Abstract. Multiple sclerosis (MS) is an inflammatory idiopathic autoimmune disease causing demyelination of central nervous system (CNS). The incidence of pediatric MS is relatively rare, affecting 0.2 to 0.64/100,000 subjects; cases with MS onset before age 10-12 years, account for less than 1% of all MS cases, while 2.7 to 10.5% of all MS cases worldwide are seen in children <18 years of age, with a strong female preponderance. The disease course of MS varies from a benign type with relatively low level of disability after a long duration (15 years) of the disease, to a malignant type of MS with severe disability or even death within few months following onset. Diagnostic criteria for pediatric MS include ≥ 2 clinical events involving more areas of CNS inflammation in the absence of encephalopathy, separated by > 30 days, along with the involvement of brainstem. Pediatric MS generally presents relapsing-remitting form of MS, with majority of the patients recovering from the first attack. Major histocompatibility complex, more specifically, mutations in the human leukocyte antigen (HLA) DRB1*15 allele, are considered most important genetic factors that are contributory to the disease. Treatment choices for pediatric MS include many disease-modifying therapies (DMT) that are currently being used for adult MS and these are interferon-β 1a/1b (IFN-β1a/1b), glatiramer acetate, teriflunomide, dimethyl fumarate, alemtuzumab, etc. However, most of these have not gone through complete testing in randomized, placebo-controlled clinical trials for pediatric MS and are being prescribed off-label by clinicians. As these studies are progressing, it is important to address if these approaches of treating pediatric MS patients have any long-term impact on patients, in particular, physical, cognitive, developmental and social outcomes of the children.

Key Words: Multiple sclerosis, Idiopathic autoimmune disease, Encephalopathy, Pediatric MS, Acute disseminated encephalomyelitis, Demyelinating syndrome, Myelin oligodendrocyte glycoprotein.

Introduction

Multiple sclerosis (MS) is an idiopathic autoimmune disease, affecting central nervous system (CNS). MS is inflammatory and causes demyelination of neuronal fibers. Approximately 2.7 to 5.4% of MS patients likely had their first episode of MS attack under 18 years of age. Disease onset of MS is generally in young adults with chronic and debilitating effects, and in a minority of population MS also start in childhood. Because of its rare occurrence, initial reports of pediatric-onset MS were described only as case reports. However, the significance of pediatric MS became rapidly evident as more reports, observations and retrospective studies poured in. Etiology of MS is not clearly understood and genetic predisposition and environmental factors, including nutritional status of vitamin D, smoking, and infections, are known to contribute to the pathogenesis of MS. The incidence of pediatric MS is approximately 0.2 to 0.64/100,000 and several population-based studies indicated that cases with MS onset before age 10-12 years, account for less than 1% of all MS cases, while 2.7 to 10.5% of all MS cases worldwide are seen in children under 18 years of age. Interestingly, it has been observed that the overall incidence of MS in both adults and children is much higher in Europe, accounting for about 50% of all MS cases, with a rapid increase in the diagnosed female patients since mid 80’s. Epidemiological studies showed that Sardinia in Italy has the highest prevalence of pediatric MS, whereas the Orkney Islands near Scotland has the highest prevalence of both adult and childhood MS, with about 300 cases per 100,000 people. There appears to be a strong female preponderance among several pediatric onset MS cases, published since 2007 that included more than 1100 patients from all across Europe, North America and Iran. The
overall female to male ratio was reported to be 4.5:1 for cases of MS onset between 12-16 years of age. This ratio is mostly even for MS onset under 10-12 years of age. In a recent study of 490 children with MS, it has been observed that the ratio of female to male to be about 1.95:1. Interestingly, the proportion of female children that developed symptoms increased from 58% at <12 years to 70% at >12 years of age. There is a possibility that children with MS are likely to have better compensatory capacity to fight against inflammatory damage to brain, even if there are high relapse rates. The relatively longer duration between the onset of MS symptoms and buildup of disability in pediatric patients as compared to adult MS patients is partly responsible for this compensatory effect. However, the neurodegenerative process from mild to severe disability seems to take about the same time – 10 years, in both children and adult MS patients, but this still affects the children at much earlier age than adults.

