Impact of MS during the critical window of brain development

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In this issue of *Neurology*®, Aubert-Broche et al.[1] study the longitudinal change in brain volume in 36 children with multiple sclerosis (MS) (mean age at scan 13.77 years) compared to 25 local healthy children and 339 healthy children from an NIH-sponsored database. This is the first study to compare the trajectory of brain growth in pediatric MS compared to normative controls. The same 1.5T MRI protocol was utilized for all study groups, and the preprocessed T1-weighted images of each time point were linearly coregistered to a subject-specific linear template. Mixed effect models, adjusting for age and sex, were used to estimate and compare growth trajectories. The major findings in the study were that brain volumes were lower in children with MS compared to healthy children of comparable age, and that, in children with MS, there was a downward trajectory in brain volume compared to the growth observed in healthy children. This downward trajectory in brain volume in the patients with MS was due to both a failure of age-expected brain growth as well as subsequent and progressive atrophy. These findings may differ from those of adult patients with MS in whom we assume that the brain is fully developed, and then atrophy ensues; however, this assumption needs to be tested through comparative studies. Deep gray matter structure volumetrics, adjusted for whole brain volume, showed lesser thalamic growth and marginal changes in the globus pallidus, compared to no change in the caudate and putamen. Higher T2 lesion load was associated with smaller thalamic volumes longitudinally. The main limitation of this study is the small number of patients assessed.

This study is notable for several reasons. First, it demonstrates that cross-sectional brain volume reductions noted in pediatric MS are associated with a longitudinal failure in brain growth and progressive atrophy. This has substantial implications for outcomes in patients with pediatric MS, and demonstrates the effect of a chronic inflammatory demyelination disease during a critical window of CNS and cognitive development.[2,3] Second, it demonstrates that thalamic volumes are reduced and that growth of this important relay structure is impaired in childhood MS. Similar studies have demonstrated an association with increased iron content in the thalamus in adolescents with MS compared to controls,[4] supporting the concept that early damage in MS is partly mediated by iron dysregulation in high iron content brain substructures.[5,6] The dissociation of these volumetric changes and the low average physical disability observed in these patients (mean Expanded Disability Status Scale score of 1.29) reinforces the importance of closely monitoring cognitive outcomes, which were not included in this study, but were evaluated by the same group in separate work demonstrating the correlation of thalamic volume and cognitive impairment in children with MS.[7] In that study, thalamic volume accounted for incremental variance in predicting global IQ, processing speed, and expressive vocabulary. Finally, the association of increased T2 lesion volume with thalamic atrophy supports the importance of effective anti-inflammatory treatment and the need for improved treatment options in children with MS.[8,9]

Future clinical trials should include whole brain and thalamic atrophy measures to assess the potential benefit of disease-modifying treatments in pediatric MS[10]; however, this should be done by carefully taking into account the issues of measuring and analyzing atrophy measures in the pediatric population as highlighted in this article, as well as pseudoatrophy and other potential confounders. Further studies are required to assess the long-term effects of impaired brain growth on clinical and cognitive measures as well as psychosocial development and achievement of educational goals in children with MS.

AUTHOR CONTRIBUTIONS

Dr. Chitnis drafted the first version of the manuscript and contributed to study concept and design. Dr. Gorman contributed to critical revision of the manuscript for important intellectual content.

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See page 2140

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