Controversies in Multiple Sclerosis

Visualisation of cortical MS lesions with MRI need not be further improved: Yes


1. Dept. of Anatomy & Neurosciences, VUmc MS Center Amsterdam, Amsterdam Neuroscience, VU University Medical Center, Amsterdam, The Netherlands.

2. Queen Square MS Centre NMR Research Unit, Department of Neuroinflammation, UCL Institute of Neurology, London, UK; National Institute for Health Research (NIHR) University College London Hospitals (UCLH) Biomedical Research Centre, UK

Corresponding author:

Jeroen J.G. Geurts, PhD
VU University Medical Center
Dept. of Anatomy & Neurosciences
O|2 building for Life Sciences
De Boelelaan 1108
1081 HZ Amsterdam
Postal address:
PO Box 7057
1007 MB Amsterdam
Email: j.geurts@vumc.nl

Acknowledgements

Declan Chard has received research support from the MS Society of Great Britain and Northern Ireland, and the National Institute for Health Research University College London Hospitals Biomedical Research Centre. The VUmc MS Center Amsterdam is funded by a program grant from the Dutch MS Research Foundation (14-358e).

Disclosures

Declan Chard has received honoraria (paid to his employer) from Ismar Healthcare NV, Swiss MS Society, Excemed (previously Serono Symposia International Foundation), Merck, Bayer and Teva for faculty-led education work; Teva for advisory board work; meeting expenses from Merck, Teva, Novartis, the MS Trust and National MS Society; and has previously held stock in GlaxoSmithKline. Jeroen Geurts has received research support or honoraria from Excemed, Novartis, Biogen, and Sanofi Genzyme. He is an Editor of Multiple Sclerosis Journal and section co-editor of the Controversies series of the same journal.
While it is now fully recognised that grey matter (GM) lesions are at least as abundant as white matter lesions in multiple sclerosis (MS), it is hard to imagine that it was only a decade ago that the first deliberate attempt was made to visualize GM lesions with magnetic resonance imaging (MRI). An initial study showed that using conventional T2-weighted and 3D fluid-attenuated inversion recovery (FLAIR) imaging, only ~5% of GM lesions were detected, [1] and this disappointing finding spurred the development of MRI techniques that would improve on this. Soon after, double inversion recovery (DIR) - which suppresses signals from both cerebrospinal fluid and white matter, making GM more conspicuous - was applied to solve this sensitivity problem, and proved superior to both FLAIR and T2 in detecting cortical GM lesions.[2] However, DIR images often exhibit artefacts that can be mistaken for GM lesions, for example small vascular structures or incompletely suppressed fluid in Virchow-Robin spaces posed a problem. A MAGNIMS study group produced consensus criteria to facilitate reliable identification of GM lesions on DIR images.[3] and using these criteria in a post-mortem study, pathological specificity was shown to be high (90%) but sensitivity lingered around a disappointing 20%.[4] So further techniques - aiming to either complement or replace DIR - were tried. 3D-T1 based techniques,[5] T2*-weighted imaging,[6] phase-sensitive inversion recovery (PSIR).[7] and creative combinations of all of the above were investigated. Whether or not any of these techniques should be considered ‘better than the other’ remains open to debate, given the often imperfect conditions of comparison, but, importantly, all of them still show only the tip of the proverbial iceberg.

Following this, researchers turned to higher field-strengths to further improve cortical lesion detection in MS. With better spatial resolution, sensitivity for cortical demyelination increased from 20% when using DIR at standard clinical field-strengths[4] to 30-50% with T2(*)-weighted imaging at 7T.[9-11] But this still means that at least half of the total number of cortical lesions are missed. Reflexively, we feel that we should improve this state of affairs; invest more research time and funds into further development of MRI techniques, higher-fields, or both. But it might be good to pause for a moment and ask ourselves to what end would we act upon this reflex. For one, conventional imaging (e.g. T2-weighted and FLAIR scans) used to detect white matter lesions, has served us well in diagnostic criteria and in treatment trials, yet still only detects between 60 and 70% of such lesions.[1]

In general, a number of clinical reasons for further improving cortical lesion visualization with MRI could be thought of: greater diagnostic accuracy, more robust prognostication, or better monitoring of therapeutic effects. So far, studying cortical lesions at clinical (1.5T and 3T) field-strengths has indeed resulted in a solid body of evidence showing an association between cortical lesions and disability, including cognitive impairment.[12] Taking cortical lesions into account appears to increase the diagnostic accuracy of MRI criteria[13] and has prognostic value.[14] The presence of cortical pathology also helps distinguish between MS and its mimics.[15] However, the question is whether or not visualizing more cortical lesions in MS patients will really make any further difference? We already know that the tip is representative of the whole iceberg.4 Unless, of course, the type of lesions that we currently see on MRI is different from the type of lesions that remain obscure. And, granted, that seems to be the case. Even at ultra-high field-strength (7T), despite being the most abundant type, subpial GM lesions are rarely seen.[9] This could be seen as a problem for those of us arguing that there is no compelling reason to further improve GM lesion visualization. However, there is no convincing evidence that subpial lesions are pathologically distinct or more (or differentially) clinically eloquent than the other types of cortical lesion that we do see more readily on MRI.
Correlations between cortical lesions and clinical deficits are certainly present but they are modest. Realising this need not drive us to improve our measurement simply to be able to confirm correlations in smaller cohorts. Instead, in a complex, multifactorial disease like MS, in which multiple different pathologies may be clinically relevant, perhaps we should aim to explain clinical variance better by integrating measures of these different pathologies rather than focusing on just one.

Of course, a different reason for wanting to improve cortical lesion visibility on MRI may be entirely scientific. For example, for the insights we may gain into the mechanisms underlying MS pathology or to provide more reliable measures of treatment efficacy. Here again, a case could be made for better detecting subpial lesions, as it is not clear that the genesis of all types of cortical lesions is the same. However, as long as what we see is in direct proportion to what we do not, the actual proportion seen may not be quite so important. Instead, improving the reliability of measures may be more relevant. With this in mind, rather than trying to improve visualisation of GM lesions by feverishly developing new MRI methods, a more cost efficient option should probably be tried first. Recent work provided a clue as to what can be done to improve lesion detection while using already existing methodology. Jonkman et al. (2015)[10] compared 7T T2*-weighted MRI with histopathology findings, and showed that although prospective scoring (i.e. without knowing where a lesion was before scoring) identified only about 30% of lesions, retrospectively (i.e., after the location of the lesion had been revealed) ~85% of lesions were visible. This serves to show that there is substantial potential for gains in lesion detection even using the scans already available to us, through better training of operators. Now may be a good time to organise an international meeting to refine the MAGNIMS consensus criteria for GM lesion marking, originally based on DIR, for use with other more recently introduced imaging methods.

In conclusion, although we recognise the potential for further improvement of cortical lesion visualisation, we should keep in mind the reasons for doing so and not simply pursue this because of the general belief that ‘more must be better’.
References


