THE ROLE OF NMR IMAGING IN THE ASSESSMENT OF MULTIPLE SCLEROSIS AND ISOLATED NEUROLOGICAL LESIONS

A QUANTITATIVE STUDY


(From the Institute of Neurology and The National Hospitals, Queen Square, London)

SUMMARY

The form and distribution of MRI abnormalities in 114 patients with clinically definite multiple sclerosis (MS) have been compared with observations on 53 apparently healthy individuals, 129 patients with isolated focal neurological lesions with which MS often presents (51 patients with optic neuritis, 44 with isolated brainstem lesions and 34 with isolated spinal cord syndromes) and 105 patients with disorders which may be confused clinically or radiologically with MS. The latter comprised 55 patients with cerebral vascular disease (including 7 cases of dementia with diffuse white matter disease), 24 with degenerative ataxic disorders, 8 with cerebellar tonsillar ectopia, 7 with sarcoidosis and 11 with a variety of other disorders.

Periventricular abnormalities were found in all but 2 patients with MS and discrete white matter lesions in all but 12. Characteristically the periventricular changes in MS were irregular in outline. Periventricular abnormalities which were often milder and of smooth outline were seen in 37/55 patients with cerebral vascular disease, 9/24 with cerebellar degeneration, 5/7 with sarcoidosis and in 2/3 apparently healthy individuals over the age of 60. The appearances in the 7 cases of dementia resembled those with advanced MS.

Cerebellar and/or brainstem atrophy characteristic of the cerebellar degenerations, in the absence of white matter abnormalities, was helpful in making the distinction from MS. Congenital anomalies and tumours in the region of the brainstem and foramen magnum were readily shown.

More than half the patients with symptoms attributable to isolated focal neurological lesions had additional lesions at presentation. MS cannot be diagnosed in these cases at presentation, but repeat scans after 5 to 20 months in 25 patients with optic neuritis and 10 with clinically isolated brainstem lesions have shown new lesions in 7 (20%). The patients with new lesions fulfil the criteria for clinically probable MS (Poser et al., 1983).

Measurements of $T_1$ and $T_2$ in vivo permitted the distinction of acute from chronic brainstem lesions. There were quantitative differences in $T_1$ and $T_2$ between the normal appearing white matter

Correspondence to: Professor W. I. McDonald, Institute of Neurology, Queen Square, London WC1N 3BG.
INTRODUCTION

The demonstration by Young et al. (1981) that nuclear magnetic resonance (NMR) imaging (MRI) is very sensitive in detecting lesions in patients with multiple sclerosis (MS) has had a major impact on the way in which patients suspected of having the disease are assessed. The original observations have been widely confirmed and it is clear that MRI is superior to other imaging techniques in demonstrating abnormalities (Young et al., 1981; Lukes et al., 1983; Runge et al., 1984; Ormerod et al., 1986a). In defining the clinical role of MRI, several questions need to be answered. What is the form and distribution of the abnormalities in MS? Are they specific? What do the abnormalities represent pathologically? What can MRI tell us about patients presenting with symptoms attributable to isolated focal lesions of the type seen in MS (hereafter referred to as isolated lesions)? What is the sensitivity of MRI relative to evoked potential methods in detecting lesions in various parts of the central nervous system?

We have addressed these questions by systematically investigating 401 individuals of whom 53 were healthy controls, 114 had clinically definite MS, 129 had isolated lesions of the kind with which MS can present (optic neuritis, brainstem or spinal cord syndromes), and 105 had a variety of conditions which may be confused clinically or radiologically with MS, including cerebral vascular disease (inflammatory and noninflammatory), intracranial sarcoidosis, cerebellar degeneration and congenital anomalies and tumours in the region of the foramen magnum, brainstem and spinal cord. Some aspects of this work based on smaller numbers of cases have been reported previously (Ormerod et al., 1984; Ormerod et al., 1986a, b, c). In this paper we review our experience of MS and the various control groups, and present serial observations on patients with isolated lesions; in addition we describe the results of an investigation of the relationship between images of postmortem brain and the form and distribution of the lesions in MS.

METHODS

Imager

The NMR imager in this study was a 0.5 Tesla Picker superconducting system which was used to form proton NMR images. A few observations were performed at a lower field (0.25 Tesla). The sequences and methods described pertain to the higher field. Following upgrade to 0.5 Tesla a number of further alterations in hardware and software resulted in a progressive improvement in image quality. These include enhanced performance in radiofrequency (RF) transmitter, frequency synthesizer (for generation of RF pulse), gradient coils, and surface receiver coils.

Brain images were all obtained using the standard head receiver coil as supplied by the manufacturer. For imaging of the optic nerve and spinal cord, closely applied surface coils were used (Axel,
1984; Bydder et al., 1985a). These coils were initially made by one of the authors (G.J.) and later supplemented by others made by the manufacturer. Surface coils give improved signal-to-noise ratio and hence permit improved spatial resolution images of specified local areas.

**Sequences**

We aimed to image as much of the brain as possible and to identify the maximum number of lesions. Multislice imaging protocols making images in the axial (transverse) plane were employed. In this way either 8 or 16 slices of 10 mm thickness and 2 mm interslice separation were examined. Later software improvements allowed the use of contiguous 10 and 5 mm slices. For imaging the spinal cord and optic nerve 5 mm slices were used either as single slice imaging or as part of the multislice protocol.

An imaging matrix of 128 x 256 was routinely employed, giving pixel dimensions of approximately 2.4 mm x 1.2 mm. For some studies, particularly of the spinal cord and optic nerve, a higher resolution (256 x 256) matrix was used, resulting in a pixel size of 1.2 mm x 1.2 mm. Each line of data collection was subject to 2 averages.

For head imaging, spin-echo (SE) and inversion-recovery (IR) sequences were used. The nomenclature for SE and IR scans are SE\(_{TR/TE}\) and IR\(_{TR/TI/TE}\), respectively, where the repetition time \(T_R\), the inversion time \(T_I\), and the echo time \(T_E\), are defined as in the glossary of NMR terms of the American College of Radiologists (American College of Radiology, Subcommittee on NMR Nomenclature and Phantom Development, 1984). On the SE sequences, lesions appear as areas of increased signal (white) relative to the underlying brain. As many of the lesions were periventricular in site their detection was facilitated by employing sequences whose imaging parameters were such that the lesions were of the highest signal and white matter was of higher signal than CSF. As the echo time of the sequence is increased the CSF tends to change from being of low signal (black) to higher signal (white), thereby potentially obscuring the periventricular lesions. Although these longer echo sequences were often less useful for identifying periventricular lesions, they sometimes enabled discrete lesions within the cerebral white matter to be visualized more easily.

With inversion-recovery sequences (apart from Short T\(_I\) Inversion Recovery (STIR) sequences, see below) the lesions appear of lower signal than brain (black), as does CSF. As a result, small periventricular lesions may be undetected and simply mistaken for partial volume artefacts around the margins of the ventricles.

No single sequence was optimal for demonstrating all the lesions (see fig. 1); this has also been the experience of other groups (Runge et al., 1984), and probably reflects differences in the water content (water proton density) and relaxation time (see Discussion) of the lesions. The use of more than one sequence, with differing dependence on \(T_I\) and \(T_2\) for the generation of contrast, allows the maximum number of lesions to be detected when multislice imaging is used with each of the sequences.

Optic nerve images were obtained using the modified IR sequence STIR (Bydder et al., 1985b) in which the signal from orbital fat is suppressed but the contrast between lesions and the surrounding optic nerve is enhanced.

For the spinal cord a variety of sequences was used. For demonstrating anatomical relationships, cord size and shape and structural abnormalities in the region of the foramen magnum, an SE\(_{500/40}\) sequence was employed. For demonstrating lesions within the cord itself sequences were used with a variety of echo times (\(T_E\) 60 ms, 80 ms, 120 ms) and repetition times (\(T_R\) 1000 ms, 1500 ms, 2000 ms).

**Measurement of \(T_1\) and \(T_2\)**

In many patients calculated images of the NMR relaxation times, \(T_1\) and \(T_2\) were formed. Algorithms supplied by the manufacturer were used to calculate these images from two SE scans and one IR scan \(\text{SE}_{2000/40}, \text{SE}_{2000/120} \text{ IR}_{2000/500(40)}\). The relaxation times could then be read from regions of interest on the displayed image. The validity of these measurements was checked using phantoms filled with MnCl\(_2\) solution (Johnson et al., 1987). Measurements were then taken from lesions and
FIG. 1. Male, aged 41 yrs, with clinically definite MS. A, axial SE 2000/40; B, axial SE 2000/120; C, axial IR 2000/300/40; D, sagittal SE 3000/60. The immediate periventricular changes are best seen with a short echo sequence (A). Discrete cerebral hemisphere lesions are better seen on a long echo sequence (B) and inversion recovery (C). There is a subcortical lesion in the right posterior parietal lesion (arrowed).

normal appearing white matter. Analysis of variance was used to compare measurements made in different sites and in different patient groups.

