Management of pediatric multiple sclerosis

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An increasing number of children and adolescents with multiple sclerosis are being identified and treated with disease-modifying therapies. As more rapid diagnosis is made possible due to the heightened awareness of pediatric multiple sclerosis among the pediatric and neurological communities, and the availability of MRI, the number of pediatric multiple sclerosis patients requiring treatment will grow over time. This review draws on information from adult and pediatric neurology sources and summarizes current available data on the management of pediatric multiple sclerosis.

Keywords: diagnosis, glatiramer acetate, interferon-β, pediatric MS, treatment

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Guiding principles in management

A number of factors are important in managing children with multiple sclerosis (MS). One key principle is that the differential diagnosis of pediatric MS differs somewhat from adult MS. A particularly challenging diagnostic concern is the distinction between MS and acute disseminated encephalomyelitis (ADEM) (**Table 1**). Additionally, pediatric MS differs on some clinical features from adult MS despite symptom overlap. For example, a greater proportion of children compared with adults have a relapsing–remitting onset, and they transition more gradually to secondary progressive MS [1,2]. MRI findings are less likely to fulfill Barkoff criteria [3,4] and these differences are even more pronounced in children less than 12 years of age [5,6]. Nonetheless, despite some clinical distinctions between children and adults, the underlying treatment principles are similar. Early initiation of disease-modifying therapy (DMT) is as important in children as in adults, and appears to be well tolerated. In the majority of cases, full doses of the different DMTs are possible following gradual dose escalation. Symptom management is an integral part of treatment and special awareness should be given to the tendency of some youngsters to under-report some important problems such as bladder incontinence. Cognitive and academic problems are particularly challenging psychosocial features of the disease. School personnel need to be educated about the child's needs and special accommodations often have to be considered. Finally, families should be reassured that despite the relative rarity of pediatric MS, they are not alone. A plethora of support networks, particularly through the National Multiple Sclerosis Society (NMSS), are available to educate and assist families.

Definition

An operational definition for pediatric MS put forth by the International Pediatric MS Study group has no lower age limit [7]. The criteria require recurrent episodes of neurological dysfunction involving separate areas of the CNS, with or without objective confirmation. An attack must be at least 24 h in duration. After the first event, either a new nonencephalopathic event or a new lesion on MRI can satisfy the dissemination in time criteria. The International Pediatric MS Study Group's consensus criteria for ADEM also made a clear distinction from clinically isolated syndromes (CIS). ADEM is multifocal and requires the presence of encephalopathy. Variants of ADEM include recurrent ADEM, in which two episodes more than 3 months apart have the same clinical symptoms as the initial episode, and multiphasic ADEM, which is also characterized by two or more episodes of ADEM, but the episodes have different clinical symptoms from one another. These variants are quite infrequent [5,8,9]. CIS can be either monofocal or multifocal, but according to the international consensus definition, lacks encephalopathy. One prospective study showed these distinctions were useful prognostic factors in the development of MS. Patients with CIS were more likely to develop MS than those with ADEM; 46 vs 8% [10]. However, others have found that encephalopathy (a major distinction between MS and ADEM) was not predictive of a subsequent diagnosis of MS. Instead, distinguishing monofocal and multifocal initial demyelinating events was more relevant in predicting a subsequent MS diagnosis [5]. One of the difficulties regarding the distinctions between ADEM and MS is that there is a subset of children, ranging from 0–28%, with initial ADEM clinical

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Table 1. Common distinctions between ADEM and multiple sclerosis.

Clinical feature	ADEM	Multiple sclerosis
Demographic profile	Females = males in frequency Age 10 and under more common	Females outnumber males Teenage years most common
Encephalopathy	Frequent	Rare
MRI	Large (1–2 cm or more), less discrete, gray matter involvement, as well as white matter, enhancement common	More sharply defined white matter lesions, gray matter involvement rare, enhancement common
CSF pleocytosis	Often present	Rare
CSF oligoclonal bands	Variable	Frequent

ADEM: Acute disseminated encephalomyelitis; CSF: Cerebrospinal fluid.

features, but who develop subsequent neurological events [11–13]. Increasingly, research is helping better define which factors increase the likelihood of MS following an initial demyelinating event. In part, the international consensus definitions have been useful in helping spur additional studies to address this issue.

