Immunopathophysiology of pediatric CNS inflammatory demyelinating diseases

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ABSTRACT

Elucidating pathophysiologic mechanisms underlying the spectrum of pediatric-onset CNS demyelinating diseases, particularly those that may distinguish multiple sclerosis (MS) from other entities, promises to both improve diagnostics and guide more-informed therapeutic decisions. Observations that pediatric- and adult-onset MS share the same genetic and environmental risk factors support the view that these conditions represent essentially the same illness manifesting at different ages. Nonetheless, special consideration must be given when CNS inflammation manifests in early life, at a time when multiple organs (including immune and nervous systems) are actively maturing. CSF analysis in pediatric-onset MS points to chronic CNS inflammation, supported by observations from limited pathologic material available for study. Emerging results implicate abnormalities in both effector and regulatory T cell subsets, and potentially immune senescence, in children with MS. Although CNS-directed antibodies (including antibodies recognizing myelin antigens; Kir4.1) can be documented in pediatric-onset MS, their pathophysiologic significance (as in adults) remains unclear. This is in contrast to the presence of serum and/or CSF antibodies recognizing aquaporin-4, which, when measured using validated cell-based assays, supports the diagnosis of a neuromyelitis optica spectrum disorder, distinct from MS. Presence of anti–myelin oligodendrocyte glycoprotein antibodies documented with similar cell-based assays may also be associated with pathophysiologically distinct disease phenotypes in children. The substantial impact of pediatric-onset MS on normal brain development and function underscores the importance of elucidating both the immunobiology and neurobiology of disease. Ongoing efforts are aimed at developing and validating biological measures that define pathophysiologically distinct monophasic and chronic forms of pediatric CNS demyelination. *Neurology*® 2016;87 (Suppl 2):S12–S19

GLOSSARY

ADEM = acute disseminated encephalomyelitis; **AQP4** = aquaporin-4; **BBB** = blood-brain barrier; **CBA** = cell-based assay; **EDSS** = Expanded Disability Status Scale; **MBP** = myelin basic protein; **MOG** = myelin oligodendrocyte glycoprotein; **MS** = multiple sclerosis; **NMO** = neuromyelitis optica; **NMOSD** = NMO spectrum disorder; **OCB** = oligoclonal band; **ON** = optic neuritis; **OPC** = oligodendrocyte precursor cell; **TM** = transverse myelitis.

There is presently limited insight into the pathophysiologic mechanisms underlying childhood-onset inflammatory demyelinating diseases. Because these disorders occur in the context of the developing immune and nervous systems, understanding the implications to both disease mechanisms and efficacy and safety profiles of potential therapeutics will help guide optimal management approaches for these children and adolescents. Elucidating the biology of pediatric-onset multiple sclerosis (MS) may provide key insights into earliest targets and processes involved in disease pathogenesis as well as into the broader spectrum of CNS demyelinating disease.

In this article, we focus on the pathophysiology of pediatric-onset MS, occasionally commenting on other conditions in the pediatric inflammatory demyelinating disease spectrum, including optic neuritis (ON), transverse myelitis (TM), neuromyelitis optica (NMO) or NMO spectrum disorders (NMOSDs), and acute disseminated encephalomyelitis (ADEM), which are discussed in