Repositioning of patients

Serial examinations were performed in many patients. Accurate repositioning was achieved as follows: three laser light sources were used to position the head. The anteroposterior (AP) angulation of the head was recorded and its position maintained by a band. The first image was a sagittal slice onto which was superimposed a grid with lines corresponding to the position of the slices in subsequent axial imaging sequences. From this pilot image the AP head angulation was recorded as the angle between the vertical and a line drawn between the nasion and the lowest point of the clivus. At subsequent examinations the same AP angulation, as measured by the laser light sources, was
used to position the patient. The level of the axial slices, as defined by the grid superimposed on the image, was adjusted to obtain the same levels as before. The maximum variation in AP angulation between two examinations, as measured from the screen images in 40 patients, was +3.6° to −4° (SD 2°).

**Assessment of the number, size and distribution of MRI abnormalities**

Abnormalities were immediately obvious in many patients, but in those presenting with clinically isolated lesions the changes were often less marked. In all patients in those groups, (optic neuritis, brainstem lesions and spinal cord lesions) and in healthy controls, each scan was assessed ‘blind’ by 4 independent assessors (I.E.C.O., G.H. du B., B.E.K., I.F.M.). In these groups of patients, only those patients whose scans were judged abnormal by all assessors were subsequently classified as such. Equivocal scans, or those where there was not a unanimous decision, were classified as normal. Areas of abnormal signal measuring less than 2 mm in their longest diameter, abnormalities appearing in parts of the image affected by artefact and areas of high signal that could represent the depths of a deep sulcus were excluded. Small areas of heightened signal are often apparent at the frontal horns in normal subjects; thus areas of increased signal in this region were only classified as abnormal if they were larger than 5 mm if symmetric, or if there was a difference of more than 2 mm between the sides.

**Quantification of abnormal images**

In order to compare the degree of abnormality in patients with MS and those with clinically isolated neurological lesions a method of quantification of the lesions was required. A method described by Runge et al. (1984) proved unsatisfactory because it depended on the assumption of an orderly progression of the distribution of the lesions for which evidence is lacking. Methods of counting individual lesions were useful in patients with only a few discrete lesions but were not suitable for those patients whose scans showed more widespread abnormalities. In such cases lesions were frequently confluent and it proved impossible to resolve reproducibly such areas into separate lesions. We therefore devised a method of assessing the degree of abnormality in a scan which did not depend upon counting individual lesions.

For each patient all slices obtained with a multislice protocol were examined. The periventricular regions were considered separately; lesions which were periventricular in part and extended out into the brain parenchyma were considered ‘periventricular’, while lesions which were apparently separate from the ventricles were designated ‘discrete cerebral lesions’. At times, however, it was difficult to differentiate reliably lesions which were in fact periventricular, protruding from the roof of the lateral ventricle, from those which were discrete from the ventricle and situated in the white matter above the roof. This was particularly the case when axial sections with the standard slice thickness were used alone. The interpretation was often clarified by using additional coronal and sagittal sections. Lesions in the brainstem and cerebellum were assessed separately.

The periventricular region was divided into 7 parts (body of lateral ventricle, frontal horn, trigone, occipital horn, temporal horn, third ventricle and fourth ventricle) and lesions in each were scored 0–3 depending on their size as measured by the maximum degree of penetration from the edge of the ventricle into the surrounding white matter (0 = no lesion, 1 = 5 mm, 2 = 6–10 mm, 3 = > 10 mm).

Discrete lesions separate from the ventricles were scored for each of 8 sites (brainstem, cerebellum, internal capsule, basal ganglia, frontal lobe, parietal lobe, temporal lobe, occipital lobe) and in each site lesions were scored 0–3 on the maximum size in any dimension.

The scores from each of the 15 sites (from each hemisphere when appropriate) were then added to give a cumulative total score, the abnormality score for that study. Scans were independently scored by 2 observers, providing an interrater reliability of 0.95.
Polyacrylamide gel electrophoresis (Dr E. J. Thompson) was carried out as previously described (Thompson et al., 1979).

Patients

Most of the patients in this investigation were attending the National Hospitals, Queen Square and Maida Vale, or the Moorfields Eye Hospital, City Road. The diagnosis in all patients was reconsidered by a clinical member of the team before the patient was included in the investigation.

RESULTS

Multiple sclerosis

Brain abnormalities

A total of 144 patients with MS were examined by MRI; 114 (aged 24–74 yrs, mean 40 yrs) had clinically definite MS and 30 (aged 24–62 yrs, mean 38 yrs) had clinically probable MS by the criteria of the Poser Committee (Poser et al., 1983). Sagittal MRI examinations of the cervical cord were made in 24 patients with definite MS. All had clinical features of a cord lesion but in none were they acute.

The results of examination of the patients with clinically definite MS are summarized in Table 1. Regions of abnormal periventricular signal were demonstrated in 112 of the 114 patients. In 1 of the 2 patients without periventricular lesions there were areas of abnormal signal only in the brainstem and in the other patient no abnormalities were seen. The former had suffered 3 clinical episodes with remission which comprised 1 episode of brainstem disturbance, 1 episode of optic neuritis and an episode of lower limb sensory disturbance. The latter patient had experienced 2 clinical episodes, 1 with clinical evidence of a cervical cord lesion; the other was an episode of acute unilateral optic neuritis.

The periventricular white matter adjacent to the trigones and bodies of the lateral

<table>
<thead>
<tr>
<th>Site of abnormalities</th>
<th>n</th>
<th>%</th>
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<tbody>
<tr>
<td>Periventricular (lateral ventricles)</td>
<td>112</td>
<td>98</td>
</tr>
<tr>
<td>Trigone</td>
<td>109</td>
<td>96</td>
</tr>
<tr>
<td>Body of lateral ventricle</td>
<td>109</td>
<td>96</td>
</tr>
<tr>
<td>Frontal horn</td>
<td>83</td>
<td>73</td>
</tr>
<tr>
<td>Occipital horn</td>
<td>95</td>
<td>83</td>
</tr>
<tr>
<td>Temporal horn</td>
<td>67</td>
<td>59</td>
</tr>
<tr>
<td>Third ventricle</td>
<td>39</td>
<td>34</td>
</tr>
<tr>
<td>Fourth ventricle</td>
<td>68</td>
<td>60</td>
</tr>
<tr>
<td>Discrete cerebral white matter</td>
<td>102</td>
<td>90</td>
</tr>
<tr>
<td>Basal ganglia</td>
<td>29</td>
<td>25</td>
</tr>
<tr>
<td>Internal capsule</td>
<td>13</td>
<td>11</td>
</tr>
<tr>
<td>Brainstem</td>
<td>77</td>
<td>68</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>56</td>
<td>49</td>
</tr>
<tr>
<td>Any cerebral abnormality</td>
<td>113</td>
<td>99</td>
</tr>
</tbody>
</table>
ventricles was most frequently involved (96%; fig. 1), followed by that around the occipital (83%) and frontal horns (73%). Lesions in the floor of the fourth ventricle were seen in 60% of patients but around the third ventricle in only 34%. Lesions discrete from the ventricles were seen in cerebral white matter in 90% (fig. 1), the majority in the white matter of the frontal and parietal lobes above the level of the bodies of the lateral ventricles, in the centrum semiovale. Lesions were present in the basal ganglia in 25% and in the internal capsule in 11%. Infratentorially, lesions were seen more commonly in the brainstem (68%) than in the cerebellar hemispheres (49%).

All 30 patients with clinically probable MS had abnormal scans. When the frequency and distribution of lesions in 30 patients with clinically definite MS were compared with those in clinically probable cases, there was no significant difference in the incidence of periventricular lesions (present in all cases) or of discrete cerebral white matter lesions between the 2 groups (P<0.2; analysis of variance). Cerebellar (P<0.005) and brainstem (P<0.05) lesions were, however, more commonly seen in patients with definite MS.

A comparison was made between the distribution of lesions in patients with and without oligoclonal IgG bands in the CSF, which were present in 37/49 (76%) of the 114 patients with clinically definite MS. Brainstem lesions were commoner (P = 0.05) in patients with oligoclonal bands, but there was no difference for lesions in other sites. The presence of oligoclonal bands was also associated with a significantly higher abnormality score (i.e., with more extensive cerebral involvement, P = 0.05). The association of oligoclonal bands with brainstem lesions probably reflects the greater likelihood of brainstem lesions being frequent in clinically

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**FIG. 2.** Serial images (IR2000/600/40) of a 30-yr-old woman with MS. The initial scan (A) was normal. Ten weeks later (B) there were 2 new lesions (arrowed) which have a 'halo' appearance.
definite disease. Oligoclonal bands were present in the 1 patient with definite MS in whom no abnormalities were seen on MRI.

