Summary

MAGNETIC RESONANCE IMAGING TECHNIQUES FOR EVALUATING BRAIN ATROPHY IN MS

There is widespread agreement that the assessment of brain atrophy by serial magnetic resonance imaging (MRI) represents a new putative tool for monitoring disease progression in multiple sclerosis (MS). In the past 5 years, several methods for the analysis of brain volume changes in MS have been proposed and implemented. More recently, these methods have been applied retrospectively to many Phase III treatment-related trials aimed at investigating the correlations between brain atrophy and other clinical/MRI parameters, and in particular to ascertain the possible effects of treatments on delaying this irreversible, destructive process. This article reviews literature on methods to quantify brain atrophy and their application in MS-treatment trials.

TECHNIQUES D'IMAGERIE PAR RESONANCE MAGNETIQUE PERMETTANT D'EVALUER L'ATROPHIE CEREBRALE DANS LA SCLEROSE EN PLAQUES

On s'accorde généralement sur le fait que l'évaluation de l'atrophie cérébrale à l'aide d'images en série obtenues par résonance magnétique constitue un nouvel instrument qui permet de contrôler l'évolution de la sclérose en plaques (SEP). Au cours des cinq dernières années, plusieurs méthodes permettant d'analyser les modifications du volume cérébral dans la SEP ont été proposées et appliquées. Plus récemment, ces méthodes ont été appliquées rétrospectivement dans de nombreux essais cliniques associés à un traitement de Phase III dans le but d'étudier les corrélations éventuelles entre l'atrophie cérébrale et d'autres paramètres cliniques et d'imagerie par résonance magnétique (IRM), et en particulier dans le but de vérifier les éventuels effets des traitements sur ce processus destructif irréversible. Cet article est une revue de la littérature sur les méthodes permettant de quantifier l'atrophie cérébrale et leur application dans les essais cliniques concernant les traitements contre la SEP.

TECHNIKEN DER BILDGEBENDEN KERNSPINTOMOGRAPHIEZUR BEWERTUNG DER HIRNATROPHIE BEI MULTIPLER SKLEROSE

Es besteht allgemein Übereinstimmung darüber, dass die Bewertung von Hirnatrophie durch serielle bildgebende Kernspintomographie (MRI) eine weitere geeignete Methode zur Überwachung der Krankheitsentwicklung bei multipler Sklerose (MS) darstellt. Während der letzten 5 Jahre wurden mehrere Methoden zur Analyse der Änderung des Gehirnvolumens bei MS vorgeschlagen und angewendet. Vor kurzem wurden diese Methoden retrospektiv auf mehrere klinische Therapiestudien der Phase III angewandt, die auf die Untersuchung der Zusammenhänge zwischen Hirnatrophie und anderen klinischen/MRI-Parametern abzielten. Vor allem sollen die Wirkung der Therapie auf die Verlangsamung der irreversiblen Hirndestruktion erfasst werden. Dieser Artikel bespricht die Literatur zu methoden der Quantifizierung der Hirnatrophie und deren Anwendung zur Verlaufsbeurteilung des Therapieerfolgs in klinischen Studien.

TECNICHE DI RISONANZA MAGNETICA PER LA VALUTAZIONE DELL'ATROFIA CEREBRALE NELLA SCLEROSI MULTIPLA

È ormai opinione diffusa che la quantificazione dell'atrofia cerebrale mediante l'uso di Risonanze Magnetiche (RM) seriali rappresenta un valido e nuovo strumento per la valutazione della progressione della malattia nei pazienti affetti da Sclerosi Multipla (SM). Nel corso degli ultimi 5 anni sono state proposte ed implementate, nell'ambito della SM, numerose metodiche per l'analisi delle modifiche del volume cerebrale. Più recentemente, tali metodiche sono state applicate retrospettivamente in vari studi farmacologici di fase III per esplorare le correlazioni esistenti tra l'atrofia cerebrale ed altri parametri clinici e di RM, ed in particolare per verificare i possibili effetti dei trattamenti utilizzati per ritardare la comparsa di questo processo distruttivo e irreversibile. Quest'articolo passa in rassegna la letteratura inerente le metodiche di quantificazione dell'atrofia cerebrale e sulla loro applicazione negli studi clinici con pazienti affetti da SM.