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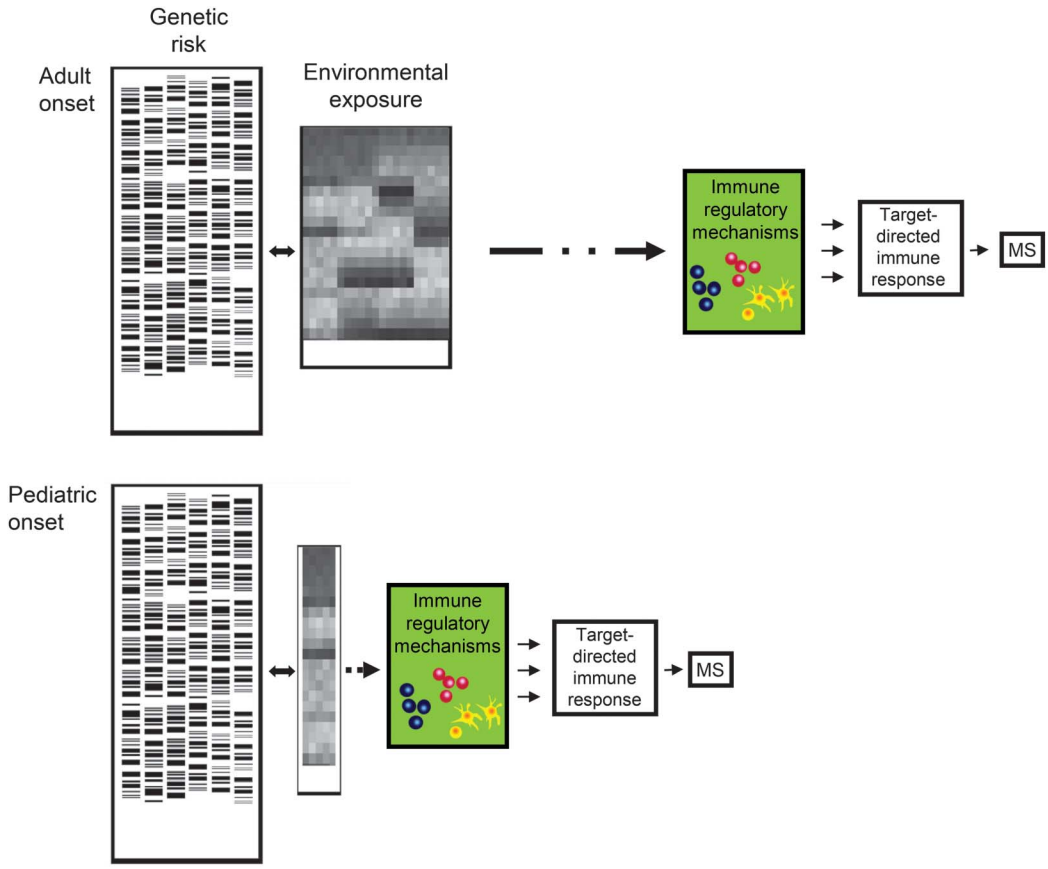
greater detail elsewhere in this supplement. We consider general implications of inflammatory CNS disease manifesting in the context of less mature immune and nervous systems. We provide an overview of genetic and environmental risk factors implicated in the development of pediatric-onset MS and discuss insights from the relatively limited body of work to date examining brain pathology, CSF profiles, CNS-reactive antibodies, and cellular immune responses in pediatric-onset MS and related disorders. In doing so, we highlight both challenges as well as opportunities in the evolving field of pediatric inflammatory demyelinating diseases.

GENERAL ASPECTS OF CNS INFLAMMATORY DEMYELINATING DISEASES MANIFESTING IN THE YOUNG As described in detail in this supplement, the same genetic and environmental risk factors implicated in adult-onset MS have been shown to contribute to MS risk in pediatric-onset MS (figure 1), supporting the view that similar pathophysiologic mechanisms underlie development of MS whether clinical onset is in early life or later. In addition, children with MS do not appear to manifest particular comorbidities that might point to a greater genetic burden—although the relatively small numbers available for study and the possibility that young individuals may not have manifested comorbid illnesses yet (and would thus be inappropriately classified) limit interpretation of such studies.[1] However, in contrast to adults with MS, both the immune and nervous systems are undergoing active development in children and adolescents developing MS or other inflammatory CNS diseases. Although much of an individual's adaptive immune system (comprising T cells and B cells) is established by early life, these immune repertoires must continue to expand and mature, such as through thymic release of newly educated T cells and bone marrow–derived B cells and plasma cells. In contrast, innate immune responses are quite intact even in a neonate. Children experience a large number of new immune challenges, including initial exposures to viruses, bacteria, parasites and fungi, during the first year of life and again during early school age. In many regions children are given vaccinations to further induce or boost particular immune responses. Recurrent infections not only stimulate the immune system but also affect the integrity of the blood-brain barrier (BBB), which in turn may increase exposure of the CNS to peripheral immune mediators. A number of infectious, parainfectious, and postinfectious inflammatory CNS syndromes occur more commonly in children than in adults. The known female predilection for MS is not seen in the youngest children (in whom the F:M sex ratio is 1:1) and appears to emerge after age 11 or so (likely reflecting puberty),[1] suggesting that both age and sex may impact an individual's early life risk of developing MS. Although "immaturity of the immune system" has been proposed as a reason that MS is less common in children than adults, the immune system in children is overall quite mature. The fact that other inflammatory conditions, both CNS-directed (e.g., myelin oligodendrocyte glycoprotein (MOG) antibody-associated disease, ADEM) and systemic (e.g., type 1 diabetes, certain rheumatologic disorders), appear more commonly in children than in adults makes this "immaturity" argument less tenable (reviewed in ref. 1 and 2).

