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CHILDHOOD MULTIPLE SCLEROSIS: A REVIEW

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Multiple sclerosis (MS) is an autoimmune demyelinating disorder of the central nervous system (CNS) that is increasingly recognized as a disease that affects children. Similar to adult-onset MS, children present with visual and sensory complaints, as well as weakness, spasticity, and ataxia. A lumbar puncture can be helpful in diagnosing MS when CSF immunoglobulins and oligoclonal bands are present. White matter demyelinating lesions on MRI are required for the diagnosis; however, children typically have fewer lesions than adults. Many criteria have been proposed to diagnose MS that have been applied to children, mostly above 10 years of age. The recent revisions to the McDonald criteria allow for earlier diagnosis, such as after a clinically isolated event. However, children are more likely than adults to have monosymptomatic illnesses. None of the approved disease-modifying therapies used in adult-onset MS have been approved for pediatrics; however, a few studies have verified their safety and tolerability in children. Although children and adults with MS have similar neurological symptoms, laboratory (cerebrospinal fluid) data, and neuroimaging findings, the clinical course, pathogenesis, and treatment of childhood onset MS require further investigation.
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Key Words: multiple sclerosis; children; clinical features; pathogenesis; therapy

Multiple sclerosis (MS) was first described more than 170 years ago in adults. Although rare, MS was recognized in children as early as 1922 [Wechsler, 1922]. Nevertheless, MS is still thought to be a disease of young adulthood, typically presenting between the ages of 20 and 40 years, and the diagnosis is rarely considered in children.

Physicians have questioned whether or not childhood MS is the same entity as seen in adults. In 1958, Gall et al. published one of the earliest retrospective studies on pediatric-onset MS [Gall et al., 1958]. Between 1920 and 1952, 40 children met inclusion criteria for the study. The patients demonstrated neurological signs and symptoms due to scattered lesions within the CNS separated by time and space and supported by objective evidence. The study concluded that children and adults with MS have similar clinical profiles, including mode of onset, symptoms, and physical and laboratory (cerebral spinal fluid [CSF]) findings. Nevertheless, diagnosing MS in children is often difficult and controversial.

EPIDEMIOLOGY

The estimated prevalence of MS worldwide is 50 per 100,000 with 2.7–5.6% of patients presenting before the age of 15–16 years [Sindern et al., 1992; Gadoth, 2003]. The calculated frequency of childhood-onset MS is 1.35–2.5 per 100,000 [Gadoth, 2003]. MS has been diagnosed during infancy and early childhood (younger than 10 years of age) accounting for 0.2–0.7% of all cases [Ruggieri et al., 1999]. There are reports of children presenting before the age of 2 years, even as early as 13 months [Cole et al., 1995]. As seen in the adult population, there is a female predominance in childhood MS ranging from 2.1–3:1 [Gall et al., 1958; Duquette et al., 1987].

CLINICAL PRESENTATION

The presenting symptoms of MS in children are similar to those reported by adults. In 1987, Duquette et al. reviewed 125 pediatric patients with MS who presented most commonly with either pure sensory symptoms or optic neuritis [Duquette et al., 1987]. Diplopia, pure motor symptoms, abnormal gait including ataxia (cerebellar or vestibular), mixed sensory and motor symptoms, and sphincter disturbances were also reported. In 1992, Sindern et al. identified 31 patients with MS using Poser's criteria (see Diagnosis section) who presented before the age of 16 years and compared them to 72 sex-matched control patients diagnosed with MS between the ages of 20 and 40 years [Sindern et al., 1992]. The most common finding at the onset of disease for both children and adults was optic neuritis, accounting for 52% and 40%, respectively. The second most common presenting symptom in children was sensory disturbance, seen in 16% of children and 15% of adults. Transverse myelitis was more common in children, whereas motor symptoms were more common in adults (18%) than in children (6%). Furthermore, in 71% of children, the initial presentation was rapid, resulting in admission to the hospital within a few hours to days. A longitudinal study by Boiko et al. confirmed Duquette's and Sindern's findings that sensory symptoms and optic neuritis were the most common initial manifestations in patients with the clinical onset of MS before the age of 16 years [Boiko et al., 2002]. In 1995, Poser et al. characterized the presentation of MS in adults (Table 1) [Poser, 1995], and the diagnosis of MS should be considered in children presenting with similar symptoms.

The clinical course of MS is divided into four subtypes: relapsing–remitting (RRMS), primary progressive (PPMS), secondary progressive (SPMS), and progressive-relapsing (PRMS).

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Table 1. Diagnostic Criteria for Dating the Clinical Onset of MS [Poser, 1995]

(A) Definite	
All symptoms must last at least 24 hr	
Optic/retrobulbar neuritis	Transverse myelitis
Useless hand syndrome	Monoparesis
Paresthesia of one limb	Trigeminal neuralgia (age <40)
Gait ataxia	Binocular diplopia
Hemifacial spasms	Scanning speech
Unilateral dysmetria	Unilateral intention tremor
Oscillopsia	Acute, painless urinary retention
Fecal incontinence	Nonpositional vertigo
Monocular color blindness	Urinary urgency/incontinence (men)
(B) Possible	
A definite symptom or abnormal sign must appear within 2 yr	
Extreme fatigue	Blurred vision
Positional vertigo	Dysarthria
Lhermitte symptom	Painless urinary frequency (men)
Facial palsy	Organic sexual impotence (men)

RRMS is the most common subtype in both adults and children.

