

Abnormal white matter development in children with multiple sclerosis and monophasic acquired demyelination

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The use of conventional MRI as a tool in the diagnosis of multiple sclerosis (MS) is well established in both adults and children and aids in the differentiation between CNS demyelination and its mimics. Conventional MR imaging is insensitive to the tissue damage, which occurs beyond the visible MS plaques, in the so-called normal appearing white matter (NAWM). In contrast to conventional MRI, diffusion tensor imaging (DTI) allows a non-invasive and indirect assessment of axonal structure and myelin integrity by characterising the diffusion properties of water molecules *in vivo* in the brain. The two most commonly used diffusion indices are the mean diffusivity (MD) and the fractional anisotropy (FA). Changes in MD and FA reflect changes in tissue microstructure and organisation of white matter fibers. Although linking changes in MD and FA to pathological abnormalities is tempting, it is likely to be an approximation, considering the complexity of the tissue microstructure and underlying pathological changes. In general, pathological processes known to occur in MS, including axonal degeneration, myelin breakdown, inflammation and increased tissue water, may lead to increased MD and reduced FA in both the lesions and NAWM¹. In addition, a reduction in white matter FA is thought to reflect reduced fiber coherence, which is responsible for a reduction in the directional bias of water diffusion.

The literature on DTI in children with MS is derived predominantly from small cross-sectional studies reporting abnormal diffusion metrics in NAWM (reduced FA and increased MD) compared to healthy controls². The literature on monophasic acquired demyelinating syndromes (ADS) is less abundant and variable, because of methodological differences and timing of data acquired in relation to the age of the child and the time from clinical presentation. Although many processes occur during brain maturation, studies of normal white matter maturation from infancy to adulthood using DTI have demonstrated a progressive increase in white matter FA and a decrease in MD suggesting an increase in axonal size with more efficient axonal transport, and myelin maturation and compaction^{3,4}.

In this current issue of *Brain* Longoni and colleagues report their prospective DTI analysis of 132 children with acquired demyelinating syndromes (ADS) and 80 healthy paediatric controls, recruited as part of the Canadian Paediatric Demyelinating Disease Study. This included 58 children with MS, 18

with acute disseminated encephalomyelitis (ADEM) and 56 with non-ADEM monophasic ADS (monoADS). Patients with monoADS were further split into monoADS with brain lesions and polyfocal symptoms (n=45), and optic neuritis or transverse myelitis (i.e. monofocal phenotype) with normal brain MRI (n=11). All participants were scanned at a single centre with a 1.5T MRI at disease onset and invited to return for a scan after 3, 4, 12 months and then yearly afterwards. In the MS group, the mean age at onset was 12.3y and the mean time from onset to DTI was 2.4y (range 0.1-14.5); the mean length of radiological follow-up in this patient group was 4.5 years. The other patient groups showed similar demographic characteristics, with the exception of ADEM cases where the mean age at onset was 6.5 y. Mean FA and MD values were computed in the NAWM and stratified into early-only analysis, which included measurements from the first two years after ADS, and late-only analysis, which referred to measurements taken more than two years after ADS. Using linear mixed effects models, that use all available data-points, and thus allow for missing data points, longitudinal changes in the NAWM diffusion indices and their associations with presenting phenotypes were evaluated.

In this very large cohort Longoni et al identified that in contrast to the biological increase in FA and reduction in MD seen in the NAWM of normally developing healthy children, children with MS demonstrated a reduction in FA and an increase in MD. These findings are likely to indicate not only abnormal white matter maturation, but also a progressive loss of tissue integrity over time. As expected, higher parenchymal T2 lesion volumes, indicative of a more active MS disease course, negatively correlated with NAWM diffusion metrics.

Interestingly, although the abnormal trajectories over time were observed in both sexes with MS (43 female and 15 males), no longitudinal changes in MD were observed in the males, reflecting a milder pathology in the NAWM. This was also observed in male participants with ADEM who showed a decrease of MD with time, with a different trajectory from that of female participants. As suggested by the authors, this may imply a relative resistance in males to axonal injury and difference in age-related myelination between the sexes. Although the overall incidence of MS is higher in females, males with MS typically show poorer recovery after the initial attack with a more rapid accrual of disability when compared to females⁵. Furthermore, functional connectivity abnormalities with impaired visuospatial memory were only detected in males with MS⁶. The inconsistency in results between adult and paediatric patients may suggest that the observed sexual dimorphism is likely to be paediatric/adolescent specific.

Children with monoADS with normal intracranial MRI showed a temporal behaviour of NAWM FA and MD that was similar to that of healthy children. Interestingly, although no significant abnormalities were detected in the early scans of children with monoADS with brain lesions, the analysis of the late time points detected significantly abnormal MD trajectories, supporting that NAWM might be perturbed by a

single demyelinating attack, if this is associated with brain lesions. Similar observations were also seen in female participants with ADEM, where no significant changes in FA and MD were detected over time, contrasting to the physiological increase in FA and decrease MD expected with age. Male participants with ADEM experienced a decrease of MD over time, with the trajectory significantly different from that of female participants, but this was not different to the healthy controls.

MRI analysis in those under 6 years of age typically requires general anaesthesia, and thus one of the obvious limitations of this study is the lack of healthy control data available for the very young children (mean age of healthy control 14.9 y). This may have affected some of the results in the ADEM group in whom the mean age of onset was much lower (6.5 y). These are critical years for myelin compaction with physiological increase in FA and decrease in MD, and comparing the ADEM group to the older healthy controls may have reduced the possibility of detecting significant differences. Differentiating between the sequelae of a single demyelinating event and on-going chronic disease pathology is particularly challenging in paediatrics as it requires comparison of patients with different ages of onset and thus different stages of brain maturation at first measurement. Correlation with clinical examination, brain volume changes and cognitive and behavioural functioning as previously reported in this cohort^{7,8} would have been informative.

Increasing availability of DTI in clinical practice may enable more accurate correlation with long-term outcome and disability. With the rarity of paediatric onset MS and the difficulties in acquiring DTI data, particularly in the very young patients, correlating the data reported here with clinical outcome measures, including treatment response, and neuropsychological data, may improve our understanding of the mechanisms of damage occurring in the brain of children with ADS. Considering that DTI indices are not widely used in adult clinical trials, it is unlikely that they will be employed in paediatric trials, so their main use, in our opinion, is to detect *in vivo* underlying pathological changes that may explain disability accumulation.

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