**Diagnosis and Clinical Presentation**

The disease course of MS varies from a benign type MS with relatively low level of disability after a long duration (15 years) of the disease, to a malignant type of MS characterized by severe disability or death within few months following onset. Diagnosis of pediatric MS starts with the identification of the onset of a CIS (clinically isolated syndrome) or occasionally ADEM (acute disseminated encephalomyelitis), as in the case of adult MS. When clinical symptoms of the 1st attack have duration longer than one day without any evidence of encephalopathy but with possible inflammatory demyelination, it is considered as CIS. It is generally agreed that patients must display minimum two demyelinating events clinically, with an interval of at least 30 days, for confirmed diagnosis of MS. Acquired demyelinating syndrome (ADS) that affects central nervous system, is the common first clinical presentation of children diagnosed with relapsing-remitting MS, and this is followed by 2 years by a second event. Apparently, the pediatric CIS disease situation is considered to be worsening if there is >1 high T2 signal in magnetic resonance imaging (MRI) of the brain, in comparison to ADEM. The new MRI McDonald 2010 MS criteria are helpful for proper pediatric onset MS diagnosis in children at the first presentation with a CIS, even though these criteria are not recommended in patients under 12 years. The specific criteria for pediatric MS diagnosis are given in Figure 1. Because of the lack of a specific biomarker for differentiating MS from monophasic ADEM or CIS, it is suggested that a combination of MRI features with information on clinical, and cerebrospinal fluid (CSF) positive oligoclonal bands to be used for correct diagnosis. Among the clinical features, it has been recently showed that occurrence of a previous infection is more frequent (about 34% cases) in younger (<12 years of age) pediatric MS cases as compared to children above 12 years of age (about 16% cases) and similar results with different magnitudes were also noted with encephalopathy and coordination problems. In this study larger number of older children (> 12 years of age) showed a spinal cord localization of the disease, along with much higher immunoglobulin G index and oligoclonal bands in cerebrospinal fluid (CSF). Other studies suggested that oligoclonal bands may show negative test at the onset of MS in children but are seen in nearly 90% of the case as the disease progresses and possibly the presence of these oligoclonal bands elevates the risk of MS. Pediatric MS presents as relapsing-remitting form of MS in most of the cases, with majority of the patients able to recover from the first attack. As mentioned before, even though there are more numbers of relapses in pediatric MS cases as compared to in adult MS cases, children display speedier recovery as well as slower progression of the disease. Among the poor prognostic factors for clinical assessment are: (1) an interval of less than one year between the first two demyelinating events elevates the risk of third attack and severe disability; (2) additional demyelinating attacks without complete recovery from previous ones, thereby increasing the cumulative disability; (3) involvement of brainstem at the onset of the disease.

**Genetic Factors in Pediatric MS**

There are nearly 200 genes that may have a role in the pathogenesis of MS, even though variants of any of these genes have not been proven to be predictive of MS. The predominant genetic loci that relates to MS among all world populations appears to be the major histocompatibility complex, more specifically, mutations in the human leukocyte antigen (HLA) DRB1*15 allele are considered the most important. The occurrence of 1 or 2 HLA-DRB1*15 alleles has been found to confer high risk for pediatric MS in a Canadian study. Apparently, the presence of
serum antibodies to myelin oligodendrocyte glycoprotein (MOG), which is an indicator of non-MS subgroup of CNS demyelination, negatively relates to the presence of higher rates of HLA-DRB1*15 allele. There is not so much difference between adult MS and pediatric MS in terms of genetic contributing factors, as 57 genetic loci, identified in a genome wide association study in adult MS patients. They have also been found to confer risk to pediatric-onset MS and it has been reported that the risk prediction of pediatric and also adult MS with the combined effect of 57 SNPs is greater than that of HLA-DRB1*15 allele alone. A recent study on the impact of genetic loci on MS familial aggregation, suggested that additional genetic variants outside the known MS-associated loci, rare variants as well as environmental, epigenetic and hormonal factors are likely responsible for disease occurrence and aggregation in families.