LABORATORY FEATURES

There are no diagnostic tests for MS. However, a lumbar puncture is routinely performed to obtain supportive evidence of CNS inflammation. In approximately 60% of patients with childhood-onset MS, the routine analysis (cell count, protein, and glucose) of CSF is normal [Duquette et al., 1987; Dale et al., 2000]. The remainder of patients has a lymphocytic pleocytosis (typically <50 cells/mm^3) and/or elevated protein (typically <75 mg/dL) [Dale et al., 2000]. Intrathecal synthesis of immunoglobulin (Ig), predominantly IgG, is also seen in patients with MS. Approximately 80% of children with MS have increased CSF IgG synthesis [Jones, 2003]. Furthermore, oligoclonal bands (OCB), markers of antibody synthesis in the CNS, are present in about 85–95% of adult patients with MS [Olek and Dawson, 2004]. In children, OCB were present in 40–87% of patients and may appear later during disease convalescence or relapse [Sindern et al., 1992; Selcen et al., 1996; Dale et al., 2000; Jones, 2003]. OCB are not specific to MS [Poser, 1983; Olek and Dawson, 2004]. They can be found in chronic CNS infections, such as subacute sclerosing panencephalitis, viral infections of the CNS, autoimmune neuropathies, cervical myelopathies, and CNS tumors [Cohen et al., 2000].

NEUROIMAGING

Magnetic resonance imaging (MRI) reveals asymmetric, multifocal white matter lesions on T2-weighted sequences and fluid-attenuated inversion recovery (FLAIR) images [Miller et al., 1990]. The lesions are most commonly located in the periventricular and subcortical white matter where they appear ovoid with extensions called Dawson fingers [Barkhof et al., 1997]. Additional lesions can be seen in the cerebellum, spinal cord, basal ganglia, and thalami [Dale et al., 2000]. New lesions may enhance with gadolinium administration. There are no longitudinal MRI studies in childhood MS to establish whether there is progressive atrophy of the brain or the appearance of "black holes" (chronic inactive lesions). Furthermore, unlike in adults, diffusion tensor imaging (DTI) and magnetization transfer ratios (MTR) have not been systematically performed. Finally, magnetic resonance spectroscopy (MRS) shows similar changes to those reported in adult MS patients with decreases in *N*-acetyl aspartate (NAA) reflecting neuronal loss, increases in choline reflecting remyelination, and increases in myoinositol reflecting gliosis [Wolinsky and Narayana, 2002].

Table 2. The Poser et al. Criteria

Clinically definite MS
Two attacks and clinical evidence of two separate lesions
Two attacks and clinical evidence of one, and paraclinical evidence of another, separate lesion
Laboratory-supported definite MS
Two attacks and either clinical or paraclinical evidence of one lesion, plus CSF OCB or elevated IgG
One attack and clinical evidence of two separate lesions, plus CSF OCB or elevated IgG
One attack, clinical evidence of one lesion, and paraclinical evidence of another, separate lesion, plus CSF OCB or elevated IgG
Clinically probable MS
Two attacks and clinical evidence of one lesion
One attack and clinical evidence of two separate lesions
One attack, clinical evidence of one, and paraclinical evidence of another separate lesion,
Laboratory-supported probable MS
Two attacks and CSF OCB or elevated IgG

Note: Paraclinical: evoked potentials, computed tomography or MRI; at least two OCB, none in serum.

DIAGNOSIS

MS remains a clinical diagnosis. In 1983, Poser et al. published guidelines incorporating laboratory, neuroimaging, and neurophysiologic data into the diagnostic criteria with four proposed subtypes: clinically definite MS, laboratory-supported definite MS, clinically probable MS, and laboratory-supported probable MS (see Table 2) [Poser et al., 1983].

In 2001, the McDonald criteria were introduced to facilitate and simplify the diagnosis of MS for patients between 10 and 59 years [McDonald et al., 2001]. The authors further defined MRI criteria and included both monosymptomatic disease and PPMS in the clinical presentations. Caution was suggested in applying these guidelines to children younger than 10 years. In fact, the sensitivity in diagnosing pediatric cases was questioned by a second panel that revised the McDonald criteria in 2005 (see Table 3) [Polman et al., 2005]. Furthermore, Hahn et al. reported that many pediatric patients did not meet the McDonald MRI criteria for dissemination in space (see Table 4) [Hahn et al., 2004].

Demonstrating dissemination in time (see Table 4) is also challenging in pediatrics due to the possibility of relapses in a monophasic disease (see Differential Diagnosis section). Nevertheless, a repeat MRI performed three months after the initial study is recommended to show dissemination in time.

DIFFERENTIAL DIAGNOSIS

Acute disseminated encephalomyelitis (ADEM), multiphasic disseminated encephalomyelitis (MDEM), and MS share similar clinical presentations, laboratory data, and neuroimaging abnormalities. Subtle differences between the

three entities have been described, such as preceding infection, encephalopathy, and bilateral optic neuritis, all of which are seen more frequently in ADEM and MDEM than MS [Dale et al., 2000]. Many patients with ADEM have an upper respiratory or nonspecific febrile illness in the weeks preceding the neurological symptoms. Measles, varicella, *Mycoplasma pneumoniae*, Epstein-Barr virus (EBV), group A (β-hemolytic) *streptococcus*, influenza B, hepatitis A and B, cytomegalovirus, enterovirus, herpes simplex virus (HSV), human herpesvirus 6 (HHV-6), human T-lymphotropic virus I (HTLV-1), human immunodeficiency virus (HIV), coxsackievirus B, *Campylobacter*, *Chlamydia*, *Legionella*, *Leptospirosis*, *Rickettsiae*, *Borrelia burgdorferi*, and *Salmonella typhi* have been detected in the serum of affected patients [Dale et al., 2000; Hynson et al., 2001; Stonehouse et al., 2003]. In addition, hepatitis B; measles, mumps, rubella (MMR); bacille Calmette-Guérin (BCG); meningitis A and C; rabies; influenza; smallpox; and Japanese B encephalitis vaccines, given within the six weeks prior to the onset of ADEM, have been suspected in triggering an autoimmune response [Dale et al., 2000].