How inflammatory responses may affect the still-developing pediatric CNS is an important and relatively poorly explored field. The early-life CNS harbors more immature cells, including oligodendrocyte precursor cells (OPCs; the potential remyelinating cells), than the adult CNS. In this regard, OPC survival and differentiation have been shown to be affected by distinct immune cell subsets implicated in MS pathophysiology, both directly and through modulation of other glial cells such as astrocytes.[3] A common theory is that the CNS of children may be more "plastic" than that of adults and that it may be better able to compensate for injury. The observation that development of substantial motor disability is relatively uncommon in children with MS in spite of considerably more active inflammatory disease may reflect improved repair mechanisms in children, although it may also reflect less loss of reserve than adults with (on average) longer-standing biological disease. It is also noteworthy that, in spite of good motor recovery, children with MS can be significantly affected in terms of cognitive functions, school performance, and socialization; therefore, the notion of greater plasticity and repair in this population should not be overestimated.

The lesser maturity of both immune and nervous systems in children with MS also has important therapeutic implications because these systems may be differentially affected by approved and emerging MS therapies compared to adults. Of particular importance is the potential impact of different immune interventions on the relatively active thymus and bone marrow, on the establishment of mature and diverse immune repertoires, and on immune surveillance including in the CNS. The fact that some immune processes (such as response to injury and repair) are actually beneficial should be considered. For the reasons outlined above, caution should be exercised in extrapolating insights and

Figure 1 Development of pediatric- and adult-onset multiple sclerosis



Genetic and environmental factors interact over time to confer risk of developing multiple sclerosis (MS). Patients with pediatric-onset MS come to clinical attention at a time that is closer on average to biological disease onset. This would be associated with a narrower range of environmental exposures acting on genetic susceptibility, providing a unique window to investigate early targets and mechanisms involved in the regulation of CNS-directed immune responses.

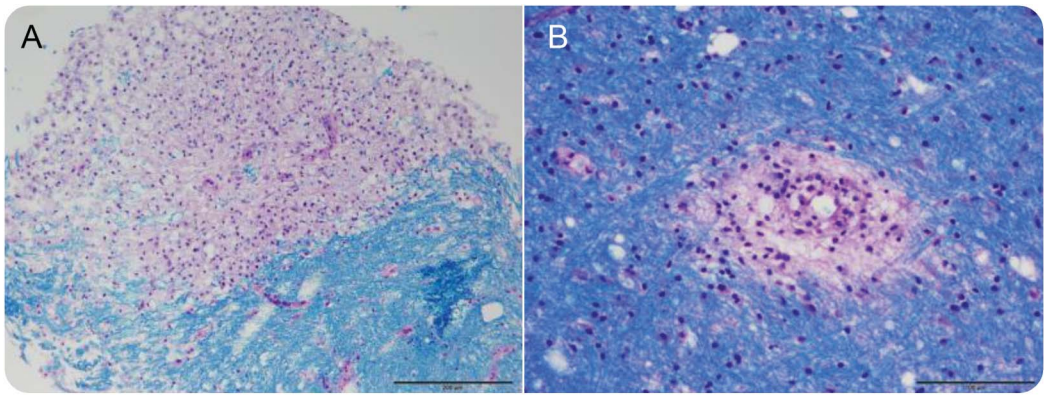
experience from adults to children with CNS inflammatory disease.

PATHOLOGY OF MS Most descriptions of MS pathology are derived from postmortem studies in progressive, long-standing MS cases. The characteristic pathologic hallmark of MS is the confluent, sharply demarcated white matter lesion showing demyelination, inflammation, gliosis, and relative axonal preservation (figure 2A and reviewed in ref. 4). Studies have demonstrated that demyelination also affects the gray matter, especially the cortical gray matter. Here, 3 different lesion types can be distinguished: the most frequent lesion type is the subpial lesion, followed by leukocortical and purely intracortical lesions. The deep gray matter is also substantially involved in the demyelinating process. Remyelination can be observed in MS lesions and may be particularly evident in early disease stages[5] and in the cortex compared to the white matter.[6]

More-detailed insight into the pathology of early disease stages is derived from studies of biopsy tissue from early relapsing-remitting MS cases. These studies have shown heterogeneity of the MS lesions,[5–7] more extensive remyelination in early disease stages,[5] and a higher degree of acute damage to axons in younger patients and those with shorter disease duration.[8]