TÉCNICAS DE IMAGEN DE RESONANCIA MAGNÉTICA PARA EVALUAR LA ATROFIA CEREBRAL EN LA ESCLEROSIS MÚLTIPLE

Existe el acuerdo generalizado de que la evaluación seriada de la atrofia cerebral mediante imagen de resonancia magnética representa una posible herramienta nueva para controlar la progresión de la enfermedad en la esclerosis múltiple. En los últimos 5 años, se han propuesto e implementado varios métodos para el análisis de los cambios del volumen cerebral en la esclerosis múltiple. Más recientemente, estos métodos se han aplicado de forma retrospectiva en muchos ensayos de tratamiento de fase III destinados a investigar las correlaciones entre la atrofia cerebral y otros parámetros clínicos y de imagen de resonancia magnética, y en particular, a establecer los posibles efectos de los tratamientos en el retraso de este proceso irreversible y destructivo. Este artículo analiza la bibliografía sobre los métodos para cuantificar la atrofia cerebral y su aplicación en los ensayos de tratamiento de la esclerosis múltiple.

MAGNETIC RESONANCE IMAGING TECHNIQUES FOR EVALUATING BRAIN ATROPHY IN MS

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INTRODUCTION

Several morphological studies of normal brain growth and atrophy have been performed since magnetic resonance imaging (MRI) was developed.[1–3] The human brain increases in size approximately four times during the first decade of life, and then declines progressively thereafter. The process of atrophy consists of a decrease in brain tissue size, involving grey and white matter, and an increase in the volume of cerebrospinal fluid (CSF). Changes in each tissue type do not necessarily happen in parallel and grey matter, white matter and CSF volumes have dynamic inter-relations throughout degenerative events.[1]

Sophisticated MRI techniques can depict subtle changes in brain structures, which has increased interest in neurodegenerative diseases including Alzheimer's disease (AD), cerebellar ataxia and multisystem atrophy, in which dramatic, short-term, pathological changes in the volume of brain structures occur.[4–7]

Traditionally, multiple sclerosis (MS) has been listed as a demyelinating disease and considered as a prototype of such disorders, but even some of the first papers on MS to be published made references to axonal damage in MS lesions.[8,9] Recent immunocytochemical studies suggest that MS may be more than a demyelinating disorder, and that it may damage axons even at an early disease stage:[10,11] this finding was documented in a report of axonal pathology and transection in MS plaques from patients with very short disease duration.[11] Following the development of new MRI techniques (including MR spectroscopy, magnetization transfer imaging and diffusion anisotrophy), there have been significant advances in the study of *in vivo* axonal pathology.[12–19] Such techniques reveal that axonal degeneration is evident within

plaques, and within normal-appearing white matter, probably as a consequence of Wallerian degeneration of axonal projections that have disconnected from their origins.

Atrophy in MS probably represents an epiphenomenon, namely the progressive, dynamic combination of focal (lesions) and global brain damage (neurodegeneration) over time. Some early MS studies used atrophy evaluation as an indicator of cognitive dysfunction;[20–23] more recent longitudinal studies, using atrophy as a surrogate marker, suggest that atrophy evaluation might be a long-term predictor of ongoing, permanent disability and a reliable putative tool for evaluating treatment influence on preventing or delaying this feature.[24–28]

Various methods to quantify atrophy have been described, such as measuring the width of the third and lateral ventricle and the corpus callosum area; measuring the spinal-cord cross-sectional area on two- and three-dimensional images; and, most recently, using three-dimensional, automated techniques to measure total brain atrophy.[25–27,29–34] This article reviews the literature where several of these methods have been used to quantify brain atrophy, and the application of such techniques in MS-treatment trials.