**Treatment Options**

There are many disease-modifying therapies (DMT) currently being used for adult cases of relapsing-remitting MS, and these include interferon-β 1a/1b (IFN-β1a/1b), glatiramer acetate, teriflunomide, dimethyl fumarate, alemtuzumab, etc. However, none of these have gone through complete testing in randomized, placebo-controlled clinical trials for pediatric MS. Even though DMT medications are used in pediatric MS setting, their use is currently off-label, particularly in patients younger than 12 years of age, as none of these drugs is approved for use in children in many countries and in fact this initiated a discussion on children with MS as “therapeutic orphans.” In order to approve current adult medications for pediatric MS use, FDA (Federal Drug Agency) of the United States, and EMA (European Medicines Agency) of European Union, have ordered 4 and 15 pediatric

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**Figure 1.** Diagnostic criteria for ascertaining pediatric MS. ADEM, acute disseminated encephalomyelitis CNS, central nervous system; DIS, dissemination in space; DIT, dissemination in time, MRI, magnetic resonance imaging.
clinical trials, respectively. Since the incidence of pediatric MS is rare and the ordered clinical trials may not be able to recruit sufficient number of patients to satisfy statistical requirements, and it is quite likely that the outcomes of these pediatric MS clinical trials will not lead to any meaningful conclusions on evidence-based drug analyses and clinical practice for the corresponding drug.\textsuperscript{35} Considering that the outcomes of such clinical trials are not meaningful, it is suggested that these forced clinical trials, in which parents of children with MS may be lured to participate, are potentially unethical. So, till these issue are resolved, clinicians have no choice to continue to use adult DMTs “off-label” for pediatric MS patients.\textsuperscript{35} Current status of industry-sponsored pediatric MS clinical trials is given in Table I.

Inasmuch as the DMT medications predominantly target inflammation, and their use in pediatric MS cases, which are associated with high rates of relapse with much elevated inflammation, is expected to be beneficial\textsuperscript{36,37}. Overall approach for treating pediatric MS should address acute management as well as prevention of relapses on long-term basis. Both IFN\textsubscript{\beta1} and glatiramer acetate are being used as first-line DMTs for pediatric MS, and these drugs reduce disability progression by 24 to 40%, with similar efficacy and side effects in pediatric and adult MS cases.\textsuperscript{38,39} Immunomodulatory drugs, which are one class of DMTs, are of two categories – first-line and second-line immunomodulatory therapeutics and the earlier use of these drugs in pediatric MS cases have been suggested according to the current practice.\textsuperscript{40} The first-line immunomodulatory therapeutics that can be given to children above 12 years of age includes IFN-\textbeta1a (Avonex\textsuperscript{®}, Rebif\textsuperscript{®}), IFN-\textbeta1b (Betaferon\textsuperscript{®}) and glatiramer acetate (Copaxone\textsuperscript{®}). These drugs have been shown to reduce the number of relapses, the degree of disability as well as disease activity.\textsuperscript{41}

