A single demyelinating attack is enough to limit brain growth in children

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Acquired demyelinating syndromes (ADS) represent acute neurologic illnesses characterized by deficits persisting for at least 24 hours and involving the optic nerve, brain, or spinal cord, associated with regional areas of increased T2 signal on conventional MRI. In contrast to the 75% of adult patients presenting with clinically isolated syndrome (CIS) who are eventually diagnosed with clinically defined multiple sclerosis (MS),1 the majority of children presenting with ADS have a monophasic illness with a good overall prognosis: more than 90% of children achieve a full neurologic recovery.2 Over the last decade, neuroimaging studies have focused on differentiating between MS and its mimics, and correlating radiologic measures with clinical outcome and neuropsychological testing in pediatric MS.3

Quantitative MRI analysis in children with MS has demonstrated that children fail to achieve the expected brain growth trajectory and show a reduced whole brain volume in adolescence; the regions more affected are the gray matter and the thalamus.3 The reduction of brain growth due to MS has been attributed to CNS inflammation, demyelination, and neurodegeneration. Brain atrophy, as measured by MRI, particularly in adults, may reflect gray matter neurodegeneration more than CNS active inflammation.4 No overlap between double inversion recovery detectable gray matter lesions and gray matter atrophy has been detected on MRI.3 Assessing brain atrophy in children is challenging; particular attention is required to take the typical expected developmental trajectory and correct for head size and age.5 In adult-onset MS, the total intracranial volume (gray matter, white matter, and CSF) is considered insensitive to atrophy; thus, the ratio of brain parenchymal volume (white and gray matter) to the total brain volume within the brain surface contour is used to measure whole brain atrophy. However, skull growth further complicates the interpretation of volume changes over time in children, which necessitates normalization of brain size to skull size in the pediatric population.3

In this issue of Neurology®, Aubert-Broche et al.7 report the prospective analysis of serial brain imaging in 83 children with monophasic ADS identified from the Canadian Pediatric Demyelinating Disease Study. These included children with acute disseminated encephalomyelitis (ADEM), CIS with brain involvement, and optic neuritis or transverse myelitis with a normal intracranial MRI. Although a relapsing disease course cannot be completely ruled out, the median period of observation of 4 years makes this unlikely. All children were invited to attend scans clinically at onset, and a subset research scans at approximately 2 weeks, then 3, 6, and 12 months, and annually thereafter. However, the numbers of children scanned at the prespecified prospective time points are not provided. Normative data were used to calculate age- and sex-specific z scores. This was particularly important in the pediatric population to control for intersubject developmental variability, and enabled the comparison of patients with different ages at onset, different stages of brain maturation at first measurement, and effect of disease duration on brain structures independent of age.

The findings presented by Aubert-Broche et al.7 demonstrate that children with monophasic demyelination have reduced age-expected brain growth, driven via reduced white matter growth. Patients with ADEM showed the most deviation from age-expected trajectory. Interestingly, unlike adults with CIS, in which atrophy rates are not different from healthy controls,6,4 reduction in age-expected brain growth was seen even in children with ADS without brain involvement on conventional MRI. In contrast with previous observations in adults and children with MS, the thalamus was not preferentially affected compared to the whole brain.

Aquaporin-4 antibodies were negative in the 63 children tested, but myelin oligodendrocyte glycoprotein antibodies (MOG-Ab) were not tested in this cohort. MOG-Ab occur in up to 50% of children with ADS and are associated with a non-MS disease course.9,10 It cannot be excluded that a proportion

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of patients reported here would have had MOG-Ab. However, the progressive loss of brain volume observed in this cohort may suggest a more chronic (neurodegenerative) disease process, which would not typically be explained by an antibody-mediated disease.

Using a brain volume modeling approach, the results reported here demonstrate that children with ADS have smaller than expected brain volumes prior to the first attack, suggesting a susceptibility to ADS in children with prior perturbations in brain growth. Although this method of extrapolating backward in time may be problematic, particularly as the exact onset and effect of the demyelinating event is difficult to judge, the findings were also present in patients whose first scan showing demyelination (research baseline scan) occurred soon after the first clinical attack. The authors suggest that children who experience acquired demyelination may have a preexisting intrinsic, but not necessarily inherited or genetic, vulnerability to the effects of immunologic attack on brain growth. These surprising findings may indicate a primary neuronal condition manifested as smaller than expected brain volume, leading to susceptibility for secondary demyelination as seen in other genetic and acquired leukoencephalopathies. While host genetic factors undoubtedly influence responses to CNS inflammatory disorders, it is unlikely that most individuals with monophasic ADS share specific genetic mutations. Further studies evaluating the complex interrelationship among genetic, environmental, and immune mechanisms in children with monophasic and relapsing ADS is likely to inform CNS-directed immunologic responses and may lead to new concepts in therapies.

With ongoing clinical trials underway in pediatric MS, these results highlight the importance of understanding the mechanism of disease in order to target potential therapeutics to children with monophasic demyelination. With encouraging results from the randomized controlled trial for the use of phenytoin in adult patients with acute optic neuritis,\textsuperscript{11} neuroprotective agents may be required beyond (or in addition to) the use of immunotherapy when evaluating treatments in children with acute demyelination. Importantly, as discussed by the authors, the use of neuroimaging as a biomarker of treatment efficacy in this population must consider the consequences of the initial inflammatory phase on brain volume prior to initiating treatment.

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**REFERENCES**