Studies on the pathology of MS in pediatric patients are extremely rare. A recent systematic analysis of pediatric MS white matter lesions analyzed the extent of acute damage to axons in relation to the amount of inflammation within the lesions and the disability of the patients.[9] The findings showed a 50% higher degree of acute damage to axons in the children with MS than the adults with MS. In addition, the degree of acute damage to axons correlated negatively with the patients' age at the time of either biopsy or autopsy.[9] The prepubertal age group in this study had the highest degree of damage to axons. Inflammation within the lesions also showed a clear age dependency. Although there was no difference in T cell numbers between pediatric and adult MS cases, macrophage/microglia numbers were highest in prepubertal MS lesions followed by

Figure 2 MS and ADEM pathology



(A) Typical multiple sclerosis (MS) lesion showing a confluent demyelinated plaque with sharp border to the periplaque white matter (×100, Luxol fast blue–periodic acid-Schiff [LFB-PAS] myelin stain). (B) Acute disseminated encephalomyelitis (ADEM) lesion showing limited perivascular inflammation and demyelination (×200, LFB-PAS myelin stain).

postpubertal MS and adult MS lesions, indicating that the innate immune reaction in pediatric MS may be significantly more extensive than that in adult MS.[9] This was also related to a higher MRI burden of T2-hyperintense lesions in these patients.[9] Moreover, a clear correlation existed between the degree of acute damage to axons within lesions and the Expanded Disability Status Scale (EDSS) score at the time of biopsy or autopsy. Remyelination was also observed in the lesions; however, a detailed quantification was not performed. In summary, these first published data on the pathology of pediatric MS highlight the substantial degree of acute damage to axons within inflammatory demyelinating lesions of children compared to such lesions in adults.[9]

The major differential diagnoses in the pathology of pediatric MS include ADEM and NMO. ADEM is characterized histopathologically by small perivascular demyelinating lesions (figure 2B). The perivascular demyelinated area is infiltrated by numerous foamy macrophages, a few lymphocytes ($CD3^-$and CD8-positive T cells, B cells, and plasma cells), and very rarely granulocytes. In contrast to MS lesions, demyelination is generally limited to perivascular areas with inflammatory infiltrates and the large confluent demyelinated lesions typical for MS do not form.[10,11] In very acute ADEM lesions, perivascular complement deposits can be found, possibly pointing toward an antibody-/complement-mediated pathogenesis.[12,13] Although NMO was once considered a variant of MS, the discovery of the autoantibody marker NMO-IgG directed against aquaporin-4 (AQP4)[14] has since established NMO as a pathophysiologically distinct entity. AQP4 is a water channel located on astrocytes and concentrated on their foot processes at the BBB. In contrast to MS lesions, NMO lesions show dystrophic astrocytes associated with perivascular deposition of IgG and complement and a striking loss of AQP4 extending beyond the area of demyelination.[15,16] In general, NMO lesions are more destructive than MS lesions, leading to extensive loss of axons and oligodendrocytes.

CSF PROFILES CSF analysis is an important tool in considering the differential diagnosis of a child with an acute inflammatory demyelinating event and can offer important insights into the pathophysiology, particularly in children with a chronic demyelinating disorder. Common features of MS in both children and adults are the intrathecal humoral immune responses characterized by the presence of CSF-restricted IgG oligoclonal bands (OCBs) and local synthesis of a limited antibody repertoire including antibodies against measles, rubella, and varicella-zoster virus—features that are not entirely specific to MS and may be absent early in the disease course, particularly in children under age 10.[17–20] IgG OCBs are more common in children with MS than in those with ADEM or other diseases mimicking MS.[17–19,21] Presence of IgG OCBs combined with an abnormal MRI was associated with a >26-fold hazard ratio for developing MS in children presenting with incident ON.[22]

CSF IgM OCBs can also be found in a subset of patients with pediatric- and adult-onset MS. In adults their presence has been associated with more active/aggressive disease,[23] but such an association has not been established in pediatric MS.[24]

Of note, CSF exhibits age-related changes independent of MS disease mechanisms, particularly around puberty. Reiber et al.[20] showed that the amount of intrathecal IgG doubles during puberty because of an increase in the albumin quotient, which

represents normal physiologic growth. Measuring the IgG index (not just IgG levels) should help avoid false interpretation of IgG synthesis rates in children and adolescents with MS.[18,20] Children with prepubertal MS appear to have a slightly higher total CSF white cell count combined with a higher proportion of neutrophils than postpubertal children,[18] although these values are still lower than those in their adult counterparts.[20] This may be due to differences in the developing immune system or reflect age-related MS-specific immune responses. With new techniques evolving, such as immunophenotyping of CSF B lymphocyte subpopulations, cell-based assays (CBAs), and measurement of proteins such as glial fibrillary acidic protein (a potential marker of astrocytic damage), the CSF profile of pediatric MS and other acquired demyelinating diseases could be studied in more detail with potential to establish biological markers that may affect diagnosis and early treatment decisions.