Clinically, ADEM is more likely to present with ataxia, encephalopathy, bilateral optic neuritis, and seizures [Hynson et al., 2001]. Children typically have a polysymptomatic presentation with sensory, pyramidal, cerebellar, and bulbar symptoms [Dale et al., 2000]. Headache, fever, meningismus, and vomiting are more often associated with ADEM [Brass et al., 2003]. Unilateral optic neuritis and internuclear ophthalmoplegia are more common in MS [Dale et al., 2000].

In ADEM and MS, the CSF can be normal, although many patients have a lymphocytic pleocytosis or elevated protein. In ADEM, the CSF white blood cell (WBC) count can be as high as 270 cells/mm^3, with a mean around 51 cells/mm^3. In MS, the cell count is lower (range, 0–130 cells/mm^3; mean, 18 cells/mm^3) [Dale et al., 2000]. The CSF protein varies from 0.1 to 3.3 g/dL (mean, 0.69 g/dL) and 0.2 to 0.99 g/dL (mean, 0.38 g/dL) in ADEM and MS, respectively [Dale et al., 2000]. OCB are seen in the CSF in more than half of patients with childhood MS but can be seen in ADEM [Dale et al., 2000; Brass et al., 2003].

With considerable overlap between clinical and laboratory findings, MRI is an important tool in determining the difference between ADEM and MS. Both can affect the periventricular, subcortical, and deep white matter; deep gray matter; brainstem; cerebellum; and spinal cord. Cortical white matter lesions are typically bilateral but asymmetric. In ADEM, lesions are less likely to be periventricular. Also, ADEM more com-

Table 3. The 2005 Revisions to the McDonald Diagnostic Criteria for MS

Clinical Presentation	Additional Data Needed for MS Diagnosis
Two or more attacks[a]; objective clinical evidence of two or more lesions	None[b]
Two or more attacks[a]; objective clinical evidence of one lesion	Dissemination in space, demonstrated by: MRI[c] or Two or more MRI-detected lesions consistent with MS plus positive CSF[d] or Await further clinical attack[a] implicating a different site
One attack[a]; objective clinical evidence of two or more lesions	Dissemination in time, demonstrated by: MRI[e] or Second clinical attack[a]
One attack[a]; objective clinical evidence of one lesion (monosymptomatic presentation; clinically isolated syndrome [CIS])	Dissemination in space, demonstrated by: MRI[c] or Two or more MRI-detected lesions consistent with MS plus positive CSF[d] and Dissemination in time, demonstrated by: MRI[e] or Second clinical attack[a]
Insidious neurological progression suggestive of MS	1 yr of disease progression (retrospectively or prospectively determined) and two of the following: a) Positive brain MRI (9 T2 lesions or 4 or more T2 lesions with positive VEP)[f] b) Positive spinal cord MRI (two focal T2 lesions) c) Positive CSF[d]

Note: If criteria indicated are fulfilled and there is no better explanation for the clinical presentation, the diagnosis is MS; if suspicious, but the criteria are not completely met, the diagnosis is "possible MS," if another diagnosis arises during the evaluation that better explains the entire clinical presentation, then the diagnosis is "not MS."
[a]An attack is defined as an episode of neurological disturbance for which causative lesions are likely to be inflammatory and demyelinating in nature. There should be subjective report (backed up by objective findings) or objective observation that the event lasts for at least 24 hr.
[b]No additional tests are required; however, if tests (MRI, CSF) are undertaken and are negative, extreme caution needs to be taken before making a diagnosis of MS. Alternative diagnoses must be considered. There must be no better explanation for the clinical picture and some objective evidence to support a diagnosis of MS.
[c]MRI demonstration of space dissemination must fulfill the criteria derived from Barkhof et al. [1997] and Tintoré et al. [2000] as presented in Table 4.
[d]Positive CSF determined using OCB detected using established methods (isoelectric focusing) different from any such bands in serum, or using an increased IgG index.
[e]MRI demonstration of time dissemination must fulfill the criteria in Table 4.
[f]Abnormal VEP of the type seen in MS.
Abbreviation: VEP, visual-evoked potential.

Table 4. The 2005 Revisions to the McDonald Diagnostic Criteria Using MRI

Three of the following are required for demonstrating dissemination in space
1. At least one gadolinium-enhancing lesion or nine T2 hyperintense lesions if there is no gadolinium-enhancing lesion
2. At least one infratentorial lesion
3. At least one juxtacortical lesion
4. At least three periventricular lesions

There are two ways to show dissemination in time:
1. Detection of gadolinium enhancement at least three months after the onset of the initial clinical event, if not at the site corresponding to the initial event
2. Detection of a new T2 lesion if it appears at any time compared with a reference scan done at least 30 days after the onset of the initial clinical event

Note: A spinal cord lesion can be considered equivalent to a brain infratentorial lesion, an enhancing spinal cord lesion is considered to be equivalent to an enhancing brain lesion, and individual spinal cord lesions can contribute together with individual brain lesions to reach the required number of T2 lesions.
Based on data from Barkhof et al. [1997] and Tintoré et al. [2000].

monly affects the thalami and basal ganglia, with a greater tendency for symmetry in the latter [Dale et al., 2000]. In ADEM, a repeat MRI scan performed more than two months after the onset of symptoms often shows partial or complete resolution of lesions with no new lesions. Enhancement after the administration of gadolinium can be seen on the initial scan; however, no lesions enhance on the follow-up MRI in ADEM. In MS, both new and enhancing lesions may be present when the scan is repeated, although the time to develop new lesions is unpredictable. In the absence of clinical symptoms, new findings on MRI are useful in differentiating MS from ADEM.

MDEM presents a challenging dilemma in diagnosing childhood-onset MS. The clinical presentation, laboratory data, and neuroimaging features of MDEM resemble ADEM, both of which are monophasic illnesses. However, patients with MDEM have a clinical relapse after their initial illness or develop new lesions on MRI, suggestive of a chronic demyelinating disease or MS. Despite the presence of new lesions on MRI, suggesting dissemination in time, some investigators believe that MDEM and MS are separate entities. A diagnosis of MDEM should be reserved for patients whose relapses are caused by the same trigger responsible for the inciting event and occur shortly after presentation or within two months of discontinuing steroids [Dale et al., 2000].

