The neurologist’s dilemma: MS is a grey matter disease that standard clinical and MRI measures cannot assess adequately – No

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Rebuttal

Multiple sclerosis (MS) affects the grey matter (GM) of the central nervous system (CNS). This has been known from the earliest clinical and pathologic description of the disease by Charcot, who reported the presence of ‘plaques located near the GM, which may spread into GM, including deep nuclei and the cortex’. Since then, several other pathologic studies have confirmed that the GM is heavily involved in patients with MS (in terms of both demyelinating lesions and a ‘dying back’ axonopathy with secondary effects in the cortex), and it became clear that many neurological manifestations of the disease likely reflect a damage of the GM rather than the white matter (WM). However, GM involvement in MS has been largely ignored by the neurological community for several decades, and MS has been traditionally classified as a ‘multifocal, demyelinating disease of the WM’. This notion has driven the application of clinical and magnetic resonance imaging (MRI) measures tailored towards the quantification of MS-related WM damage. As a consequence, such measures are at present considered as ‘standard’ and/or ‘conventional’ for the assessment of these patients and, by definition, are only suboptimal in the detection and quantification of GM damage present in this disease. Therefore, an important issue is to define what is ‘standard’. We believe that this term should apply to measures that are sensitive, easily available, practical and standardized. If such a definition is accepted, several measures are available to assess GM damage in patients with MS.

The two measures most frequently applied to monitor clinical activity and progression in MS patients are relapse rate and clinical disability quantified using the Expanded Disability Status Scale (EDSS). Both of these metrics do not account or account only partially for GM involvement. More recently, several scales and tests have been developed or ‘borrowed’ from other conditions to evaluate aspects of MS clinical manifestations which are likely to reflect an involvement of the GM, such as cognitive impairment, fatigue, and depression. Since these manifestations are not routinely evaluated in daily-life clinical practice, the wrong notion that we do not have adequate clinical measures to assess them is strengthened.

Considering the MRI point of view, focal T2 hyperintense lesions and gadolinium enhancing lesions are the measures most commonly used in MS patients, which, once again, are not or very poorly sensitive to GM damage. During the past decade, several other MRI sequences have been developed and applied in the clinical arena, which have the potential to improve our ability to detect focal GM lesions in vivo. The most promising among these are double inversion recovery (DIR) sequences, which, however, are not routinely used and which require an ad hoc training for a correct assessment. As long as these lesions, DIR sequences have shown GM lesions in all the major MS clinical phenotypes, and in patients at presentation with clinically isolated syndromes (CIS) suggestive of MS those at a high risk of evolution to definite MS. In addition, in patients with MS an association has been found between the extent of GM lesions and cognitive impairment as well as their predictive role for subsequent development of irreversible disability.

Measuring atrophy of the whole brain GM or of selected brain GM structures is also of clinical relevance. GM atrophy is associated with locomotor disability, cognitive disturbances, and depression. Longitudinal studies have shown an increased rate of cortical tissue loss in patients...
with progressing disability in comparison with those with a stable disease, as well as an accelerated GM atrophy from the relapsing through the progressive forms of MS. Another study has suggested that, 20 years after the onset of MS, clinical outcomes are more closely related to GM atrophy than WM lesions. Turning to the evaluation of the regional patterns of GM involvement, hippocampal atrophy has been associated with a poor performance in memory encoding task and depression, patients with cerebellar dysfunction show a reduced cerebellar GM volume, and thalamic atrophy has been correlated with long-term accumulation of disability in patients with relapse-onset MS. It is worth noting that whole GM atrophy and atrophy of selected GM structures, such as the hippocampus, are assessed routinely in patients with dementing conditions and they also contribute to the diagnostic work up of these patients. The application of these metrics should become a ‘standard’ approach in MS, too.

In addition, a number of quantitative structural and functional MRI techniques have been used in research studies to estimate GM involvement of the brain and the cervical cord in MS. Even if this effort has improved our understanding of the pathophysiology of the disease and the mechanisms related to the accumulation of ‘fixed’ clinical disability, these techniques are currently implemented only in specialized centres and they cannot be considered part of the ‘standard’ evaluation of these patients. Nevertheless, they might become ‘standard’ in the near future.

To conclude, MS affects the GM of the CNS and clinical and MRI measures that can assess this adequately are already available, although not routinely applied. As a consequence, their use in the clinical arena should be fostered. Clearly, a reliable assessment of MS damage should also include measures able to quantify and monitor WM involvement. Albeit the precise interplay between GM and WM damage and the way they influence each other still need to be defined, a few longitudinal studies have shown a relationship between accumulation of T2 hyperintense lesions over time and the progression of GM atrophy. An additional research question is whether focal GM lesions can result in secondary degenerative phenomena in the WM.

Although the field is rapidly evolving and therefore it is still not fully clear to what extent we will be able to assess MS-related GM damage in future daily-life clinical practice, we believe that it is not only a matter to discuss whether or not ‘standard’ clinical and MRI measures can or cannot assess adequately GM damage in MS, but rather to define what we mean by ‘standard’ in this context.

**Conflict of interest**

None declared.

**References**