Differential diagnosis

Establishing a diagnosis of pediatric MS requires exclusion of other potential etiologies. In some instances the differential diagnosis can be very difficult. As mentioned, the most challenging differential diagnostic entity is ADEM. However, there are other conditions that should also be excluded. For example, neuromyelitis optica (NMO) must be excluded in patients with longitudinally extensive spinal cord lesions and optic neuritis. The differential diagnosis of pediatric MS has been reviewed in detail elsewhere [14–16]. **Table 2** summarizes some of the most common diagnostic categories, representative disorders and screening laboratory tests in the blood to include in the evaluation.

Cerebrospinal fluid (CSF) collection is also necessary in the work up. Many studies have found that oligoclonal bands and elevated immunoglobulin G (IgG) index are more common in patients with subsequent demyelinating events and with MS [5,17]. However, there is some overlap in their relative frequency in MS and ADEM [8,11,18,19]. Nonetheless, CSF studies should include oligoclonal bands, IgG index, white and red cell count, protein and glucose. CSF lactic acid helps screen for metabolic disorders; angiotensin-converting enzyme in serum and CSF tests for CNS sarcoidosis; and in hyperendemic areas for Lyme disease a Lyme titer in serum and CSF is useful. In patients with possible encephalitis, PCR for herpes virus, cytomegalovirus, enterovirus and Epstein–Barr virus are appropriate.

Treatment with DMT

Prognostic features relevant to management

One unresolved question in pediatric MS management is whether to consider treatment with DMT for children with a very high risk for MS. Patients at risk for MS include those with CIS who have monofocal disease, MRI features consistent with Barkhof's criteria or lesions that are discrete and are perpendicular to the corpus callosum, positive oligoclonal bands and a positive family history. Experience with treating adult CIS with DMT has shown that this can delay the MS diagnosis. The observations with interferon (IFN)-β1b (Betaseron®) [20], IFN-β1a intramuscular (Avonex®) [21] and IFN-β1a subcutaneous (Rebif®) [22] all show a delay in reaching the second MS defining relapse, as well as favorably affecting MRI lesion burden. These treatments should be given serious consideration in older children with CIS with strong risk factors. Greater caution should be used in children under the age of 10 years, as their clinical and radiologic features can be less specific [5,6]. It is unclear whether a controlled clinical trial will be performed to answer the question of whether treatment using DMT in CIS in children is effective due to ethical concerns of withholding therapy from individuals who might need it.

To assist in the decision of how early to treat patients with established pediatric MS, incorporation of prognostic factors may be useful. Two preliminary studies suggest that children with MS who are African–Americans or of Hispanic ethnicity may do worse or have a greater disease burden on MRI [23,24]. Cases of pediatric MS associated with a short duration between two demyelinating events is also a potentially worrisome prognostic sign [2]. Another consideration influencing treatment is that while children with MS transition more gradually to secondary

progressive MS, they reach disability levels such as requiring ambulatory assistance at an earlier age than adults [1,2].

Overview of DMT in established MS

Once the diagnosis is established and conveyed to the family, issues related to treatment become the next focus of management. Since almost all patients in the childhood and adolescent age groups present with relapsing MS, and since this is the form of MS for which proven treatment is available, educating the family regarding the importance and benefits of DMT is a mainstay of management. As shown in **Table 3**, each of the first-line DMTs has been successfully given to children and adolescents with few serious adverse events, and has been associated with a decrease in relapse rate on treatment compared with baseline. However, none of the clinical experience published on children and DMT are based on randomized clinical trials. Hence, information on treatment of pediatric MS with DMT is largely from small samples and from extrapolation of the treatment studies in adult MS.

The concept of regular injections is difficult for many children (and adults), and parents may struggle with the idea of administering injections to their child. Extensive training with qualified MS nurses can help parents and children adapt to the injections and facilitate use of proper techniques. In our experience, younger children tend to cope well with injections. Many teenagers quickly learn how to administer the injections independently; others have compliance issues. The auto injector, available for IFN-β1b subcutaneous, IFN-β1a subcutaneous and glatrimer acetate (GA), is frequently preferred, but in some children (and occasionally in teens or adults) the clicking noise can be bothersome.