Nine patients with clinically definite disease had lesions in which the centre was of different signal intensity from the periphery, producing a halo-like appearance (fig. 2). On the SE sequences (SE<sub>2000/120</sub>) these lesions had a centre of higher signal than the periphery with the reverse effect on the IR sequence (IR<sub>2000/600/40</sub>). These findings suggested that the centre of the lesion was of longer T<sub>1</sub> and T<sub>2</sub> than the periphery, a prediction confirmed by measurement of T<sub>1</sub> and T<sub>2</sub> from calculated images. In 2 of the 9 patients there was evidence that the lesions may have been of recent origin. The patient illustrated in fig. 2 had a previous episode of optic neuritis and was scanned after an episode attributable clinically to a lesion in the spinal cord. A repeat examination ten weeks later showed 2 new areas of abnormal signal which were not present in the same slice at the earlier examination. The patient had suffered no new symptoms in this period. These findings are further considered in the discussion.

**Spinal cord abnormalities**

All 24 patients in whom a satisfactory examination of the cervical spinal cord was achieved had periventricular lesions and 20 also had discrete lesions in the cerebral white matter.

SE images of the cervical cord were made in the sagittal plane using the standard head receiver coil as supplied by the manufacturer, rather than surface receiver coils. Areas of high signal within the cord, probably due to an increased T<sub>2</sub> (although relaxation times were not calculated), were seen in 14/24 patients. In 1 patient there was an apparent fusiform enlargement of the cervical cord. The areas of altered signal were of varying appearance: in 8 patients the abnormalities extended longitudinally over one or more segments (fig. 3), in 2 the whole transverse diameter of the cord appeared abnormal, and in 6 the lesions were more rounded in shape and did not appear to extend along the long axis of the cord.

**Follow-up MRI examinations**

Seventeen patients with clinically definite MS had repeat MRI examination performed approximately three months following the first examination (8–19 wks, mean 12 wks). The patients were carefully repositioned (see Methods) and the sequences used for the first examination repeated. Seven showed lesions on the second scan which had not been on the earlier study (fig. 2). In 2 the follow-up scan failed to demonstrate a lesion which had been seen on the first examination, although both showed new lesions which had not been seen on the first examination.

Many of the lesions showed changes in signal intensity or size when the images of the two studies were compared. Change in intensity alone was difficult to evaluate since it is dependent on a number of factors and T<sub>1</sub> and T<sub>2</sub> of the lesions were not measured in all cases. Minor changes in size of the lesions were also difficult to
evaluate as slight alterations in section level might cause considerable alterations in the appearance of the lesion. The results of reexamining patients with clinically probable MS will be reported in a later paper.

Measurement of relaxation times ($T_1$ and $T_2$)

Measurements of relaxation times were made in 34 patients with clinically definite MS and in the 18 control subjects in whom the necessary sequences had been performed. In the patients, readings were taken from the areas of visibly abnormal signal intensity and from apparently normal brain, in both white matter and grey matter (Tables 2, 3, 4). There was a wide variation in relaxation times of the lesions. For periventricular lesions, $T_1$ ranged from 455 ms to 1785 ms and $T_2$ ranged from 125 ms to 405 ms, while for discrete lesions within the cerebral white matter $T_1$ ranged from 185 ms to 480 ms and $T_2$ ranged from 110 ms to 220 ms. The relaxation time values were longer for lesions which were periventricular in site than for those which were in the cerebral white matter (analysis of variance, $P<0.05$).

The values obtained for $T_1$ and $T_2$ in the healthy controls are shown in Tables 3 and 4, respectively. A comparison of these values of $T_1$ and $T_2$ with those for the normal appearing white matter in the patients with MS was made. The values in the patients were significantly higher in all cerebral hemisphere lobes studied (Tables 3, 4). The implications of these results are considered in the Discussion.
### Table 2. Mean Relaxation Times of Lesions in the Brain in 34 Patients with Multiple Sclerosis*

<table>
<thead>
<tr>
<th>Brain region</th>
<th>$T_1$</th>
<th>$T_2$</th>
<th>$T_1$</th>
<th>$T_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temporal lobe</td>
<td>489 (92)</td>
<td>127 (28)</td>
<td>714 (202)</td>
<td>205 (82)</td>
</tr>
<tr>
<td>Occipital lobe</td>
<td>486 (19)</td>
<td>112 (21)</td>
<td>623 (137)</td>
<td>164 (49)</td>
</tr>
<tr>
<td>Frontal lobe</td>
<td>541 (57)</td>
<td>139 (23)</td>
<td>627 (172)</td>
<td>179 (86)</td>
</tr>
<tr>
<td>Parietal lobe</td>
<td>567 (87)</td>
<td>150 (53)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brainstem</td>
<td>608 (72)</td>
<td>129 (22)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebellum</td>
<td>542 (56)</td>
<td>106 (14)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Mean values in ms; SD in brackets.

### Table 3. Mean $T_1$ Measurements (in ms, SD bracketed) of Apparently Normal White and Grey Matter in Multiple Sclerosis Patients ($n=34$) and Control Subjects ($n=18$)

<table>
<thead>
<tr>
<th></th>
<th>White matter</th>
<th>Grey matter</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MS</td>
<td>Controls</td>
</tr>
<tr>
<td>Temporal lobe</td>
<td>429 (31)$^1$</td>
<td>400 (22)$^1$</td>
</tr>
<tr>
<td>Occipital lobe</td>
<td>430 (44)$^2$</td>
<td>395 (21)$^2$</td>
</tr>
<tr>
<td>Frontal lobe</td>
<td>421 (37)$^3$</td>
<td>385 (21)$^3$</td>
</tr>
<tr>
<td>Parietal lobe</td>
<td>427 (35)$^4$</td>
<td>397 (20)$^4$</td>
</tr>
</tbody>
</table>

$^1 P = 0.05; ~ ^2 P = 0.001; ~ ^3 P = 0.01$.

### Table 4. Mean $T_2$ Measurements (in ms, SD bracketed) of Apparently Normal White and Grey Matter in Multiple Sclerosis Patients ($n=34$) and Control Subjects ($n=18$)

<table>
<thead>
<tr>
<th></th>
<th>White matter</th>
<th>Grey matter</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MS</td>
<td>Controls</td>
</tr>
<tr>
<td>Temporal lobe</td>
<td>94 (10)$^1$</td>
<td>87 (9)$^1$</td>
</tr>
<tr>
<td>Occipital lobe</td>
<td>93 (17)$^2$</td>
<td>88 (10)$^2$</td>
</tr>
<tr>
<td>Frontal lobe</td>
<td>95 (10)$^3$</td>
<td>86 (7)$^3$</td>
</tr>
<tr>
<td>Parietal lobe</td>
<td>98 (12)$^4$</td>
<td>90 (9)$^4$</td>
</tr>
</tbody>
</table>

$^1 P = 0.1; ~ ^2 P = 0.1; ~ ^3 P = 0.04; ~ ^4 P = 0.01$.

**MRI of postmortem brains**

It is obvious that the distribution of lesions at MRI corresponds with that recognized pathologically (Cruveilhier, 1829–1842; Charcot, 1868; Gowers, 1893; Dawson, 1916; Hallervorden, 1940; Fog, 1965; Lumsden, 1970; Allen, 1984). It was nevertheless important to establish in individual cases whether the abnormal areas on the images do indeed correspond to plaques. There is no published example of histological confirmation of the nature of lesions recognized in vivo by MRI in a patient with MS. Stewart et al. (1984) showed that reasonable images can be obtained from postmortem material. We therefore examined 6 formalin-fixed brains.
from patients dying with clinically definite MS; 4 were male (aged 51, 52, 56 and 78 yrs) and 2 female (56 and 67 yrs). After removal the brains were weighed and examined for the presence of external abnormalities and quickly immersed in 30% neutral formaldehyde. After a period of fixation varying between 2 and 3 wks, the brains were further examined and subsequently secured, vertex down, to the base of a perspex cradle. The imaging plane was perpendicular to the base. Serial near-contiguous images were obtained in an approximately coronal plane using the multislice technique and SE sequences (SE$_{1500/40}$).

After the NMR observations the brains were cut. The first coronal section was made through the mamillary bodies while the brain was still attached to the base and care was taken to cut exactly perpendicularly to the base of the apparatus. After the first cut, 0.5 or 1 cm thick sections were cut through the whole brain. Each section was examined and matched with the corresponding NMR picture (fig. 4). Finally, blocks were taken from various regions which included areas with normal-looking myelin and plaques. From paraffin embedded blocks, sections were cut and stained with haematoxylin and eosin, haematoxylin-van Gieson, luxol fast blue, Glees-Marsland silver impregnation for axons, and Holzer for glial fibres. Some blocks were embedded in celloidin and sections from them stained for myelin.

