Brain (1996), **119**, 2009–2019

Progressive cerebral atrophy in multiple sclerosis
A serial MRI study

N. A. Losseff,[1] L. Wang,[1] H. M. Lai,[1] D. S. Yoo,[2] M. L. Gawne-Cain,[1] W. I. McDonald,[1] D. H. Miller[1] and A. J. Thompson[1]

[1] *NMR Research Unit, Institute of Neurology, and*
[2] *Department of Medical Physics and Bio-Engineering, University College London, UK*

Correspondence to: Dr A. J. Thompson, NMR Research Unit, Institute of Neurology, Queen Square, London WC1N 3BG, UK

Summary
Recent studies of the spinal cord and cerebellum have highlighted the importance of atrophy in the development of neurological impairment in multiple sclerosis. We have therefore developed a technique to quantify the volume of another area commonly involved pathologically in multiple sclerosis: the cerebral white matter. The technique we describe extracts the brain from the skull on four contiguous 5 mm periventricular slices using an algorithm integrated in an image analysis package, and quantifies their volume. Intra-observer scan–rescan reproducibility was 0.56%. We have applied this technique serially to 29 patients with multiple sclerosis selected for an 18-month treatment trial with a monoclonal antibody against CD4+ lymphocytes (deemed clinically ineffective). A decrease in volume beyond the 95% confidence limits for measurement variation was seen in 16 patients by the end of the 18-month period. The rate of development of atrophy was significantly higher in those who had a sustained deterioration in their Kurtzke expanded disability status scale (EDSS) score compared with those who did not (respective means: –6.4 ml year^{-1} and –1.8 ml year^{-1}, $P < 0.05$) but in both groups these changes differed significantly from baseline ($P < 0.05$). Baseline T_2 lesion load, change in T_2 lesion load over 18 months and the volume of new gadolinium enhancing lesions on monthly scans for the first 10 months showed no correlation with the development of atrophy. This study demonstrates that progressive cerebral atrophy can be detected in individual patients with multiple sclerosis, correlates with worsening disability and gives additional information to that obtained with conventional MRI. The effect of putative therapies aimed at preventing disability could be objectively assessed by this measure.

Keywords: multiple sclerosis; MRI; disability; cerebral atrophy; gadolinium enhancement; lesion load; clinical measurement.

Abbreviation: EDSS = expanded disability status scale

Introduction
Recent studies have shown strong correlations between disability and both spinal cord (Losseff *et al.*, 1996*a*) and cerebellar atrophy (Davie *et al.*, 1995). The most striking example (Losseff *et al.*, 1996*a*) demonstrated a strong graded correlation between spinal cord area measured at the C2 level and the EDSS (Kurtzke, 1983), which is heavily weighted towards locomotion. Given the relationship between spinal cord dysfunction and locomotor deficit, this study underlines the importance of atrophy as a process associated with or responsible for fixed functional deficit. Another area commonly involved in multiple sclerosis is the cerebral white matter (Brownell and Hughes, 1962) and the significance of atrophic changes to this area has been, in part, addressed by studies of cerebral atrophy. These studies have given conflicting results as to the clinical significance of cerebral atrophy (Loizou *et al.*, 1982; Rao *et al.*, 1985; Hageleit *et al.*, 1987; Huber *et al.*, 1987; Comi *et al.*, 1993; Gross *et al.*, 1993), possibly because of their cross-sectional design, and the large intersubject variations in normal brain size (Blatter *et al.*, 1995). To date, there has been no definitive serial study of the measurement and significance of progressive cerebral atrophy in multiple sclerosis and the relationship of the development of atrophy to either progressive disability or MRI markers of disease activity (change in number and area of lesions and volume of gadolinium enhancing lesions). This question could be most appropriately answered by

studying the cerebral white matter, in view of the predilection for lesions at this site and its accessibility to high definition MRI.

We have developed a new technique to quantify the volume of a region of the cerebral hemispheres and have applied this to a group of 29 patients with multiple sclerosis participating in an 18-month treatment trial with a monoclonal antibody against CD4+ lymphocytes. This multicentre, phase II, double blind, placebo-controlled study was set up to evaluate the effect of sustained suppression of CD4+ T lymphocytes with the chimeric monoclonal anti-CD4 antibody cMT412 (Centocor) on disease activity as measured with gadolinium enhanced MRI. No reduction in MRI activity was seen (van Oosten *et al.*, 1996). The detailed immunological and MRI aspects of the anti-CD4 trial are the subject of other publications in preparation.

We have used the data collected at our centre during this trial to ascertain if progressive atrophy could be detected in individual patients outside the 95% confidence limits for measurement variation and if so, what the relationship was to change in disability. The relationship of atrophy to lesion load, change in lesion load and volume of gadolinium enhancement detected during this serial study was also explored.

Methods

Patients

Twenty-nine patients were included in the London arm of the anti-CD4 trial, of which 27 completed the trial. One patient dropped out because of increasing disability at month 9 and one at month 12. The inclusion criteria included: (i) clinically definite multiple sclerosis which followed a relapsing–remitting or secondary progressive course; (ii) evidence of clinically active disease (either two relapses within the 12 months prior to inclusion, one of which was in the preceding 6 months, or deterioration of at least one point on the EDSS within the preceding 18 months); (iii) current EDSS 3–7.

Exclusion criteria included primary progressive multiple sclerosis, significant cognitive impairment and treatment with corticosteroids within the last month. All patients gave informed written consent to enter the study which had been approved by the ethical committee of the National Hospital for Neurology and Neurosurgery.

MRI protocol

All imaging was performed on a Signa 1.5 T machine (General Electric, Milwaukee, Wisc., USA) using a standard quadrature head coil. Patients were imaged monthly from month −1 to month 9 and then at 12 months and 18 months with the following sequences: (i) dual echo T_2-weighted (TR = 3000 ms, TE = 30 and 80 ms); (ii) T_1-weighted (TR = 600 ms, TE = 20 ms) 10 min post-injection with gadolinium DTPA 0.1 mmol kg^{-1}.

All sequences were acquired as axial contiguous 5 mm slices, 256^2 image matrix, 24 cm field of view. Repositioning was ensured by four oblique pilots.

Clinical

At each of the above timepoints the patients underwent a full neurological and general examination by one observer (H.M.L.) who scored them on the EDSS. A definite change in EDSS was defined as progression of greater than or equal to 1 point for patients entering with a score below EDSS 5.5, or greater than or equal to 0.5 points for patients entering with a score greater than or equal to EDSS 5.5 (Goodkin, 1991). Any change had to be sustained for three months or more.