LINEAR INDEXES

In the 1980s, linear indexes and area evaluations (e.g. third and lateral ventricular width and the area of corpus callosum; Figure 1) were applied in several MS[26] studies, to establish the relationship between cerebral atrophy and cognitive impairment.[20–23] In a longitudinal Phase III treatment trial that started in the late 1980s, this technique was introduced as a prospective natural history method to evaluate cerebral atrophy and compare findings with disability progression.[27] The results documented that atrophy could be detected over 1-year intervals, and proposed a relationship between lesion-enhancing and other MRI evaluations of atrophy within a 3-year period.[27] Although this method appears to be less sophisticated and less reproducible (coefficient of variation, ≈ 3%) when compared with three-dimensional automated techniques, it provides similar information[27] and analyses parameters (such as the third or lateral ventricle) which have a close association between clinical features and pathological signs.

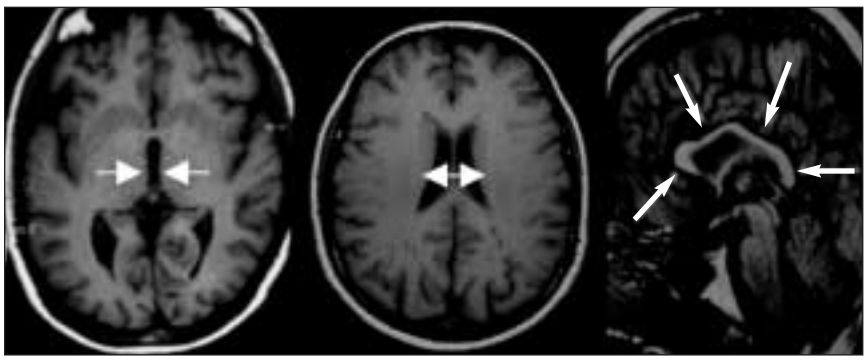

Figure 1.
Atrophy measures based on T1-weighted images. Left panel: arrows indicate level and location used for third ventricle measure. Middle panel: arrows indicate maximum lateral ventricle measure. Right panel: arrows depict corpus callosum measure, using best mid-sagittal section.

TWO-DIMENSIONAL TECHNIQUE

This regional method is a two-dimensional technique that consists of quantifying brain volume in four contiguous selected slices, up to the velum interpositum (Figure 2). This technique combines histogram-based automatic thresholding with sequences of morphological operations that distinguish brain from surrounding tissue and CSF. Although analysis is restricted to the axial plane and to four selected slices, which leads to a lack of image registration and a possible partial-volume effect, the high scan-rescan reliability (coefficient of variation, <1%)[24,25,28] and the high level of automation limit the risk of operator-dependent error and measurement drift over time.

The regional method was first used in 29 MS patients included in the London arm of the anti-CD-4 trial; Losseff *et al.*[24] demonstrated that progressive cerebral atrophy could be detected in individuals with MS and correlated with worsening disability. Other studies using the regional method have claimed that the acute inflammatory process may cause an inevitable pathological cascade, with demyelination and axonal loss as the final events.[24,25,27] Once established, any treatment may have little effect on this neurodegenerative process.

Another study performed in 52 patients with early relapsing–remitting MS documented brain atrophy as an early MRI finding, closely related to the burden of black holes.[29] In this study, Losseff's technique[24] was applied to the infratentorial structures, and the high reliability of the regional

method was confirmed (coefficient of variation, 0.23%; Figure 3). The technique was also applied in 95 patients with secondary progressive MS, participating in the European multicentre, double-blind, placebo-controlled trial of interferon beta-1b.[28] This study documented a lack of significant treatment effect in reducing brain atrophy progression, although a possible concomitant effect might have been due to the anti-inflammatory/antioedematous action of interferon beta-1b: the rate of tissue loss may have been overestimated in the patients receiving interferon.

WHOLE-BRAIN AUTOMATED TECHNIQUES

The brain boundary shift integral

The brain boundary shift integral (BBSI) uses image co-registration to calculate the total difference in brain volume between two MRI scans, performed at different times. This technique is highly automated, sensitive and reproducible, probably because it removes major obstacles to brain volume measurement – image-analysis time and problems related to observer dependence and segmentation error.

