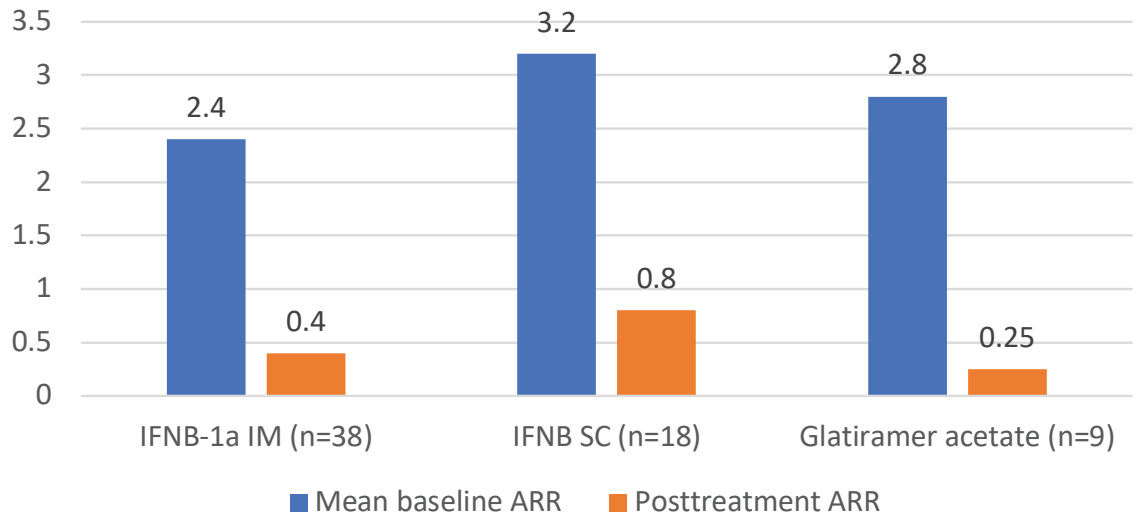

Figure 2: Change in ARR from baseline with injectable DMTs in pediatric MS.

Ghezzi A, et al. *Mult Scler.* 2005;11(4):420-424.[32]
ARR=annualized relapse rate; IFNB=interferon beta; DMTs=disease-modifying therapies

ety (NMSS) at the first visit and tell them we can plan to regroup in a few weeks to make a decision together. During the intervening few weeks any necessary screening labs can also be performed.

Jennifer Boyd: The treatment approach has to be family based. We need to make sure we address any language or cultural barriers. The family should be aware that there is a care team supporting them to help them manage this disease. Social work support can be key in dealing with all the levels of complexity involved—helping families get resources and counseling if they need it, and ensuring school support.

DISCUSSION

Selecting a DMT

Ann Yeh: Although it may seem surprising, some families prefer an intramuscular injection over an oral DMT, especially for younger children. Many kids will not swallow a pill or don't like to have a medication that must be taken every day. Much of the decision making is lifestyle-based, especially for kids with a lot of extracurricular activities.

Jennifer Boyd: It is also age-dependent, with the potential to change as the child matures. Under the age of 10, it's difficult to assume that an oral is going to be taken with a high degree of adherence, compared to an injection once or twice a week administered by the parents. If it's an interferon, the parents might give the injection on a Friday night or Saturday night so any side effects do not cause the child to miss school.

Jennifer Graves: Although we think of the injectable agents as being the least-potent drugs for adults with MS, for a young child who has a smaller body habitus, the dosage is often reasonable. These are also the agents with the most well understood safety profile and have appeal to those with low risk tolerance. However, higher-potency drugs may be necessary for disease control in some children. Oral drugs may be difficult to administer in very young children due to their reluctance to swallow pills, but become more popular choices once the child is past puberty. Adherence is a very important consideration in this unique population of MS patients.

What Can Myelin Oligodendrocyte Glycoprotein [MOG] Antibodies Reveal in Pediatric MS?