Lesion load and gadolinium volumes

The total lesion load on the mildly T_2-weighted image (SE 3000/30) was calculated at baseline and 18 months. The volume of new gadolinium enhancement was calculated on each monthly scan for the period from month 0 to month 9. These calculations were all performed, using the image display program Dispunc (D. L. Plummer, University College London, UK) with a contouring technique (Grimaud *et al.*, 1996), by one observer (H.M.L.) who was blind to the scan identity and using the image display program Dispune (D. L. Plummer, University College, London) with a contouring technique (Grimaud *et al.*, 1996).

Measurement of cerebral volume

The basis of our method has been to extract the brain from the skull and CSF spaces and to quantify the volume represented in the extracted image. Brain extraction was performed on the gadolinium enhanced T_1-weighted images for months 0, 6, 12 and 18 (for the two patients who dropped out at months 9 and 12, images were analysed for months 0, 3, 6 and 9 and 1, 4, 8 and 12, respectively) using an algorithm integrated in a window-based image analysis package (e*XK*ull © D. S. Yoo, Department of Medical Physics and Bio-Engineering, University College London, UK). Before brain extraction, the scans were examined by an experienced radiologist (M.L.G.-C.) blind to the clinical details to ensure that repositioning was satisfactory by using current accepted treatment trial criteria (Polman *et al.*, 1995). This inspection is important as progressive atrophy of areas of the brain used as landmarks for repositioning (e.g. the corpus callosum) may result in spurious movement of numbered slices. Following this, the radiologist selected four contiguous slices from each scan with the most caudal at the level of the velum interpositum cerebri. This approach was chosen as it was the most reproducible method covering the region of interest. Of the 116 scans examined, five were

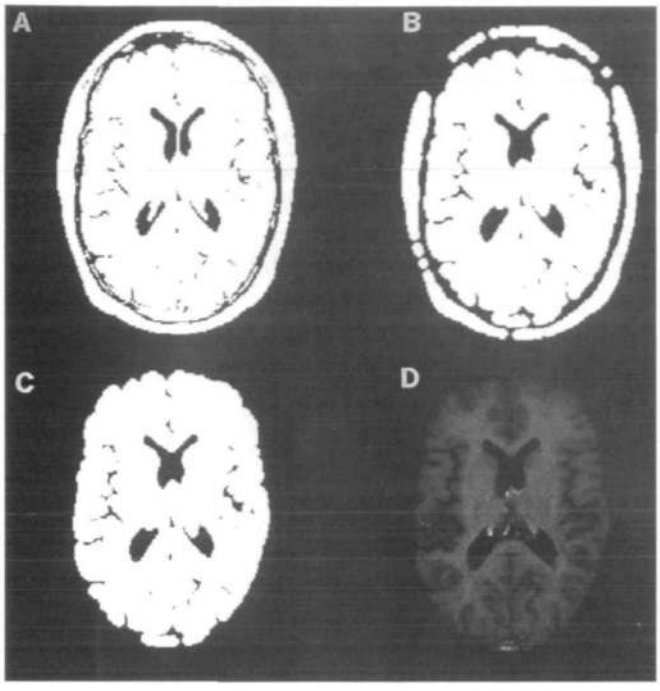

Fig. 1 A brain extraction using the e*XK*ull program. Following automatic thresholding, a binary image is produced (**A**), and the morphological opening separates the brain from the scalp and skull (**B**). The brain is determined as the largest component by connected component analysis (**C**), and finally the cerebral tissue is extracted by masking the binary brain image to the original grey image (**D**).

excluded from analysis as repositioning was considered unsatisfactory. No patient had fewer than three timepoints for analysis after rejection of unsatisfactory images. Three patients were not represented at month 18 as two had dropped out and in one other the scans were rejected as repositioning was unsatisfactory.

The cerebral tissue was extracted from the head using a method adapted from earlier work on skull segmentation (Yoo *et al.*, 1995). Our method combines histogram-based automatic thresholding with sequences of morphological operations that distinguish the brain from surrounding tissues as illustrated in Fig. 1. The following four-stage procedure was performed. (i) Automatic thresholding by discriminant analysis of the histogram: a histogram of image intensities represented in a complete slice is formed. It is then assumed that all pixels in the given slice belong to one of two classes, background or brain. Discriminant analysis searches for the optimal grey level that best separates these two classes by variance optimization. Once the optimal threshold has been found, this is applied to classify the pixels into one of two classes: background or brain, thus creating a binary image (Fig. 1A) for the next step. (ii) Morphological opening operation: the opening (dilation after erosion) is used to correct imperfections in the thresholded binary image by separating the brain from the undesired components in the head (e.g. bone, muscle and scalp) with a circular structuring element. The size of the structuring element is fixed through the whole process (Fig. 1B). (iii) Connected component analysis which consists of three main operations: (a) connection of components with non-zero pixels (the CSF spaces and areas previously occupied by tissues associated with the skull now have zero image intensity); (b) labelling and counting the connected components; (c) selecting the largest connected component as the brain (Fig. 1C).

(iv) Masking operation: the resulting binary image of the brain is masked to the original grey image and finally the brain is extracted from the head (Fig. 1D).

As T_1-weighted images were used, the CSF has grey levels close to background and is thus thresholded out. Hence, progressive enlargement of the ventricles and CSF spaces can be sensitively detected. The whole process was checked by a reviewer but in 2% of all slices the process failed, resulting in small islands of skull being left. These undesired regions were removed manually by an operator blind to the patients' identity. The process also commonly leaves extra cerebral tissue such as choroid plexus and small areas of sagittal or straight sinus enhancement. These appeared consistent in any given patient and were not removed.

Following extraction and editing the volume was calculated using in house software (Calc-Vol, L Wang, Institute of Neurology, University College London, UK) which simply counts the number of non-zero pixels remaining and multiplies them by their size. Progressive atrophy was expressed as change in millilitres per year.

Quality assurance

The method we describe would be susceptible to changes in the size of the image field of view produced by gradient fluctuations. Examination of phantom data collected during the time period of the treatment trial show that these are small (<1%), predominantly in the z-direction and random. No systematic drift was observed.