Fig. 4. Coronal brain slices. A. MRI. B. fixed brain. The abnormalities seen in the hemisphere white matter and in the corpus callosum in A are confirmed in B. C is a section through the right frontal lobe stained with luxol fast blue-cresyl violet showing several plaques which correspond in location to the abnormal images in A.
All the brains were of normal shape but 2 of them (both males, aged 51 and 78 yrs) were moderately atrophic (1195 and 1110 g, respectively). The leptomeninges were thin and transparent; the atrophic brains had wide sulci. At the base the vessels were of normal configuration and, on occasion, showed slight to moderate atherosclerosis. The cranial nerves were normal. In 2, plaques could be seen on the ventrolateral surface of the pons: they appeared slightly depressed, grey and, in places, serpiginous. In all the cases the cortical ribbon and deep grey matter looked normal. The lateral ventricles showed a mild degree of dilatation; plaques were
seen in all cases, some of them deeply situated in the hemisphere white matter, while others were arranged around the lateral ventricles. When they involved the corpus callosum this was thin and grey. Occasionally, plaques were also seen to impinge into the cortical and subcortical grey matter which appeared pearl grey.

Histological examination of the plaques showed a varying degree of myelin loss, which was in places complete, as well as astrocytic gliosis. Comparing sections stained for myelin and glial fibres (fig. 5b, c) it appeared that in the same plaque the loss in myelin staining corresponded to a proportional increase in intensity of the glial proliferation. The transition between myelinated and demyelinated areas was usually abrupt, but occasionally there was an intervening zone in which the myelin stain was pale but still present. Silver impregnation showed the axons to be relatively spared although in some areas of myelin pallor or loss they were severely reduced in number or almost completely absent. Oligodendrocytes were also reduced in number. Indeed, in some of the most severely affected areas they were completely absent, and the only cells present were fibrillary astrocytes (fig. 6) whose processes formed a delicate network of fibres, particularly dense around blood vessels and in periventricular regions. In the areas of most severe myelin loss, blood vessels appeared singly or forming small groups; they had thick fibrous walls and were surrounded by enlarged spaces; some of them were cuffed with lymphocytes and occasional plasma cells.

As fig. 4 shows, there was a good correspondence between the areas of abnormality in the NMR images and the histological lesions, although the outlines were not precisely the same. This difference is to be expected, since the NMR image represents averaging of the signal over a slice 10 mm thick whereas the histological sections were 30 μm thick.

We conclude that MRI abnormalities originated from chronic plaques of MS.
Optic neuritis

Optic neuritis is one of the commonest isolated manifestations of MS. In the United Kingdom, the majority of patients presenting with this clinical syndrome ultimately develop the generalized disease (McDonald, 1983). It is therefore of considerable interest to know the frequency with which multiple lesions are found at presentation. We have investigated 51 patients fulfilling the criteria of Gould et al. (1977) for acute optic neuritis. Those with symptoms of previous ocular disease or neurological symptoms, and those with evidence of other causes for optic neuropathy (e.g., ischaemia) were excluded. Further details of some aspects of our observations on a smaller series of patients have been reported previously (Ormerod et al., 1986c).

Particular interest attaches to the adult patients presenting with their first episode of acute 'isolated' unilateral optic neuritis. Of such patients, 29/42 scanned 1 to 40 wks after onset (mean 9 wks) had multiple brain lesions (fig. 7). In 28 there were periventricular abnormalities; 21 patients showed additional discrete lesions elsewhere in the cerebral white matter; 1 patient showed only discrete lesions.

In order to assess the sensitivity of MRI in detecting multiplicity of lesions the results were compared with those obtained from somatosensory (SEP) and brainstem auditory (BAEP) evoked potentials in 29 patients. The overall incidence of EP abnormalities (8/29, 28%) was similar to that reported by others (Matthews

![Fig. 7. SE_{t2} T_{1} axial images showing brain lesions in 2 patients with isolated optic neuritis. A, a 27-yr-old male with acute unilateral optic neuritis of 1 w's duration. B, a 41-yr-old male with bilateral sequential optic neuritis. There is involvement of the optic radiation.](https://brain.oxfordjournals.org/content/oxfordjournals.brain.oxfordjournals.org.full/doi/10.1093/brain/110.5.879/F10031402692)
et al., 1982; Sanders et al., 1984) and much lower than that detected by MRI (19/31, 61%). In contrast, the evoked potential method was more sensitive than MRI in detecting lesions in the optic nerve itself: visual evoked potentials (VEPs) were abnormal in all our patients. At the time of our previous paper (Ormerod et al., 1986c) we had failed to demonstrate any abnormalities in the optic nerve by MRI. However, the recent application of the STIR sequence and surface coils have enabled us to obtain good axial and coronal images of the optic nerves, and we have so far seen 10 lesions in 14 patients following an attack of acute unilateral optic neuritis (fig. 8) (Miller et al., 1986).

Serial observations

Because of the similarity between the frequency of MS after isolated optic neuritis in the United Kingdom (range 42–85%, higher frequencies being observed with longer follow up; McDonald, 1983) and the frequency of finding multiple lesions...
in MR images at presentation, it is tempting to suggest that the patients with multiple lesions already have MS. This conclusion is not, however, justified at present on the basis of a single scan, since the frequency with which optic neuritis may be the sole symptomatic manifestation of what in reality is a multifocal but nevertheless monophasic pathological process (i.e., a form of acute disseminated encephalomyelitis) is unknown. There is evidence that such cases can occur in children in whom the subsequent development of MS is very uncommon (Meadows, 1969; Parkin et al., 1984). If after an interval of greater than one month (in keeping with the diagnostic criteria of Poser et al., 1983) new lesions could be demonstrated, the diagnosis would become more likely. We therefore undertook a serial clinical and MRI study of the patients presenting with optic neuritis.

Twenty-five adults have been rescanned after 5 to 20 months (Table 5). Five showed unequivocal evidence of new abnormalities in the images. In these patients, the criteria for a diagnosis of clinically probable MS are fulfilled (Poser et al., 1983).

<table>
<thead>
<tr>
<th>TABLE 5. FOLLOW-UP STUDIES IN OPTIC NEURITIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>New lesions</td>
</tr>
<tr>
<td>(follow-up brain MRI)</td>
</tr>
<tr>
<td>Clinical relapse</td>
</tr>
<tr>
<td>---------------------------------------------</td>
</tr>
<tr>
<td>Abnormal initial MRI (17)</td>
</tr>
<tr>
<td>Normal initial MRI (8)</td>
</tr>
</tbody>
</table>

Six other patients had experienced a relapse attributable to a lesion outside the optic nerve, although none of these had a new lesion visible at follow-up; in these cases, the criteria for a clinically definite diagnosis were fulfilled: all 6 had multiple brain lesions at presentation. None of the 8 with a normal initial scan had further symptoms at follow-up.

Isolated brainstem lesions

An isolated brainstem disturbance is a common initial manifestation of MS. However, it is not known what proportion of patients presenting with such a brainstem disturbance will ultimately develop MS. MRI is clearly of interest in such patients to identify the symptomatic lesion and to establish the frequency of multiple lesions at presentation. We therefore examined 44 consecutive patients with clinical evidence of an isolated brainstem abnormality by MRI. None had had previous neurological disturbances. All were in the age range where the first episode of MS could be the cause of their illness (15—55 yrs).

Of the 44 patients scanned, a diagnosis other than MS was made in 4; 3 of these had sixth cranial nerve palsies with additional long tract signs. One female with a 2-wk history of diplopia had a pontine angioma; another female with a 6-month history of diplopia had a brainstem glioma (fig. 9A); and a 38-yr-old male with a 5-wk history of progressively worsening diplopia had a pontine haematoma (fig. 9B).
The fourth patient, a female of 20 yrs who had respiratory failure and upbeat nystagmus, had extensive lesions in the medulla and in both thalami thought to be due to Leigh's disease.

The remaining 40 patients had a variety of brainstem disturbances (Table 6). For example, all those with downbeat or torsional nystagmus had nystagmus in other directions and 3 with gaze palsies had a one-and-a-half syndrome. The severity of the abnormalities varied. Thus some patients with an internuclear ophthalmoplegia had a full range of adduction of the eye on the affected side but velocity was reduced, while others had a complete failure of adduction.