EFFECTOR AND REGULATORY T CELLS IN PEDIATRIC MS A simple model of the immune pathogenesis of MS can be conceptualized based on results from studies of immune responses in adults with MS, insights from use of experimental therapies that target particular immune responses, and complementary data from animal model studies.[25,26] An early step is thought to involve peripheral activation of $CD4^+$ T cells in response to some stimulating antigen, during which the profile of molecules including costimulatory signals and cytokines influences activated T cell responses and their capacity to interact with and transmigrate across the BBB.[26] This transmigration involves adhesion, chemoattraction, and active infiltration of the activated immune cells into the CNS thought to contribute to perivascular inflammatory injury of the CNS.[26] The process by which the injury may cause additional CNS antigens to be exposed, thereby resulting in the recruitment of T cells with specificities for additional CNS antigens, has been called "epitope spreading," which may also serve to propagate a chronic immune response.[25,26] The initial antigenic targets in MS are unknown; the "molecular mimicry" hypothesis postulates this to be an infectious antigen, triggering T cell responses that are cross-reactive with CNS antigen. Compact myelin antigens such as myelin basic protein (MBP) and proteolipid protein, as well as MOG, have been traditionally considered leading candidates, largely based on the experience from the commonly used animal model experimental autoimmune encephalomyelitis. An exploratory CSF proteomic analysis comparing a small number of children with MS to children with monophasic disease failed to detect differences in compact myelin antigens while surprisingly implicating the axoglial apparatus (the small region where the oligodendrocyte myelin membrane attaches to the axonal node of Ranvier) as a potential target of early injury in pediatric MS.[27]

A number of abnormalities in T cell phenotype and function have been reported in adults with MS (reviewed in ref. 25 and 26), whereas relatively limited cellular immunology data are available in children. An early study suggested that children with early MS exhibited abnormally heightened circulating T cell responses to CNS autoantigens, although so did children with remote CNS injury, highlighting the challenge of distinguishing immune responses that contribute to injury from those that may develop as a response to injury.[28] A subsequent study assessed responses of T cells of both adult and pediatric patients with MS to MBP and MOG[29] and found that both groups mounted preferential and similar responses to particular antigenic epitopes, including MBP 83–102, 139–153, and 146–162 and MOG 1–26, 38–60, and 63–87.[29] The authors noted that T cells of both children and adults with MS mounted limited responses to fetal MBP. A significant number of children on immunomodulatory treatments were included in these 2 studies, which may have influenced results. Two groups have since evaluated T cell responses in pediatric MS. In one study, $CD4^+$ T cell responses to a composite of 7 myelin peptides were increased in a group of untreated pediatric patients with MS compared to adults with MS as well as healthy control children.[30] Children with MS also exhibited higher frequencies of proliferating memory $CD4^+$ T cells and higher levels of interleukin-17 secretion in response to myelin peptides than healthy children, suggesting that this T cell population may be relevant to pathogenesis of pediatric MS.[30] Another group found an increased proportion of memory cells and fewer recent thymic emigrants (particularly regulatory T cells) in children with MS compared to healthy children, suggesting early immune senescence in patients with pediatric MS.[31] This study also found that the suppressive function of Foxp3 regulatory cells was impaired in patients with pediatric MS. The extent to which peripheral immune measures may (or may not) reflect the immune profile within the pediatric MS CNS remains to be elucidated.

