A Practical Guide to Pediatric Multiple Sclerosis

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Abstract

During the past 10 years much knowledge has been gained about multiple sclerosis in the pediatric population. This article summarizes the information relevant to the neurologist and pediatric neurologist concerning the diagnosis, differential diagnosis and therapy for pediatric MS.

Introduction

3–5% of patients with multiple sclerosis (MS) have an onset of disease equal or prior to the age of 16 and less than 1% before 11 years of age [7,11,16,38]. However until the 1990s it was largely unknown that MS even existed in this age group. In the past 10 years the knowledge on pediatric MS has increased immensely and many excellent reviews have been published recently [1,45,49]. This article, therefore, does not attempt to give an overview of the subject but instead summarizes the practical consequences that arise from the recent gain in knowledge for a physician not primarily involved in the treatment of pediatric MS. Since there are no approved guidelines for the diagnosis and treatment of pediatric MS, the information in this article is based where possible on the results of studies or consensus papers; where no such studies or papers were available the current proceedings in use in the Center for Multiple Sclerosis in Childhood and Adolescents, Göttingen, Germany are described.

Definition and Diagnosis

The International Pediatric MS Study group has formulated in 2007 consensus definitions for pediatric MS [21]. As in adults, the term clinically isolated syndrome (CIS) is applied to the first demyelinating event. This event can be monofocal meaning that the clinical features can be attributed to a single CNS lesion or multifocal but should not be associated with encephalopathy. Encephalopathy has been defined as the occurrence of behavioral changes (e.g. confusion or excessive irritability) or alteration in consciousness (lethargy or coma). The presence of encephalopathy does not exclude CIS but rather speaks for the diagnosis of acute demyelinating encephalomyelitis (ADEM).

The term "pediatric MS" is applied to children with MS (< 10 years of age) and adolescents (< 18 years of age). Following the revised McDonald criteria for adult MS the diagnosis requires at least 2 episodes of CNS demyelination disseminated in space and time. Dissemination in time means that at least 30 days must separate the onset of the first attack and a second attack. Dissemination in space requires the objective clinical evidence of 2 or more lesions [27,37]. However, both diagnostic criteria, dissemination in time and space, can be met by MRI and laboratory findings alone allowing the diagnosis after the first attack. Dissemination in time can be stated in the absence of a second clinical attack when new T2-bright or gadolinium enhancing lesions develop 3 months following the initial event. Analogously to the McDonald criteria, dissemination in space is present when 3 of the following 4 features are found in the MRI: 1) 9 or more white matter lesions or one gadolinium enhancing lesion, 2) 3 or more periventricular lesions, 3) 1 juxtacortical lesion, 4) 1 infratentorial lesion. Alternatively, the dissemination in space criteria can be fulfilled by combination of oligoclonal bands or an elevated IgG index in CSF and 2 lesions on the MRI, of which one must be in the brain.

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Clinical Presentation

In most patients the onset of MS is post-pubertal but it can also occur in infancy [41]. Interestingly the male/female ratio is equal in the prepubertal group while a preponderance of females is seen following puberty, as in adults [2,41]. The majority of patients (>95%) with pediatric MS present with a relapsing remitting course and frequently a complete remission of symptoms occurs after a course of steroids [3,41]. In our Göttingen cohort of 166 patients the annual relapse rate was 1.95% in the first year and dropped down to 0.23% in the 5th year after the first attack [41]. Most frequently the attacks affected the cranial nerves in particular the optic nerve (43%). Other frequent symptoms are sensory and motor deficits or cerebellar dysfunction. Less frequent symptoms in our cohort were pain, fatigue and cognitive problems.