PATHOGENESIS

MS is a neurodegenerative disease that affects young adults and children, often women. Linkage and twin studies demonstrate that individuals carry a genetic susceptibility to this disease [Rice, 2004]. A susceptibility locus for MS has been identified on chromosome 6, specifically the major histocompatability complex (MHC) class II alleles human leukocyte antigens (HLA) DR15 and DQ6. This association is seen in all populations. In Sardinians, there is an additional association with DR4, and, in Turks, there is an association with DR2 and DR4. In Finns, there is an association of MS with myelin basic protein (chromosome 18); however, neither this association nor an association with any other myelin genes has been noted in non-Finnish populations [Kenealy et al., 2003]. Aside from the MHC locus, other regions of interest identified from the United Kingdom study for MS susceptibility are located on chromosomes 1, 5, 6p, 7p, 14q, 17q, 19q, and Xp [Chataway et al., 1998]. Some of the genes in these regions include tumor necrosis factor [TNF]α, interleukin [IL]-1Ra, IL-4, and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4).

Aside from the genetic predisposition for MS, epidemiological data indicates that an environmental factor also plays a role [Compston, 2003]. For some time, an infectious agent has been suspected in triggering an autoimmune response. This theory was supported by apparent epidemics that occurred in the Faroe Islands and Iceland following World War II [Rice, 2004]. Additional support for an infectious etiology was provided by further studies that showed elevated antiviral titers (measles, rubella, mumps, varicella/zoster, EBV, influenza/parainfluenza,coronavirus, HTLV-1, Borna, etc) in the CSF of MS patients during an acute exacerbation [Sibley et al., 1985; Panitch, 1994]. Presumably, the elevated titers represent nonspecific activation of B cells in the nervous system. In addition, the MS literature is replete with the isolation of viruses from the brains of patients with MS including measles, coronavirus, retroviruses, HTLV-1, HHV-6, and scrapie agent. Current focus on infectious agents includes EBV, HHV-6, endogenous retroviruses such as HERV-W, and *Chlamydia pneumoniae* [Johnson and Major, 2003].

Oldstone postulated that an environmental trigger activates the immune system by "molecular mimicry" in which an infectious agent has sequence homology to a myelin protein. Following the infection, tolerance is broken and an immune response ensues with the appearance of autoreactive T cells (CD4 and CD8) [Oldstone, 1998]. Alternatively, the pathogen activates Toll receptors that then initiate the cellular immune response with the production of IL-12 and IL-23 [Vasselon and Detmers, 2002; Frohman et al., 2006].

The earliest pathological change seen in an MS lesion is oligodendrocyte apoptosis with microglial activation but lacking infiltrating lymphocytes [Barnett and Prineas, 2004; Matute and Pérez-Cerdá, 2005]. Older lesions have perivascular infiltration by lymphocytes, plasma cells, and macrophages; loss of myelin and oligodendrocytes; axonal damage; and reactive astrocytes. Chronic lesions are sharply demarcated with a hypocellular center and axonal loss, perivascular infiltration by lymphocytes, and increased number of oligodendrocytes. In chronic silent lesions, there is a loss of axons and oligodendrocytes. Lucchinetti et al. have grouped the neuropathological lesions into four types, each containing T cells [Lucchinetti et al., 1996, 1999, 2000]. Type 1 is characterized by a predominance of macrophages, Type II by the deposition of immune complexes, Type III by oligodendrocyte malfunction, and Type IV by oligodendrocyte death. There is insufficient data to describe the pathology of MS in children.

MS is an organ-specific autoimmune disease mediated by Type 1 helper T cells (T_H1) that recognize components of myelin and induce an inflammatory process by recruiting other inflammatory cells such as macrophages. In patients with MS, myelin-reactive T cells found in the blood stream produce a cytokine profile consistent with T_H1 cells. In demyelinating lesions, T_H1 cytokines, such as interferon γ, TNF-α, and IL-2, are expressed by these leukocytes. The chemokine profile also suggests a T_H1-mediated inflammatory process. Nevertheless, MS is likely to be more than a purely T_H1-mediated disease because it is likely that CD4 cells, macrophages, B cells, and a paucity of regulatory T cells also play a role [Merrill, 1992; Sorensen et al., 1999; Frohman et al., 2006].

TREATMENT

Therapy in MS targets four different aspects of a child's illness. First, disease-modifying drugs, or immunomodulators (ID), are used to alter the biological activity of the disease, thereby preventing neurological disability. Second, additional medications help alleviate symptoms such as fatigue, spasticity, bladder dysfunction, and depression. Third, neuroprotective agents are being studied to prevent and repair nerve injury. Finally, rehabilitation is needed to overcome physical handicaps. Disease modifying, symptomatic, and neuroprotective therapies will be described in this review.

In evaluating effectiveness of therapies that modify the biological activity of the disease in children, a major challenge is the inability to predict the outcome of the disease and the lack of good outcome measures. The goal of any disease-altering therapy is to prevent long-term disability which evolves over many years [Goodin et al., 2002]. The efficacy of the newer therapies has predominantly been studied over a short time period. Moreover, the expanded disability status scale (EDSS) that is used as an outcome measure in adult studies has not been validated for use in children. Children with MS may have cognitive dysfunction, which has not been evaluated as an outcome measure, although the MS functional composite (MSFC) places

some weight on mental functioning. Once again, the utility of this scale has not been established in children. Currently, most studies use the short-term attack rate as an outcome measure as well as MRI data to assess T2 disease burden, cerebral atrophy, and the appearance of T1 black holes. Although there are very few trials that have included children, in this article we review therapies that are recommended for adults and, where data is available, highlight the pediatric studies.