The mean age of these 40 patients was 33 yrs (20–52 yrs); 20 were male and 20 female. There was a wide range in the duration of the brainstem dysfunction (1 wk–12 yrs), but this range fell into two clear groups without overlap. Twenty-six patients had had symptoms for less than 3 months (mean 3.6 wks) and 14 patients
Table 6. Clinical Features in 40 Patients with Isolated Brainstem Lesions

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Horizontal nystagmus*</td>
<td>23</td>
<td>58</td>
</tr>
<tr>
<td>Upbeat nystagmus*</td>
<td>14</td>
<td>35</td>
</tr>
<tr>
<td>Downbeat or torsional nystagmus*</td>
<td>7</td>
<td>18</td>
</tr>
<tr>
<td>Internuclear ophthalmoplegia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unilateral</td>
<td>6</td>
<td>15</td>
</tr>
<tr>
<td>Bilateral</td>
<td>7</td>
<td>18</td>
</tr>
<tr>
<td>Gaze palsy</td>
<td>6</td>
<td>15</td>
</tr>
<tr>
<td>One-and-a-half syndrome</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Unilateral VI nerve palsy</td>
<td>5</td>
<td>13</td>
</tr>
<tr>
<td>Bilateral VI nerve palsy</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Unilateral VII nerve palsy</td>
<td>5</td>
<td>13</td>
</tr>
<tr>
<td>Bilateral VII nerve palsy</td>
<td>2</td>
<td>5</td>
</tr>
</tbody>
</table>

* 1st, 2nd, or 3rd degree.

had symptoms for more than 9 months (mean 20 months). There was no significant difference in the ages of the two groups, the former having a mean age of 31 yrs (20–47 yrs) and the latter 34 yrs (22–52 yrs).

Thirty-five of the 40 patients (88%) had a lesion demonstrated in the brainstem by MRI (Table 7). There was a good correlation between the clinical picture and the site of the lesion in the case of cranial nerve palsies (6th, 7th) and the one-and-a-half syndrome (fig. 10). The majority of patients with internuclear ophthalmoplegia also had lesions that could involve the medial longitudinal fasciculus (fig. 11), but care must be exercised here as lesions in the floor of the fourth ventricle were so common that a lesion is likely to be found in the region of the medial longitudinal fasciculus even in those patients who do not have an internuclear ophthalmoplegia. Thirty of the 40 undiagnosed patients (75%) had MRI evidence of disseminated lesions in the periventricular region, or discretely in the cerebral hemisphere, or usually both (Table 7). The distribution resembled that seen in MS. The presence of multiple lesions was unrelated to the duration of symptoms.

Table 7. MRI Abnormalities in 40 Patients with Isolated Brainstem Lesions

<table>
<thead>
<tr>
<th>BS</th>
<th>C</th>
<th>Only P</th>
<th>Only DC</th>
<th>P + DC</th>
<th>Any cerebral abnormality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of symptoms less than 3 months (n = 26)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number</td>
<td>23</td>
<td>6</td>
<td>5</td>
<td>1</td>
<td>14</td>
</tr>
<tr>
<td>%</td>
<td>88</td>
<td>26</td>
<td>19</td>
<td>4</td>
<td>54</td>
</tr>
</tbody>
</table>

| Duration of symptoms greater than 9 months (n = 14) |    |        |         |        |                         |
| Number | 12 | 3  | 1  | 0    | 9    | 10                       |
| %     | 86 | 21 | 7  | 0    | 64   | 71                       |

BS = brainstem; C = cerebellum; P = periventricular; DC = discrete cerebral.
FIG. 10. A, axial slice (SE$^{2,000/60}$) from a 25-yr-old male with a 4-wk history of diplopia and ataxia. Examination revealed a left one-and-a-half syndrome, and left facial weakness. There is a left-sided lesion in the floor of the fourth ventricle, extending to the midline. B, axial slice (SE$^{2,000/60}$) of a 29-yr-old female with a 2-wk history of diplopia, ataxia and left facial numbness. Examination revealed horizontal and upbeat nystagmus and left facial sensory loss. There is a lesion in the floor of the fourth ventricle extending into the left posterolateral pons. C, axial, and D, sagittal slices (SE$^{2,000/60}$) of a 30-yr-old male with bilateral sixth nerve palsies of 2 wks duration. There is a midline lesion in the floor of the fourth ventricle (arrowed).

The sensitivity of MRI in detecting lesions was compared with that of evoked potential methods. In the brainstem itself lesions were detected by BAEPs in 7 of the 32 patients and by SEPs following median nerve stimulation at the wrist in 5 of 31 patients, 4 of whom also had an abnormal BAEP (Table 8). MRI, which was...
abnormal in 88%, was obviously more sensitive. Evoked potentials were also less sensitive in detecting lesions outside the brainstem: abnormal VEPs were found in 4/23 patients with symptoms for less than 3 months and 7/14 with symptoms for more than 9 months.

As for optic neuritis, the question arises as to whether the patients with multiple lesions at presentation already have MS, and for the same reason, the question cannot be answered now. However, 14 of the 31 patients who underwent lumbar puncture (45%) had oligoclonal IgG bands in the CSF at electrophoresis, irrespective of the duration of their symptoms (Table 8). These patients have an increased probability of developing MS (Moulin et al., 1983).

**Serial observations**

These were performed on 10 patients after 6 to 12 months and revealed new lesions in 2 (fig. 12), neither of whom had new symptoms. However, the appearance of such new lesions on follow-up scans allows a diagnosis of clinically probable MS on the criteria of Poser et al. (1983).

Quantitative measurements of T₁ and T₂ of the brainstem lesions were made in 17 patients because concurrent experimental work (Barnes et al., 1986) had suggested that it might be possible to distinguish acute from chronic lesions in this way. The results have been reported in detail elsewhere (Ormerod et al., 1986b). In summary, T₁ and T₂ were increased in both acute and chronic lesions, but the increase was significantly greater in the acute lesion. The implications of these findings for the diagnosis of MS is discussed below.
Isolated spinal cord syndromes

Thirty-four patients with clinically isolated lesions of the spinal cord were examined, 23 with a chronic progressive syndrome (aged 25–50 yrs, mean 41), and 11 with an acute presentation, that is, evolution of the syndrome over less than 2 wks (aged 15–35 yrs, mean 27). In those with a chronic syndrome the most common presentation was with a progressive spastic paraparesis or tetraparesis without a sensory level and often with little alteration in sensation. Of those with an acute presentation all had sensory symptoms and 7/11 had a sensory level detectable at some stage in the illness. Only 1 had a syndrome of complete transverse

<p>| TABLE 8. RESULTS OF EVOKED POTENTIAL AND CSF EXAMINATION IN PATIENTS WITH BRAINSTEM LESIONS |
|-----------------------------------------------|------------------|------------------|------------------|
| VEP  | AEP  | SEP  | Oligoclonal CSF IgG bands |</p>
<table>
<thead>
<tr>
<th>N</th>
<th>A</th>
<th>N</th>
<th>A</th>
<th>-</th>
<th>+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of symptoms less than 3 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number</td>
<td>19</td>
<td>4</td>
<td>18</td>
<td>3</td>
<td>17</td>
</tr>
<tr>
<td>%</td>
<td>83</td>
<td>17</td>
<td>86</td>
<td>14</td>
<td>90</td>
</tr>
<tr>
<td>Duration of symptoms greater than 9 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number</td>
<td>7</td>
<td>7</td>
<td>4</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>%</td>
<td>50</td>
<td>50</td>
<td>64</td>
<td>36</td>
<td>75</td>
</tr>
</tbody>
</table>

VEP = visual evoked potential; AEP = auditory evoked potential; SEP = somatosensory evoked potential; N = normal; A = abnormal.
myelitis. Patients with a previous history of neurological disturbance or with physical signs suggestive of lesions outside the spinal cord were excluded. All patients with chronic syndromes and 7/11 with acute syndromes had myelography. Those in whom external compression of the cord had been demonstrated were excluded. The patients underwent MRI examination of the spinal cord and the brain. The results were compared with those obtained from evoked potential studies and with the CSF findings.

MRI demonstrated lesions within the brain in 4/11 patients with acute syndromes and in 14/23 with a chronic syndrome. The form and distribution of the abnormalities in the brain were similar to those in MS.

Visual, auditory and somatosensory evoked potential examinations were performed in 23 patients including 12/18 in whom lesions were seen on the cerebral MRI examinations (Table 9). Evoked potential abnormalities indicating lesions outside the clinically affected pathways were found in 0/5 patients with acute syndromes and in 3/18 of those with chronic syndromes. Thus MRI was more sensitive than BAEP and VEP combined in demonstrating the presence of clinically unsuspected lesions outside the spinal cord.

In the patients with an acute syndrome MRI revealed an area of abnormal signal intensity within the cervical cord in 5/7 patients, in 2 of whom the cord appeared swollen. In no patient with a clinically localized lesion of the thoracic cord did MRI demonstrate a lesion within the cord. Two patients with cord abnormalities demonstrated by MRI had no cerebral abnormalities visible. SEPs failed to demonstrate a lesion within the spinal cord in any of the patients with an acute syndrome.