Reproducibility

We initially explored the reproducibility of different slice prescriptions from five patients with clinically definite multiple sclerosis scanned weekly for 5 weeks with an identical MRI protocol. These patients were participating in a separate study set up to ascertain if weekly scanning detects significantly more enhancing lesions than monthly scanning. We assessed scan–rescan reproducibility by comparing week 2 with week 1, week 3 with week 2, etc. in each patient, which gave a total of 20 scan–rescan observations. The assumption was that real changes in brain volume over a period of 1 week would be very small compared with apparent changes produced by measurement variation. From these patients, we ascertained that the best reproducibility containing the region of interest was obtained using four contiguous slices with the most caudal at the level of the velum interpositum cerebri, thus encompassing the lateral ventricles and associated white matter. Reproducibility was

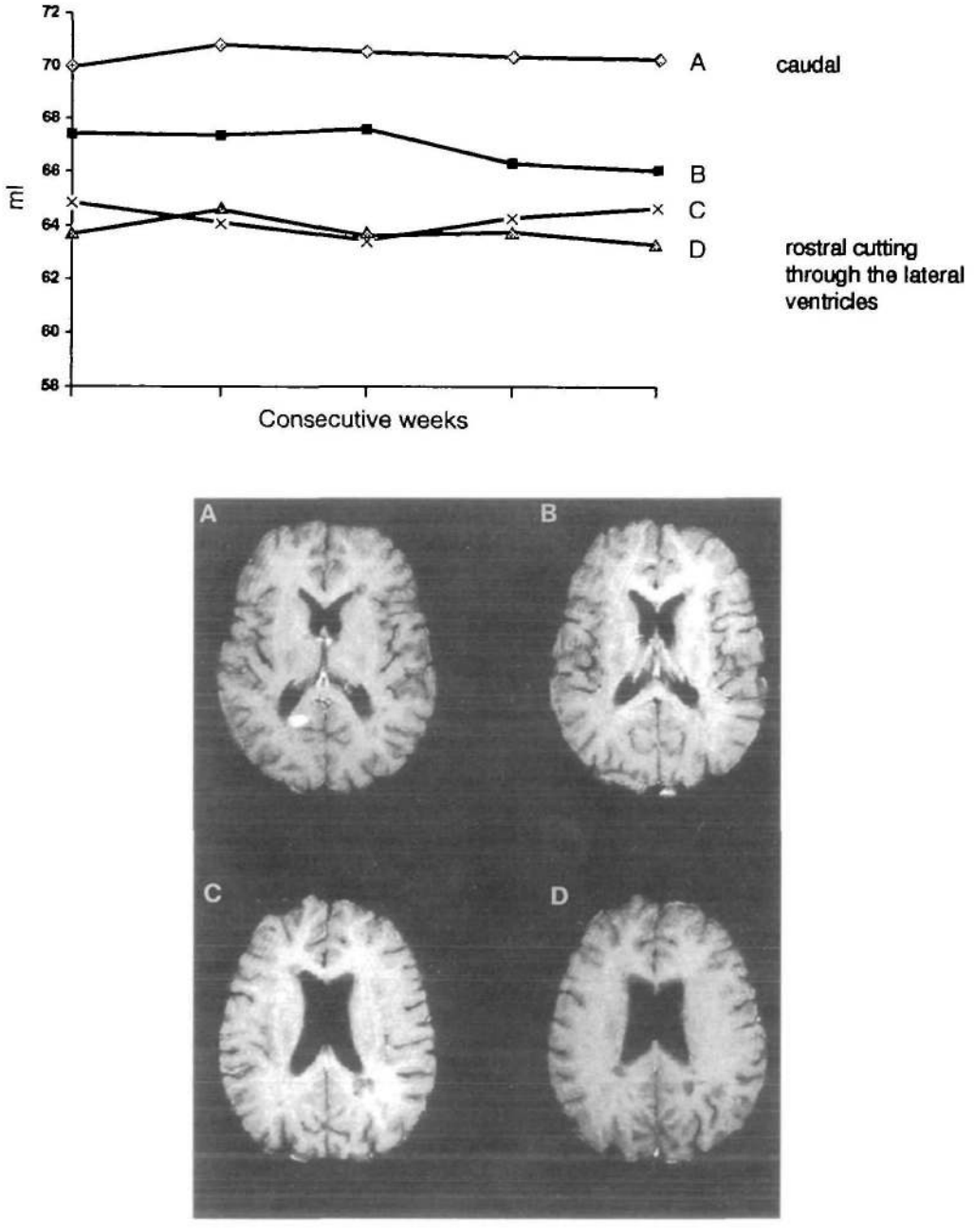

Fig. 2 Reproducibility assessed with weekly scanning. The volume of four individual slices is illustrated in a subject scanned weekly, labelled **A**, **B**, **C** and **D** with the extracted images shown below.

expressed both as the standard deviation of measurement variation (British Standards Institution, 1979) and the coefficient of variation (Goodkin *et al.*, 1992). An example of the volume of the four individual slices is illustrated in Fig. 2 for a single patient over 5 weeks.

Statistics

Paired and unpaired Students *t* test or the Mann–Whitney/Wilcoxon test was used as appropriate for group analysis. Spearman's Rank Correlation Coefficient was used to assess the relationship between baseline EDSS and cerebral volume.

Results

Reproducibility

Mean cerebral volume in the four slices for the five patients studied was 299 ml (range 265–319). For any given series of slices, the volume calculated from repeated brain extraction and non-zero pixel counting was identical. For scan–rescan

analysis, which takes into account repositioning, radiological selection and any editing, the mean coefficient of variation was 0.56% (range 0.15–1.5) with a mean standard deviation of measurement variation of 1.67 ml (range 0.4–4.5). Hence changes as little as 1.1% would be outside the 95% confidence limit for that occurring by chance due to measurement variation.

Baseline characteristics (month 0)

There were 29 patients of mean age 38 years (range 26–53 years), 13 male and 16 female, 13 had relapsing–remitting multiple sclerosis while in 16 it was secondary progressive. Mean disease duration was 8.8 years (range 1–29 years). Mean EDSS at entry was 5 (range 2–7). Mean cerebral volume in the four slices was 302 ml (range 270–346 ml). Males had significantly larger cerebral volumes than females (mean 316 ml compared with 291 ml, $P < 0.01$). There was no significant difference between the cerebral volume of the relapsing–remitting group and the secondary progressive group, though the latter group contained proportionately more men. There was no cross-sectional correlation between cerebral volume at baseline and the EDSS or its functional system subscores.

Serial results

Mean EDSS at exit for all patients was 5.9 (range 1–8.5). The mean rate of brain volume change by the end of the study for all patients was −3.4 ml year^{-1} ($P < 0.001$ comparing month 0 with exit).