IFN-β1a intramuscular (Avonex®)

IFN-β1a intramuscular at a dose of 30 µg once weekly is usually well tolerated in children with MS. In the largest study to date, a total of 53 children under the age of 16 were started on therapy and followed for a mean of 43 ± 20 months [25]. Of this group, 19 discontinued treatment. Reasons for discontinuing were most often due to a switch to what was considered a more effective therapy (n = 13). The most common adverse events were similar to adults, and included flu-like symptoms (33%), headache (29%) and myalgia (21%). Laboratory abnormalities were in most cases transient and most commonly included leukopenia, which in one patient, due to persistent abnormality, led to discontinuation. Overall, persistent adverse events developed in only 8%. For the total group there was a drop in annual relapse rate from pretreatment to during therapy of 1.9 to 0.4 [25].

Table 2. Evaluation of suspected pediatric multiple sclerosis.

Blood test	Conditions to evaluate in differential diagnosis
MRI of brain, cervical and thoracic spinal cord	CNS mass lesion, e.g., lymphoma; and test also provides measure of MS burden of disease
Chest x-ray	Inflammatory disorders: e.g., sarcoidosis, Wegners granulomatosis
ESR, C-reactive protein	Vasculitis, e.g., CNS angitis
ANA	SLE
CBC	Anemia e.g., macrocytic anemia from vitamin deficiency
B12, folate	Vitamin deficiency associated with white matter changes in CNS
TSH	Thyroid disorders, e.g., Hashimoto thyroiditis
Angiotensin-converting enzyme	Sarcoidosis
Genetic studies for mitochondrial and dysmyelinating disorders	Onset of progressive cognitive decline associated with other neurologic deficts including peripheral nervous system dysfunction, e.g., metachromatic leukodystrophy
Mitochondrial testing (Notch 3 mutations)	Stroke-like episodes and migraine (CADASIL)
NMO-IgG	Optic nerve or spinal cord involvement, prominent features, e.g., neuromyelitis optica
Lyme titer	In endemic areas or early-summer onset
Mycoplasma titer	Mycoplasma infection

In the Blood test column, routine tests are bolded – otherwise the tests are applicable for specific clinical presentations only.
ANA: Antinuclear antibody; CADASIL: Cerebral autosomal dominant arteriopathy; CBC: Complete blood cell count; ESR: Erythrocyte sedimentation rate; IgG: Immunoglobulin G; NMO: Neuromyelitis optica; SLE: Systemic lupus erythematosus; TSH: Thyroid-stimulating hormone.

Table 3. First-line disease-modifying therapies in pediatric multiple sclerosis (selected studies).

Drug	Number of children per study (n)	Duration of treatment (months)	Most frequent adverse events	Decrease in relapse rate from pretreatment (%)	Ref.
IFN-β1a im. (Avonex®) 30 mg im. once a week	13	12	Flu-like symptoms, injection-site reactions, transient abnormal liver enzymes	NA	[28]
	52	43	Flu-like symptoms, headache, mylagia	79	[25]
	9	17	Flu-like symptoms, injection site reactions	NA	[27]
IFN-β1b (Betaseron®) 8 mU sc. every other day	43	29	Flu-like symptoms, LFT increase, injection site reactions	50	[31]
IFN-β1a SQ (Rebif®) sc. 22 µg or 44 µg three-times per week	16	41	Flu-like symptoms, laboratory abnormalities*	73	[35]
	51	22	Injection site reactions, flu-like symptoms, abnormal blood counts	58	[29]
	24	44	Flu-like symptoms, injection site reactions, abnormal liver enzymes	Significant	[30]
Glatiramer acetate (Copaxone®) 20 mg sc. daily	7	24	Systemic reaction	100	[34]
	9	33	None reported	91	[35]

Side effects includes two patients on IFN–β1b.

im.: Intramuscular; LFT: Liver function test; sc.: Subcutaneous.

Similar positive treatment effects with IFN-β1a intramuscular were noted in a small placebo-controlled study (n = 16), which showed improvement in IFN-β1a intramuscular relative to placebo over a 48-month period [26]. Others have also found good tolerability and an improved relapse rate with treatment [27,28].