Prognosis

The risk of developing MS after CIS has been estimated at 43–57% in the pediatric population [30,31]. It is higher in patients with an age at onset ≥10 years, a positive family history of optic neuritis or MS, an absence of encephalopathy at onset, optic nerve lesions, an MS-suggestive initial MRI and oligoclonal bands or an elevated IgG index present in CSF. It has been found that time period between the first and second attack is longer in children under the age of 10 (median 6 years) compared to older children (median 1 year) [30]. Long term follow-up of patients with pediatric MS has shown that the median time from onset of disease to secondary progression and irreversible disability (defined as a Expanded Disability Status Scale (EDSS) >4) is 10 years longer than in adults. However, due to the younger age at onset this stage of the disease is reached 10 years earlier than in adults, at a median age of 41 years [38]. Pediatric MS is therefore, although less dramatic at the beginning, by no mean a harmless disease.

Differential Diagnosis

Many disorders in childhood that present with neurological symptoms are associated with white matter lesions on cranial MRI. The differential diagnosis at the time of the first attack therefore includes a large number of infectious, autoimmune, neoplastic, vascular and metabolic disorders. Especially in childhood where MS is very rare and the first presentation often atypical a very careful evaluation is warranted. The following signs and symptoms should wake the awareness that MS is an important differential diagnosis:

1. *A previously healthy child develops a neurological symptom within hours or days.* In most metabolic disorders and in brain tumors the careful history taking will reveal that the child had subtle symptoms like developmental delay, headaches, vomiting, weight loss or behavioral problems prior to first presentation. Moreover, in most of these disorders the symptoms will develop over weeks or even month and not within days.
2. *The presenting symptom is optic neuritis.* Optic neuritis is a very frequent symptom of pediatric MS. Pediatric patients with optic neuritis should therefore always get a complete diagnostic work-up including cranial MRI and CSF studies.
3. *The symptoms resolve after high dose steroids*. Children with vascular disorders, tumors or leukodystrophies might show some improvement after steroid treatment but in most cases not complete and sustained recovery.
4. *The course of the disease is remitting recurrent*. Very few neurological disorders of childhood have a remitting recurrent course. One exception are mitochondrial disorders that often present during or after infections and may show resolution of symptoms like seen in MS. However, the MRI pattern in these patients is often atypical for MS, and the lactate in CSF is elevated in many.

In the following paragraph we will discuss those disorders that are in the eyes of the authors the most important differential diagnoses. A comprehensive set of differential diagnoses can be found in the publication of the International Pediatric Study Group in 2007 [17].

Acute demyelinating encephalomyelitis: ADEM is an immune-mediated inflammatory disorder of the CNS that is monophasic in most but may be multiphasic in some patients [43]. Typically it begins within days or weeks after an infection presenting with a rapid onset encephalopathy and multifocal neurological deficits. On cranial MRI large poorly marginated T2-bright lesions that affect gray and white matter are seen. The differentiation between ADEM and MS can be difficult or impossible especially in young children as the latter can also present with encephalopathy and large lesions on MRI. It is therefore not surprising that 10–29% of patients with an initial diagnosis of ADEM are later diagnosed with MS [29,30,42].

Neuromyelitis optica (NMO): NMO is a rare disorder characterized by either monophasic or recurrent attacks of optic neuritis and longitudinal extensive transverse myelitis [48]. In some pediatric cases of recurrent NMO antibodies directed against aquaporin-4 can be detected which seems to be a marker for a more severe clinical course [6]. Cranial MRI is either normal or shows large cloudy T2-bright lesions distinguishing it from most cases of MS [32]. It is very important not to misdiagnose NMO because in many patients recurrent NMO has a very poor prognosis leading to disability or even death within 5–10 years. Moreover NMO does not respond to the disease-modifying therapies using interferon beta or glatiramer acetate but instead requires early treatment with immunosuppressant drugs.

Optic neuritis (ON): ON can be the first symptom of MS but it can also be a monophasic or recurrent disorder unrelated to MS often associated with infections. The risk of developing MS after an episode of ON has been estimated 15–42%, it is higher in patients with bilateral or recurrent ON and lower in those with an infection within 2 weeks prior to onset of ON [20,24,39]. An MRI showing white matter lesions suggestive of MS is also very indicative of a high risk for developing MS [8].

