

Brain atrophy measurements should be used to guide therapy monitoring in MS? No

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Word count 960 / 1000 max

References 10 / 10 max

Disclosures and acknowledgements

FB received consultancy fees from Bayer-Schering, Roche, Merck-Serono, Genzyme, TEVA, Synthon, Biogen-IDEC and Novartis for serving on steering committees, advisory boards and data-safety monitoring committees.

MRI plays an important role in MS to secure an early diagnosis and monitor treatment by revealing the inflammatory lesions typical of the disease. In terms of predicting outcomes, the most relevant MRI markers include those depicting neurodegenerative features such as brain volume (BV) loss – or “atrophy” [1]. The cross-sectional predictive value of BV is fairly good at a group level, especially for outcomes like cognition, although the predictive value in individual patients has not been studied in great detail and there are consistent differences between software packages used for BV analysis [2].

With the advent of high-field imaging and robust image segmentation techniques, the scan-rescan precision of brain atrophy measures has become high enough to detect minute MRI-based BV changes on a group level that are clinically meaningful after 5 to 10 years of follow up [3]. Atrophy measures are increasingly used to determine treatment effects in randomized clinical trials of MS [4]. Various drugs have been shown to favourably affect the rate of atrophy development, though some drugs are associated with an initial acceleration of BV loss (sometimes referred to as “pseudo-atrophy”). On a meta-analytical level, the effects on disability in such trials can be accounted for to a substantial degree by their effects on brain atrophy [5].

Inspired by the important observations regarding predictive value in natural history studies of MS and the possibility to alter atrophy rates favourably by drug treatment, the next logical step would be to apply BV measurements to individual patients in routine clinical care [6]. For the inflammatory demyelinating aspects of the disease, the usage of MRI has been successfully operationalized for diagnostic purposes through the McDonald criteria that encompass detailed criteria for assessment and validated cut-off values (2 or more lesion locations). Progress is also being made regarding the evaluation of treatment efficacy by means of MRI on an individual level: finding 2 to 3 or more active lesions on yearly MRI scans under first-line treatment seems a reliable indicator of treatment failure [1]. Do similar validated cut-of values exist for BV measures of cerebral atrophy?

The rate of atrophy in MS patients is on average 3 to 5 times faster than in normal aging [<http://www.msbrainhealth.org/>]. The normal rate of BV change with aging varies from <0.1% per year in young adults but increases to 0.5% per year in

subjects over 65 years of age. Since the age of MS patients varies between these 2 extremes, age-dependent cut-offs are needed that yet have to be defined. The first crude attempt to look at cut-off values for BV changes was based on repeated MRI scans from 35 healthy volunteers scanned 2-4 times over periods up to 12 years [7]. Based on the histograms of the observed variability in BV variability in healthy controls and MS, a pathological threshold of 0.37% per annum was only 80% specific and a cut-off of 0.52% was needed to separate groups with 95% specificity. The problem is easily understood when figure 1 of that paper is inspected, showing marked within-subject variability not only in MS patients, but also in healthy volunteers, despite being scanned on the same scanner with the same protocol. We can only speculate as to the source of this variability, but it likely includes true biological variability in BV change (e.g. related to time of day [8], water intake, hormonal effects), as well as technical imperfections (such as placement of the subject within the scanner, movement artefacts).

In real-life practice, the amount of within-subject variability is likely to be aggravated by uncontrolled technical variability, such as changes of scanner, gradients, RF homogeneity, receiver coils, pulse-sequences and methods of analysis. In my own experience, a major gradient upgrade of one of the scanners led to a 1.49% change in BV in a group of 10 health volunteers, even though visually images and their segmentations appeared identical. Such measurement variability is on the order of a 2 to 3 year change observed in MS patients and painfully illustrates the problems of interpreting BV changes in individual subjects.

What would be needed to allow more accurate and precise BV measurements in MS and make more credible inferences about the development of atrophy and the effects of treatment? First of all, more work is needed to understand the sources of biological variability in BV in healthy aging and MS, especially around hydration status. Secondly, image acquisition should be standardized by employing better (multi-contrast) pulse-sequences and should be monitored using quality assurance and control programs, which may entail phantom scanning for calibration. Thirdly, image segmentation and quantification techniques should be developed that are more robust in accommodating variations in acquisition, but also are more wide available (preferably on the scanner console) to obviate the need for dedicated workstations or

other prohibitive off-line processing strategies. Lastly, more normative data are needed to plot our patients relative to normal aging and untreated MS and better statistical models should be developed to model the expected (rate of) BV loss as a function of age, disease and treatment.

In conclusion, while being a keen proponent of quantitative neuroimaging and having witnessed the developing potential of BV measurements, I have to sadly conclude that despite decades of hard work in the field, atrophy measurements are not reliable enough to guide treatment in individual MS patients yet [9]. Hopefully, the items listed above can be addressed through a collaborative effort between manufacturers and academia to furnish MS patients of the future with reliable means to better guide treatment of the neurodegenerative aspects of the disease. To this end, even when technical implementation would be sufficiently robust, a clear algorithm needs to be developed – and accepted by regulators and payers – that incorporates BV changes in therapeutic decisions alongside clinical data and MRI lesion changes [10].

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