Dosing

No published information is available on the dosing of IFN-β1a intramuscular in the pediatric age range. However, the standard adult dose of 30 µg, intramuscular once per week has been used effectively even in some children aged 10 years and under. In our experience, a slow gradual titration of IFN-β1a intramuscular is usually best tolerated. Depending on the age of the child, we have used the following schedule: 5 µg × 2–4 weeks, 10 µg × 2–4 weeks and, finally, the full dose of 30 µg (the volume to be injected depends upon whether the prefilled or lyophilized form is being used). The same injection sites used for adults can be used in children. In one case where the family of a 5-year-old girl misunderstood the instructions and on the first day of treatment injected a full dose, marked vomiting occurred for the duration of a day. Once the titration schedule was initiated, she tolerated the medication well, but because of her small size did not go beyond a half dose.

IFN-β1a subcutaneous (Rebif®)

Interferon-β1a subcutaneous has been administered to MS patients in the pediatric age range with good effect. Among 51 children under the age of 16 years started on IFN-β1a subcutaneous therapy, treatment was well tolerated [29]. Six patients withdrew due to adverse events, two patients due to injection phobia and one from suspected lack of efficacy. The mean annual relapse rate decreased from 1.9 prior to initiation of therapy to 0.8. Adverse events on treatment were usually mild flu-like symptoms (65%) and laboratory changes similar to those reported in adults, which included elevated transaminases (35%) and leukopenia (27%) [29]. Smaller studies of IFN-β1a subcutaneous have also noted good tolerability [25,28,30].

In a study of 24 children with a mean age of 9 years who were treated for an average of 40 months, IFN-β subcutaneous was associated with two serious adverse events (arthritis and suicide attempt). More commonly, side effects are minor. Among the 24 children studied, these included flu-like symptoms (58%), myalgia (17%) and injection-site reactions (75%) [30]. Expanded Disability Status Scale (EDSS) was decreased among children aged under 10 years during therapy compared with pretreatment levels [30]. In the author's experience, the one serious adverse event that developed was with a teenager who continued to self-inject in an area of skin breakdown, developing a severe cellulitis that ultimately required skin grafts. Fortunately, the vast majority of children do extremely well with IFN-β subcutaneous However, as is the case for all therapies, close monitoring of compliance and adverse events, as well as laboratory testing, is necessary.

Dosing

The standard dose for IFN-β1a subcutaneous for children can be the same as adults: 44 µg three-times a week with a minimum of 48 h between each dose. However, one study used 22 µg three-times a week with good tolerability. The dosing schedule of IFN-β1a subcutaneous is somewhat simplified by the availability of different sized doses. For children, dependent on their age, we escalate at 8.8 µg three-times a week × 2–4 weeks, 22 µg three-times a week × 2–4 weeks and 44 µg thereafter at three-times a week.

Interferon β 1b subcutaneous (Betaseron®)

A multicenter collaborative effort to examine experience with IFN-β1b subcutaneous was completed among 43 individuals who all began therapy prior to their 18th birthday [31]. There were no serious adverse events. Flu-like symptoms (35%), elevated liver function tests (25%) and injection-site reactions (21%) were the most frequent side effects. Most of the side effects were similar to those seen in adult MS patients. Only one patient discontinued treatment due to an adverse event: an injection-site reaction. However, some patients switched to different therapies or failed to continue therapy due to poor adherence or continued disease progression [31].

This overall positive experience regarding ability to tolerate IFN-β1b subcutaneous is also supported by a case report [32]. For example, one 7-year-old boy who experienced multiple relapses between the ages 3 and 7 years who started IFN-β1b subcutaneous tolerated the medication well. No subsequent relapses occurred during the 3-year follow-up period and there were no serious adverse events [32].

Dosing

The standard dose of IFN-β1b subcutaneous is 1.0 cc of 8 million IU, self-administered every other day. It is important to titrate gradually and to monitor for adverse events and laboratory changes during this process. One approach is to begin a dose of 0.25 cc (2 million IU) × 2–4 weeks followed by 0.5 cc (4 million IU) × 2–4 weeks, followed by 0.75 cc (6 million IU) × 2–4 weeks and then titrated to full dose. The same injection sites used for adults can be used in children. There are no known drug interactions with the IFNs. The concurrent use of steroids and symptomatic therapies were not associated with adverse events in any of the clinical trials.