In those patients with a chronic syndrome, 2 with clinical evidence of a lesion within the cervical spinal cord had abnormalities within the cord on MRI. In neither of these were SEPs recorded. The SEPs revealed a cord lesion in 1/5 patients who were examined with a cervical cord syndrome and in 3/13 in whom there was clinical evidence of a thoracic cord lesion.

Oligoclonal IgG bands were found in the CSF in 5/17 patients with chronic syndromes but in 0/9 with acute syndromes.

Table 9: Incidence of Abnormalities in CSF and Evoked Potentials in Clinically Isolated Spinal Cord Syndromes

<table>
<thead>
<tr>
<th></th>
<th>Oligoclonal CSF IgG pattern</th>
<th>VEP</th>
<th>AEP</th>
<th>SEP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cervical</td>
<td>0/5</td>
<td>0/3</td>
<td>0/3</td>
<td>0/3</td>
</tr>
<tr>
<td>Thoracic</td>
<td>0/4</td>
<td>0/2</td>
<td>0/2</td>
<td>0/2</td>
</tr>
<tr>
<td>Chronic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cervical</td>
<td>2/4</td>
<td>0/5</td>
<td>0/5</td>
<td>1/5</td>
</tr>
<tr>
<td>Thoracic</td>
<td>3/13</td>
<td>1/13</td>
<td>2/13</td>
<td>3/13</td>
</tr>
</tbody>
</table>

VEP = visual evoked potential; AEP = auditory evoked potential; SEP = somatosensory evoked potential.
Spinal syndromes are a common mode of presentation of MS and it is likely that an appreciable proportion of patients with disseminated lesions at presentation have this disease. The probability is increased in those with oligoclonal bands in the CSF (Moulin et al., 1983), but even these cases do not at presentation fulfil the criteria of the Poser Committee (Poser et al., 1983). The implications of multiplicity of lesions at MRI are considered in the Discussion.

Comparison of MRI in MS and isolated lesions

The distribution of the additional abnormalities seen in all three types of isolated lesion resembled that of MS. A quantitative comparison of the abnormality (calculated as for MS) showed that there were more abnormalities in known MS than in the patients presenting with clinically isolated lesions ($P<0.001$) although there was some overlap in that the lowest score in a patient with clinically definite MS was 9 and the highest score in a patient with an isolated syndrome was 42. There was no significant difference between the scores in the three groups of patients with isolated lesions.

Cerebral vascular disease

Although cerebral vascular disease is infrequently confused with MS clinically, it may be when there is an acute onset, for example, of a hemiparesis or brainstem lesion. Moreover, the periventricular lucencies seen on x-ray CT scans in diffuse cerebral vascular disease (Rosenberg et al., 1979; Goto et al., 1981) and MS (Radue and Kendall, 1978, Hershey et al., 1979) may be very difficult to distinguish, as may the small lucencies in the cerebrum seen in lacunar infarction and MS. In order to determine whether there are reliable features which can be used to separate some of these conditions we have studied the NMR images in 55 patients with a variety of syndromes attributable to cerebral vascular disease, and compared them with images obtained in MS. The ages of these patients with vascular disease ranged from 14 to 80 yrs (mean 50 yrs); 13 had late onset epilepsy associated with lacune-like abnormalities on CT scans in the white matter of the cerebral hemispheres; 11 had the clinical picture, confirmed on CT scanning, of cerebral infarction in the territory of a major vessel; 8 had Behçet’s disease (according to the criteria of Haim and Gilhar, 1980); 6 had systemic lupus erythematosus (SLE) (as classified according to the American Rheumatism Association Revised Criteria, Tan et al., 1982); 4 had other forms of vasculitis; 3 had the syndrome of transient global amnesia; 2 had intracerebral haemorrhage demonstrated by CT scanning; and 1 had venous infarction. Finally, 7 patients had progressive dementia with evidence on CT scans of diffuse white matter abnormality (Valentine et al., 1980). The nosological status of this last condition is at present difficult to define. It is sometimes referred to as subacute arteriosclerotic encephalopathy or Binswanger’s disease (Janota, 1981; Kinkel et al., 1985). However, patients with this syndrome may also have evidence of lacune-like lesions on CT scans (Goto et al., 1981),
Fig. 13. Cerebral vascular disease. A, axial slice (SE<sub>2000/60</sub> at 0.25 Tesla) of a 43-yr-old male with a left middle cerebral artery infarct. B, axial slice (SE<sub>2000/60</sub>) of a 65-yr-old male with episodes of vertebrobasilar ischaemia. There is smooth change along the body of the lateral ventricles and a discrete lesion in the left corona radiata (arrowed). C, axial slice (SE<sub>2000/60</sub>) of a 40-yr-old woman with Behçet's disease and transient episodes of vertigo and ataxia. There is a lesion at the left trigone (arrowed). D, axial slice (SE<sub>2000/60</sub>) of a 40-yr-old woman with established SLE who presented with an episode of confusion. There are several discrete lesions in the right frontal white matter.
raising the question of overlap with multi-infarct dementia (Hachinski, 1983). Since
the pathogenesis of subacute arteriosclerotic encephalopathy is not established,
although there is good evidence that the end result is infarction (Goto et al., 1981;
Janota, 1981), we have preferred to use the term ‘dementia with diffuse white matter
abnormality’ suggested by Dr David Drachman (personal communication).

All 37 patients with noninflammatory (i.e., nonvasculitic) disease had previously
undergone CT and abnormalities were found in 36. In no case were abnormalities
seen on CT not visible also on MRI. MRI showed evidence of cerebral abnor-
malities in 10 patients who had shown no such abnormality on CT. Focal abnor-
malities were seen with MRI in all 37 and ranged in size from small lacune-like
regions of altered signal to large lesions corresponding with the distribution of a
major cerebral vessel in those with stroke (fig. 13A, B); 27 patients had evidence of
periventricular abnormalities on the SE sequences (fig. 13B). Such abnormalities
were seen in all patients with dementia with diffuse white matter abnormality and
in 12/13 with lacune-like lesions.

Periventricular abnormalities were least common in patients with infarction in
the territory of a fairly large cerebral vessel; the ages of the subjects in this group
were lower with a mean age of 46yrs (range 24–77 yrs). If the 3 patients in this
group over the age of 60yrs are excluded, none had periventricular areas of
abnormal signal intensity.

Of 18 patients with inflammatory disease (i.e., Behçet’s disease, SLE or another
vasculitic disorder) 10 had periventricular changes and 8 had small discrete lesions
in the cerebral hemispheres (fig. 13C, D). There were infarcts in the territory of a
major cerebral artery in 2 patients, and 1 had small peripheral wedge-shaped lesions
suggesting infarction.

It was important to try to distinguish the appearances of the periventricular
abnormalities in cerebral vascular disease from those in MS. Of the 37 patients
with such changes, 10 had a smooth line of increased signal around the bodies of the
ventricles (fig. 13B) which differed from the irregular periventricular abnormalities
found in 112/114 patients with MS. Smooth outlining of the ventricles was seen in
all subgroups of patients with cerebral vascular disease except those with dementia
with diffuse white matter abnormality. The remaining 27 cases showed irregularities
in outline more or less resembling those seen in MS, although often the changes
were milder. The changes reached an extreme degree in the 7 patients with dementia
with diffuse white matter abnormality (fig. 14). In this group the changes resembled
those seen in advanced MS although there was a tendency for the abnormalities in
the latter to be more marked posteriorly and in the former to be evenly distributed.
White matter changes extending into the centrum semiovale were seen in both
conditions. Abnormalities were more frequently seen in the basal ganglia in patients
with dementia with diffuse white matter abnormality than in those with MS
\(P<0.001\). The differences in the distribution of abnormalities in other sites did
not reach statistical significance although the number of patients with dementia
with diffuse white matter abnormality was small.
In a further attempt to discriminate between the MRI abnormalities in dementia with diffuse white matter abnormality and those in MS, the relaxation times $T_1$ and $T_2$ were measured from computed images of abnormalities around the bodies of the lateral ventricles on each side and anteriorly and posteriorly (4 readings) using the computer reformatted images of relaxation times $T_1$ and $T_2$ (see Methods). The values obtained from the periventricular abnormalities taken from the patients in the former group were compared with those from 35 patients with MS. There was considerable overlap between the values obtained from the two groups and no statistically significant difference between them was found by analysis of variance.

It is thus clear that each of the individual features we have analysed which are seen in MS are also seen in cerebral vascular disease. Nevertheless, the pattern of MRI abnormalities was usually strongly suggestive of the correct diagnosis. Kortman et al. (1985) reached the same conclusion.

Cerebellar degeneration

An episode of unsteadiness of gait is not uncommon as the initial manifestation of MS. Progressive ataxia is less common but when it occurs in the absence of a family history it may be difficult to distinguish clinically from the cerebellar degenerations of middle life. We therefore undertook a study of MRI in this group of disorders, examining 12 cases with a recognizable genetic syndrome and 12 with idiopathic late onset cerebellar ataxia (Harding, 1984). The patients ranged in age from 24 to 64 yrs (mean 42 yrs).

