Journal of the Neurological Sciences 311 S1 (2011) S16–S23

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

MRI measures of neuroprotection and repair in multiple sclerosis

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ARTICLE INFO

Keywords:
Multiple sclerosis
Magnetic resonance imaging
Neurodegeneration
Demyelination
Clinical trials

SUMMARY

Magnetic resonance imaging (MRI) has had an enormous impact on multiple sclerosis, enabling early diagnosis and providing surrogate markers for monitoring treatment response in clinical trials. Despite these advantages, conventional MRI is limited by lack of pathological specificity and lack of sensitivity to grey matter lesions and to microscopic damage in normal appearing tissue. Quantitative MRI techniques such as measures of parenchymal volume loss, magnetisation transfer imaging, diffusion tensor imaging, and proton magnetic resonance spectroscopy have enhanced our understanding of the nature and mechanism of tissue injury and repair in multiple sclerosis, and provided more specific correlates of neurological deficits and disability accrual. Some of these techniques may be of potential use in clinical trials as surrogate outcome measures for measuring treatment effects on neurodegenerative injury, which is currently difficult to quantify in clinical trials. In this respect, measures of brain volume, T1 hypointensity and magnetisation transfer ratio, and optical coherence tomography appear to be the most promising in the short term.

The evidence for a role of neurodegeneration in the pathogenesis of multiple sclerosis, and particularly in the accumulation of irreversible disability, has become increasingly strong over recent years. This has prompted the search for new treatments that can effectively slow down, halt or even reverse such neurodegenerative processes, and in this way restore nervous system function. For this reason, there has been much interest in the development and validation of surrogate markers of neurodegeneration and neuroprotection for use in clinical trials. Advances in magnetic resonance imaging (MRI) technology have allowed the development and implementation of a number of methods that may be promising in this respect.

To assess the utility of these methods and to identify needs for further research, sixty experts in neuropathology, clinical measurement, imaging and statistics participated in a meeting held in Amsterdam in 2008 under the aegis of the National Multiple Sclerosis Society. In the proceedings of the meeting, published in 2009 [1], brain volume changes, T1 hypointensity, magnetisation transfer ratio and optical coherence tomography were deemed the most promising measures for screening the neuroprotective capacity of new agents. Other MRI techniques, such as DTI, ^{1}H-MRS and functional MRI, although potentially useful, require more observational data to help determine the optimal trial design.

This article will review some of the issues that were discussed at this meeting, and present some of the imaging techniques that were considered to be the most promising.

Neuroprotection and repair in multiple sclerosis trials

The development of new treatments for multiple sclerosis (MS) involves several stages. The main goal of Phase I clinical trials is to evaluate the general safety of a new treatment in humans. In Phase II trials, an attempt is made to gain first proof of efficacy in a relatively small group of patients with limited exposure to the treatment. In MS, these trials are typically of four to six months' duration. Since it is very difficult to obtain an unambiguous clinical outcome within this timeframe, biomarkers are generally used as surrogate outcome measures for the primary outcome of the study. The best example of this is the use of MRI to track gadolinium-enhancing (Gd) lesions in the CNS as a surrogate marker of inflammatory activity. If a new treatment reduces the appearance of new Gd-enhancing lesions, this is strongly supportive of an anti-inflammatory effect that may be of clinical benefit in MS. In the context of neuroprotection, there is a compelling need for an MRI metric of neurodegeneration that will be as useful and as practical as gadolinium enhancement MRI is for following inflammatory activity. In order to be approved by regulatory authorities as a valid surrogate outcome measure for future neuroprotective

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Table 1
Criteria for imaging outcomes to fulfil in order to be used as surrogate markers for proof of concept studies of neuroprotection in multiple sclerosis. Taken from Barkhof et al., 2009 [1].

1. Pathological specificity
2. Reproducibility
3. Sensitivity to change
4. Clinical relevance
5. Response to treatment

treatments, such an MRI metric has to be sufficiently reliable and sensitive. In addition, it needs to be sufficiently straightforward to be incorporated into simple, standardised MRI protocols and allow rapid and efficient testing of promising new treatments. The 2008 task force on imaging measures for neuroprotection [1] established a checklist of five criteria that a given MRI metric would be expected to fulfil in order to meet these goals (Table 1). These were used to gauge available MRI techniques as potential surrogate outcome markers for neuroprotection in proof-of-concept Phase II trials in MS. For some MRI techniques, such as brain atrophy measurements, quantification of T1 hypointense lesions and magnetisation transfer imaging, there are available data that can be used to design proof-of-concept studies of neuroprotective therapies. For other MRI techniques, such as diffusion tensor metrics and functional MRI more observational data are needed to optimise trial design.

Evolution of new lesions into permanent T1 hypointense lesions

Permanent T1 hypointense lesions, or 'black holes' are characterised by extensive demyelination and axonal loss. In a *post mortem* study in which MRI features of 109 MS lesions were compared with axonal density determined by histopathology [2], a good correlation was observed ($r = 0.74$; $p < 0.0001$) between the extent of lesion hypointensity (or contrast ratio) and axonal density (Fig. 1). The 'black holes' need to be distinguished from the acute transient T1 hypointense lesions, characterised by oedema related to inflammatory activity. Serial MRI studies have shown that persistence over a period of at least six months is required for a hypotense lesion to qualify as a 'black hole' [3].