Glatiramer acetate (Copaxone®)

Glatiramer acetate (GA) represents another treatment option, which has an advantage in that it does not require laboratory monitoring and is not associated with flu-like symptoms as a possible adverse event. However, this advantage is somewhat counterbalanced by the need for daily subcutaneous administration and, as with the IFNs, there exists a possibility of injection-site reactions. In a web-based survey of MS patients, supported by Teva Neuroscience, MO, USA, 96 subjects reported they were 18 years or younger. Of these 96 individuals, 84 (88%) were prescribed a DMT. GA was the most frequently prescribed medication in 51% of respondents, followed by IFN-β1a intramuscular (28%). Only one patient on GA reported discontinuation due to side effects. A total of 86% of individuals were started on DMT within 6 months of diagnosis [33].

In a study of seven patients aged 9–16 years who were treated with GA, all tolerated the medication well at standard doses and without escalation. A total of two out of seven remained relapse-free during a 2-year follow-up period while on treatment. The median pretreatment relapse rate of 4 (range: 2–6) dropped to 1 (range: 0–4) the year following treatment, and to 0 (range: 0–4) in the subsequent year [34]. In another study examining children on different DMTs, there were seven patients treated with GA who were under the age of 16 years [35]. In this group, the annual relapse rate decreased from 2.5 to 1.0 after a mean treatment duration of 14.7 months [35]. The experience with GA is less well documented in pediatric MS compared with the other DMTs. However, the adult experience is informative. In controlled clinical trials of adults, the most commonly observed adverse experiences associated with the use of GA were: injection site reactions, vasodialation, chest pain, asthenia, infection, pain, nausea, arthralgia, anxiety and hypertonia. These side effects have also been reported in children.

Dosing

Dosing of GA for children is the same as adults at 1 cc subcutaneous (20 mg) daily, and can be initiated at full dose from the onset of treatment. There are no known drug interactions with GA. The concurrent use of steroids and symptomatic therapies were not associated with adverse events in the pivotal clinical trials. GA is contraindicated in patients with known hypersensitivity to GA or mannitol.

Breakthrough disease

Unfortunately, some children treated with first-line DMTs experience breakthrough disease and need to be switched to either another first-line treatment or to second-line therapies. In a preliminary study of 164 treated children, 25% had breakthrough disease. Of these, eight children were switched to chemotherapy, two went on natalizumab (Tysabri®) and two were treated with pulse intravenous immunoglobulin [36].

Experience with natalizumab (Tysabri®)

There are only anecdotal reports regarding the use of natalizumab in pediatric MS. A 12-year-old who had not responded to DMT experienced a decrease in relapse frequency with natalizumab [37]. In open discussions during the Teen Adventure Weekend for MS, out of 42 teen campers who were less than 18 years of age with MS, five had been treated with natalizumab. One came off therapy due to either an infusion or hypersensitivity reaction. The other youngsters reported that they tolerated treatment without complication and felt well with the therapy. Nonetheless, this second-line treatment must be used with great caution until further information has accrued regarding safety. At the time of this review, out of the approximate 30,000 adults with MS who have been treated with natalizumab, four cases of progressive multifocal leukoencephalopathy (PML) have developed, of which two have been fatal.

Management of acute attacks

Children with MS in the midst of an acute relapse can be successfully treated with corticosteroids. Steroid therapy is most appropriate when the relapse is associated with sufficient neurological impairment to interfere with daily activities. Usual doses of methylprednisolone are

10–30 mg/kg up to a dose of 1000 mg administered intravenously once daily in the morning for 3–5 days. However, in adults with MS, oral prednisone may be as effective as intravenous treatment [38]. High-dose prednisone seems very effective in managing acute relapses [39]. High-dose oral prednisone (up to 1200 mg/day) has also been found to have good bioavailability compared with intravenous therapy [40]. High-dose prednisone as an alternative to intravenous steroids has not yet been studied in pediatric MS. Adverse effects of steroids are most likely to develop after prolonged use and include insomnia, mood disturbance, hyperglycemia and hypertension. Prolonged steroid use can also possibly retard growth in youngsters. Attention to the possibility of acute psychosis is also important. Despite its long-term risks, short courses of steroid therapy are reasonably safe and well tolerated by most children.