Partial transverse myelitis: Like ON partial transverse myelitis can be the presenting symptom of MS. However the risk to develop MS is much lower than in ON (8%) [30]. In adults it has been shown that T2-bright lesions in the brain, oligoclonal bands or a raised IgG-index in CSF are associated with a higher risk of developing MS [40].

Cerebral vasculitis: The various forms of cerebral vasculitis are very rare in childhood. However, they can present with

recurrent episodes of focal neurological symptoms accompanied by T2-bright lesions on MRI that are not unlike those seen in MS [23]. MR angiography may or may not show abnormalities in cerebral vasculitis. In many patients with cerebral vasculitis the erythrocyte sedimentation rate will be elevated which is uncommon in MS.

Neoplasms: In some cases CNS neoplasms or metastasis can present with focal neurological symptoms and MRI lesions indistinguishable from those seen at the first attack of MS. CNS lymphoma is the most frequent neoplasm that can be mistaken for MS. CSF analysis, serial MRIs and MR-spectroscopy will in most cases clarify the diagnosis. In the remaining patients brain biopsy has to be performed [26].

Neuroborreliosis: In about 10% of patients that are infected with Borrelia burgdorferi the disorders enters a second stage often with neurological symptoms. Most commonly these patients present with meningitis and or facial nerve palsy. Here the differentiation between neuroborreliosis and MS is unproblematic. In some cases, however, neuroborreliosis causes other neurological symptoms like transverse myelitis, ataxia, chorea or peripheral neuritis and these symptoms may even show a remitting relapsing course. In these cases cranial or spinal MRI often reveals white matter lesions similar to those found in MS. The exclusion of borreliosis by determination of antibodies against borrelia burgdorferi in CSV is therefore always indicated especially in areas where Lyme disease is prevalent.

Diagnostic Testing

The mainstay of the diagnostic procedures for MS is the history taking and the neurological examination. For evaluating whether dissemination in time is present one has to keep in mind the definition of an MS attack. An attack is a neurological symptom that lasts at least 24 h, occurs ≥ 30 days after the previous attack and is not accompanied by fever or infection. The instruments developed for follow-up and evaluation of therapy e.g. the Expanded Disability Status Scale (EDSS) or the Multiple Sclerosis Functional Composite Scale (MSFC) has been standardized for adults. They can and should be used in adolescents but are less useful in younger children.

MRI: The MRI is the most important diagnostic tool in pediatric MS. It allows exclusion of many differential diagnoses, can demonstrate the dissemination in time and space necessary for the diagnosis if clinically not present or unclear and is sometimes useful for the evaluation of the disease-modifying therapies. Following the recommendation of the International Pediatric MS Study Group the examination should include a cranial and a spinal MRI with and without gadolinium [17]. The pattern of lesions on cranial MRI in pediatric MS is similar to that seen in adults. It has been reported that children have fewer lesions and less gadolinium enhancing lesions when compared to adults, however this finding has not been reproduced in a more recent study [5, 46]. In children under 11 years T2-bright lesions are less well defined and have a tendency to vanish on follow-up imaging while adolescents show an accumulation of lesions. It has also been found that in children more lesions include the deep gray matter [10].

Cerebrospinal fluid (CSF): CSF analysis has a role in the initial diagnostic procedure in a child suspected to have MS but does not play a role for follow-up or therapy evaluation. Many pediatric MS patients show pleocytosis with up to 60 leucozytes/mm^3 during the first attack [34]. Higher levels would rather indicate an infection or vasculitis. Oligoclonal bands are frequently positive in pediatric MS and therefore very sensitive but in some patients they develop later in the course of the disease [34]. However, negative oligoclonal bands do not exclude MS while positive oligoclonal bands can also be found in several immunological disorders as well as in chronic or acute infections [28]. As in adults the IgG index is raised in most pediatric MS patients but this has been found to be less sensitive than oligoclonal bands [34].

