

**Title page:**

**Clinical monitoring of MS should routinely include spinal cord imaging- YES**

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MAGNIMS guidelines on the use of magnetic resonance imaging (MRI) to monitor multiple sclerosis (MS) disease activity, published in 2015, concluded that the use of spinal cord MRI in addition to brain MRI is not recommended for routine monitoring of patients (in contrast to MS diagnosis) and should be limited to certain clinical situations (such as unexplained and/or unexpected spinal cord symptoms).<sup>1</sup> Are these guidelines still valid or has anything changed? There are five points that we would like to discuss.

First, a recent study has addressed the independent value of spinal cord MRI in monitoring disease evolution in patients with clinically stable relapsing-remitting MS.<sup>2</sup> The authors showed that 25.2% of relapsing-remitting MS patients developed at least one new asymptomatic spinal cord lesion over a median follow-up of 17 months. Although this was a lower percentage than that of patients who developed at least one new asymptomatic brain lesion (43.7%), adding spinal cord MRI to the follow-up protocol identified about 10% of patients who had disease activity that would have been otherwise neglected.<sup>2</sup> A study carried out in the late 1990s showed that although the total number of new spinal cord lesions occurring over a period of one year was lower than that in the brain (there were 8.78 brain lesions for any single new spinal cord lesion), two-thirds of spinal cord lesions were asymptomatic.<sup>3</sup> Additionally, it has been demonstrated that spinal cord lesions may develop independently of brain lesions.<sup>4</sup> Therefore, although with a lower sensitivity than brain MRI, routine spinal cord MRI in stable relapsing-remitting patients detects disease activity that does not correlate with brain activity and does not always manifest clinically.

Second, it has been demonstrated that the presence of asymptomatic spinal cord lesions has a more important role than brain lesions in predicting clinical outcome.<sup>5,6</sup> For example, in patients with a non-spinal clinically isolated syndrome (CIS) not fulfilling the McDonald

criteria on their brain MRI, the presence of spinal cord lesions allowed for early diagnosis.<sup>7</sup> The presence of lesions in the spinal cord MRI of patients with CIS, independently of the presence of brain MRI lesions, increased the risk of conversion to clinically definite MS threefold if there was only one lesion and almost sixfold if there was more than one lesion.<sup>8</sup> In addition, in patients with CIS, baseline asymptomatic spinal cord lesion number and change in cord lesion number over time explained the variability in disability after 5 years more than baseline brain lesion load.<sup>5</sup> Therefore, the detection of asymptomatic spinal cord lesions in patients with CIS is important because it may change their treatment plan.

Third, technical developments have led to improved spinal cord imaging, which is becoming less challenging; short protocols for spinal cord MRI (i.e., 6-7 minutes acquisition time) with increased image resolution can be routinely acquired on clinical scanners.

Fourth, the detection of a new asymptomatic spinal cord lesion causes more concern in the treating neurologists than a new asymptomatic brain lesion, since spinal cord damage is crucial for the development of progression in MS. Spinal cord lesions are more numerous in progressive MS than relapsing remitting MS.<sup>9</sup> All patients with radiologically isolated syndrome who later developed primary progressive MS over time showed asymptomatic spinal cord lesions at onset versus 64% of those who develop a CIS or relapsing remitting MS.<sup>10</sup> Therefore, the presence of asymptomatic spinal cord lesions on MRI helps neurologists to understand the disease course and disease activity of individual patients and, therefore, formulate the most effective treatment plan.

Fifth, there may be clinical situations in which routine spinal cord MRI should be considered. In addition to cases of unexplained and/or unexpected spinal cord symptoms, patients with large brain lesion loads, which make it difficult to detect new asymptomatic brain lesions, could be monitored with spinal cord MRI.

In conclusion, spinal cord MRI for routine monitoring may be of added value to brain imaging in the diagnosis and monitoring of MS. However, we acknowledge that the cost of adding spinal cord MRI to routine brain MRI protocol should be fully evaluated and further longitudinal studies assessing the impact of asymptomatic spinal cord lesions on disease course and clinical management should be carried out.

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