<table>
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<tr>
<th>Drug</th>
<th>Study Design</th>
<th>Phase</th>
<th>Primary outcome</th>
<th>No. of patients to be enrolled</th>
<th>Proposed end date</th>
<th>NCT number/ Sponsor</th>
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<td>Annualized relapse rate</td>
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<td>Teriflunomide (Aubagio)</td>
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<td>3</td>
<td>Time to first clinical relapse after randomization</td>
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<td>NCT0220108/Sanofi</td>
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<tr>
<td>Dimethyl fumarate (Tecfidera)</td>
<td>Open-label, randomized</td>
<td>3</td>
<td>Time to first clinical relapse</td>
<td>172</td>
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<td>NCT02428218/Biogen Idec</td>
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<tr>
<td>IR902 TCR peptide formulation in IFA BV5S2, BV6S5 BV13S1 (Neurovax)</td>
<td>Randomized, double-blind</td>
<td>1</td>
<td>New MRI Gd1 lesions; WBC measurements</td>
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<tr>
<td>Betaferon (IFN-\beta1b; Betaseron)</td>
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<td></td>
<td>307</td>
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Table I. Current clinical trials in pediatric multiple sclerosis.
ferons by binding to their cognate receptors modulate the cytokine networks of lymphocytes towards anti-inflammatory effect via reducing B-cell mediated antigen presentation, shifting the polarization of Th1/Th2/Th17 cells to an anti-inflammatory state, and also by enhancing the regulatory T-cell and B-cell activity. Major side effects due to subcutaneous injections of IFN-β1a are injection site reactions, blood cell disorders such as thrombocytopenia, hepatic disorders, thyroid dysfunction, etc. Glatiramer acetate, which is generally tolerated better on long-term use, acts through the blockade of specific effector T-lymphocytes and modulating the function of antigen-presenting B-cells and suppressor T-lymphocytes. Side effects of glatiramer acetate include tachycardia in association with transient flushing-like reaction. The main second-line immunomodulatory drug, which is still in clinical trials, is natalizumab (Tysabri®), a humanized monoclonal antibody that blocks the migration, across the blood-brain barrier, of activated B-and T-lymphocytes by targeting the µ4 subunit of µ4β1-integrin on the cell surface, thereby preventing their inflammatory activity and disease process in CNS. Even though natalizumab is approved for adult MS, it is contra-indicated in Europe by EMA for pediatric MS due to lack of sufficient clinical trials. This drug has not been approved by FDA for pediatric use in the United States. However, several clinical studies indicated the effectiveness of natalizumab in pediatric cases despite the occurrence of some side effects including hypersensitivity, progressive multifocal leukoencephalopathy, and infections. A return of disease activity clinically in terms of relapses and MRI activity was reported upon discontinuation of natalizumab in pediatric MS patients. Another antibody based therapeutic that showed some efficacy is rituximab, which is an anti-CD20 chimeric monoclonal antibody. Rituximab targets CD20 receptor on the surface of activated B-lymphocytes and was found to reduce relapses in pediatric MS cases with reasonably good tolerance. However, the possibility of developing progressive multifocal leukoencephalopathy (PML) as noticed in few cases as an unwanted side effect, remains to be addressed. Other drugs such as mitoxantrone (type-II topoisomerase inhibitor), fingolimod (modulates sphingosine-1-phosphate receptor), teriflunomide (reversible inhibitor of mitochondrial dihydroorotate dehydrogenase), cyclophosphamide (immunosuppressor), dimethyl fumarate (modulator of Nrf2 antioxidant pathway) and daclizumab (targets IL2-receptor µ-chain), are still being tested clinically, but appear to have several side effects in children and more clinical trials are needed for assessing their efficacy. General approaches for the treatment of relapse in pediatric MS patients include high doses of corticosteroids (e.g., methylprednisolone) given intravenously, along with gastroprotective drugs. Corticosteroid treatment suffers from several side effects including mood disorders, hyperglycemia, insomnia, etc., and in cases where this treatment fails or unacceptable, administration of immunoglobulins intravenously, is recommended. MS patients suffer from pain that is of neuropathic origin and the recommended treatments include tricyclic antidepressants, pregabalin, lidocaine, etc. Some of the novel approaches that are being developed to treat MS condition in general are remyelinating therapies and neuroprotective therapies. An important aspect that should be addressed for all the approaches to treating pediatric MS patients, is the long-term impact of these therapies on the patients, as well as parents, with particular attention to physical, cognitive, developmental and social outcomes of the children.

Conclusions

Multiple sclerosis (MS) is an inflammatory idiopathic autoimmune demyelinating disease of central nervous system (CNS). The incidence of pediatric MS is relatively rare, with 2.7 to 10.5% of all MS cases in children <18 years of age, with a strong female preponderance. Pediatric MS generally presents as relapsing-remitting form of MS with ≥ 2 clinical events involving more areas of CNS inflammation in the absence of encephalopathy, separated by > 30 days, along with the involvement of brainstem. Disease-modifying therapies that are currently available for adult MS, such as IFN-β1a/1b, glatiramer acetate, teriflunomide, dimethyl fumarate, alemtuzumab, are being prescribed off-label by clinicians for pediatric cases as most of these drugs have not gone through complete testing in randomized, placebo-controlled clinical trials for pediatric MS. It is important to address if these approaches of treating pediatric MS patients have any long-term impact on the patients, in particular, physical, cognitive, developmental and social outcomes of the children.
Conflict of Interests:
The authors declared no conflict of interest.

References


Childhood multiple sclerosis