Recent studies have reported the presence of high-titer serum IgG antibodies to myelin oligodendrocyte glycoprotein (MOG), mainly in pediatric patients with acquired demyelinating diseases.[1-3] Presence of MOG antibodies seems to distinguish between patients with clinically isolated syndrome or confirmed MS (MOG-negative) and those with a monophasic episode or another relapsing demyelinating condition that is not MS (MOG-antibody positive). The latter could include acute disseminated encephalomyelitis (ADEM), followed by episodes of optic neuritis, multiphasic demyelinating encephalomyelitis, and recurrent optic neuritis. Presence of MOG antibodies may be associated with a better prognosis in pediatric patients. MOG antibodies have also been observed in cases of neuromyelitis optica spectrum disorder (NMOSD) with certain biomarkers, specifically patients who are negative for aquaporin-4 (AQP4) antibodies.[4] The significance of MOG antibody status remains uncertain, so before presence or absence of MOG antibodies is used in the laboratory diagnosis of pediatric MS, these tests should be further validated and the immunoassays improved.

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Management Approaches for Aggressive Cases of Pediatric MS

Childhood MS often follows an aggressive course. Suboptimal response to an initial DMT has been reported frequently in the pediatric MS population.[11] The International Pediatric MS Study Group defined indicators of active disease (signifying a need for therapeutic escalation) as:[11]

1) Patient has been fully compliant for least 6 months on full-dose standard DMT
   AND
2) Occurrence of at least one of the following:
   1. Increase, or no reduction, in relapse rate
   2. New T2 or contrast enhancing lesions on MRI compared with pre-treatment period
   3. ≥2 confirmed relapses (clinical or MRI relapses) within a 12-month period or less

Early and effective treatment is necessary to limit long-term damage, and some experts advocate an induction approach (starting with more potent agents) to avoid missing the crucial window of opportunity to treat developing brain before irreversible injury occurs. Problems with access to therapy can delay treatment for some patients. If the particular DMT is off-label and not reimbursed by the payer, it may be necessary to apply for compassionate use.

Natalizumab

Natalizumab is a potential option for patients with pediatric MS with an aggressive course or whose disease remains active despite use of other agents. Data on the use of natalizumab involving large groups of pediatric patients or over long-term periods are limited. A 2007 Italian study based on registry data evaluated 101 patients under age 18 (mean age 14.7 ±2.4 years) who received natalizumab for a mean of 34 months. Treatment was associated with a decrease in ARR from 2.3 ± 1.0 to 0.1 ± 0.3 ($P<0.001$) and decreases in mean EDSS score and new T2 or enhancing lesions on MRI.[41] No relevant adverse events were recorded during the study. Safety concerns appear

to be similar to that of adults, although the presence of antibodies for JCV is probably less common in the pediatric population.[42,43] Use of natalizumab in patients with pediatric MS should be overseen by providers who have experience with this agent.

Alemtuzumab

There are no published studies on the use of alemtuzumab in pediatric MS. There is clinical history in the pediatric population, because this agent is approved as an immunoablative induction agent for children undergoing transplant procedures such as kidney or bone marrow transplant.[44,45] A trial of alemtuzumab in patients with treatment-resistant pediatric MS (LEMKIDS) is under way.[37] Until more data are available, this therapy should be reserved for severe cases not responding to other treatment approaches. The potential for development of secondary autoimmunities such as thyroid dysfunction is an important consideration in this population.

Rituximab

Rituximab, a monoclonal antibody targeting CD20 on B cells, has been assessed in pediatric MS in a few observational studies. Swedish investigators assessed rituximab therapy in 14 patients with MS (median age at treatment 16.5 years).[46] Patients received rituximab 500 to 1,000 mg once every 6 or 12 months for a median duration of 23.6 months. During treatment, no relapses were observed, and only 1 new lesion was detected on MRI. EDSS scores remained stable or decreased in 13 of 14 cases, and no serious adverse events were reported.[46]

Investigators from the Pediatric MS Clinic at the University of California San Francisco reported on a retrospective case series of 11 patients with pediatric demyelinating disease who received at least one infusion of rituximab at the center.[47] Patients had either NMO (n=8) or MS (n=3, one with secondary progressive MS) and received a median of 3 rituximab cycles per patient. Relapse rates were reduced in 9 of the 11 patients (82%). No serious infections were reported, but infusion reactions occurred in 3 patients which were subsequently managed with pretreatment of dexamethasone and diphenhydramine and a slower infusion rate.[47]

