An asymptomatic new lesion on MRI is a relapse and should be treated accordingly - No

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In the diagnosis and treatment of relapsing remitting (RR) multiple sclerosis (MS), a relapse is a sentinel event. At least one clinical episode is necessary for a diagnosis of RRMS to be made [1], and - in the UK - one or more relapses are required before most MS disease modifying treatments can be prescribed. An MS relapse is diagnosed on clinical grounds, however magnetic resonance imaging (MRI) studies have shown that about 5 to 10 new white matter (WM) lesions accrue per relapse diagnosed [2], highlighting that symptomatic events substantially underestimate MS inflammatory activity. Further, as asymptomatic lesions seen in MRI strongly predict the subsequent development of MS on clinical grounds (for example [3]), a new lesion seen using MRI is now considered essentially equivalent to a relapse when making a diagnosis of RRMS [1]. However, while MRI evidence can substantially decrease the time needed to make a diagnosis of MS, it does so at the expense of clinical specificity [4].

When considering MS disease modifying treatments, MRI has played a very important role in drug development, and at a group level a treatment effect on WM lesion accrual predicts the effect on relapses, and does so in much smaller and shorter trials [5]. However, at the level of an individual with MS, we think asymptomatic lesions seen on MRI should be regarded with greater caution. While mindful that the early use of higher potency agents reduces risk of, or at least delays onset of, secondary progressive MS [6], even if we agree that the aim of MS disease modifying treatment is to suppress all inflammatory activity (some have argued that early relapses play a relatively minor role in longer-term disability progression), there are several reasons to consider MRI findings with some caution. The main issue is that lesion appearances on MRI are not pathologically specific, for example vascular and MS lesions can look the same. Further, normal ageing is associated with brain lesion accrual, and more are seen in people with cardiovascular risk factors or a history of migraine. As such, not all new brain lesions seen in a person with MS are necessarily due to MS. Lesion location may provide clues about aetiology (for example lesions occurring in non-watershed regions are more likely to be MS-related), but this still does not offer certainty.

Beyond this, the work of Rio and colleagues [7] suggests that defining treatment failure purely on MRI grounds may lead to treatment escalation without the prospect of clinical benefit. In their study in people on beta interferon, they found the accrual of ≤ 2 MRI visible lesions over a year, or the presence of a single gadolinium contrast enhancing lesion within a year, was not associated with a greater risk of increasing disability over the next ~7 years. They did not assess lesion location, but we think this should also be considered when guiding people with MS in their treatment choices, as lesions are not necessarily prognostically equal. For example lesions in the posterior fossa, when compared with elsewhere in the brain, appear to be associated with more disabling outcomes [8].

This said, symptoms are a far from an ideal marker of MS inflammatory activity. Tallantyre and colleagues [9] found that symptoms leading a patient to attend an MS relapse clinic were ultimately not thought to be due to an MS relapse in ~40% of cases. Where there is doubt about the source of symptoms, MRI can be used to look for a potentially causative lesion, but the absence of a lesion does not mean that an episode of symptoms is unrelated to inflammation: about 30% to 40% of WM, and nearly all grey matter, MS lesions will be overlooked on conventional MRI scans [10]. Given this, we argue that even with an absolute approach to suppressing inflammation, a nuanced weighing of clinical and radiological evidence is needed.

In conclusion, we do not think that asymptomatic MRI-detected lesions can be regarded as equivalent to a relapse. Instead, they should be considered alongside rather than as a substitute for clinical findings, with the rate of accrual and location of lesions, and co-morbidities, also taken into account. Further, we believe that the prognostic value of clinical and MRI evidence should be balanced against a frank assessment of the risks and benefits of each treatment. A mechanical approach, where any new lesion seen on MRI leads to treatment initiation or escalation, may result in more harm than good and for a person with MS may exhaust their treatment options unnecessarily.

References

1. Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, Comi G, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol 2018;17(2):162–73.

2. McDonald WI, Miller DH, Thompson AJ. Are magnetic resonance findings predictive of clinical outcome in therapeutic trials in multiple sclerosis? The dilemma of interferon-beta. Ann Neurol 1994;36(1):14–8.

3. O'Riordan JI, Thompson AJ, Kingsley DP, MacManus DG, Kendall BE, Rudge P, et al. The prognostic value of brain MRI in clinically isolated syndromes of the CNS. A 10-year follow-up. Brain 1998;121(Pt 3):495–503.

4. Filippi M, Preziosa P, Meani A, Ciccarelli O, Mesaros S, Rovira A, et al. Prediction of a multiple sclerosis diagnosis in patients with clinically isolated syndrome using the 2016 MAGNIMS and 2010 McDonald criteria: a retrospective study. Lancet Neurol 2018;17(2):133–42.

5. Sormani MP, Bruzzi P. MRI lesions as a surrogate for relapses in multiple sclerosis: a meta-analysis of randomised trials. Lancet Neurol 2013;12(7):669–76.

6. Brown JWL, Coles A, Horakova D, Havrdova E, Izquierdo G, Prat A, et al. Association of Initial Disease-Modifying Therapy With Later Conversion to Secondary Progressive Multiple Sclerosis. JAMA. American Medical Association; 2019 Jan 15;321(2):175–13.

7. Río J, Rovira A, Tintoré M, Otero-Romero S, Comabella M, Vidal-Jordana A, et al. Disability progression markers over 6–12 years in interferon-β-treated multiple sclerosis patients. Mult Scler 2018;24(3):322–30.

8. Tintore M, Rovira A, Arrambide G, Mitjana R, Rio J, Auger C, et al. Brainstem lesions in clinically isolated syndromes. Neurology 2010;75(21):1933–8.

9. Tallantyre EC, Causon EG, Harding KE, Pickersgill TP, Robertson NP. The aetiology of acute neurological decline in multiple sclerosis: experience from an open-access clinic. Mult Scler 2015;21(1):67–75.

10. Geurts JJG, Bö L, Pouwels PJW, Castelijns JA, Polman CH, Barkhof F. Cortical lesions in multiple sclerosis: combined postmortem MR imaging and histopathology. AJNR Am J Neuroradiol 2005;26(3):572–7.

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