Disease-Modifying Therapies

Glucocorticoids

Glucocorticoids, such as intravenous (IV) methylprednisolone, are the mainstay of treatment for acute attacks or relapses in MS [Goodin et al., 2002]. They suppress the immune system in many ways, such as altering cytokine profiles, inhibiting the synthesis of matrix metalloproteinases, and reducing CSF antibodies to MBP and OCB [Kupersmith et al., 1994]. In 1970, a multicenter trial compared adrenocorticotropic hormone (ACTH) (80 U/day given intramuscularly [IM] for four days with a 7-day taper) against placebo in 197 patients with acute MS [Rose et al., 1970]. After four weeks, the authors found that ACTH accelerated clinical improvement, although there was no significant difference in the outcome. In another study, ACTH (80 U/day for one week followed by a taper) was compared with 1 g of IV methylprednisolone for three days. In this study, there was no significant difference between the two treatment arms [Thompson et al., 1989]. Subsequently, a number of studies have been published using glucocorticoids for optic neuritis, most notably the Optic Neuritis Treatment Trial. This multicenter study compared IV methylprednisolone for three days followed by oral prednisone for 11 days against a 14-day course of oral prednisone and a placebo group. For both primary (visual fields and contrast sensitivity) and secondary (visual acuity and color vision) endpoints, the group that received IV methylprednisolone had an accelerated recovery of visual function compared to the placebo group. The rate of recovery for the group receiving oral prednisone was in between the IV and placebo groups. At six months, there was no difference between the treated and the placebo groups [Beck, 1988]. Furthermore, the group receiving oral steroids had an increased number of recurrences of optic neuritis. In addition to their use in optic neuritis, high-dose steroids are also known to enhance the resolution of gadolinium-positive MRI lesions [Barkhof et al., 1991; Burnham et al., 1991]. Finally, abrupt discontinuation of steroids can lead to severe clinical, radiographic, and histopathologic relapses; therefore, an oral taper is recommended. Although these studies were performed in young adults with RRMS and CIS, IV steroids (15–30 mg/kg/day given daily for 3–5 days followed by an oral taper over 14 days) are used in children with acute attacks that impair function.

Interferon β

Interferons (IFNβ-1a and IFNβ-1b) are recombinant proteins, which inhibit the adhesion and the migration of WBC across the blood–brain barrier, thereby blocking antigen presentation and the synthesis and transport of matrix metalloproteinases [Harris and Halper, 2004]. In addition, they may cause a shift from a T_H1 to a T_H2 response. In adult-onset MS, IFN-β has a beneficial effect on the clinical and radiological outcome measures. Because the drug is not marketed for the pediatric population, there are no recommendations available for dosing children. For older children and adolescents, adult doses are most often used. Interferon β-1a (INFβ-1a) is available in a weekly IM injection (Avonex, 30 μg) or a subcutaneous (SC) injection given three times a week (Rebif, 22 μg or 44 μg). Interferon β-1b (INFβ-1b, Betaseron, 8 million international units (MIU) or 250 μg) is given SC every other day. For smaller teens or children younger than 10 years, the doses are often adjusted to minimize adverse events and increase tolerability, such as starting with a half-dose of Avonex or Betaseron or using the lower dose for Rebif.

In 2006, Banwell et al. retrospectively studied dosing, safety, and tolerability of IFNβ-1b in 43 children diagnosed with MS who had been treated for an average of 29.2 months [Banwell et al., 2006]. Treatment was initiated at full dose (8 MIU or 250 μg) in 15 children, all of whom were older than 10 years of age. Younger children were started at 25–50% of the full dose and slowly increased; two children, both under the age of 10 years, were unable to tolerate the dose escalation. None of the children had any serious adverse events. Therapy was discontinued in 25 of 43 patients after being treated for a mean duration of 111 weeks for various reasons, such as perceived lack of efficacy, cost of medication, lack of adherence, injection pain, and change in diagnosis. Nevertheless, of the 38 patients with confirmed MS, the annualized relapse rate was reduced by a mean of 50%.

The side effects of INFβ in children are similar to those reported by adults. Fever is the most common side effect, reported in 50% of the patients [Ghezzi et al., 2005]. Additional side effects include headache, myalgia, flu-like symptoms, injection site reactions, fatigue, nausea, and asthenia [Waubant et al., 2001; Banwell et al., 2006]. The majority of these symptoms are transient. To alleviate side effects, children may be pretreated with acetaminophen, ibuprofen, or naproxen. Laboratory abnormalities, such as elevations of liver function tests, can also occur. When present, a temporary discontinuation of the medication is recommended. Often, the INFβ can be restarted without a recurrence of the elevated transaminases [Banwell et al., 2006].

Glatiramer acetate (GA, Copaxone)

GA is a random polypeptide composed of four amino acids (L-glutamic acid, L-lysine, L-alanine, and L-tyrosine) resembling myelin basic protein (MBP). This drug has a number of effects on the immune system including inhibition of antigen presentation, competition and displacement of bound MBP, conversion of CD4 T cells from T_H1 to T_H2 type cells, and induction of brain-derived neurotrophic factor (BDNF) expression [Teitelbaum et al., 1992; Neuhaus et al., 2001; Aharoni et al., 2003; Azoulay et al., 2005]. It also induces antigen-specific suppressor T cells which release anti-inflammatory cytokines thereby generating tolerance to self-antigens [Harris and Halper, 2004]. There are no trials similar to those conducted in adults that have primarily focused on the efficacy of this drug in children with MS. There are, however, reports of using this drug in children who were given 20 mg SC daily, the standard dose for an adult. In one child treated with GA, chest pain was reported; however, no other clinical or laboratory abnormalities were identified [Ghezzi et al., 2005].