DISCUSSION

Monitoring and Follow-up

Jennifer Graves: Clinically it is helpful to see patients 3, 6 and then 12 months after diagnosis in the first year and then every 6 months at minimum thereafter. I recommend a follow-up MRI 6 months after diagnosis, as I would with an adult patient. For untreated patients suspected to have MS, this allows us to catch recurrent disease quickly. For those on treatment, we can reassess baseline MRI activity after starting a DMT. The frequency of MRI is not necessarily based on the child's age, but we do need to be cognizant of the need for anesthesia for a very young child undergoing an MRI and minimize this exposure. Since traveling can be difficult for families who don't live close to the pediatric MS center, we would adjust their monitoring schedule as needed.

Ann Yeh: For those families whose child cannot be followed at a specialized center, a shared relationship with a local practitioner is the best model. At our center we engage in ongoing relationships with primary care or general neurology providers who are closer geographically to the patient. We offer telemedicine in combination with yearly visits to the clinic (more often if needed) and frequent check-ins. These partnerships are very important. We have kids receiving high efficacy IV therapies at a distance. Because the monitoring for these therapies is highly specialized, these therapies should be administered in consultation with providers who have experience managing pediatric MS.

Part 3. Comprehensive Care of Pediatric and Adolescent MS: Partnering With the Patient and Family

In the management of pediatric MS, a comprehensive, long-term approach is critical and must emphasize family involvement. The parent-child relationship is key to treatment decisions. DMT selection must take into account the child's psychosocial development and familial relationships.

Adherence to therapy requires that the family and patient accept diagnosis and agree with treatment plan. Poor adherence to therapy has been well documented in the pediatric MS population.[48] Medication adherence problems can arise when teens try to rebel because they want to feel "normal" and they don't understand the how the therapy may be helping them. Poor adherence among children with MS can result from:[48]

- family conflicts or a difficult household environment
- limited education about the disease
- incomplete understanding about the purpose of therapy
- belief that MS is transient or that natural therapies are preferable
- economic barriers and lack of access to care

Psychosocial Issues

Psychosocial adjustment difficulty can be a concern for patients with pediatric-onset MS. Fatigue is a major issue that affects children and teens with MS. Behavioral problems and perceived cognitive difficulties may be related to fatigue.[49] MS symptoms like fatigue as well as relapses may cause children to miss school, sports, and social activities, which heightens feelings of being alienated and different from their peers. Depression and anxiety disorders have been reported in 46% of adolescents studied.[50] Additionally, cognitive dysfunction affects about one-third of children and adolescents with MS and may interfere with academic achievement.[51,52]

DISCUSSION
Managing Cognitive Symptoms and Mood Disorders

Ann Yeh: Fatigue and depression are among the major issues affecting our patients with pediatric MS. A high percentage of our patients have depression and/or anxiety, but many don't want to see a psychiatrist because they feel they have already seen enough doctors.

Jennifer Graves: I agree. Many pediatric patients have good motor function, even after relapses. But the number one complaint is usually something in the realm of cognitive or mood changes. School performance is an issue in many cases. We conduct neuropsychological testing and evaluations every 2 to 3 years to help with school recommendations and to monitor this over time to make sure kids are meeting cognitive and developmental milestones.

Jennifer Boyd: It is important to work collaboratively with other members of the health care team and community services to ensure young people with MS and their families receive necessary treatment and support. This may include the primary care provider, neuropsychologist, clinical psychologist, social worker, psychiatrist, school staff and MS Society. Counseling can be very helpful. There are many feelings these kids may not be expressing including stress, anxiety, peer pressure—particularly the adolescents. Camps established for young people with MS help them feel less isolated and promote friendships with those who share similar experiences and feelings. Adolescence is difficult enough without having MS. Sometimes the parents can benefit from counseling as well.