Blood: There are no established biomarkers in serum or plasma to date that would help to support or disprove the diagnosis of MS. The investigations in serum and plasma are therefore only directed to exclude other disorders. According to the International Pediatric MS Study Group the investigations in blood should include a complete blood count with differential, erythrocyte sedimentation rate and antinuclear antibodies [17]. All other investigations should be guided by the clinical presentation and MRI pattern.

Neurophysiological testing: In the initial work-up of a patient with suspected MS visual and auditory evoked potentials as well as somatosensory evoked potential are useful because they help to objectify neurological symptoms and even detect clinically silent lesions [35]. Due to the high frequency of optic neuritis the visual evoked potentials should also be part of the follow-up investigations.

Therapy

Since pediatric MS in contrast to adult onset MS is a rare disorder neither double blind, randomized controlled studies nor prospective single arm studies on the treatment of pediatric MS have been performed so far. The available data on currently used medications is summarized below. Because the intention of this article was to provide a practical guide, the current treatment procedures used at the German Center for Multiple Sclerosis in Childhood and Adolescents in Göttingen, Germany are also provided.

Treatment of the acute attack

No studies known to the authors have been performed on this subject. The International Pediatric MS Study Group recommends the treatment of significant neurological impairment with methylprednisolone 20–30 mg/kg/day as a 1–2 h infusion in the morning for 3–5 days. A subsequent oral tapering should be restricted to patients with insufficient resolution of symptoms. For children with severe relapses that do not improve after high dose steroids they suggest plasma exchange might be beneficial.

Procedure in Göttingen: All patients that experience an attack are treated with 20 mg/kg/day (up to a maximum of 1 gr/day) iv methylprednisolone for 3–5 days without subsequent tapering. If symptoms do not improve within 14 days a second course of high dose steroids is administered. In case of severe worsening of symptoms after the first course or no improvement of severe symptoms after the second course a plasma exchange or immu-

noadsorption is performed. In 2009 only 3 patients with pediatric MS had to be treated with either plasma exchange or immunoadsorption and in all of them it resulted in a significant improvement of symptoms.

Disease modifying therapy (DMT)

It has been shown that DMT reduces the relapse rate and progression of disease in most cases [13,14]. According to the International Pediatric MS Study Group a disease modifying therapy should be initiated in all patients with active remitting recurrent disease. This has been defined as more than one relapse in a period of 1–2 years and new T2-bright lesions or gadolinium enhancing lesions. To avoid treating patients with ADEM in patients whose initial episode included encephalopathy the therapy should not be started until the second or third attack [36].

Procedure in Göttingen: In all patients in whom the diagnosis of MS is established according to the McDonald criteria the patients and parents are informed about DMT. We do not recommend starting a DMT in patients with the diagnosis MS based on MRI findings if the symptoms of the first attack resolved completely and a low lesion load (<6 T2-bright lesions, <2 gadolinium enhancing lesions) is present on cranial MRI. This recommendation is reviewed every 6 months. If a second attack happens during the following 2 years or there are signs of active disease on follow-up MRI a DMT is recommended.

Disease modifying drugs

Like in adults the disease modifying drugs used in pediatric MS include subcutaneous and intramuscular interferon-β1a (INFB-1a), subcutaneous interferon-β1b (INFB-1b) and glatiramer acetate (GA). However, no randomized controlled trials are available that show the effectiveness of these therapies in pediatric patients. There are also no comparative studies that show that either of the agents is superior to the others. The choice of drug therefore varies from clinic to clinic and country to country.

Procedure in Göttingen: All 4 treatment options are discussed with the patient and the parents. Since only retrospective studies with small patient numbers [4,33,44,47] are available on the effectiveness the information about the route of administration (subcutaneous or intramuscular) the rate of administration (daily, every second day or once weekly) and the expected side effects guide the individual choice.

