Brain Atrophy in Multiple Sclerosis

Clinical Relevance and Technical Aspects

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KEYWORDS

• Multiple sclerosis • MR imaging • Brain atrophy • Gray matter • Biological confounding factors • Disability

KEY POINTS

- Brain volume decreases can be observed in patients with all disease phenotypes, and seem to proceed at a faster pace in gray matter than in white matter.
- Brain volume measurements are associated with the clinical status of patients and are independently predictive of their clinical evolution.
- Progressive loss of whole or regional brain volume can be detected in vivo in a sensitive and reproducible manner by MR imaging, mainly with the use of quantitative measures acquired by automated techniques.
- Several physiologic and multiple sclerosis–related confounding factors and sources of error related to image acquisition and processing can affect brain volume measurements.
- In spite of encouraging evidence in favor of the use of brain volume measurement as a treatment monitoring tool, confirmatory studies at the patient level are still needed before this can become clinical practice.

INTRODUCTION

The neurodegenerative nature of multiple sclerosis (MS) was reappraised in 2 studies published in the late 1990s, in which an immediate connection between the inflammatory process and axonal loss was confirmed,[1,2] providing a strong rationale for the use of the antiinflammatory therapies that had been widely shown to affect clinical outcomes in MS trials. Axonal loss, and as a consequence brain tissue loss, had previously been considered mostly as the final outcome of the long-standing inflammatory damage to myelin and, therefore, a pathologic process that could only be seen and measured at the very late stages of MS. In parallel, the first MR imaging studies performed in patients with MS to measure the magnitude of brain atrophy already showed significant atrophy evolution over short periods of time and clinical correlations of atrophy changes.[3] Altogether, brain atrophy became attractive from the clinical point of view and measurable from the technical perspective and so research interest in this area increased exponentially. In consequence, in the last 20 years, a growing number of studies have further increased the knowledge of the neurodegenerative phenomenon in MS through MR imaging

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volumetric techniques; a succinct summary of the evidence gathered to date is presented later.

BRAIN ATROPHY IN MULTIPLE SCLEROSIS: A PATHOLOGIC PROCESS

Even though brain volume loss occurs naturally in healthy people and it is regionally variable,[4] pathologic changes well beyond what is seen in controls have been observed in many studies in patients with MS of different phenotypes.[5–8] In those studies it was early observed that not only white but also gray matter was also importantly affected, thus challenging the earlier concept of MS being fundamentally a white matter disease and in accordance with contemporaneous pathology work.[9] Posterior studies have shown,[10,11] using different methods, that such changes seem to be more relevant in certain gray matter areas, including the basal ganglia bilaterally, the precentral and postcentral regions bilaterally, and the cingulate bilaterally.[10] Overall, it has been well established that pathologic brain volume decreases can be observed in patients with MS, of all disease phenotypes, and that those losses are not uniformly widespread but mostly caused by tissue damage in particular gray matter regions.

NATURAL HISTORY OF BRAIN ATROPHY IN MULTIPLE SCLEROSIS

In accordance with cross-sectional research, many studies have shown that the rate of brain volume loss is also higher in patients with MS compared with healthy controls[12] soon after disease onset.[13–15] In this regard, a large study[16] indicated that brain volume loss seems to proceed at a similar pace in patients with clinically isolated syndromes compared with those with progressive (primary and secondary) forms of MS, challenging the view that brain tissue loss only occurred as a late neurodegenerative phenomenon in this disease and in accordance with the pathologic studies mentioned before.[1,2] Longitudinal studies have also shown, in all clinical subtypes of MS, that measurable tissue loss seems to proceed at a faster pace in gray matter compared with white matter.[13–15,17] In these studies it was also shown that the degree of inflammation affects white matter volume measurements in a way that increased inflammation produces spurious increases in white matter volume and that gray matter volume changes seem to be independent of the amount of white matter lesions and of changes in their volume.

A recent study has tried to obtain a cutoff for the rate of brain tissue loss that may be useful to differentiate patients with MS from healthy individuals.[18] In this study, 207 patients with different clinical phenotypes (relapsing-remitting, secondary, and primary progressive) showed an annualized percentage brain volume change of −0.57% compared with −0.27% in healthy controls. The cutoff point to maximize discrimination between both groups was −0.37%, with a sensitivity of 67% and a specificity of 80%. However, application of such cutoff at an individual level remains challenging.

CLINICAL RELEVANCE OF BRAIN ATROPHY IN MULTIPLE SCLEROSIS: CONCURRENT AND PREDICTIVE VALUE

From the early studies, clinical associations of brain volume measurements were evident.[3] Losseff and colleagues[3] described, in a group of 26 patients with relapsing-remitting and secondary progressive MS, a significant difference in brain volume loss between those with definite disability progression, measured with the Expanded Disability Status Scale (EDSS), and those without, favoring the latter. Posterior studies have shown this to be applicable to all disease phenotypes, early from disease course and for different clinically relevant disease end points. Early in the disease evolution, Pérez-Miralles and colleagues[19] showed that brain volume loss in the first 9 months after a first attack of MS is associated with the presence of a second attack in the short to medium term and Di Filippo and colleagues[20] showed that brain volume loss in the first year after a first attack was associated with disability after 6 years. Note that the role of gray matter volume loss seems to be central for these correlations, as was shown by Dalton and colleagues,[13] and more recently by Pérez-Miralles and colleagues.[19] Even before any clinical symptom has appeared, recent evidence suggests that brain volume may already be associated with cognitive performance on formal neuropsychological testing, as shown by Amato and colleagues[21]; this study also showed a significant decrease in the brain volumes in this group of extremely early patients compared with healthy individuals. Significant associations between clinical findings and brain volume changes both globally and for gray matter have been shown in many studies not only for global quantitative measures but also using regionally specific techniques.[10]

From a clinical point of view, it is of utmost importance to show whether brain volumetry techniques may predict disease evolution. This importance has been shown by several studies from early in the disease course[19] but, most