Transition to Adolescence and Adulthood

A key aspect of managing pediatric MS is adjusting the approach during the transition into adolescence and the teen years. As the young patient matures, there is a need to encourage more independent decision-making and responsibility. Better adherence to therapy is linked to whether the young adult chooses to take responsibility for his or her own self-care.[53] Teens whose MS was diagnosed earlier in childhood may require re-education about their disease, since much of the earlier education was directed toward the parents. Teens and young adults will face new situations, such as deciding whether or when to disclose the diagnosis of MS to their friends, intimate partners, teachers, and employers. In addition, there are many new medical issues related to puberty and adulthood, including birth control and family planning, and expanded exposure to substances such as cigarettes, drugs, or alcohol.

Comorbidities affect young patients with MS as well as adults. Obesity is a major concern affecting an increasing number of people with MS and may be involved in pathophysiology of pediatric MS.[54] Obesity increases the risk for serious comorbidities such as diabetes, further expanding the complexity of MS management, drug-drug interactions, and adherence problems. Mobility limitations that limit exercise opportunities and tolerance contribute to weight problems, while excess weight may be part of the vicious cycle of overweight/obesity and MS.[54]

Conclusion

Diagnosis of pediatric MS is increasing, mainly due to the availability of more information about this condition, more specific diagnostic criteria, and access to MRI. Pediatric MS can be managed in the community in consultation with a specialized pediatric MS center. Careful differential diagnosis is critical and may be informed by an expanding number of biomarkers for other conditions with characteristics that may resemble MS. Early, effective treatment is essential to minimize permanent damage, especially since pediatric MS often has a highly active inflammatory course with frequent relapses and lesion activity. Fingolimod is approved for treatment of MS in children under the age of 18. Some other DMTs have been used off-label, and clinical trials in pediatric MS are ongoing for many of the available therapies.

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Appendix A. Pediatric MS Centers in the U.S. and Canada

Alabama
- Center for Pediatric-Onset Demyelinating Disease
- Children's Hospital of Alabama
- Birmingham AL, 205-996-7850

Arkansas
- University of Arkansas For Medical Sciences Department Of Pediatrics
- Arkansas Children's Hospital
- Little Rock 501-364-1850

California
- UCSF Regional Pediatric MS Center
- San Francisco, CA 415-353-3939
- Pediatric Multiple Sclerosis Center
- Loma Linda University Children's Hospital
- San Bernardino, CA 909-835-1810
- Kaiser Permanente San Francisco
- San Francisco, CA 415-833-3092
- Kaiser Permanente Walnut Creek Medical Center
- Walnut Creek, CA 925-295-4070
- Harbor- UCLA
- Torrance, CA 310-222-2345
- Rady Children's Hospital
- University of California San Diego
- San Diego, CA 858-966-5819

Colorado
- University of Colorado, Denver Children's Hospital, Rocky Mountain MS Center
- Aurora, CO 720-848-2080

Connecticut
- Long Ridge Medical Center/ Yale New Haven Health
- Stamford, CT 475- 619-7353

District of Columbia
- Children's National Medical Center
- Washington, DC 202-476-5000

Florida
- Baptist Neurology
- Jacksonville Beach, FL 904-249-1041
- Memorial Neuroscience Institute
- Hollywood, FL 954-265-9500
- University of Miami MS Center of Excellence
- Coral Gables, FL 305-243-3100
- Vero Beach Neurology and Research Institute
- 772-492-705 *teens and up
- Univ. of FL Health Jacksonville MS Center
- Jacksonville, FL 904-383-1022
- University of South Florida Multiple Sclerosis Center
- Tampa, FL 813-396-9478
- UF Health Neurology
- Gainesville, FL 352-265-8408

Georgia
- Savannah Neurology Specialists
- Savannah, GA 912-354-7676

Illinois
- Lurie Children's Hospital of Chicago
- Chicago, IL 800-543-7362

Indiana
- JWM Neurology-
- Indianapolis, IN 317-537-6088

Kentucky
- University of Louisville Physicians, MS Center
- Louisville, KY 502-588-4800

Massachusetts
- Partners Pediatric MS Center
- Massachusetts General Hospital for Children
- Boston, MA 617-726-2664
- Pediatric Multiple Sclerosis and Related Disorders Program
- Boston Children's Hospital
- Boston, MA 617-355-2751

