Serial proton magnetic resonance spectroscopy of normal-appearing gray and white matter in MS

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In multiple sclerosis (MS), gray and white matter that appear normal on conventional MRI may be affected, even in early phases of the disease.[1] This has been ascertained with techniques such as proton magnetic resonance spectroscopy (^{1}H-MRS), which has the specificity to detect and differentiate between neuronal and glial abnormalities in the absence of overt structural injury. Interpretation of ^{1}H-MRS results across studies is not straightforward, however, because of a number of confounding technical issues.

The spatial resolution of ^{1}H-MRS is poor: typically a few cm^3, compared with mm^3 for high-resolution T1-weighted sequences. This results in varying amounts of tissue types in the volume of interest and hence an inability to sample pure white and (especially) gray matter.[2] Brain coverage is also an issue, because most protocols cover less than 10% of the brain, leaving open the question whether a finding there is globally representative. Finally, the use of metabolic ratios, rather than absolute values, underutilizes the data, because it is not known whether levels of the numerator or those of the denominator are changing. Ratios also risk missing differences altogether if both metabolites change in the same direction.[2] These factors affect the certainty with which results can be extrapolated from one cohort to another and the ability to assemble a clear picture of the temporal metabolic changes in the evolution of MS.

In this issue of *Neurology*®, Kirov et al.[3] tackle these issues and present data of both cross-sectional differences and medium-term longitudinal changes of spectroscopic markers in early MS. They use a relatively large volume of interest (360 cm^3), covering approximately 30% of the brain (more than other studies), and try to reduce partial volume effects by combining the gray and white matter segmentation obtained from T1-weighted images with ^{1}H-MRS data. Two values per metabolite are reported: its level in the global gray and global white matter within the volume of interest. These were collected for 18 patients semiannually over 3 years and annually for 10 controls. At baseline, the patients had an average time from diagnosis of 2.7 years and an Expanded Disability Status Scale score of 1.3, which remained relatively stable at 1.4 at the study's end. Each patient was treated based on an individualized regimen. Comparison over all time points revealed that gray matter metabolic levels in patients were not different from controls. In patients' white matter, however, levels of the glial markers creatine (Cr), choline, and *myo*-inositol were increased, whereas the axonal marker *N*-acetylaspartate (NAA) was lower. Although this suggested both glial and axonal abnormalities, the former were found to predominate as levels of Cr, choline, and *myo*-inositol were consistently greater than the NAA deficit. Previous cross-sectional studies report glial abnormalities, but the dynamics of NAA reduction are still unclear.[4,5] The results obtained by Kirov et al. suggest that the white matter NAA deficit in early MS is subtle and therefore not always detectable.

During the longitudinal observation, patients' glial abnormalities progressed, whereas axonal values were stable. Almost all previous serial ^{1}H-MRS studies in patients on immunomodulatory medication report stable or recovering white matter NAA, and Kirov et al. also attribute it to treatment effect. This likely is the case, because in untreated patients NAA decreases.[5,6] The observation of increasing glial abnormalities, however, is novel and may have been masked in previous serial studies by the use of NAA/Cr ratios. Overall, the results suggest that treatment had a presumed effect on axons, but not on glial markers, which showed the greater abnormalities.

Lower NAA as a neuronal marker is not specific to cell death or dysfunction. This study suggests that the latter dominates, based on the normal gray matter NAA (indicating sparing of the soma) and the recovery of the white matter NAA deficit. It is likely that some dysfunction is mitochondrial, because NAA is synthesized there and levels likely represent mitochondrial activity, which may be decreased in MS.[7] The accumulating glial abnormalities likely reflect gliosis; less likely, but still possible, is the contribution of de/remyelination and activated microglia to this signal. To date, it remains unclear how the ^{1}H-MRS findings relate to the better-studied, lesion-based metrics of disease progression and the Expanded Disability Status Scale.[8]

Despite the fact that the ^{1}H-MRS volume of interest covered a substantial brain volume, there are limitations

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with respect to both gray and white matter coverage. Only approximately 20% of the brain's gray matter was covered (vs 40% of the brain's white matter), and, more important, cortical and deep gray matter were not differentiated. Therefore, heterogeneous or local injury in each gray matter compartment may not be detectable with this approach, explaining why no gray matter metabolic abnormalities were found. Similarly, normal- and "dirty"-appearing white matter were considered a single entity, although the latter is known to share histologic characteristics of lesions.[9]

The main limitation of the approach, however, is that in its current form it uses in-house software and requires lengthy postprocessing. And despite its improved sensitivity, its variability is large, precluding monitoring medication response in individual patients. But the study is also motivation for the development and application of new techniques to accelerate spectroscopic imaging for clinical research.[10]

Nevertheless, the study is a step forward in our understanding of gray and white matter metabolism outside of the MRI-visible lesions, which in early MS constitute just a few percent of total brain volume. Much more is known about lesions, however, and their natural history. The study by Kirov et al. is a timely contribution about the status and evolution of the other 99% of the brain in MS.

DISCLOSURE

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