In each patient, we constructed graphs illustrating their measured cerebral volume at the four time points, two examples of which are given in Fig. 3A showing change inside and outside of the 95% confidence limits for measurement variation. Four individuals had developed a significant

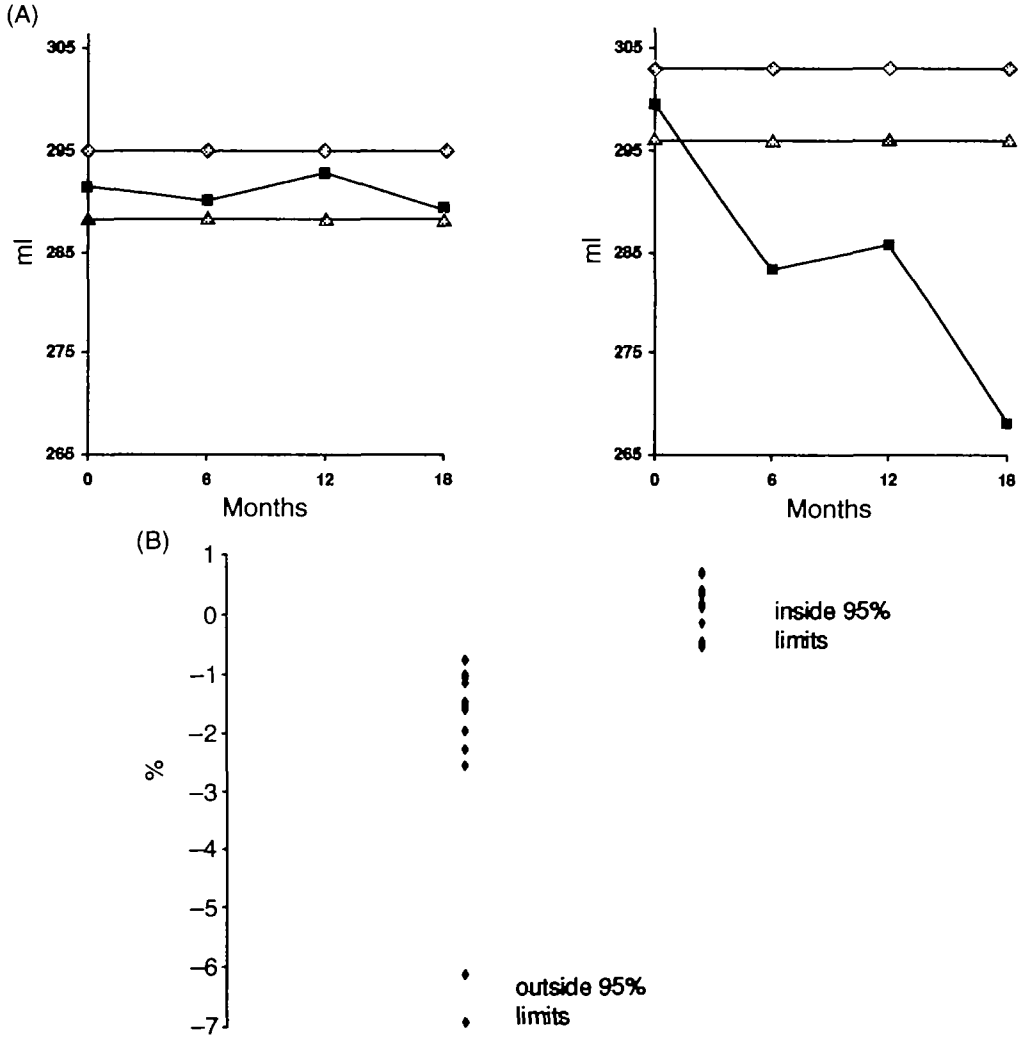

Fig. 3 (**A**) Serial measurement over 18 months. Two patterns are illustrated, showing no significant (*left*) and significant (*right*) change in two patients over 18 months. The straight lines mark the 95% confidence limits for measurement variation. (**B**) Change per year in all patients.

Table 1 *Clinical and MRI characteristics stratified by the development of progressive atrophy*

	Definite cerebral volume change	No definite volume change	*P*
Numbers	16	13	
Mean age (years)	38	39	0.7
(range)	(32–50)	(26–53)	
Sex (male, female)	8 M, 8 F	5 M, 8 F	0.8
Disease subtype	11 SP, 5 RR	5 SP, 8 RR	0.2
Mean disease duration (years)	9	8	
(range)	(2–29)	(1–26)	0.4
Mean baseline EDSS: month 0	5.4	4.9	
(range)	(3.5–7)	(2–7)	0.2
Mean exit EDSS	6.6	5	
(range)	(3–8)	(1–8.5)	<0.01
Mean baseline cerebral volume (ml)	298	309	
(range)	(269–345)	(271–377)	0.18
Mean baseline T_2 lesion load: month 0 (ml)	53	32	
(range)	(13–161)	(2–97)	0.06
Mean change in T_2 lesion load (month 18) (ml)	+6.3	+0.8	
(range)	(−17 to 41)	(−6 to 9) 0.31	
Mean detected new gadolinium volume (ml) (months 0–9)	6.7	4	
(range)	(0.47–34)	(0.2–14)	0.6

Range for 'definite cerebral volume change' = −2.3 to −21 ml year^{-1} and for 'no definite volume change' = +2.1 to −1.9 ml year^{-1}.
SP = secondary progressive; RR = relapsing–remitting.

reduction in brain volume by 6 months, eight by 12 months and 16 by 18 months. Both patients who dropped out had a significant reduction in brain volume by 3 and 4 months, respectively. The remaining 13 patients did not show individual change outside the measurement variation at 18 months.

There were five occasions out of a total of 109 separate timepoints in which the upper limit for measurement variation was exceeded (none at 18 months) compared with 44 separate occasions in which the lower limit was exceeded. We have stratified patients into two groups: those who did (n = 16) or did not (n = 13) develop change outside of the 95% confidence limits for measurement variation at the end of the study. The change in cerebral volume in % is illustrated for these two groups in Fig. 3B and their full clinical and MRI characteristics are described in Table 1. Patients in whom progressive atrophy was detected were more likely to have secondary progressive multiple sclerosis (11 out of 16) and tended to have smaller brains at entry, though this was not statistically significant. A significant change in EDSS score ($P < 0.05$) was seen in the group with progressive atrophy and this group had a slight tendency toward greater disability at baseline (mean EDSS 5.4 compared with 4.9 for the group without progressive atrophy, P = 0.2). These changes in EDSS were not accounted for by the acute effects of a relapse. Of the group in whom we detected progressive atrophy eight out of 16 had a sustained change in EDSS while in the group which did not have progressive atrophy only two out of 13 had a sustained change. The 10 patients who had a sustained change in EDSS had a significantly higher rate of progressive atrophy when compared with the group without a sustained EDSS change (–6.4 ml year^{-1} compared with –1.8 ml year^{-1}, respectively, $P < 0.05$). However, both groups showed a significant change in cerebral volume from baseline ($P < 0.05$) (Fig. 4).