Michigan
- Memorial Center for Multiple Sclerosis
- Owosso MI 989-723-1390

Minnesota
- Mayo Clinic Pediatric MS Center
- Rochester, MN 507-293-0378

Missouri
- Washington University, Pediatric MS and other Demyelinating Disease Center
- St. Louis, MO 314-454-6120
- Pediatric MS & Demyelinating Diseases Center
- St. Louis Children's Hospital
- St. Louis, MO 314-454-6120

New Mexico
- UNM Multiple Sclerosis Specialty Clinic At The Clinical Neuroscience Center
- Albuquerque, NM 505-272-3160

New York
- Pediatric MS Center of the Jacobs Neurological Institute
- Buffalo, NY 877-878-7367
- Pediatric MS Center at New York University Langone Medical Center
- New York NY 646-501-7500
- University of Rochester Pediatric Neuroimmunology and Multiple Sclerosis Center
- Rochester, NY 585-275-2808
- Elmwood Health Center
- Buffalo, NY 716-874-4500
- Cayuga Neurologic Services
- Ithaca, NY 607-273-6757

North Carolina
- Brenner Children's Hospital/ Wake Forest Baptist Pediatric Neurology
- Winston Salem, NC 336-716-4101
- Raleigh Neurology Associates
- Raleigh, NC 919-782-3456
- Wake Forest Baptist Health Multiple Sclerosis Center
- Winston Salem, NC 336-716-4101

Ohio
- Cleveland Clinic, Mellen Center for Multiple Sclerosis
- Cleveland, OH 216-444-5559

Pennsylvania
- Children's Hospital of Philadelphia
- Philadelphia, PA 215-590-1000
- Wellspan Neurology
- York, PA 717-851-5503

South Carolina
- Premier Neurology
- Greenville, SC 864-655-4005

Texas
- The Blue Bird Circle Clinic for Multiple Sclerosis
- Texas Children's Hospital
- Houston, TX 832-822-5046
- Cook Children's Neuroscience Clinic
- Ft Worth, TX 682-885-2500
- Children's Medical Center Dallas
- University of Texas Southwestern
- Dallas, TX 214-645-8800

Tennessee
- Vanderbilt Multiple Sclerosis Center
- Nashville, TN 615-343-1176

Utah
- Eccles Primary Children's Outpatient
- Salt Lake City, UT 801-213-3599
- Primary Children's Hospital Outpatient Services at Riverton
- Riverton, UT 801-213-3599
- Utah Valley Neurological Center/ Intermountain Healthcare
- Provo, UT 801-357-7420

Virginia
- James Q Miller Consultative Multiple Sclerosis Clinic
- Charlottesville, VA 434-924-8668

Washington
- Center for Healing Neurology
- Seattle, WA 206-379-1213
- Seattle Children's Hospital
- Seattle, WA 206-987-2078

Wisconsin
- Marshfield Clinic MS Clinic
- Marshfield, WI 800-699-3377
- University of Wisconsin Hospital & Clinic Neurology/MS Clinic
- Madison, WI 608-263-1300
- Aurora Health Care
- Milwaukee, WI 414-546-5460
- Dean Neurologic Institute & Spine Center
- Madison, WI 608-260-3425

West Virginia
- Marshall University School of Medicine Department Of Neurology
- Huntington, WV 304-691-1787
- CANADA
- University of Ottawa Department of Pediatrics
- Ottawa, Ontario, Canada 613-737-7600
- Hospital for Sick Children (SickKids)
- Toronto, Ontario, Canada 416-813-1500
- University of British Columbia
- Vancouver, British Columbia, Canada 604-806-8206

Source: National Multiple Sclerosis Society

Post-test

Pediatric Multiple Sclerosis: Sourcebook for MS Care Professionals

To receive credit, please read the program in its entirety, answer the following post-test questions, and complete the program evaluation. A certificate will be awarded for a score of 75% (6 correct answers) or better. A certificate will be emailed (or mailed) to you within 2 weeks. There is no charge for CME/CNE credit.

