

BREAKDOWN OF THE BLOOD-BRAIN BARRIER PRECEDES SYMPTOMS AND OTHER MRI SIGNS OF NEW LESIONS IN MULTIPLE SCLEROSIS

PATHOGENETIC AND CLINICAL IMPLICATIONS

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SUMMARY

From an extensive serial magnetic resonance imaging (MRI) study in multiple sclerosis (MS) we have identified 4 cases in which disruption of the blood-brain barrier, as detected by gadolinium-DTPA enhancement, preceded other MRI abnormalities and in 1 case clinical evidence of the new lesion. This supports the view that a defect in the blood-brain barrier, and therefore inflammation, is an early and possibly crucial event in the pathogenesis of the new lesion in MS. These cases showed a marked discrepancy between MRI abnormality and symptoms. The mechanisms contributing to this disparity are discussed, and it is concluded that far from being surprising it is to be expected.

INTRODUCTION

The sequence of events in the development of the acute lesion in multiple sclerosis (MS) remains unresolved. Histological data has been inadequate as few postmortem or biopsy studies have been performed in the context of an acute relapse (Prineas *et al.*, 1987). While an inflammatory component has been recognized for many years (Dawson, 1916; Greenfield and King, 1936) its precise role remains unclear, some authors regarding it as secondary to myelin breakdown produced by an independent mechanism (Calder *et al.*, 1989), while others consider it to be pathogenetically related to demyelination (Adams *et al.*, 1985; Hafler and Weiner, 1989). Over the last 15 yrs evidence has accumulated that a perivascular inflammatory infiltrate is characteristic of the acute lesion (Adams, 1975; Guseo and Jellinger, 1975). Such perivascular inflammation has also been seen in normal-appearing white matter of the brain and in the retinal venules in the absence of subjacent parenchymal inflammation (Arnold *et al.*, 1984; Lightman *et al.*, 1987), leading to the conclusion that perivascular inflammation in MS can occur in the absence of myelin breakdown, and the suggestion that a vascular event is a necessary preliminary to the development of structural damage.

Magnetic resonance imaging (MRI) provides a noninvasive means of studying disease

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activity in MS (Young *et al.*, 1981; Ormerod *et al.*, 1987; Paty *et al.*, 1988). Gadolinium-DTPA (Gd-DTPA) enhancement signifying breakdown of the blood-brain barrier (Hawkins *et al.*, 1990) has been shown to be a consistent finding in new lesions in relapsing/remitting and secondary progressive MS (Grossman *et al.*, 1986; Miller *et al.*, 1988a; Thompson *et al.*, 1989a). Similar studies in chronic relapsing experimental allergic encephalomyelitis have shown that the enhancement seen in acute lesions only occurs at sites of active inflammation (Hawkins *et al.*, 1990). The important question regarding the evolution of the acute MS lesion is: How early does blood-brain barrier breakdown occur? We have had the opportunity to try to answer this question in the course of a serial study comparing primary and secondary progressive MS and in a study of brainstem symptomatology in demyelinating disease. Gd-DTPA enhancement was detected either before other evidence of white matter involvement or before the development of clinical signs in 4 patients. Three patients were part of a larger cohort of 12 patients with secondary progressive MS who were taking part in a study comparing the pattern and time course of enhancement in new lesions with patients who were progressive from onset (primary progressive). In the secondary progressive group multiple enhancing lesions are frequently seen, many of which do not relate to the patient's symptoms (Thompson *et al.*, 1989a). The fourth patient presented with brainstem symptoms.

METHODS

Magnetic resonance imaging

MRI was performed on a Picker 0.5T superconducting MR imager as part of a serial study in MS. Cases 1, 2 and 3 had T₂ weighted MRI of brain (SE_{2000/60}), with 5 mm contiguous slices and a 128×256 image matrix. Case 4 had T₂ weighted MRI of brain (SE_{2000/40} and SE_{2000/120}) with 10 mm slices and a 256×256 image matrix. Scanning plane in Cases 1, 2 and 3 was determined by 4 oblique pilots (transverse, coronal, sagittal and a final check transverse pilot) to ensure consistency of the imaging plane over the course of the serial study (MacManus *et al.*, 1989). All had T₁ weighted precontrast images (SE_{500/40}), followed by intravenous injection of Gd-DTPA (0.2 mmol/kg in Cases 1 and 4, 0.1 mmol/kg in Cases 2 and 3). Post Gd-DTPA images were obtained using SE_{500/40}. MRI was repeated between 10 and 14 days later in the first 3 cases and 28 days later in Case 4.

A full neurological examination was carried out at the time of each scan and disability was scored on Kurtzke's Expanded Disability Status Scale (EDSS) (Kurtzke, 1983). Scans were examined by D.P.E.K. and B.E.K. without knowledge of the patient's clinical condition.