Although INFβ and GA have been used in practice, the long-term tolerability, side effects, and overall efficacy in the pediatric population is not yet known. In a multicenter Italian study published in 2005, Ghezzi et al. focused on effectiveness and tolerability of interferons and glatiramer acetate in patients treated before the age of 16 [Ghezzi et al., 2005]. Sixty-five cases were reviewed. The majority was treated with Avonex (38), followed by Rebif (18), Betaseron (16), and

Copaxone (9). Relapses were defined as the occurrence of new symptoms lasting more than 24 hr with objective findings of CNS involvement in a previously unaffected patient or the acute worsening of preexisting symptoms lasting more than 24 hr and causing an increase of at least 1 on the EDSS. All four of the drugs substantially reduced the relapse rate with combined data showing a decrease from 2.8 to 0.5 relapses per year and similar results for the individual medications. The change in EDSS was not significantly different when comparing the first and last visit in the INFβ subgroups; however, a statistically significant difference was seen in the GA subgroup (baseline: 1.1 ± 0.5, posttreatment: 0.6 ± 0.5, $P = 0.007$). It should be noted that the patients on GA had overall lower disease duration when compared to the other groups and EDSS at entry was lower than that in the Avonex and Rebif/Betaseron groups.

Natalizumab (Tysabri)

Natalizumab is a recombinant monoclonal antibody directed against α4-integrin. In Experimental Autoimmune Encephalitis (EAE), the animal model for MS, the expression of T-cell surface receptors (integrins) promotes adhesion and transport of these cells through capillary endothelial cells. This antibody against α4-integrin blocks the adhesion of activated T lymphocytes to endothelial cells thereby preventing these cells from entering the nervous system. This is the only selective immunomodulating drug for the treatment of MS. The results from the Natalizumab Safety and Efficacy in Relapsing Remitting Multiple Sclerosis (AFFIRM) and Safety and Efficacy of Natalizumab in Combination with Interferon β-1a in Patients with Relapsing Remitting Multiple Sclerosis (SENTINEL) studies in adult patients indicate that the annualized rate of clinical relapses was reduced by 68%, the number of new and enhancing MRI lesions was reduced by 83%, and a decrease occurred in progression and prolongation of the interval before neurological deterioration, demonstrating the usefulness of the drug [Polman et al., 2006; Rudicket al., 2006]. Although natalizumab had significant short-term beneficial effects, unfortunately, three patients who received this drug developed progressive multifocal leukoencephalopathy (PML). The relative risk of developing PML in MS patients on natalizumab is 1 in 1,000 [Ropper, 2006]. Moreover, the use of this drug may have other long-term effects, such as unmasking latent viral infections as well as other diseases that are dampened by immune surveillance. In children who have a malignant course of MS, the use of this drug on a short-term basis may be warranted.

Campath-1H (Alemtuzumab)

Campath-1H binds CD52 antigen, which is present on the surface of all B and T lymphocytes, as well as some monocytes. It is a lympholytic antibody that has been shown to prevent relapses and the formation of new MRI lesions in MS; however, it does not seem to have any effect on disease progression [Paolillo et al., 1999]. Furthermore, when Campath-1H was initially used in patients with MS, a transient worsening of symptoms occurred due to the release of cytokines and nitric oxide (NO) [Moreau et al., 1996]. In vitro studies demonstrated that NO can cause conduction blocks that could account for the transient worsening of symptoms with treatment initiation. Pretreating with steroids can avert the cytokine release.

Rituximab (Rituxan)

Rituximab is a humanized monoclonal antibody directed against CD20 and antigens found on B lymphocytes [Valentine et al., 1989]. B-cell proliferation, as well as an increase in the mutations of their receptors, has been shown in the CSF of MS patients. The B-cell response reflects the presence of a specific antigen in the CNS. Thus, the B cells have become another therapeutic target in MS. Rituximab, a drug that depletes B cells, is currently being investigated in the treatment of MS [Reff et al., 1994; Frohman et al., 2006].

Mitoxanthrone (Novantrone)

Mitoxanthrone is an anticancer drug that acts by intercalating into DNA thereby producing DNA strand breaks and interstrand crosslinking. In the immune system, it causes the elimination of lymphocytes and reduction of T_H1 cytokines. The major side effects include cardiac toxicity, presenting as a cardiomyopathy with irreversible congestive heart failure, and increased risk of developing malignant tumors. Nevertheless, this drug reduced the attack rate of patients with RRMS by 66%, reduced the number of gadolinium-enhancing and new lesions on the MRI, and reduced the clinical rate of progression of the disease [Millefiorini et al., 1997]. Given the toxicity profile, this is not a first-line drug for the treatment of MS in children.

Cyclophosphamide (Cytoxan)

Cyclophosphamide is a powerful immunosuppressive agent that has been used to treat relapsing–remitting and progressive forms of MS. Side effects include alopecia, nausea and vomiting, hemorrhagic cystitis, sterility, and long-term risk of malignancy. The use of IV Cytoxan (400–500 mg/day with WBC counts about 4,000 per microliter) did not show any benefit for patients with progressive MS at 1- and 2-year follow-up after the initiation of therapy [Hauser et al., 1983; Likosky et al., 1991]. In a Canadian study using 1,000 mg of Cytoxan with a 3-year follow-up of patients with progressive MS, there was no significant benefit from use of this drug [Canadian Cooperative MS Study Group, 1991]. Nevertheless, in a study of 256 patients with progressive MS, younger patients derived some benefit from the use of Cytoxan [Weiner et al., 1993].

Methotrexate (Rheumatrex)

Methotrexate acts as a folate antagonist, thereby affecting DNA synthesis in immune cells. It decreases proinflammatory cytokines and enhances suppressor T-cell function. The major side effects are nausea, headache, diarrhea, liver damage, and the risk of developing non-Hodgkin's lymphoma. A small, double-blinded study of low-dose methotrexate revealed a benefit for patients with RRMS but not for patients with the progressive forms of the disease [Currier et al., 1993]. However, in another study of 60 patients with chronic progressive MS, low-dose methotrexate was found to be beneficial and showed a reduction in the T2 diseased burden [Goodkin et al., 1995].