Interferon beta (INFB): Retrospective studies and open label studies have shown safety and tolerability of subcutaneous and intramuscular INFB-1a and INFB-1b in pediatric MS [4,33,44,47]. As in adults the most frequent side effects were flu-like symptoms, headaches, abnormal liver function tests and injection site reactions. The International Pediatric MS Study Group has recommended that the dose should be adjusted in pediatric MS, especially in children below age 10 years [36]. The initial dose might be decreased to 25–50% of the adult dose and then stepwise increased every 2–4 weeks to full or maximum tolerable dose. Flu-like symptoms can be treated with ibuprofen 10 mg/kg prior to administration of INFB.

Procedure in Göttingen: Most patients in Göttingen decide to use subcutaneous IFNB-1a or INFB-1b. However, especially in patients with needle phobia or problems with compliance, once weekly intramuscular INFB-1a has been successful. Most adolescents will tolerate the full dose after a stepwise increase. In children below 10 years of age the treatment is started with 10% of the adult dose and slowly increased to the maximum tolerable dose. Most patients experience transient flu-like symptoms during the first 3 months of treatment.

Glatiramer acetate (GA): GA has been found to be safe and well tolerated in pediatric MS patients [19,22]. Most frequent side effects were pain and induration at the injection site and transient systemic reactions. According to the International Pediatric MS Study Group no dose escalation is needed [36].

Procedure in Göttingen: Only few patients decide initially to use GA because it means daily injections. The patients that do use it report less side effects than the patients treated with INFB (personal observation).

Follow-up and therapy evaluation

Follow-up: In patients treated with INFB it is recommended that CBC with differentiation, AST and ALT are obtained monthly until the full dosage is reached and thereafter every 3 months and when the patient is feeling unwell [36].

Therapy evaluation: To evaluate therapy efficiency neurological examination should be performed 1, 3 and 6 months after therapy initiation and then every 6 months. MRI scans should be obtained prior to DMT initiation and 6 months after. In patients with stable disease MRI scan should be repeated yearly [36] (**Table 1–4**).

Change of treatment

A change of treatment is necessary when serious side effects occur, when the side effects are not tolerable for the patient leading to reduced compliance or when the currently used therapy is not effective enough. In adults suboptimal response to DMT treatment has been defined as a relapse rate of either 1/year or unchanged from pretreatment rates, incomplete recovery from multiple attacks, evolution of polyregional neurologic involvement, recurrent brainstem or spinal cord lesions, and cumulative loss of neurologic function sufficient to disrupt daily activities [12]. Recently similar guidelines have been suggested for pediatric MS [15].

Table 1 Diagnostic criteria for pediatric MS according to Krupp et al. 2007 [7].

Diagnostic criteria for pediatric MS are fulfilled after
– 2 attacks
– disseminated in time (At least 30 days separate the first from the second attack) **and**
– disseminated in space (Objective clinical evidence of 2 or more lesions)
– 1 attack
– when new T2-bright or gadolinium enhancing lesions develop 3 month following the initial event **and**
– first or second MRI show three of the following four features
– 9 or more white matter lesions or 1 gadolinium enhancing lesion
– 3 or more periventricular lesions
– 1 juxtacortical lesion
– 1 infratentorial lesion
– **or** 2 lesions on MRI, one of which must be in the brain and oligoclonal bands or an elevated IgG index in CSF

Procedure in Göttingen: In patients in whom the DMT treatment leads to intolerable side effects the therapy is switched from either INFB to GA or vice versa. The change in therapy is done without overlap or a time delay. When INFB is newly introduced, the dosage is increased stepwise as described above. The decision that DMT treatment has a suboptimal response is not made before 6 month after commencement of one of these therapies and is based on the above mentioned recommendation for adults but does not follow a strict algorithm instead it is an individual decision for each patient.

Escalation therapy

Cyclophosphamide, mycophenolate mofetil, daclizumab, mitoxantrone, rituximab and natalizumab have been used in pediatric MS patients [9,18,25,49]. However no recommendations for their use are available.