Originally, BBSI was applied to study AD;[5,6] more recently it has been used to characterize changes in brain volume in MS.[31] Using this approach, over a 1-year period the rate of cerebral atrophy in the subjects with MS was three-times greater than that found in age-matched control subjects, and the rate of ventricular enlargement was five-times greater. The authors, however, did not find a relationship between changes in brain or ventricular volume and changes in clinical disability. As they suggest, this could be related either to the slight degree of worsening in the group or to the fact that the clinical measures used to evaluate disease progression[35] tend to quantify locomotor function impairment and, to a lesser extent, the cognitive changes that might reflect brain atrophy.

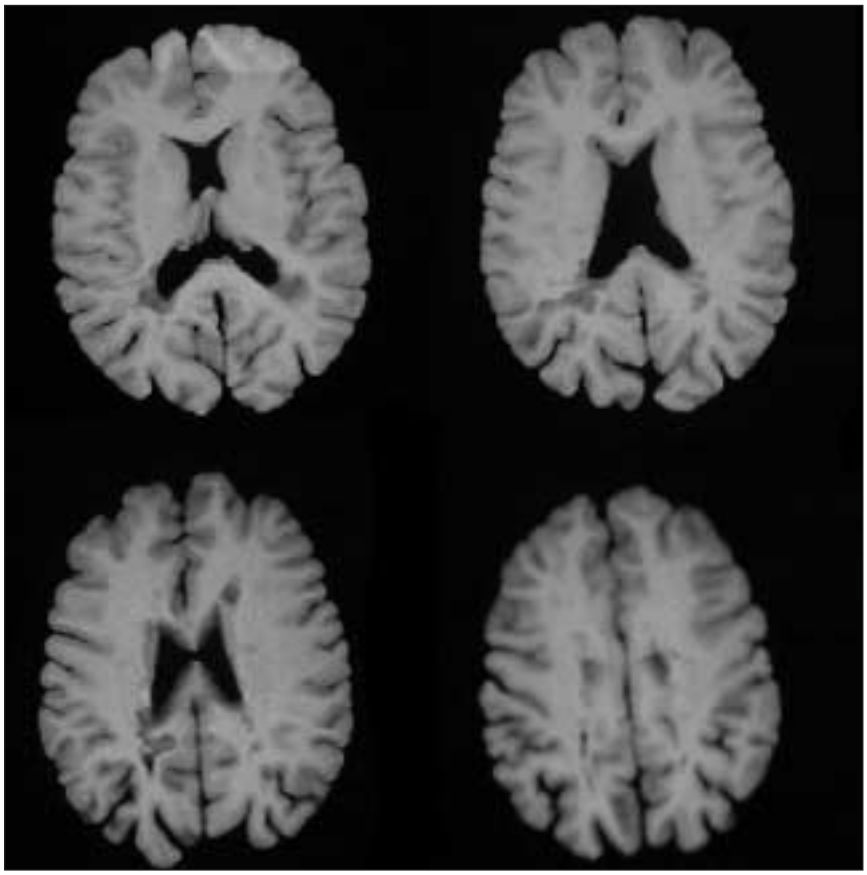

Figure 2.
Axial T1-weighted image. Brain volume is measured using four individual slices, up to the velum interpositum.

Brain parenchymal fraction

Brain parenchymal fraction (BPF) is a size-normalized estimate of total brain atrophy.[32] BPF is calculated as the ratio of the volume of brain parenchymal tissue to the total volume within the outer surface of the brain. Both

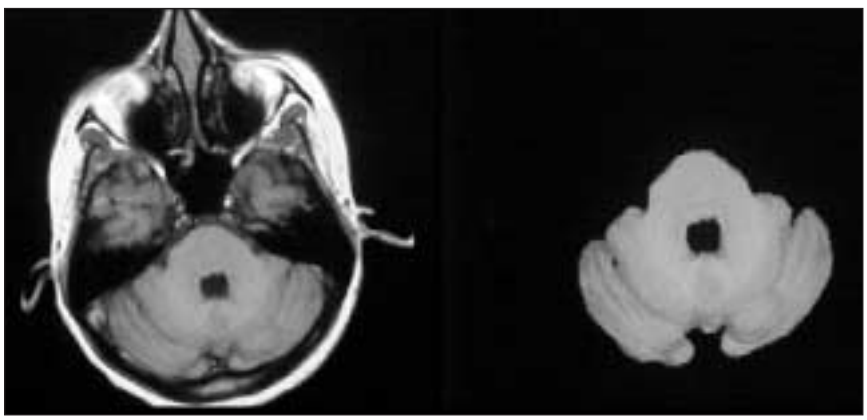

Figure 3.
Axial T1-weighted image. Infratentorial brain volume measure obtained in a single slice.