Azathioprine (Imuran)

Azathioprine is an analog of 6-mercaptopurine that inhibits purine synthesis, thereby impairing DNA and RNA synthesis in B cells, T cells, and macrophages. Its side effects are anemia, lymphopenia, alopecia, liver dysfunction, pancreatitis, reactivation of latent infections, and the risk of developing malignancies. In a retrospective analysis of seven studies that had enrolled 793 patients, use of Imuran reduced the number of relapses; however, the drug did not seem to affect the course of patients with progressive MS or their disability [Yudkin et al., 1991].

Cyclosporine (Sandimmune)

Cyclosporine is a potent immunosuppressive agent that selectively inhibits

helper T cells. Side effects include hirsutism, headaches, nausea, hypertension, edema, paresthesias, nephrotoxicity, and abdominal pain and discomfort. Studies conducted in London and Amsterdam showed no benefit on the relapse rate but did show some effect on slowing the progression of the disease [Rudge et al., 1989]. Given the side effects of this drug, its use in MS is very limited [Goodin et al., 2002].

Cladribine (Leustatin)

Cladribine, an adenosine deaminase-resistant purine nucleoside, is a potent immunosuppressive drug that is selective for lymphocytes. Side effects include nausea, diarrhea, fever, fatigue, and leukopenia. Although cladribine does not have a significant effect in reducing the relapse rate, it may slow the degree of disability. In addition, it reduces the appearance of gadolinium-enhancing lesions on MRI [Beutler et al., 1996; Rice et al., 2000].

Statins

3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, also called statins, have been recently studied in a variety of CNS disorders, including MS. Statins disrupt the activation of proinflammatory T-cells by inhibiting signals from MHC Class II molecules [Neuhaus et al., 2002]. They also decrease migration of leukocytes into the CNS, expression of inflammatory mediators by T-lymphocytes and in the CNS [Stüve et al., 2003]. Statins, such as simvastatin (Zocor) and atorvastatin (Lipitor) have been shown to inhibit and reverse chronic and relapsing EAE [Stüve et al., 2003]. Atorvastatin induces STAT6 phosphorylation and enhances the secretion of T_H2 cytokines (IL-4, -5, and -10 and transforming growth factor [TGF] β) while inhibiting STAT4 phosphorylation and secretion of T_H1 cytokines (IL-2, -12, IFN-γ, and TNFα) [Youssef et al., 2002]. In small, short-term studies, Zocor decreased the number and size of gadolinium-positive lesions on MRI scans without effect on progression and disability [Vollmer et al., 2004]. The immunomodulatory effects of the statins offer promise in the treatment of MS, and their usefulness is being further investigated [Neuhaus et al., 2004].

Vaccination therapies

Vaccination therapies are currently being developed that would alter the treatment of MS. Vaccinations that promote the development of tolerance have been effective in EAE [Robinson et al., 2003]. In addition, T cell and T cell receptor peptide vaccinations have been studied in humans with MS [Correale et al., 2000; Bourdette et al., 2005]. None of the vaccines have been studied in children.

IV immune globulin

IV Immune Globulin (IVIg) blocks Fc receptors on macrophages, alters the cytokine profile, and has antiidiotypic effects. IVIg is typically used as an adjunct for acute relapses; however, its recurrent use has been studied in RRMS. In a multicenter, double-blind, placebo-controlled study of 148 RRMS patients given IVIg (0.125–0.2 g/kg) monthly for two years, a reduction in the clinical attack rate (−49%) with a possible reduction in the degree of disability (not significant) was observed [Fazekas et al., 1997]. In a separate study, the number of total and enhancing lesions seen on MRI was decreased by more than 60% in patients treated with IVIg compared with placebo [Sorenson et al., 1998]. Thus, it appears that IVIg may reduce the attack rate in RRMS but probably has little effect in slowing the progression of the disease.

Plasmapheresis (plasma exchange)

Although it does not alter the long-term course in MS, plasma exchange has been used to treat acute relapses, presumably by removing harmful antibodies. Several groups have investigated this particular therapeutic modality for treatment of patients with progressive MS [Hauser et al., 1983]. For some patients who had not responded to IV steroids, plasma exchange performed every other day for a total of 14 days provided a greater degree of improvement when compared with a sham-treated group [Weinshenker et al., 1999]. Some patients receiving plasma exchange improve very rapidly, which is unlikely due to the repair of the injured tissue. Instead, the rate of recovery may be due to the rapid shifts in electrolytes that result in improved axonal conduction or the possible removal of an antibody that affects transmission of electrical impulses.

Symptomatic Treatment

Fatigue

Although fatigue is a common and debilitating symptom is adults, children rarely complain of this symptom. The mechanism for fatigue is multifactorial and includes depression, excessive effort due to muscle weakness or spasticity, release of cytokines, and sleep disturbance. Therapies for fatigue in MS include the use of amantadine, modafanil, and pemoline. All have been shown to have modest beneficial effect in adults.

Spasticity

When patients have involvement of the corticospinal tracts, whether it be due to lesions in the spinal cord or higher, treatment should include physical therapy, splints to prevent contractures, and stretching exercises combined with pharmacological treatments, such as diazepam (Valium), tizanidine (Zanaflex), baclofen (Lioreseal), and dantroline (Dantrium). Less well established is the use of tetrahydocannabinol. For contractures that do not respond to stretching, alternatives include serial casting, Botox injections, and tenotomy. In more severe cases, a baclofen pump, or rhizotomy or myelotomy, may be considered.

