Preventing brain atrophy should be the gold standard of effective therapy in MS (after the first year of treatment): No

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Rebuttal

Multiple sclerosis (MS) is a complex and heterogeneous disease in which different pathological substrates, including inflammation, demyelination, remyelination, gliosis, and axonal loss, all contribute, simultaneously or consecutively, to its clinical manifestations and accumulation of irreversible disability. At present, magnetic resonance imaging (MRI) is the most sensitive and accurate tool to monitor disease evolution, either natural or modified by treatment.

There is large amount of evidence that measuring focal T2 lesions that form during the course of the disease and their volume changes over time is not enough to properly profile MS clinical heterogeneity and monitor its progression. Likewise, suppressing inflammation with available disease modifying treatments does not seem to affect the neurodegenerative aspects of the disease.1,2 During the past few years, a considerable effort has been spent to develop new therapeutic avenues for neuroprotection and repair, and to identify MRI outcomes to be included in clinical trials of such agents. Among the different MRI measures considered,3 the one that is seen as the most promising by many investigators, is the quantification of brain atrophy. The most probable reasons for this are: 1) brain atrophy is a sort of “summary measure” of the most destructive pathologic processes of MS, including irreversible demyelination and axonal/neuronal loss; 2) it is highly reproducible and sensitive to disease-related changes over time; and 3) it correlates with MS locomotor disability and cognitive impairment.3 Based on these considerations, brain atrophy has already been included as a secondary or exploratory MRI outcome in several MS clinical trials.4

Despite the afore-mentioned advantages, there are at least two aspects that need to be considered carefully if one wishes to use brain atrophy as the “gold standard” of effective therapy in MS. The first one is that in patients with active disease (i.e., presence of multiple gadolinium enhancing lesions), who are usually those included in clinical trials or under consideration for treatment decisions, the presence of inflammation and edema can cause a paradoxical increase of brain volume. Thus, the loss of brain volume frequently observed in the early phase of treatment institution in these patients may simply reflect decreased inflammation and edema (pseudatrophy).4 This would suggest that quantification of brain atrophy is likely not to be the ideal outcome measure of treatment response in short duration (one year or less) studies.

The second, and even more critical, aspect is that atrophy is an end-stage phenomenon, which can take several years before being objectively quantifiable and clinically meaningful. As a consequence, the exclusive use of this measure might limit our ability to grade neurodegeneration properly and early enough. Indeed, natural history longitudinal studies in patients at presentation with clinically isolated syndromes or early relapsing-remitting MS (who are the target populations of the majority of nowadays clinical trials) gave conflicting results when the development of brain atrophy was assessed: some studies found significantly decreased brain volume over time, while others did not.4 This suggests that a follow up of several years may be required to be able to capture adequately brain volume modifications, and clearly this clashes with the typical trial durations, usually ranging from 4-6 months for phase II to 1-2 years for phase III trials.

Since atrophy quantifies an end-stage phenomenon, there are other pathological abnormalities occurring in the MS brains, which might be better detected by advanced MR techniques, such as magnetization transfer (MT) MRI, diffusion tensor (DT) MRI, and proton MR spectroscopy (1H-MRS). Indeed, these techniques are characterized by a higher pathological specificity than atrophy quantification3

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and can provide a reliable assessment of MS-related abnormalities not only in focal T2 lesions, but also in the normal-appearing white matter (WM) and gray matter (GM). Regrettfully, while the potential of these techniques in the research setting has been and is continuously being investigated and their acquisition in multi-centre studies has been standardized, they still need to be validated and evaluated in the context of clinical trial monitoring.

It is also worth emphasising that brain atrophy in MS occurs in a distributed pattern, which involves both the WM and GM, and that atrophy of the spinal cord is also likely to be clinically important. Thanks to improvements in methods of analysis, the quantification of the extent of tissue loss in GM and WM separately is now feasible. Several longitudinal studies have shown that while WM atrophy is relatively stable over the course of the disease, GM atrophy occurs since the early stages, worsens over time, and predicts the subsequent clinical evolution. As a consequence, measuring GM atrophy instead of whole brain atrophy has the potential to result in the identification of more robust measures of neuroprotection and treatment efficacy. Several recent trials have already included GM atrophy quantification as an outcome measure to assess the neuroprotective effect of available MS treatments. An important observation from one of these studies is that pseudoatrophy seems to affect WM volume measurements, but not GM volume modifications. Measuring cervical cord area in a multi-centre setting using a rapid and highly reproducible method has also been shown to be feasible and likely to contribute to the monitoring of MS evolution. If confirmed, these findings might have important implications for the set up of future clinical trials.

In conclusion, quantification of brain atrophy is one of the available outcome measures to assess treatment efficacy on MS-related neurodegeneration, but it is not the best one at our disposal. Indeed, the assessment of brain atrophy progression might result in an overlook of more fundamental and earlier disease pathological processes. We have better metrics available, including measurement of GM and cervical cord atrophy, and quantification of damage to the normal-appearing brain tissues. As a consequence, there is an urgent need to move these possible outcome measures from research to treatment monitoring, in order to identify which of them would be the gold standard of effective treatment in future clinical trials.

Conflict of interest
The authors declare that there are no conflicts of interest.

Disclosures

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References