volumes are obtained automatically by software developed to segment the brain in standard MRI. The algorithm is based on a sequence of three-dimensional image-processing operations to depict the outer surface of the brain and, subsequently, the parenchymal tissue within that outer surface. Rudick *et al.*[36] reported the use of BPF in an MS trial, and reported the association between disability evaluation and baseline BPF. This study also demonstrated the effect of treatment with once-weekly interferon beta-1a in delaying the rate of atrophy progression during the second year of follow-up.[36] As possible explanations for this effect, first the authors hypothesized a delayed therapeutic action and, secondly, the time-course of the appearance of atrophy. Indeed, the reduction and eventual suppression of disease activity during the first year of treatment did not stop atrophy, whereas the persistence of reduced activity may have resulted in a slower rate of brain atrophy in the second year. Despite the large sample size, in this trial there was a poor correlation between changes in disability and progression of atrophy. [36]

More recently, Fisher *et al.*[37] applied BPF to investigate brain volume changes in an MS cohort[36] over 8 years, and reported a significant correlation between decrease in brain volume and worsening in Expanded Disability Status Scale (EDSS) score from Year 2 onwards.

3DVIEWNIX (Udupa's method)

This program, developed by the Medical Image Processing Group of the University of Pennsylvania,[33] determines whole-brain parenchyma and CSF volumes. The CSF-only image is obtained by creating an 'angle image' of CSF, using an equation. The angle image shows a relatively homogeneous CSF signal intensity value that can be segmented by thresholding. The brain parenchyma image is generated and the volume is calculated by subtracting the CSF-only images and volume data from the intracranial contents after segmentation.

This method was used in 36 untreated MS patients (27 relapsing–remitting, nine secondary progressive), followed up for a median period of 2.5 years (range, 1–7 years).[38] The method documented a high reliability, with a median coefficient of variation of 0.23% for brain parenchyma volume and 0.45% for CSF volume. The authors found a significant correlation between brain atrophy and changes in EDSS scores in patients with secondary progressive MS, but not relapsing–remitting disease.

Brain to intra-cranial capacity ratio

The brain to intra-cranial capacity ratio (BICCR) is a fully automated method, developed by the Montreal Neurological Institute, which estimates whole-brain volume in MS patients. The BICCR is calculated by applying the following automatic processing steps on proton density (PD) and T2-weighted images:[39] correction of image intensity non-uniformities; stereotaxic registration and resampling of the MRI data; intensity normalization to a standard average PD or T2 volume; cropping the inferior and superior slices to yield an automatically equivalent 80-mm-thick volume in all subjects; digital morphology for intracranial-cavity identification; Bayesan tissue classification into grey matter, white matter, CSF, lesion and background voxels within the brain mask. The coefficient of variation for this method is approximately 0.21%.

When applied to a cohort of 46 patients with relapsing–remitting and 22 with secondary progressive MS, the BICCR was significantly lower in the people with secondary progressive MS than in those with relapsing–remitting disease, or healthy controls.[39] Moreover in the group with secondary progressive MS, the BICCR was inversely correlated with EDSS and disease duration. Subjects in this cohort also underwent proton MRI spectroscopy, to assess decreased axonal density and axonal metabolic dysfunction, by measuring the resonance intensity of *N*-acetyl aspartate (NAA) relative to creatine (Cr). The BICCR in people with relapsing-remitting MS was slightly lower than in the control subjects, in spite of a significantly lower NAA/Cr ratio in the patients compared with controls. This finding suggests that in the early phase of MS, axonal injury and atrophy processes proceed independently.[39]