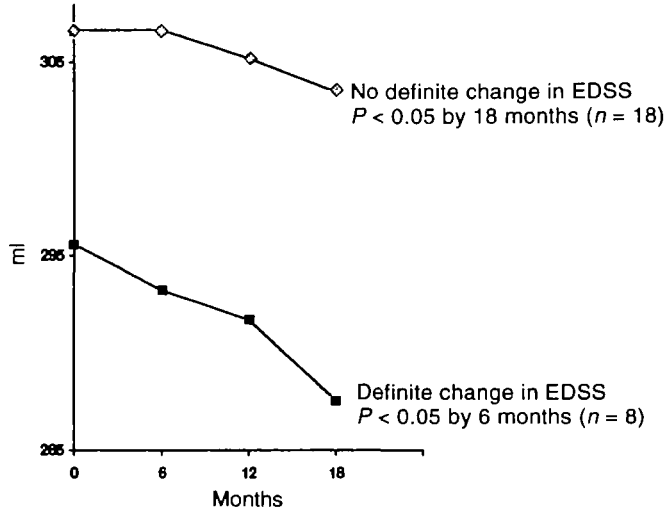

Fig. 4 Mean decrease in cerebral volume over 18 months stratified by a definite sustained change in EDSS. Three patients are excluded as there were no measurements in month 18.

Baseline T_2 lesion load, T_2 lesion load changes (over 18 months) and gadolinium volumes (over 10 months) did not correlate with progressive atrophy (millilitres per year) but there were trends suggesting a higher baseline lesion load (P = 0.06), greater change in lesion load and higher volumes of gadolinium enhancement in the group that developed progressive atrophy. As gadolinium volumes were only measured for the first 10 months, we also examined their relationship to the development of atrophy between 0 and

12 months, but no significant correlation was found. Development of marked atrophy was seen both in patients who had minimal gadolinium enhancement detected over the initial 10 months and those with intense activity (Fig. 5). Gadolinium volumes were significantly higher for the group that had a definite sustained change in EDSS ($P < 0.05$) and there were trends to suggest a higher baseline T_2 lesion load and change in T_2 lesion load in this group.

The mean rate of development of atrophy in those who received anti-CD4 antibodies was −3.6 ml year^{-1} and in those who received placebo was −3.1 ml year^{-1} ($P = 0.77$).

Discussion

This is the first study to demonstrate progressive cerebral atrophy by serial MRI scanning in individual patients with multiple sclerosis. The results suggest that atrophy correlates with worsening disability and, although it may be present in patients who do not have measurably increasing disability, it progresses at a significantly slower rate than in those who do. These findings suggest that this measure is clinically relevant, gradable, objective and practical enough for inclusion in treatment trials. It may also have greater sensitivity in detecting clinically relevant changes than some currently used disability scales and MRI measures.

The presence of cerebral atrophy in excess of what might be expected for age is well described in multiple sclerosis both with CT and MRI (Loizou *et al.*, 1982; Noseworthy *et al.*, 1984; Rao *et al.*, 1985; Hageleit *et al.*, 1987; Huber *et al.*, 1987; Comi *et al.*, 1993; Gross *et al.*, 1993). However, investigators have differed in their interpretation of the clinical significance of such changes. Most studies have specifically investigated the relationship between cerebral atrophy and dementia in a cross sectional design and of these some have found a positive correlation (Rao *et al.*, 1985; Comi *et al.*, 1993) and others a weak correlation or trend (Hageleit *et al.*, 1987; Huber *et al.*, 1987). More recently, a CT study (Gross *et al.*, 1993) has suggested that the development of brain atrophy early in the course of the disease is a poor prognostic sign in relation to the development of disability and identified a 'malignant' subgroup with detectable atrophy on CT within a year of diagnosis. In the present study we have detected early progressive atrophy in five out of 13 relapsing–remitting patients with a mean disease duration of 7.2 years (range 2–12 years).

Relationship of atrophy to disability

There is growing evidence that atrophy *per se* is a clinically relevant entity in multiple sclerosis and this has been demonstrated by studies of functionally sensitive areas such as the spinal cord (Losseff *et al.*, 1996*a*) and the cerebellum (Davie *et al.*, 1995) in which atrophy has been correlated with locomotor dysfunction and ataxia, respectively. It seems unlikely that progressive cerebral atrophy is the primary cause of worsening motor disability as measured by the EDSS; in this regard, changes in the spinal cord are likely to be more relevant. However, it is a process which runs in parallel with clinical disease progression and is therefore a sign of poor prognosis. We have not had the opportunity to analyse the relationship between cerebral atrophy and progressive cognitive impairment as the only data available is the Kurtzke functional system mental score, which is very limited and has poor reliability (Francis *et al.*, 1991). In addition, patients with significant cognitive impairment were excluded from the trial. Previous investigators have demonstrated a relationship between serial psychometry and change in MRI lesion load (Feinstein *et al.*, 1993), hence future investigation with regard to atrophy will be of considerable interest.

It is now well recognized that most current imaging techniques are poorly predictive of outcome and the development of disability. There is thus a need to include imaging methods into treatment trials that clearly relate to the development of disability and that give additional information to conventional MRI measures. Our present and previous investigations (Davie *et al.*, 1995; Losseff *et al.*, 1996*a*) suggest that measurement of atrophy of the brain and spinal cord provides such indices.