Procedure in Göttingen: Patients that need an escalation of treatment are treated with natalizumab at a dose ranging from 3–5 mg/kg as an infusion every 4 weeks. So far, 6 patients have been treated and in all of them it has successfully reduced the relapse rate and disease progression. However, natalizumab is not licensed under age 18 years and leads in some patients to progressive multifocal leukoencephalopathy (PML). Commencement of this treatment should therefore be restricted to specialized centers. Since natalizumab was effective in all patients treated so far, we do not have patients treated with cyclophosphamide, mycophenolate mofetil, daclizumab, mitoxantrone or rituximab.

Table 2 Diagnostic workup in patients with suspected pediatric MS.

– MRI
– axial T2, sagittal T2, axial T1, axial Flair
– axial T1 with gadolinium
– spinal T2 and T1 with gadolinium
– CSF
– cell count with differentiation
– total protein
– IgG index
– oligoclonal bands
– borrelia antibodies
– Blood
– blood count with differentiation
– ESR
– ANA
– Neurophysiology
– visual evoked potentials

Conclusions

Pediatric MS is often considered a more benign disorder than adult MS and in fact in most patients the gain of permanent disabilities is slow. However due to the young age at onset pediatric MS patients reach a comparable degree of disability 10 years sooner than adult MS patients. It has been shown in adults with relapsing remitting MS that an early start of DMT leads to permanently slower disease progression. No such studies have been performed in pediatric MS but there is no indication that this should not also be true in this population. Early treatment is only possible if the diagnosis is not delayed. It is therefore important that especially pediatricians are aware that MS is not restricted to adult patients but can already occur in early childhood. The treatment of patients with pediatric MS should be overseen by centers that are experienced in the field as in many patients the therapy is not straight forward. This will be even truer in the near future because a whole array of new drugs is about to be licensed for the treatment of MS. Examples are immunmodulatory drugs for oral application like cladribine, fingolimoid and laquinimod. In clinical trials for adult MS many of these drugs have been shown to be more potent than the cur-

Table 4 Algorithm for therapy of pediatric MS. INFB: Interferon beta; GA: Glatiramer acetate.

Therapy of the acute attack:
– iv methylprednisolone 20 mg/kg/day (max. 1 gr/day) for 3–5 days
– reevaluation 7 days later
– improvement of symptoms
– no further treatment
– no improvement or worsening of mild or intermediate symptoms
– repeat methylprednisolone
– reevaluation 7 days later
– no improvement or worsening of symptoms
– plasmapheresis
– no improvement or worsening of severe symptoms
– plasmapheresis
Disease modifying therapy
– INFB or GA
– reevaluation after 6 months
– no disease progression, little or no side effects
– continuation of treatment
– no disease progression, but severe side effects
– change from INFB to GA or vice versa
– disease progression or severe side effects
– escalation therapy

Table 3 Differential diagnosis of pediatric MS.

Disorder	Distinguishing features		
	Clinical	MRI	Laboratory
Acute demyelinating encephalomyelitis	encephalopathy	large T2 bright lesions also affecting grey matter	negative for oligoclonal bands
Recurrent optic neuritis	no other symptoms	normal	negative for oligoclonal bands
Neuromyelitis optica	no other symptoms	longitudinal extensive myelitis large cloudy T2 bright lesions	aquaporin-4 antibodies in serum
Transverse myelitis	no other symptoms	cranial MRI normal	negative for oligoclonal bands
Cerebral vasculitis	poor recovery of symptoms	pathological MR-angiography in some patients	elevated erythrocyte sedimentation rate
Neoplasms	progressive course	persistent or growing lesions on MRI	tumor cells in CSF
Neuroborreliosis	monophasic	normal in most patients	borrelia burgdorferi antibodies in CSV

rently available DMTs but also harbor the risk of serious side effects including the development of tumors. These new drugs will allow more individualized therapy for patients with MS but will demand even more experience from the physician that commences them.

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