CNS-DIRECTED ANTIBODIES IN PEDIATRIC DEMYELINATING DISEASE A growing number of CNS-reactive autoantibodies are emerging as useful diagnostic markers in the context of CNS inflammatory diseases, including pediatric demyelinating disorders. The method used to measure the CNS-autoreactive antibodies is an important consideration. For autoantibodies that bind to the extracellular domains of proteins such as AQP4 (in NMO[14]) and MOG,[32] CBAs have emerged

as the preferred approach, as these present the antigen in its conformational state at the cell surface, which is likely to be more representative of the in vivo interaction.[33] In contrast, antibody assays that alter proteins (by unraveling them) or expose antigens or linear epitopes that are not present at the cell surface are less likely to measure antibodies that are pathophysiologically relevant in vivo. It remains unknown whether antibodies are primary contributors to pediatric CNS demyelinating disease immunopathogenesis, modify pathogenesis, or merely represent secondary epiphenomenon of immune activation. The classic autoantibody-mediated CNS demyelinating disease is NMO, in which presence of the AQP4 targeting Ig in serum or CSF is associated with a typical perivascular staining pattern reflecting antibody binding to the foot processes of astrocytes around blood vessels.[34] The anti-AQP4 antibody is thought to exert direct pathogenic functions (both complement- and Fc receptor–mediated), resulting in the hallmark autoimmune astrocytopathic picture distinguishing NMO from MS pathology.

Anti-MOG antibodies occur more frequently in children than in adults and have been described (using different assays which, as noted above, may affect findings) in pediatric patients with a variety of autoimmune demyelinating disease phenotypes, including those of ADEM, MS,[32,35–37] relapsing ADEM, relapsing ON,[38,39] relapsing ADEM-ON,[40] and relapsing ON-longitudinally extensive TM (NMO-like).[36,37] The normal function of MOG, which resides at the cell surface of oligodendrocytes, is not well understood. There is a dominant epitope involved in MOG IgG binding on the extracellular domain[13] and evidence of MOG IgG pathogenicity including alteration of oligodendrocyte cytoskeleton,[38] as well as implication in both complement-dependent and cell-based cytotoxicity.[35,41,42] A recent pathology report demonstrated antibody and complement deposition in an adult case of anti-MOG antibody-associated demyelination.[43] Compared to AQP4 IgG-associated disease, CBA seropositivity for MOG IgG appears to be associated with less severe disease, including better resolution and less likelihood to relapse,[44] and may also be associated with a non-MS disease phenotype.[45]

A serum antibody binding to KIR4.1 (the ATP-sensitive inward rectifying potassium channel found primarily on glial cells) has been reported in 47% of adults with MS as well as in a subset of children with acute CNS demyelination.[46,47] Presence of this antibody was not associated with particular clinical features and its significance is uncertain at this time. Studies that have not replicated the original report[48,49] underscore the challenge of assay differences and the value of direct assay comparisons.[33]

One study using a custom antigen array of epitopes from candidate proteins including myelin antigens reported different IgG and IgM binding in serum of children with MS compared to those with ADEM.[50] Another study applied an antigen array to samples obtained from children at time of presentation with incident episodes of CNS inflammatory demyelination as well as 3 months later.[51] Children were subsequently diagnosed with either MS or monophasic disease. Although some differences were again noted in serum antibody patterns between children with MS and controls, of particular note was the observation that the range of CNS-directed antibodies detected in the children with MS increased substantially between the 2 time points, whereas the range decreased in children with monophasic disease. Although the pathogenic significance of particular serum antibodies detected using such antigen arrays is unclear, the general pattern and changes over time are consistent with a process of humoral "epitope spread," distinguishing the ongoing MS injury process from monophasic disease mechanisms.

CONCLUDING COMMENTS Information regarding the pathology and immunopathogenesis of pediatric-onset MS and other early-life CNS inflammatory demyelinating conditions remains limited. Pediatric- and adult-onset MS share genetic and environmental risk factors, suggesting that they represent essentially the same disease clinically manifesting at different ages rather than pathophysiologically distinct entities. Nonetheless, a number of differences exist. Children tend to experience more-frequent relapses and higher MRI lesion burden (more "inflammatory" disease, at least early on), have better motor recovery from acute relapses (with a slower progression on the EDSS scale), and experience an important impact on cognitive realms. Whether these differences reflect the lesser states of maturation of the immune and nervous systems in children, including differences in early-life CNS resiliency and/or repair capacities, is unknown. Studies of hypomyelinating conditions and leukodystrophies may provide additional insights into mechanisms of myelin injury and repair of particular relevance to pediatric-onset MS.[52] Of concern are hints from imaging studies that progressive disease mechanisms are already in play at the earliest stage of the pediatric MS spectrum.[53,54] Atrophy is present at the initial clinical presentation of children with MS, and their skull sizes appear on average smaller than controls, raising the question of how early the CNS injury process actually starts in these children.[55] Therefore, patients with pediatric MS require treatments that would target both aberrant immune responses as well as the neurobiology of disease. Both current and future treatments must consider the impact of intervention on the still-developing immune and nervous systems.

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