Motor weakness

Hemiplegia in children is disabling, particularly because of the loss of dexterity. Sensory impairment further aggravates movements of the hand. Such children do not use the affected hand, which results in learned nonuse of that hand. Recent studies indicate that such children benefit from intensive practice and forced use; restraint of the noninvolved arm appears to improve function of the affected hand, probably due to functional reorganization of the nervous system.

Paroxysmal symptoms

Patients with MS have a variety of paroxysmal symptoms that last seconds to minutes and are not associated with alterations in consciousness or any electroencephalogram correlate for seizure. Paroxysmal sensory symptoms and motor symptoms, such as ataxia and Lhermitte's sign, respond to low doses of carbamezapine, phenytoin, and acetazolamide. Heat-sensitive symptoms can respond to potassium channel blockers with the caveat that these drugs can induce seizures.

Pain including headaches

This is not an uncommon symptom in some children. Nonsteroidal antiinflammatory agents are recommended. If they are not sufficient, gabapentin (Neurontin), carbamezapine (Tegretol), or amitriptyline (Elavil) can be beneficial.

Neuroprotection and Repair

Neuroprotection

In MS, axonal injury occurs early in the course of the disease with eventual

transection of axons. Factors that have been associated with axonal injury are cytokines, NO, superoxide radicals, proteases, CD8 T cells, cholesterol breakdown products, abnormal expression of sodium channels and function of the sodium–calcium exchanger, and glutamine excitotoxicity [Waxman et al., 2004].

When an axon is demyelinated, there is abnormal expression of voltage-gated sodium channels with increased influx of sodium in an attempt to restore conduction. To compensate for this, there is a reversal of the sodium/calcium exchanger with efflux of sodium and an influx of calcium. This could result in calcium-mediated neuronal degeneration. This hypothesis has received some support from work on EAE models where sodium channel blockers, such as flecainide and phenytoin, help preserve axons [Lo et al., 2003; Bechtold et al., 2004].

In patients with MS, MRS has demonstrated increased glutamate concentration, providing the underpinning for considering glutamate excitotoxicity. The increased glutamate could result from a decrease in glutamate transporters in glial cells and elevation of glutaminase, a glutamate-synthesizing enzyme, in microglia [Werner et al., 2001]. However, increased glutamate acting through the α-amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid (AMPA) and/or *N*-methyl-D-aspartate (NMDA) receptors, which are present on neurons and oligodendrocytes, can result in calcium-mediated cell death. Riluzole, a glutamate antagonist that has been used in infants with spinal muscular atrophy, blocks NMDA and sodium channels and reduces the number of T1-weighted hypointense lesions on the MRI scans of patients with MS [Frohman et al., 2006].

Because axonal damage is a feature of MS, promoting neurite outgrowth could be beneficial. However, axonal sprouting is inhibited by activation of the Nogo receptor by agonists such as Nogo, oligodendrocyte-myelin glycoprotein (OMgp), and myelin-associated glycoprotein (MAG). Thus, blocking the Nogo receptor could represent a therapy that would be of value in promoting axonal sprouting [Wang et al., 2002].

Therapies to help remyelination

In acute MS plaques, there is clear-cut evidence for remyelination; however, this is minimal in chronic lesions. The recruitment of oligodendrocyte precursor cells to areas of demyelination is mediated via chemokine and cytokine receptors, a pathway that appears to be intact. Once attracted to areas of damage, these precursor cells recapitulate the differentiation process; however, full differentiation of these cells may be dampened by macromolecules that are negative regulators of this process, such as activation of the Notch pathway due to reexpression of the ligand Jagged or the Nogo receptor interacting protein. In the future, both of these targets may be sites for therapeutic intervention that will aid the process of remyelination. In addition, transplantation of stem cells or oligodendroglial progenitor cells may be a consideration [John et al., 2002; Mi et al., 2005; Frohman et al., 2006].

PROGNOSIS

MS is best recognized for its relapsing and remitting clinical course. In fact, in both children and adults, RRMS is the most common form, followed by the secondary and primary progressive forms. However, the prognosis for pediatric MS remains controversial. The EDSS has been used to quantify the disability associated with MS by assigning a functional score for multiple systems (pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, and cerebral) [Kurtzke, 1983]. Patients with a score of 0 have a normal neurological exam. Scores between 1.0 and 3.5 are fully ambulatory, whereas 4.0–5.5 are ambulatory for short distances without aid or rest. Patients with scores greater than 6 require assistance with ambulation as well as other activities of daily living. In 2002, Boiko et al. compared the time to EDSS of 3.0 (mild disability in at least three domains or moderate disability in one area) and 6.0 (requiring intermittent or constant unilateral assistance to walk 100 meters with or without resting) in adult- and pediatric-onset MS [Boiko et al., 2002]. On average, adults had a 50% risk of reaching EDSS scores of 3.0 and 6.0 in 10 and 18 years, respectively, after onset whereas disability in children was much slower, taking 23 and 28 years, respectively. In addition, 53.1% of children with RRMS progressed to SPMS after an average of 17.7 years (SD 1.17 years). The 50% risk for conversion from RRMS to SPMS was 23 years in children, whereas it was 10 years in adults. Although this data suggests a slower disease course in children, the overall morbidity is typically greater when children reach adulthood. Children have higher EDSS scores when compared to adults with MS of the same age [Ghezzi et al., 2005].

CONCLUSIONS

MS is under-recognized in the pediatric population and presents new challenges in diagnosis and treatment. Despite significant advances in neuroimaging, MS remains a clinical diagnosis. New guidelines allow earlier diagnosis, but they have not been reliably established in children, especially those younger than 10 years of age. In addition, these guidelines may not be sufficient to prevent the inclusion of monosymptomatic demyelinating disorders, which do not require long-term treatment. Early diagnosis and treatment with immunomodulatory agents are critical to reducing the morbidity and mortality associated with this disease. Although these drugs have been used in practice, more data is needed on long-term tolerability, side effects, and overall efficacy in the pediatric population. ■

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