Measurement of cerebral atrophy

The technique described is relatively simple to apply, has high serial reproducibility and is not time consuming. We chose this particular slice prescription for a number of reasons. First, slices below the level of the velum interpositum cerebri commonly include orbital tissue which interferes with the extraction necessitating extensive manual editing. Secondly, the most rostral of the selected slices tends to be situated at the level of the roof of the lateral ventricles. Beyond this point, the increasing convexity of the brain means that small changes in positioning lead to large changes in measured volume, reducing reproducibility. However in slices positioned through the ventricles even where the brain surface is becoming convex, there is little change in measured volume with repositioning: it appears that as the brain circumference gets smaller, so do the ventricles and hence the measured volume remains relatively constant (*see* Fig. 2) with small positioning changes. Thirdly, this area is a very common site for disease activity and for the development of atrophy, evidenced both as ventricular and sulcal enlargement (*see* Fig. 5). Sensitivity to detect change is thus maximized. Gadolinium enhanced T_1-weighted scans were chosen for two reasons. Firstly, the grey level of CSF is close to background and hence automatically thresholded out. Secondly, this type of imaging forms an essential part of ongoing treatment trials in multiple sclerosis (Polman *et al.*, 1995). Administration of gadolinium results in small amounts of sinus enhancement but this is consistent across time in any given patient. Ideally, in future studies, non-gadolinium enhanced scans should be used and the

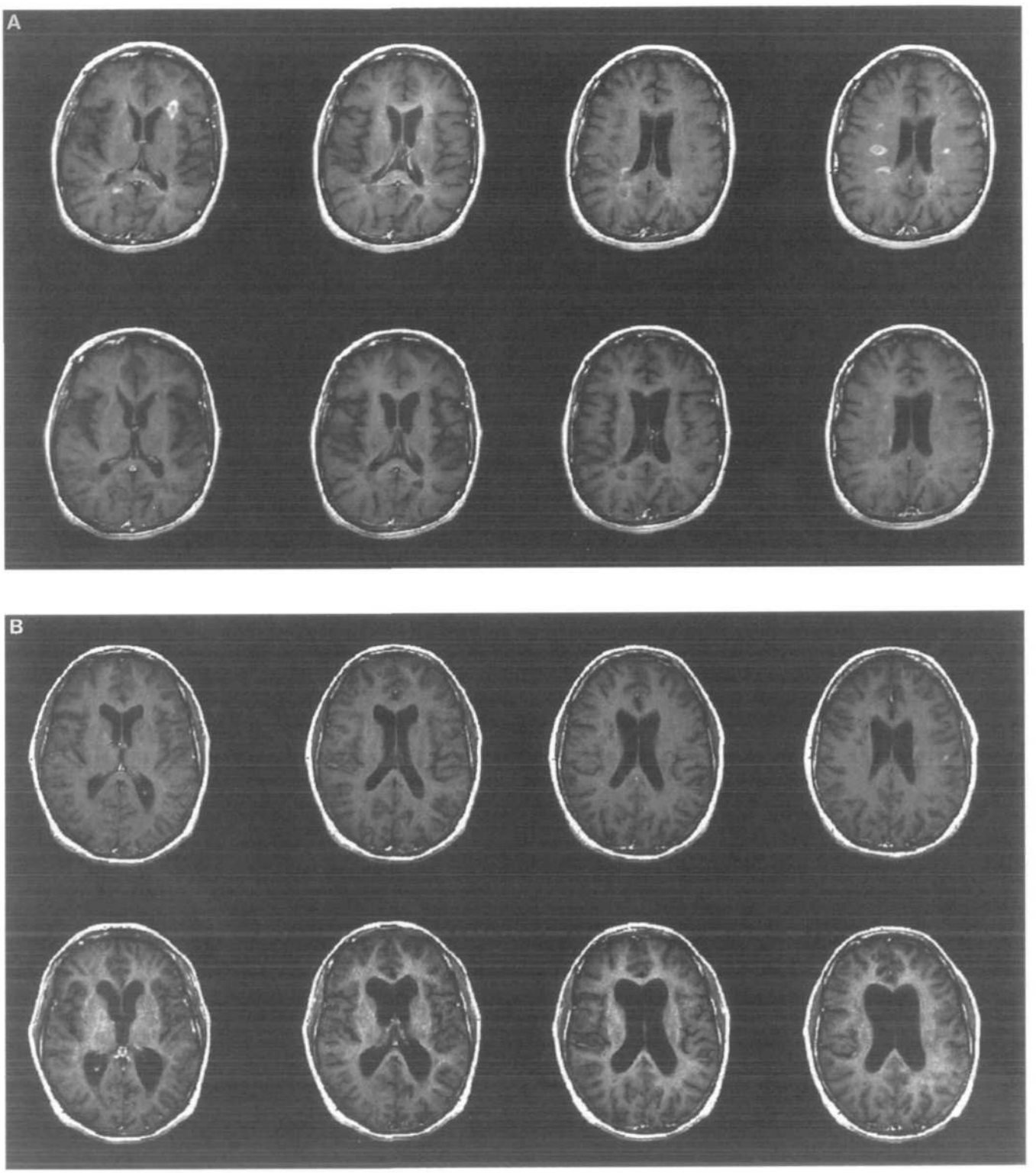

Fig. 5 Development of cerebral atrophy. **(A)** Matched scans from month 0 (*top row*) and month 9 (*bottom row*). A patient with marked enhancement detected shows changes in the ventricles and sulci over the 9-month period. The volume of new gadolinium enhancement detected over month 0–9 was 34 ml. **(B)** Matched scans from month 0 (*top row*) and month 18 (*bottom row*). This patient had minimal enhancement detected at month 0 (0.4 ml) and none during months 1–9, 12 and 18. There is marked dilation of the ventricles over 18 months with increased differentiation of the grey/white matter. The atrophy had evolved gradually with a graded increase evident at months 6 and 12.

technique could further be improved by volume acquisition. This would overcome repositioning errors, probably the major factor affecting reproducibility, and may allow segmentation of the white and grey matter as they would have better differentiation. The high reproducibility allows changes in individual patients to be categorized with some degree of confidence. However it is important to be aware of the fact that there may be a difference between short-term reproducibility as defined in the study of patients scanned weekly and long-term reproducibility, when other factors, such as gradient drift and the effects of normal ageing, need to be considered.

Pathological implications

The underlying pathological mechanism of atrophy has been discussed previously (Losseff *et al.*, 1996*a*) and the most potent contributor is probably axonal loss, a likely underlying cause of fixed functional deficit in multiple sclerosis. In our patients we have seen that atrophy is the result of both ventricular and sulcal enlargement (Fig. 5) but the extent to which grey matter involvement contributes to this sulcal change is uncertain without formal measurement. The changes we have observed in most patients are diffuse and symmetrical but in some the ventricles are enlarged with a degree of asymmetry unexpected from normal biological variation, suggesting a focal pathology. We have occasionally noted the presence of periventricular T_1 hypointense lesions at the tips of the lateral ventricular horn, the functional significance of which has been discussed recently (van Walderveen *et al.*, 1995) but we have not been able to follow the direct evolution of a hypointense lesion to 'atrophy' over this time period. It seems possible that these hypointense lesions may (in some cases) be an intermediate stage in the development of atrophy, as current evidence suggests they have less tissue structure than lesions visualized by T_2-weighted imaging only. Atrophy is only detectable by observing change at the edges of the brain and spinal cord with the CSF spaces. This suggests that the CNS responds to tissue destruction by contracting and reorganizing itself to fill areas devoid of tissue due to previous damage. If so, considerable tissue destruction may occur but not appear as a focal abnormality.