Friedreich's ataxia is readily distinguished from MS by its clinical and electrophysiological features and autosomal recessive pattern of inheritance (Harding,
Four patients were studied. In all there was brainstem atrophy and 1 also showed cerebellar atrophy. In none was there evidence of cortical atrophy.

The remaining 8 cases with inherited ataxic syndromes comprised 5 with autosomal dominant inheritance (Type 1 of Harding, 1982) and 3 with recessive disorders (1 with Kjellin's syndrome, 1 associated with spastic paraplegia and 1 with extrapyramidal features; see Harding, 1984). Cerebellar atrophy was present in all except the patient with Kjellin's syndrome. Brainstem atrophy was present in 4/5 dominantly inherited cases but in only 1 of recessive type. Cerebral cortical atrophy was seen in 3/5 with dominantly inherited syndromes and all of those with recessive syndromes.

Periventricular lesions were present in 2/3 with recessively inherited disease, 1/4 with Friedreich's ataxia, and 3/5 with autosomal dominantly inherited disease (fig. 15A). In all, the lesions differed from those seen in MS by being smooth in outline. No case with Friedreich's ataxia or other recessively inherited ataxia had discrete cerebral lesions, but 3/5 of those with a dominant syndrome did (fig. 15A).

Broadly similar findings were present in the sporadic cases of late onset cerebellar degeneration in none of whom was there clinical or investigative evidence of MS. Cerebellar atrophy was present in 10/12 compared with 7/12 of the 'definitely genetic' cases (fig. 15B). Brainstem atrophy was present in 6/12 (5/12 of the genetic cases). Cerebral cortical atrophy and smooth periventricular changes were rather less frequent: 2/12 compared with 6/12 of the genetic cases for each. Discrete

![Fig. 15. A. axial slice (SE<sub>2000,40</sub>) from a 64-yr-old male with a dominantly inherited cerebellar degeneration. There are smooth periventricular changes and discrete lesions in the cerebral white matter. B. sagittal image (IR<sub>2000,90,40</sub>) showing marked cerebellar atrophy in a 22-yr-old female with a 7-yr history of progressive ataxia and a negative family history.](image-url)
cerebral lesions were also less frequent: 1/12 sporadic compared with 3/12 in the genetic cases.

It was of particular interest to see whether the cases with regions of periventricular abnormality or discrete abnormalities in the cerebral white matter had other evidence that would raise the possibility of MS. Oligoclonal IgG bands in the CSF have not been described in cerebellar degeneration; they were tested for in 8 of the present series and found in none.

The numbers of cases in the individual subgroups of this series of patients is too small to permit characterization of the MRI changes in each of them. Considered as a whole however, the findings show important differences from patients with MS. The most clear-cut finding is that in the majority abnormalities were not seen in the periventricular region and when they were, the smoothness of outline differed from that seen in MS. Since periventricular changes are almost always present in MS it is reasonable to conclude that in patients with established progressive cerebellar ataxia, the absence of such changes, especially in a setting of cerebellar and/or brainstem atrophy, makes a diagnosis of MS highly unlikely.

The frequency and distribution of atrophy in this series of patients is in accord with the pathological description (reviewed by Oppenheimer, 1979; Harding, 1984). Periventricular and focal white matter lesions have not been described, and their significance remains to be determined.

Other conditions

Structural abnormalities in the region of the brainstem, foramen magnum and spinal cord not infrequently cause diagnostic difficulty in patients with progressive spasticity or ataxia in middle life. We have scanned 14 patients aged 17 to 65 yrs (mean 42 yrs) with Chiari types I and II malformations (8), brainstem glioma (2), spinal cord tumour (2), prepontine epidermoid (1) and cervical spondylitic myelopathy (1). Cerebellar ectopia, syringomyelia, and tumours of the brainstem and spinal cord were readily revealed (figs 16, 9A), although bony abnormalities per se were not because of the small number of water protons present in cortical bone. However, bony abnormalities of cancellous bone containing marrow were often obvious, as were protrusions of intervertebral discs.

We have had the opportunity to scan small numbers of patients with neurological manifestations of histologically proved sarcoidosis (7), chicken pox encephalitis (2) and metachromatic leucodystrophy (2). Our experience is insufficient to define the MRI characteristics of these conditions, but in the context of the present paper it is worth noting that in each group we have seen patients with periventricular changes and discrete cerebral abnormalities (fig. 17).

The findings in the 2 cases of chicken pox encephalitis are noteworthy. Both patients were scanned in the symptomatic phase and multiple cerebral white matter abnormalities were visible. A follow-up scan in one of these patients after 18 months showed the lesions persisting. The possibility thus arises that such appearances in
apparently healthy individuals (see below) and in some patients with neurological
disease may reflect past illness and be unrelated to the patient’s present condition.
Because of our interest in the possibility that the MRI changes in chronic lesions
reflect gliosis, we scanned 1 patient who had had a stereotactic prefrontal leucotomy
15 yrs previously (fig. 18A). Morphologically, the sites of leucotomy are char-
acterized by the presence of cystic cavities, foci of nerve fibre loss, reactive gliosis
and in cases examined shortly after the operation, extensive haemorrhage (Meyer

Fig. 16. Sagittal image (SE$_{300,40}$) from a 15-yr-old female
with ataxia and downbeat nystagmus. The cerebellar tonsils
extend down to C2. The medulla is depressed and impressed.

Fig. 17. Axial image (SE$_{200,40}$) in a 25-yr-old
female with progressive dementia from meta-
chromatic leucodystrophy.
and Beck, 1945). The image in fig. 18A shows evidence of a cyst on one side and areas of increased signal on both. The spin-echo characteristics of the latter are indistinguishable from those of lesions in MS or cerebral vascular disease.

Healthy controls

When the present investigation began (April 1984), relatively little had been published about the findings in apparently healthy individuals. It was obviously important to establish the range of appearances encountered in 'normal' people of different ages using the sequences that were used to investigate patients with neurological disease. We scanned 53 men and women who believed themselves to be fit and in whom no evidence of past or present neurological disease was found on a general health questionnaire; they were not, however, examined neurologically. The ages ranged from 17 to 68 yrs (mean 46 yrs). In 48, no abnormalities were detected. In 2 of 3 individuals over the age of 60 yrs there was smooth altered signal in the periventricular region, as others have described (Brant-Zawadski et al., 1985). In 2, aged 54 and 45 yrs, there were a few small areas of abnormality without periventricular changes. The origin of these changes is uncertain, but, as already mentioned, they could be a consequence of cerebral involvement in the childhood exanthemata or of occult vascular disease. One healthy individual showed extensive periventricular changes and discrete white matter abnormalities indistinguishable from those in MS (fig. 18B). We do not know whether this patient has MS or not, but the occasional finding of such abnormalities in normal individuals is in keeping
with the observations of Gilbert and Sadler (1983), who found evidence of 'unsuspected' MS at postmortem in 5 of 2450 brains examined at routine necropsy.

**DISCUSSION**

This investigation has shown that characteristic periventricular and discrete abnormalities in the white matter were seen on NMR images in 99% of patients with clinically definite MS, which corresponded to the distribution of plaques at postmortem. Similar multiple MRI abnormalities were seen at presentation in between a half and two-thirds of patients with clinically isolated lesions of the kind seen in MS, such as optic neuritis, acute brainstem lesions and progressive spastic paraplegia. Although the changes in MS were not specific, more or less similar abnormalities being frequent in a variety of other conditions, their distribution was characteristic.

These observations provide a basis for assessing the role of MRI in the differential diagnosis of MS. Comparison of the images obtained in the different clinical groups showed that although no change was specific to any single disease process, the form and distribution of abnormalities could point strongly to particular diagnoses. The outline of the periventricular abnormalities was almost invariably irregular in MS, reflecting the finger-like extensions of the lesions (Dawson, 1916) along the cerebral veins (Fog, 1965) whereas, with the notable exception of dementia with diffuse white matter abnormalities, the periventricular changes in cerebral vascular disease and in ageing were sometimes smooth in outline, and often less extensive. Like Kortman *et al.* (1985), we found that discrete brainstem lesions were more common in MS than in cerebral vascular disease. This finding was, however, of little value on its own in the individual patient. Abnormalities conforming to the distribution of major cerebral vessels of course provided strong evidence of vascular disease.