Plasmapheresis is a reasonable alternative when intravenous steroids fail to improve a severe relapse. The use of this modality is based on its success in some adult cases [41].

Treatment with plasmapheresis for steroid unresponsive severe relapses in pediatric MS is a consideration, as plasmapheresis can be safely given to children with other immune-mediated disorders [42]. Among children in whom it is difficult to wean off steroids, one approach is to administer pulse intravenous immunoglobulin at a dose of 0.4 g/kg × 5 days and to continue 1 day per month at 0.4 g/kg. This therapeutic approach has been studied in only small samples of ADEM and its variants [43,44].

Symptom management

There are no specific studies of symptomatic management in pediatric MS. Therefore, most of the following suggestions are either based on adult studies or anecdotal reports. Most of the common MS symptoms associated with adult MS also occur in children [45]. These include problems with fatigue, cognitive impairment, mood disturbance, paroxysmal spasms, bladder/bowel dysfunction and motor impairments.

Fatigue

Fatigue is a consistent problem and has been reported in 40–70% of pediatric MS patients [46,47]. A fatigue scale designed for children and adolescents showed that over half the children with pediatric MS reported fatigue and three-quarters of their parents described fatigue in their children [48]. Using the fatigue severity scale (FSS), the frequency of fatigue was lower in children with MS [47]. However, the FSS was developed for adults and is likely to be less sensitive in pediatric MS. Fatigue can be severe and can interfere with completing homework, performing well in school and getting to classes in a timely fashion. While there are no studies addressing treatment of fatigue in pediatric MS, there are a few clinical trials examining the efficacy of fatigue therapies in adults with MS [49–54]. The most numerous address the role of amantadine, but a recent Cochrane database review concluded that there is inadequate data to address the efficacy of amantadine for fatigue [55]. Studies concerning modafinil have yielded conflicting results [56,57]. However, given the frequency of sleep problems in MS, it is not surprising that this agent might be effective for some patients with MS fatigue. Nonpharmacologic approaches include exercise, conservation of energy, improved sleep hygiene and rescheduling the more demanding academic activities in the early morning when fatigue is often less severe. On the other hand, keeping children and teens socially engaged and involved in sports activities to the extent possible are important to self image. Often, parents need reassurance that sports are appropriate for MS.

Cognition

Cognitive problems are another major concern for children. In the earliest study addressing this issue, duration of disease was associated with greater impairments [58]. In a comprehensive study of 63 pediatric MS patients and 57 healthy controls, 53% of the MS group failed at least two tests, and 31% failed three tests. These results showed significant cognitive dysfunction in pediatric MS relative to healthy controls [47]. Another study showed that approximately a third of children with pediatric MS had deficits relative to normative samples [59]. The most prominent deficits among children with MS are memory, complex attention and executive function, a pattern of cognitive impairment similar to the deficits of adults with MS [47,59]. However, unlike adults, the affected children also have impairments in linguistic abilities [47,59]. One analysis of cognitive impairments in pediatric MS found no clinical predictors of cognitive deficit other than IQ. Others have noted that cognitive impairment was associated with disease duration, relapse frequency and EDSS [58,59]. Comprehensive longitudinal studies are required to determine the progression of cognitive deficits

in children and the effect, if any, of DMT. Unfortunately, one small study of children on DMT found that declines over short periods such as 1–2 years are common [60].

There are few studies demonstrating consistent benefits with either pharmacologic or nonpharmacologic interventions for cognitive deficits in adults. However, no studies have been done in children. For example, among adults, a randomized control clinical trial demonstrated that donepezil (Aricept®) 10 mg/day was associated with improved memory [61]. Whether or not such treatment should be considered in cognitively impaired children is unknown. Cognitive rehabilitation has shown some benefits on overall cognitive functioning in adults [62] with MS, but has not been studied in children.

Depression

Mood disorders are another issue, which requires special attention. In a subset of 12 patients who underwent psychiatric evaluation, almost half were diagnosed with depression or an anxiety disorder [59]. However, using self-report measures others have found low levels of depressive symptoms in children [47]. Overall, healthcare providers should be attentive to changes in school performance and the possibility of depression or anxiety. The use of antidepressant therapy has not been examined in children with pediatric MS, but has been studied in children with major depression [63]. The one agent with the most consistent benefit is fluoxetine. The usual dose ranges from 10–40 mg [63]. The other selective serotonin reuptake inhibitors (SSRIs) have shown less consistent results [63]. While there is a risk of suicide in teenagers treated for depression, the risk of untreated depression is also severe. Some untreated as well as treated children are severely depressed to the point of expressing suicidal ideation and have required psychiatric hospitalization.