It is also important to be aware of other factors that may influence cerebral volume such as excessive alcohol intake (Ron *et al.*, 1982), anorexia (Kohlmeyer *et al.*, 1983), corticosteroid administration (Bentson *et al.*, 1978) and acute dehydration (Mellanby and Reveley, 1982). None of the patients in the trial had evidence of severe dehydration, malnutrition or alcohol abuse as evidenced by clinical examination, normal blood urea and electrolytes, albumin and liver enzymes. Eight patients received intravenous methylprednisolone (1 g once daily for 3 days) but no steroids were given within a month of any scan. The rate of progressive atrophy in those patients who received steroids was not significantly different from those who did not. It is also possible that the anti-CD4 antibodies may have distorted the natural history of the development of atrophy either by influencing disease activity or by a direct effect on brain volume. This seems unlikely in view of the overall similarity between treated and untreated groups. In addition we have no control group (as the imaging analysis was post-gadolinium) and hence we cannot be sure what contribution normal ageing makes over this time period. A study using a similar technique to ours and examining the effect of ageing from the third to the eighth decade (in a cross-sectional design) has quantified the cerebral volume represented in seven 5 mm slices with the most caudal slice just above the orbits (Pfefferbaum *et al.*, 1994). An average decrease in cortical grey matter volume of 0.7 ml $year^{-1}$, stable cortical white matter volumes and an increase in ventricular CSF of 0.3 ml $year^{-1}$ was found. Given that the volume of brain examined in the earlier study is far greater than that represented in our technique, it seems unlikely that normal ageing makes a significant difference to our findings. All serial studies would be subject to ageing effects and this would not influence the fact that atrophy develops at a significantly higher rate in those with worsening disability.

Relationship to other MRI parameters

The group who developed atrophy had a slightly smaller cerebral volume at baseline (despite having proportionately more men). However this was not significant but may reflect the fact that this group was more disabled at baseline and that the atrophic process was already established. The lack of a strong relationship between atrophy and other MRI measures of disease activity, such as gadolinium enhancing lesion volume, T_2 lesion load or change in T_2 lesion load is of particular interest. There are at least three possible reasons for this. First, the extent and duration of enhancement (indicating blood–brain barrier breakdown) may not always result in the same degree of tissue destruction. Secondly, we do not know the precise pathophysiology of atrophy and its temporal relationship to episodes of blood–brain barrier breakdown. Thirdly, we have examined the relationship of enhancement over 10 months to the development of atrophy over 12 and 18 months. It is possible that this is misleading and that the development of atrophy may be a response to events that have occurred some time before or after the period of scanning with gadolinium. Nevertheless current opinion favours the view that the greater the activity (as evidenced by gadolinium enhancement) the worse the prognosis with regard to the development of disability. This is supported by a recent study suggesting that the frequency of gadolinium enhancing lesions detected over a 6-month period in a group of secondary progressive patients was predictive of increase in disability measured 5 years later (Losseff *et al.*, 1996*b*) and the fact that, in the present study, gadolinium volumes were significantly higher for those who developed a definite sustained EDSS change; an observation similar to a previous study (Smith *et al.*, 1993). To detect gadolinium enhancement visually one needs sufficient

contrast from surrounding tissues. Of interest is the observation that one of the patients illustrated in Fig. 5 displays a diffuse change in the grey–white matter differentiation over 18 months (G. Du Boulay, personal communication) despite no focal enhancing lesions having been detected during months 1–9, month 12 and month 18. One possible explanation for this is the presence of diffuse enhancement which we are not including in the measurement of gadolinium volumes.

However, in this study we have observed patients who have progressive atrophy and disability despite absent or minimal MRI activity. A previous study (Kidd *et al.*, 1996) has made a similar observation. Hence current MRI activity measures may not be reflecting or predicting all functionally relevant pathological change.

Both baseline T_2 lesion load and change in T_2 lesion load over 18 months showed trends towards increased volume and change in volume for the group who subsequently developed atrophy. This trend was strongest for baseline T_2 lesion load but was not statistically significant ($P = 0.06$). It is possible that the development of atrophy may interfere with the serial measurement of lesion load, by changes in brain structure affecting repositioning and by 'loss' of existing lesions which become part of the CSF spaces. This seems unlikely unless progressive atrophy is extreme, as seen in Fig. 5.

Progressive cerebral atrophy was a frequent finding in this study of patients selected for a treatment trial, it may be detected in individual patients over a short period of time and may appear at an early stage in the disease. Cerebral atrophy may develop at a rapid rate, despite the static appearance of the patients measured disability and absent MRI activity. Our results suggest that the technique we have used to measure cerebral atrophy is objective and yields clinically relevant information of prognostic value. It would be possible to apply this technique in currently ongoing treatment trials and completed trials of putative agents for the treatment of multiple sclerosis. To date analysis in these trials has focused on lesion load, MRI activity measures (Miller *et al.*, 1996) and assessment of locomotor disability. A reliable method for the measurement of atrophy may yield more relevant information with regard to changes of functional significance. It may also allow us to further elucidate the relationships between inflammation and tissue destruction in multiple sclerosis.

Acknowledgements

We wish to thank David MacManus, Stephanie Webb and Helen Gallagher for carrying out all the imaging, to Dr Gareth Barker and Stephanie Webb for examination of the phantom data and to Dr Nick Silver for allowing us to study his weekly patients. We are also very grateful for the helpful advice and comments of Professor George Du Boulay and Dr Paul Tofts. The NMR Research Unit is supported by a generous grant from the Multiple Sclerosis Society of Great Britain and Northern Ireland. N.A.L. is supported by the Brain Research Trust.

References

Bentson J, Reza M, Winter J, Wilson G. Steroids and apparent cerebral atrophy on computed tomography scans. J Comput Assist Tomogr 1978; 2: 16–23.