Alfano method

This fully automated MRI segmentation method is based on a relaxometric characterization of brain tissues, calculated using R_1 (=1/T1), R_2 (=1/T2) and proton density (N[H]) maps from spin-echo studies. Originally this method was applied to AD,[7] but it has now been used in people with MS (Figure 4), where its reliability for the measurement of de-myelinated plaques and different brain tissue types (grey and white matter, CSF and ventricles) has been described.[40]

In this study, segmentation of normal tissues and lesions was obtained from their relaxation rate and proton density maps. For MS lesion depiction, three-dimensional lesion shape and surrounding tissue composition were also included.[40] The Alfano method is a multispectral, relaxometric, segmentation procedure that provides accurate classification of MS lesions in serial fashion, as well as reliable estimates of lesion burden. The technique can also be used as a repeatable, supervised method to monitor disease progression or assess treatment effect. Currently, the Alfano method is being applied in many clinical longitudinal MS trials.

Structural image evaluation using normalization of atrophy

Structural image evaluation using normalization of atrophy (SIENA) is a fully automated, highly accurate method (approximately 0.2% brain volume change error). The input consists of two cranial MRI scans, taken at different time-points; the output consists of a change image, along with an estimate of brain volume change. SIENA segments brain from non-brain automatically (and assesses the skull's outer surface), can be undertaken for a range of slice thicknesses and MRI sequences, and performs a correction for scanner drift.[41] When applied in people with MS, SIENA documents a close correlation between brain volume and EDSS score, particularly when a categorical distribution is used.[41]

Voxel based morphometry

Voxel based morphometry (VBM) is a fully automated whole-brain technique to measure regional volume and tissue 'concentration'

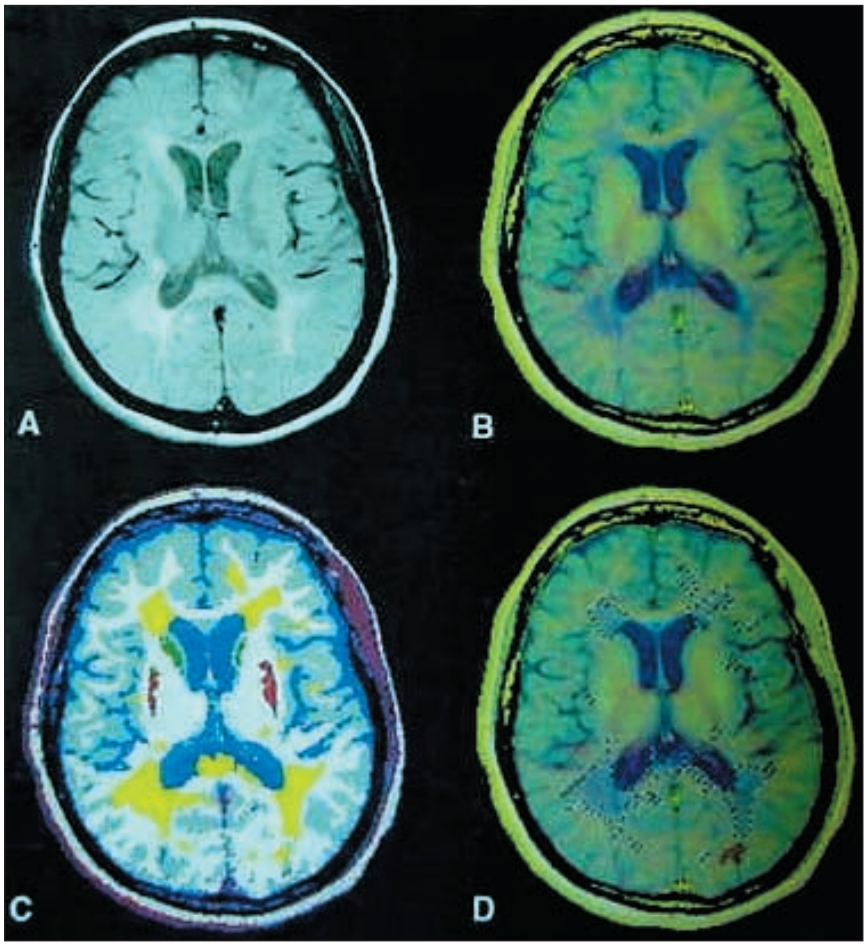

Figure 4.
Axial slice at the level of the lateral ventricles in a person with multiple sclerosis (MS). (A) Proton density-weighted image. (B) Corresponding multifeature quantitative magnetic colour image; MS lesions are violet. (C) Corresponding unsupervised segmented image; MS lesions are yellow. (D) Verification of the performance of unsupervised selection of MS lesions. This automatic program can quantify cerebrospinal fluid and ventricles (coloured blue), grey and white matter (coloured grey and white, respectively), and lesions (coloured yellow). Reproduced from reference 40 with permission.