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PLEASE SELECT THE BEST ANSWER

1. Multiple sclerosis (MS) onset before the age of 18 occurs in approximately ____ of all MS cases.

A. 1%
B. 5%
C. 10%
D. 25%

2. Diagnostic criteria for pre-pubescent patients with pediatric MS:

A. Are the same as McDonald diagnostic criteria for adults with MS
B. Differ from the adult diagnostic criteria in the typical distribution of lesions
C. Differ from adult criteria in the requirements for dissemination of time and space
D. Differ from adult criteria in reference to nonencephalopathic inflammatory events

3. In the blood workup for children with suspected demyelinating disorders, a positive serum test for AQP4 is indicative of:

A. leukodystrophies such as CADASIL
B. neuromyelitis optica spectrum disorder (NMOSD)
C. acute disseminated encephalomyelitis (ADEM)
D. presence of MOG antibodies

4. Relative to adults, inflammatory activity in pediatric MS tends to manifest as:

A. higher relapse rates
B. higher MRI burden with little to no relapse activity
C. full recovery following acute relapses
D. higher relapse rates and higher disease burden on MRI

5. Disease-modifying therapies (DMTs) approved for children with MS age 10 and up include:

A. interferon beta and glatiramer acetate
B. teriflunomide
C. fingolimod
D. all DMTs approved in adult MS

6. International Pediatric MS Study Group indicators of a need for therapeutic escalation in children with MS include:

A. increase in relapse rate or ≥2 relapses in 12 months
B. new T2 or contrast-enhancing MRI lesions
C. either A or B above
D. both A or B must be present

7. Among the most common and debilitating issues affecting children and adolescents with MS are:

A. fatigue, depression and anxiety
B. cognitive dysfunction
C. denial in the MS diagnosis
D. balance and gait dysfunction

8. The significance of MOG antibodies in pediatric MS relates to:

A. Positive MOG antibodies may suggest ADEM or a condition other than MS
B. Presence of MOG antibodies may signal better prognosis
C. Positive MOG antibodies may occur in conjunction with NMOSD
D. all of the above

Evaluation Form

Pediatric Multiple Sclerosis: Sourcebook for MS Care Professionals

Please answer the following questions by circling the appropriate rating:

5 = Outstanding 4 = Good 3 = Satisfactory 2 = Fair 1 = Poor

Extent to Which Program Activities Met the Identified Objectives: *After completing this activity, participants should be better able to:*

1) Apply currently recommended criteria for the differential diagnosis of MS in pediatric patients. 5 4 3 2 1
2) Interpret recent evidence for disease-modifying treatment in patients with pediatric MS, including treatment selection, dosage, frequency, and need for monitoring. 5 4 3 2 1
3) Plan and implement a comprehensive care plan for the patient with pediatric MS that emphasizes partnership with the patient and family. 5 4 3 2 1

To what extent was the content:

4) Well-organized and clearly presented 5 4 3 2 1
5) Current and relevant to your area of professional interest..... 5 4 3 2 1
6) Free of commercial bias..... 5 4 3 2 1
7) Clear in providing disclosure information 5 4 3 2 1

General Comments

8) As a result of this continuing education activity (check only one):

❒ I will modify my practice. (If you checked this box, how do you plan to modify your practice?) _____

_____

❒ I will wait for more information before modifying my practice.
❒ The program reinforces my current practice.
❒ No, I will not modify my practice.

Please indicate any barriers you perceive in implementing these changes:

❒ Cost
❒ Lack of time to assess/counsel patients
❒ Lack of administrative support
❒ Cultural or language barriers
❒ Reimbursement/insurance issues
❒ Concerns about patient safety/well being

9) This activity will assist in the improvement of my (check all that apply):

❒ Competence ❒ Performance ❒ Patient outcomes

Suggestions for future topics/additional comments: _____

_____

Follow-up

As part of our continuous quality-improvement effort, we conduct postactivity follow-up surveys to assess the impact of our educational interventions on professional practice. Please check one:

❒ Yes, I would be interested in participating in a follow-up survey.
❒ No, I would not be interested in participating in a follow-up survey.

There is no fee for this educational activity.

Post-test Answer Key	1	2	3	4	5	6	7	8

Request for Credit ***(Please print clearly)***

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THE CONSORTIUM OF
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