Blatter DD, Bigler ED, Gale SD, Johnson SC, Anderson CV, Burnett BM, et al. Quantitative volumetric analysis of brain MR: normative database spanning 5 decades of life. AJNR Am J Neuroradiol 1995; 16: 241–51.

British Standards Institution. Precision of test methods I: guide for the determination and reproducibility for a standard test method (BS 5497, part 1). London: British Standards Institution, 1979.

Brownell B, Hughes JT. The distribution of plaques in the cerebrum in multiple sclerosis. J Neurol Neurosurg Psychiatry 1962; 25: 315–20.

Comi G, Filippi M, Martinelli V, Sirabian G, Visciani A, Campi A, et al. Brain magnetic resonance imaging correlates of cognitive impairment in multiple sclerosis. J Neurol Sci 1993; 115 Suppl: S66–S73.

Davie CA, Barker GJ, Webb S, Tofts PS, Thompson AJ, Harding AE, et al. Persistant functional deficit in multiple sclerosis and autosomal dominant cerebellar ataxia is associated with axon loss. Brain 1995; 118: 1583–92.

Feinstein A, Ron M, Thompson A. A serial study of psychometric and magnetic resonance imaging changes in multiple sclerosis. Brain 1993; 116: 569–602.

Francis DA, Bain P, Swan AV, Hughes RAC. An assessment of disability rating scales used in multiple sclerosis. Arch Neurol 1991; 48: 299–301.

Goodkin DE. EDSS reliability [letter; comment]. Neurology 1991; 41: 332. Comment on: Neurology 1990; 40: 971–5.

Goodkin DE, Ross JS, Medendorp SV, Konecsni J, Rudick RA. Magnetic resonance imaging lesion enlargement in multiple sclerosis. Disease-related activity, chance occurrence, or measurement artifact? Arch Neurol 1992; 49: 261–3.

Grimaud J, Lai M, Thorpe J, Adeleine P, Plummer D, Barker G, et al. Quantification of MRI lesion load in multiple sclerosis: a comparison of three computer-assisted techniques. Magn Reson Imaging 1996. In press.

Gross KR, Tomberg TA, Kokk AA, Kaasik AE. [The prognosis of multiple sclerosis: computed tomographic comparisons]. [Russian]. Zh Nevropatol Psikhiatr Im S S Korsakova 1993; 93: 32–5.

Hageleit U, Will CH, Seidel D. Automated measurements of cerebral atrophy in multiple sclerosis. Neurosurg Rev 1987; 10: 137–40.

Huber SJ, Paulson GW, Shuttleworth EC, Chakeres D, Clapp LE, Pakalnis A, et al. Magnetic resonance imaging correlates of dementia in multiple sclerosis. Arch Neurol 1987; 44: 732–6.

Kidd D, Thorpe JW, Kendall BE, Barker GJ, Miller DH, McDonald WI, et al. MRI dynamics of brain and spinal cord in progressive multiple sclerosis. J Neurol Neurosurg Psychiatry 1996; 60: 15–19.

Kohlmeyer K, Lehmkuhl G, Poutska F. Computed tomography of anorexia nervosa. AJNR Am J Neuroradiol 1983; 4: 437–8.

Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 1983; 33: 1444–52.

Loizou LA, Rolfe EB, Hewazy H. Cranial computed tomography in the diagnosis of multiple sclerosis. J Neurol Neurosurg Psychiatry 1982; 45: 905–12.

Losseff NA, Webb SL, O'Riordan JI, Page R, Wang L, Barker GJ, et al. Spinal cord atrophy and disability in multiple sclerosis: a new reproducible and sensitive MRI method with potential to monitor disease progression. Brain 1996a; 119: 701–8.

Losseff NA, Kingsley DPE, McDonald WI, Miller DH, Thompson AJ. Clinical and magnetic resonance imaging predictors of disability in primary and secondary progressive multiple sclerosis. Multiple Sclerosis 1996b; 1: 218–22.

Mellanby AR, Reveley MA. Effects of acute dehydration on computerized tomographic assessment of cerebral density and ventricular volume [letter]. Lancet 1982; 2: 874.

Miller DH, Albert PS, Barkhof F, Francis G, Frank JA, Hodgkinson S, et al. Guidelines for the use of magnetic resonance techniques in monitoring the treatment of multiple sclerosis. Ann Neurol 1996; 39: 6–16.

Noseworthy JH, Paty DW, Ebers GC. Neuroimaging in multiple sclerosis. Neurol Clin 1984; 2: 759–77.

Pfefferbaum A, Mathalon DH, Sullivan EV, Rawles JM, Zipursky RB, Lim KO. A quantitative magnetic resonance imaging study of changes in brain morphology from infancy to late adulthood. Arch Neurol 1994; 51: 874–87.

Polman CH, Dahlke F, Thompson AJ, Ghazi M, Kappos L, Miltenburger C, et al. Interferon beta-1b in secondary progressive multiple sclerosis—outline of the clinical trial. Multiple Sclerosis 1995; 1 Suppl. 1: S51-S54.

Rao SM, Glatt S, Hammeke TA, McQuillen MP, Khatri BO, Rhodes AM, et al. Chronic progressive multiple sclerosis. Relationship between cerebral ventricular size and neuropsychological impairment. Arch Neurol 1985; 42: 678–82.

Ron MA, Acker W, Shaw GK, Lishman WA. Computerized tomography of the brain in chronic alcoholism: a survey and follow-up study. Brain 1982; 105: 497–514.

Smith ME, Stone LA, Albert PS, Frank JA, Martin R, Armstrong M, et al. Clinical worsening in multiple sclerosis is associated with increased frequency and area of gadopentetate dimeglumine-enhancing magnetic resonance imaging lesions. Ann Neurol 1993; 33: 480–9.

van Oosten BW, Lai M, Hodgkinson S, Barkhof F, Miller DH, Moseley IF, et al. Treatment of multiple sclerosis with the monoclonal anti-CD4 antibody cM-T412: results of a randomized, double-blind, placebo-controlled, MR-monitored phase II trial. Neurology 1996. In press.

van Walderveen MA, Barkhof F, Hommes OR, Polman CH, Tobi H, Frequin ST, et al. Correlating MRI and clinical disease activity in multiple sclerosis: relevance of hypointense lesions on short-TR/shortTE (T_1-weighted) spin-echo images. Neurology 1995; 45: 1684–90.

Yoo DS, Lemieux L, Arridge SR, Tofts PS. Segmentation of skull contours in MR head images. Proc Soc Magn Res 1995; 2: 707.

Received April 16, 1996. Revised July 29, 1996.
Accepted August 5, 1996