It is clear that MRI is the most sensitive means currently available for detecting lesions in MS. The relative lack of specificity of the changes, however, limits the role of the technique at present to an anatomical one, namely that of determining whether multiple lesions are present. It is likely that with increasing experience, detailed analysis of the appearances and distribution of lesions will provide a useful contribution to differential diagnosis. Evoked potentials have a similar anatomical role, but sensitive though they are to defects in the pathways subserving them, they are less useful than MRI in establishing multiplicity of lesions because they sample such small fractions of the central white matter. In essence, the present contributions of MRI and evoked potentials to the assessment of patients suspected of having MS are similar: they can detect the presence of a lesion (provided it is greater than a certain minimum size) but the interpretation of its significance depends on the clinical context.

In patients scanned once at presentation with a single acute neurological episode (e.g., optic neuritis) the presence of multiple lesions cannot of itself be used as a
basis for the diagnosis of MS, even though the distribution of lesions may be highly suggestive. In high prevalence areas such as the United Kingdom it is of course likely that most patients with multiple lesions at presentation will subsequently develop clinically manifest dissemination of lesions, but at present the risk that an individual patient will do so is not established. The diagnosis of MS becomes clinically probable (Poser et al., 1983) if subsequent scans reveal new lesions, provided that appropriate precautions to ensure precise repositioning of the head have been taken and the same sequences are used. The timing of subsequent scans is a matter for judgement, but in conformity with the criteria of Poser et al. (1983) they should not be used for diagnostic reassessment until at least one month has elapsed, and on the whole we recommend an interval of about six months to minimize the risk of misdiagnosing a case of rather slowly evolving encephalomyelitis as MS.

MRI is of particular value in certain kinds of patient. First, there are those in the less definite categories of MS. In the patient with a history of several episodes of neurological disturbance but with clinical evidence of only a single lesion, the finding of multiple lesions enables a clinically definite diagnosis to be made.

A second group of patients in which MRI is useful is that with progressive ataxic and spastic syndromes in middle life. Congenital anomalies, tumours and cysts in the region of the foramen magnum, spinal cord and brainstem are easily recognized. The finding of brainstem or cerebellar atrophy in patients with an established picture of progressive ataxia in the absence of abnormalities in the white matter provides strong evidence for a diagnosis of cerebellar degeneration and against a diagnosis of MS. The presence on a single scan of irregular periventricular changes and discrete lesions in the intracranial white matter is not sufficient to diagnose MS. As for acute isolated lesions, a clinically probable diagnosis on MRI evidence requires the demonstration of the development of new lesions by serial scanning, provided of course that there is no better explanation for them.

The results derived from a comparison of quantitative data on the relaxation times $T_1$ and $T_2$ in acute and chronic brainstem lesions encourage us to think that further development of this approach may permit the differentiation of such lesions in a single scan, thereby permitting earlier diagnosis. It is important to stress, however, that this work is in an early stage of development and that since the values for $T_1$ and $T_2$ are influenced by the characteristics of the individual scanner our data cannot be applied directly to the interpretation of data from other sources.

A notable feature of our investigation, as of others, was the frequency with which there were discrepancies between the clinical features and the location and number of lesions as detected by MRI in MS and the clinical syndromes attributable to 'isolated lesions'. This is what should be expected from a knowledge of the pathophysiology of the disease. The complex issues involved are discussed by McDonald (1986).
Origin of MRI abnormalities

The study of postmortem brains provided convincing evidence that the abnormalities seen on MRI correspond with plaques. The question now arises as to the origin of the abnormal signals. Any explanation must account for the similarities between the abnormal images in MS, a predominantly demyelinating disease, and the various forms of cerebral vascular disease in which both axons and myelin are destroyed (Janota, 1981; Allen, 1984).

The signal intensity in proton NMR images depends upon many different factors of which proton density and the relaxation times, $T_1$ and $T_2$, are usually the most important. Since the signal from normal brain is largely derived from water protons (Bottomley et al., 1984), and since $T_1$ and $T_2$ are strongly influenced by the macromolecular environment of that water, image abnormalities will result from changes in both the quantity of tissue water and its macromolecular environment. There are a number of possible mechanisms for the observed signal changes. The effects of demyelination on image appearances are difficult to predict: both the constituent lipid protons of myelin, and the water associated with it are effectively invisible in NMR images due to their very short $T_2$ relaxation times. It would be expected, therefore, that demyelination per se would have little effect on the image appearances. Following the loss of myelin, however, there remains a larger proportion of the tissue which may be occupied by water molecules of longer $T_2$ relaxation times which are able to generate a detectable signal. Thus, it is possible that demyelination may lead to secondary changes in the tissue NMR parameters, and so to image intensity of white matter.

In the chronic lesion of MS (fig. 4) and in dementia with diffuse white matter abnormality, gliosis is as striking as the myelin loss (see fig. 2, McDonald, 1986). Electron microscopy shows that in the plaque of MS the space created by the disappearance of myelin is filled by the cytoplasm-rich fibrillary astrocytic processes; the appearance is well illustrated in fig. 4 of Prineas and Connell (1978). The expectation that these changes would result in an increase in water content per unit volume is supported by the measurements of Tourtellote and Parker (1968) who showed that there is a significant increase of water content in plaque tissue compared with normal white matter. It is therefore likely that the abnormalities in MR images to some extent reflect gliosis by virtue of the increase in water protons. It is also possible that differences between the macromolecular environment of water in astrocyte processes and in the normal tissue water spaces contribute.

The origin of the halo-like abnormalities seen in some patients is at present uncertain, and more than one mechanism may be involved. One possibility is that they represent lesions undergoing centrifugal enlargement with an outer rim of active myelin breakdown and a core of established gliosis and demyelination (see Prineas and Connell, 1978). Alternatively they might represent new lesions with active central myelin breakdown accompanied by oedema and cellular infiltration which progressively diminishes peripherally.
It is generally believed that water passes from the CSF into brain substance, particularly under conditions in which the balance between intraventricular pressure and brain compliance is disturbed. The contribution of this water, diffusing from the ventricle to the periventricular high signal area, might be substantial and find its way especially to neighbouring regions of damaged brain.

Data on the cerebral water content are not available for dementia with diffuse white matter abnormality or the lesion produced by leucotomy, but from the histological similarities it seems likely that the MRI abnormalities in these conditions have a similar origin. The observation that the gliosis following experimental vasogenic oedema in the cat is accompanied by similar MRI abnormalities suggests that gliosis is in part responsible for the abnormal MR images of a variety of affections of white matter (D. Barnes, W. I. McDonald, D. N. Landon, G. Johnson, unpublished observations).

The origin of the MRI abnormalities in the acute lesions of MS (e.g., in the brainstem) is probably more complex. Experimentally, both the acute vasogenic oedema of the lesion produced by cortical freezing and the cytotoxic oedema of acute triethyl tin intoxication are associated with striking MRI abnormalities (Barnes et al., 1986, 1987). The two types of acute oedema can be distinguished from each other (reflecting their different protein content) and from the chronic (gliotic) cold lesion by the pattern of alterations in the measured value of $T_1$ and $T_2$. Adams (1983) has described oedema in association with the acute lesions of MS and it seems likely that the MRI changes in such lesions reflect alterations in the quantity and distribution of tissue water. A relative increase in intracellular water per unit volume due to the accumulation of macrophages and the activation and proliferation of astrocytes might also play a part, though a smaller one.

It is of interest that serial imaging in experimental vasogenic oedema has shown that the acute image abnormalities disappear after about a week, coincident with the resolution of the oedema, only to become abnormal again after two to four months, corresponding with the development of gliosis (D. Barnes, W. I. McDonald, D. N. Landon, G. Johnson, unpublished observations). These observations have implications for the interpretation of MR images in MS. The failure to identify an abnormality after the acute development of a symptom may not mean that none was present earlier or that none will be obvious later; and the apparent disappearance of a lesion (spontaneously or during treatment) need not imply resolution of the pathological changes with restoration of normal structure. Serial studies in patients with acute lesions made at short intervals will be necessary to determine how important these considerations are in human disease.

Much of the white matter between the plaques in MS appears macroscopically normal both at postmortem and by MRI. Nevertheless we found quantitative differences in $T_1$ and $T_2$ between the normal-appearing white matter in MS and in healthy individuals. The explanation probably lies, at least in part, in the limited resolution of our MRI system with the scan times used (voxel size approximately 30 mm$^3$). Established plaques and oedematous regions smaller than this would not
be visible on the images but might change the values of $T_1$ and $T_2$. It is also possible that changes in the density and macromolecular environment of protons caused by the diffuse increase in the number of astrocytes present in normal-appearing white matter in MS (Allen 1984), and the presence of myelin breakdown products in scattered microscopic lesions play a part. The quantitative data thus provides a more accurate reflection of the diffuseness of pathological changes in MS than the visual impression gained from the MR images or naked eye examination of the cut brain or stained sections. Both the natural history of the individual plaque and the background changes in the intervening white matter are of great interest in relation to the pathogenesis and pathophysiology of the disease. MRI offers the possibility of investigating the changes serially as resolution improves and quantification becomes more sophisticated.

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REFERENCES


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