differences in structural MRI images. It permits unbiased comparison of all areas of the brain, thus offering an opportunity to assess anatomical differences throughout the brain. Regional differences between groups can be compared and, in serial studies, a measurement of volumetric change over time can be obtained. It may be difficult to use VBM to depict changes in areas with high natural variance (e.g. the peri-Sylvian region), and aspects of the algorithm (such as registration to a template and smoothing) will decrease sensitivity to longitudinal changes. Recently, VBM was applied in patients with clinically defined early relapsing MS (mean delay from first clinical symptoms to scan, 1.8 years). Using this method, MS patients showed a significant lower grey matter (GMF), white matter (WMF) and brain parenchymal fraction (BPF) when compared with healthy subjects.[42] Lesion load as expressed by T2 hyperintense lesions and T1 hypointense lesions was inversely correlated with both BPF and GMF, but not with WMF. This suggests that pathological changes in white matter may happen

through mechanisms which are at least partly independent from obvious lesion genesis in early MS.[43]

CONCLUSION

Atrophy measurement appears to be one of the most promising methods for detecting disease progression in clinical treatment-related trials. Most of the methods presented in this review are automated and reliable, sensitive to subtle changes in brain structures, may reflect treatment effects, and may act as potential indicators of the global, long-term effects of MS on the brain. Their use may also provide information that helps to prevent or delay the neurodegenerative component of MS.

Several questions must be answered regarding the use of atrophy measurements in MS. First, it is unclear which types of methods should be applied, although a workshop* held to discuss these issues agreed that automated three-dimensional methods, obtained on whole brain, appear to be more reliable and sensitive to subtle atrophic changes. Secondly, we need to ask what role the anti-inflammatory properties of treatments play in determining the reduction in brain volume. Thirdly, we do not understand what the neurodegenerative component of MS depends on. Fourthly, we need to establish the correlation between the appearance of atrophy and focal abnormalities (lesions) in different stages of MS; and finally, we need to establish whether there is a correlation between brain atrophy and permanent disability. Answers to these questions may be obtained by performing long-term trials, because atrophy phenomena become progressively more apparent over time.

*A workshop, entitled *Measuring Atrophy in MS*, was held at the Institute of Neurology, Queen Square, London WC1N 3BG, UK, in December 2000. A detailed review article was published in *Brain*, August 2002: Miller DH, Barkhof F, Frank JA, Parker GJM, Thompson AJ. Measurement of atrophy in multiple sclerosis: pathological basis, methodological aspects and clinical relevance. *Brain* 2002; **125:** 1676–1695.

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A MULTIGENERATIONAL FAMILY WITH MS

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We report a family with 15 individuals affected with multiple sclerosis (MS) in three and possibly four generations. The segregation of MS within this pedigree is consistent with an autosomal-dominant mode of inheritance with reduced penetrance. Clinical characteristics of the affected individuals are indistinguishable from those seen in sporadic MS. Eleven of 14 cases were positive for the known MS-associated major histocompatibility complex Class II HLA DRB1*15 allele. Parametric linkage analysis gave a non-significant LOD score of 0.31 (theta; = 0.33) for the DRB1 gene. However, among 11 affected children with at least one DRB1*15 bearing parent, all 11 received at least one copy of this known susceptibility allele. A transmission disequilibrium test analysis was significant for the DRB1*15 allele within this family; P=0.0054. This inheritance pattern suggests the presence of a single major locus responsible for MS susceptibility, with DRB1 acting as an important modifier. This family could be important for the identification of an MS susceptibility gene.