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Multiple Sclerosis in Children and Adults: Does Age Matter?

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Pediatric-onset multiple sclerosis (MS) patients, in comparison with adults, show a higher relapse rate, a more rapid accrual of lesions on MRI early in the disease course, and an increased risk of cognitive and physical disabilities in the long term[1]. Despite the higher inflammation, pediatric-onset MS patients demonstrate a slower rate of disability accrual compared to adult-onset patients. In a comparative study between 710 adult-onset and 83 pediatric-onset MS patients, the pediatric group had a lower Expanded Disability Status Scale (EDSS) at the last clinical examination, despite a longer disease duration[2]. This has been hypothesized to result from greater plasticity of the developing brain in children and consequently greater capacity for repair.

In this current issue of *Neurology,* Bonacchi et al[3] investigated the "pure effects" of age at disease onset on MRI measures by comparing both gray matter volume and white matter structural changes in adults with relapsing-remitting MS who either had pediatric-onset (POMS) or adult-onset (AOMS) disease.

In this cross-sectional exploratory study, the authors included a cohort of pediatric-onset MS patients (n=67) matched in terms of disease duration to adult-onset MS patient cohort (n=143). MRI analyses included conventional approaches providing T2 lesion load and gray matter volumetric measures and DTI providing white matter structural measures. Healthy controls (n=208) were also included to provide a z-score for brain tissue measures to exclude the confounding factor of age.

POMS patients had a mean age of disease onset of 15 years compared to 32 years for patients with adult-onset disease (17 years difference). Similarly, patients with AOMS were 15-16 years older (46 years) than those with pediatric-onset MS (~30 years). Using this large sample of cross-sectional data, the authors reconstructed a pseudo-longitudinal study assessing the evolution of brain tissue injury in the two different groups from the first clinical stage of the disease.

The results of this study demonstrate that early in the disease course, white matter (WM), fractional anisotropy (FA), and gray matter volume (GMV) were abnormal in AOMS but not in POMS patients. Over the disease course, POMS patients acquired more severe brain damage with longer disease duration, manifesting as a loss of WM integrity, followed by GM atrophy and finally clinical disability. Although POMS patients had higher PASAT-2 z scores and took longer to reach EDSS 3, they did so at a younger age compared to AOMS patients.

Using a brain-modeling approach, the data reported here indicate that the interaction between the age of disease onset and disease duration occurred at a cross-over point at 15-years disease duration for WM FA and 19-years for GMV. This is indicative of the fact that disruption of WM integrity may precede GM atrophy in POMS as disease accumulates. Although this method of extrapolating backward only provides indirect evidence, the results of this study are in keeping with natural history studies of POMS, demonstrating that it takes approximately ten years longer for POMS patients to reach irreversible disability; however, reaching these landmarks at a biological age around ten years younger than their counterparts with adults-onset disease[4]. Interestingly, despite the effects of age on disease course, AOMS patients in this study had twice the percentage of SPMS than those with POMS and higher disability. With recent paradigm shifts in MS management resulting in earlier diagnosis, shorter time to treatment initiation, and higher efficacy therapies, it is likely that the POMS patients have been treated with more effective treatments earlier in their lifetime because they were born later.

A critical methodological challenge in studies when calculating disease duration in MS is that the disease processes start before the first clinical presentation. Additionally, Bonnachi and colleagues[3] have only had access to cross-sectional data, and the interpretations are primarily based on extrapolating results based on statistical models. MRI can detect brain volume loss in children with MS compared to healthy controls, already at the time of first clinical presentation[5-7]. In the early stages of the disease, despite the development of brain atrophy, cognitive problems may not be apparent[4]. As clearly demonstrated here, the compensatory mechanisms observed initially in the younger patients start failing over the disease course, with higher rates of WM and GM damage accrual in POMS compared to AOMS patients. This is postulated to be due to the greater plasticity of the developing brain and consequently a greater capacity for repair. This greater capacity for repair

may also be due to the better remyelination seen in younger patients[8] and may suggest a therapeutic window in which appropriate early treatment may prevent future disabilities. Although the reduction in WM FA (reflecting WM inflammation and microstructural damage) occurred prior to GMV loss (reflecting neuro-axonal loss), time will tell if reducing inflammation with higher efficacy treatments will prevent neurodegeneration in POMS or if it is white matter immaturity in younger patients that is driving the greater microstructural tissue damage.

The data reported here provide some explanation to the apparent mismatch seen in children with MS early in the disease course, between stable disability measures and ongoing clinical and radiological disease activity. A more robust recovery from clinical attacks seen in children can also be misleading when assessing disease severity. Current clinical markers of disease activity, including the EDSS and Annualised Relapse Rates (ARR), are not sufficiently sensitive to reflect disease activity and do not accurately predict disease progression. With the growing number of clinical trials and real-world studies evaluating treatment response, understanding the impact of age on the patient's clinical state is crucial. This raises key questions regarding the use of age-specific outcome measures clinically. With the rarity of paediatric MS, validating these is likely to be challenging; however, utilizing advanced imaging techniques and modelling approaches, with patient age taken into account, may be the best way forward. Future longitudinal studies should corroborate the key hypotheses arising from this study.

References

1. Hacohen Y, Banwell B, Ciccarelli O. What does first-line therapy mean for paediatric multiple sclerosis in the current era? Mult Scler 2020:1352458520937644.
2. Simone IL, Carrara D, Tortorella C, et al. Course and prognosis in early-onset MS: comparison with adult-onset forms. Neurology 2002;59:1922-1928.
3. Bonacchi R, Meani A, Pagani E, et al. Association of Age at Onset With Gray Matter Volume and White Matter Microstructural Abnormalities in People With Multiple Sclerosis. Neurology 2021;XX:xx-xx.

4. Renoux C, Vukusic S, Mikaeloff Y, et al. Natural history of multiple sclerosis with childhood onset. N Engl J Med 2007;356:2603-2613.
5. De Meo E, Meani A, Moiola L, et al. Dynamic gray matter volume changes in pediatric multiple sclerosis: A 3.5 year MRI study. Neurology 2019;92:e1709-e1723.
6. Aubert-Broche B, Fonov V, Narayanan S, et al. Onset of multiple sclerosis before adulthood leads to failure of age-expected brain growth. Neurology 2014;83:2140-2146.
7. Bartels F, Nobis K, Cooper G, et al. Childhood multiple sclerosis is associated with reduced brain volumes at first clinical presentation and brain growth failure. Mult Scler 2019;25:927-936.
8. Neumann B, Segel M, Chalut KJ, Franklin RJ. Remyelination and ageing: Reversing the ravages of time. Mult Scler 2019;25:1835-1841.

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