The correlation between 'black hole' lesion load and clinical disability is stronger than that observed for T2 lesion load, which is probably to be accounted for by the higher pathological specificity of the former for irreversible tissue damage [4]. For example, in a prospective study of 46 MS patients followed for a period of forty months [6], the 'black hole' volume was better correlated with EDSS score at inclusion (r = 0.41; $p = 0.005$) and at study end (r = 0.37; $p < 0.012$) than was the T2 lesion load (r = 0.33 [$p < 0.025$] and r = 0.27 [NS] respectively). Moreover, in the subgroup of patients with secondary progressive MS (SPMS), the percent change in 'black hole' load was highly correlated with the change in EDSS score (r = 0.81; $p < 0.0001$). A number of subsequent studies have reported similar associations between 'black hole' volume and disability (reviewed in [4]).

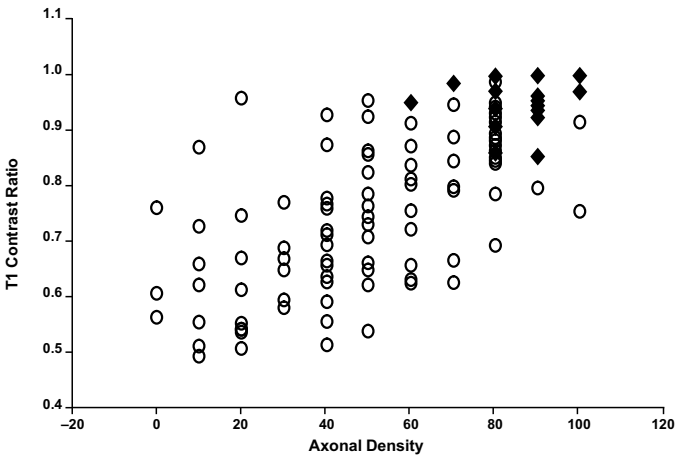

Fig. 1. Relation between T1 contrast ratio and axonal density in a series of 109 lesions from 17 patients with multiple sclerosis examined *post mortem*. Reproduced from Barkhof et al., 2000 [5].

The number of new Gd-enhancing lesions evolving into 'black holes' can change in response to treatment. This was first demonstrated in a *post hoc* analysis of the data from the European/Canadian randomised, placebo-controlled trial of glatiramer acetate (GA) in relapsing–remitting MS (RRMS) [7]. In this study, patients underwent monthly MRI scans for eighteen months. After nine months of treatment, the patients originally randomised to placebo were all switched to GA. All new Gd-enhancing lesions that appeared during the first three months of the trial were followed for the remaining six months of the double-blind phase and the proportion that evolved into black holes was determined in both the active treatment arm and placebo arm. The analysis showed that treatment with GA was associated with a reduction of fifty percent in the proportion of new Gd-enhancing lesions evolving into black holes compared to the placebo group ($p = 0.002$). This suggests that, in addition to its well-characterised anti-inflammatory effect, GA may also have a tissue-protective activity. Subsequently, such an approach has been used for other MS treatments. For example, a 42% relative reduction in 'black hole' formation was reported from a placebo-controlled study of natalizumab [8].

Studies with interferon-β have yielded equivocal results. In the pivotal Phase III study of interferon-β 1a *im*, 'black holes' were evaluated in a subgroup of 160 patients. A lower rate of appearance of 'black holes' was observed in the active treatment group than in the placebo group, but the difference failed to reach statistical significance [9]. Several observational studies have reported reductions in overall 'black hole' load in interferon-β treated patients compared to pre-treatment values [10–12]. However, these studies are difficult to interpret in the absence of a control group and since the fate of individual lesions was not tracked. More recently, three randomised controlled trials have compared interferon-β 1a *sc* [13] and interferon-β 1b [14,15] to GA over a two-year treatment period. The two largest of these trials failed to demonstrate a significant between-group difference in the number of new 'black holes' developing during the study [13,15], whereas the third trial, which used an 'enhanced' protocol for the detection of new lesions, reported a significantly lower percent conversion rate ($p = 0.02$) in patients treated with interferon-β 1b (9.8%) compared to those receiving GA (15.2%) [14].

In an attempt to estimate the number of patients required in a clinical trial to demonstrate a significant treatment effect on the emergence of 'black holes' [16], the rate of evolution of contrast-enhancing lesions into 'black holes' in untreated patients was determined in a cohort of 169 RRMS patients followed for three months and found to be 21.2%. In order to see a reduction of between 50% and 90% in the rate of formation of 'black holes' over a three-month period, it would be necessary to include between 200 and 30 patients per arm to obtain sufficient statistical power [16].

With respect to operational application in clinical trials, one issue with the measurement of 'black holes' is that its definition is rather qualitative. For example, there is no validated threshold of contrast ratio to define what distinguishes a 'pathological' hypointense T1 lesion from an isointense one. One way to overcome this problem is to associate the measure of lesion intensity change to a more quantitative measure, such as the magnetisation transfer ratio (MTR) in the same lesion. A reduction in MTR has been shown