Urinary/bowel dysfunction

Urinary dysfunction is a critical issue for individuals with MS, affecting both adults and children of both genders. Among children participating in open discussions regarding their MS, many admitted they were reluctant to disclose this problem to their healthcare providers. Special awareness and specific questioning are important in assessing the problem. As reviewed elsewhere, 32–97% of adults with MS experience symptoms of urinary dysfunction, which are most often detrusor and sphincter disorders [64]. These symptoms most often appear on average 6 years after the onset of the disease (range: 5–9.5 years) [64]. Doses for medications commonly used in adults are oxybutynin (Ditropan®) 5–10 mg everyday, twice daily as needed. Tolterodine (Detrol®) 2–4 mg everyday, twice daily as needed and solifenacin succinate (Vesicare®) 5 mg daily.

Bowel problems can be treated with a bowel training regimen which includes taking a food diary to see which foods trigger a problem. Sometimes a laxative taken in the morning can allow a patient to set a morning time to eliminate. This would then permit the patient to function normally the remainder of the day. Patients should avoid caffeine, spicy foods and fried foods. Carbonnated beverages should also be avoided as they can cause flatulence. Anticholinergic medication can be a consideration in selected cases.

Spasticity

Spasticity is a problem that can be addressed with multidisciplinary treatment. Physical therapy and exercise are helpful in adults and should be considered for children as well. In children, oral baclofen (0.36–1.5 mg/kg), can be used in MS, as well as those with other neurological disorders. However, very young patients have a risk of seizures [65]. The experience of intrathecal baclofen in patients with cerebral palsy (25–50 µg/day) is in general positive, and in severely spastic MS children might be a consideration in those failing oral baclofen [66]. Another oral therapy effective for spasticity is tizanidine (2–24 mg/day).

Paroxysmal spasms

Paroxysmal spasms are most typically characterized by trigeminal neuralgia and can occur in children with MS as they can in adults. For trigeminal neuralgia, the most consistently effective medication in adults with the disease is carbamazepine [67]. The pediatric dose is 10–35 mg/kg/day. Other agents used successfully include gabapentin 10–50 mg/kg/day, tizanidine or baclofen.

Motor impairments

Motor problems are common in pediatric MS. Physical therapy and exercise are the main therapeutic interventions. In adults, the medication fampridine sustained release (SR) has been associated with improved walking speed and strength [68]. This medication is still experimental and has not been studied in children.

Supporting the family

Multiple sclerosis affects the entire family including the parents, siblings and grandparents. Support, education and reassurance is needed by both the parents and patient. We believe that the diagnosis should be shared with both the parents and the patient regardless of the age. There are a variety of different support systems available to assist in breaking the diagnosis to the family. Educational materials available through the National Multiple Sclerosis Society (NMSS) include *Children get MS too: A guide for parents*, *Children and Teens with MS: A Network for Families* and *Mighty Special Kids – an activity book for children with MS*. More information, additional services and online networking for parents and teens are available at the website of the NMSS [101] or by phone (+1 866 – KIDS WMS [866 543 7967]). Additional information can also be found at the National Pediatric MS Center Website [102].

Conclusion

Pediatric MS is a chronic disorder that requires early intervention and a multidisciplinary treatment approach. The management includes educating and reassuring the family, using medications to modify the disease course and addressing the daily symptoms and psychosocial consequences of the disease. Most children appear to do reasonably well and do not develop a progressive course until decades later [2]. However, ongoing support and assistance in transitioning to adulthood as the children become older are all elements of the treatment.

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Executive summary

- Establishing the correct diagnosis is essential, as well as considering those prognostic factors for a multiple sclerosis (MS) diagnosis following an acute demyelinating event.
- Disease-modifying therapy is well tolerated and appears effective despite the lack of controlled clinical trials in pediatric MS.
- Attention should be given to the consequences of cognitive impairments and the management of MS-associated symptoms.

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