CASE REPORTS

All cases had clinically definite MS (Poser *et al.*, 1983) with oligoclonal IgG bands in the CSF. The first 3 cases had relapsing/progressive MS (secondary progressive) and the fourth was still in the relapsing/remitting phase. All 4 patients were studied during an acute relapse.

Case 1

A 25-yr-old female with a 6 yr history of MS and a disability score of 4.5 on the EDSS became severely ataxic with marked weakness of her left leg such that she was only able to walk a few feet. Seven days later MRI showed numerous new lesions in both cerebral and cerebellar hemispheres with a large new lesion in the right precentral gyrus consistent with her left-sided weakness (fig 1A). Twenty-seven areas of Gd-DTPA enhancement were seen, including several small areas of enhancement within the much larger region of abnormality on the T₂ weighted MRI in the right precentral gyrus (fig. 1B). One enhancing region in the left frontal lobe did not correspond to any lesion on the T₂ weighted MRI (figs 1C, D). Ten days later a lesion was clearly seen on T₂ weighted MRI in the left frontal lobe (fig. 1E). T₂ weighted MRI

2 months later showed that the large precentral gyrus lesion had shrunk and was now of similar proportion to the original areas of enhancement (fig. 1F).

Case 2

A 29-yr-old male who had a 3 yr history of MS and moderate disability (EDSS = 4) developed paraesthesiae in both legs with marked pyramidal weakness and a sensory level to touch and pin prick at T8. T₂ weighted MRI 7 days later showed a new lesion adjacent to the left sylvian fissure. Gd-DTPA enhanced images showed enhancement in the new lesion, in a left periventricular lesion still enhancing from 2 wks previously, and in the left internal capsule which did not correspond to any lesion on the T₂ weighted MRI (figs 2A, B). Fourteen days later a lesion was seen on the T₂ weighted MRI in this position (fig. 2c). No enhancement was seen after injection of Gd-DTPA on this occasion.

Case 3

A 54-yr-old male, who had MS for 7 yrs and now had moderate disability (EDSS = 5), developed numbness in both hands, increasing weakness of both legs with a T10 sensory level of touch and pin prick, and urinary frequency. Five days later an MRI of brain revealed 2 new lesions known from serial scans to be less than 14 days old: 1 left frontal and 1 left thalamic. There was also a possible lesion in the right posterior temporal lobe which was barely visible (fig. 3A). After Gd-DTPA, 5 enhancing areas were seen. Two lesions (left occipital and left periventricular) were already enhancing 4 wks previously; (1 was 4 weeks old and the other was an older reactivated lesion). The 2 new lesions (left frontal and left thalamic) were also enhancing. A fifth enhancing area was seen in the right posterior temporal lobe which corresponded to the faint lesion on the T₂ weighted MRI (fig. 3B). Fourteen days later this lesion was clearly visible on the T₂ weighted MRI (fig. 3c).

Case 4

A 47-yr-old man with a 4 yr history of MS developed a rapidly progressive right-sided hearing loss following a 2 wk history of vertigo and nausea when lying on the right. Examination revealed abnormal extraocular movements with saccadic pursuit and first degree nystagmus to left and right and downwards. There was reduced perception of light touch but not pin prick in the area of the right fifth nerve, mild right facial weakness and a moderate spastic ataxia of all four limbs with brisk tendon reflexes and extensor plantar responses. There was mild impairment of vibration sense at the left hallux, Romberg's test was positive and his gait was grossly ataxic. Caloric testing demonstrated a total canal paresis on the right. Audiometric testing revealed absent hearing on the right and the pure tone audiogram was equivocal on the left. The auditory brainstem responses were absent bilaterally. Over the next 7 days auditory acuity declined rapidly on the left and then slowly improved over the next 3 wks. The right ear also began to improve and had returned to normal 1 month after presentation. The auditory brainstem responses remained absent. A initial MRI showed an enhancing lesion in the right pons extending towards the root entry zone of the eighth nerve (figs 4A, B). There was also a faint lesion in the left root entry zone which was more obvious on the enhanced scan (figs 4B, C). One month later the left-sided lesion was clearly visible on the T₂ weighted scan and continued to show enhancement (fig 4D). The right-sided lesion persisted but showed less enhancement. Thus enhancement preceded the development of clinical deafness on the left.

DISCUSSION

The serial scans of the first 3 patients show that blood-brain barrier breakdown can precede the appearance of new lesions on T₂ weighted MRI (Cases 1, 2); Cases 3 and 4 show that prominent enhancement precedes the development of the marked increase in signal on T₂ weighted MRI characteristic of the established unenhanced lesion, and in the fourth case blood-brain barrier breakdown preceded the clinical expression of the new lesion. In addition a clear discrepancy between MRI abnormalities and clinical symptoms was seen in the 3 secondary progressive cases. These observations have important implications for our understanding of the pathogenesis of MS and raise questions

about the relationship between MRI abnormalities and the development of symptoms.

Do these observations help to decide if the inflammation seen in MS is a primary or secondary event? In chronic relapsing experimental allergic encephalomyelitis

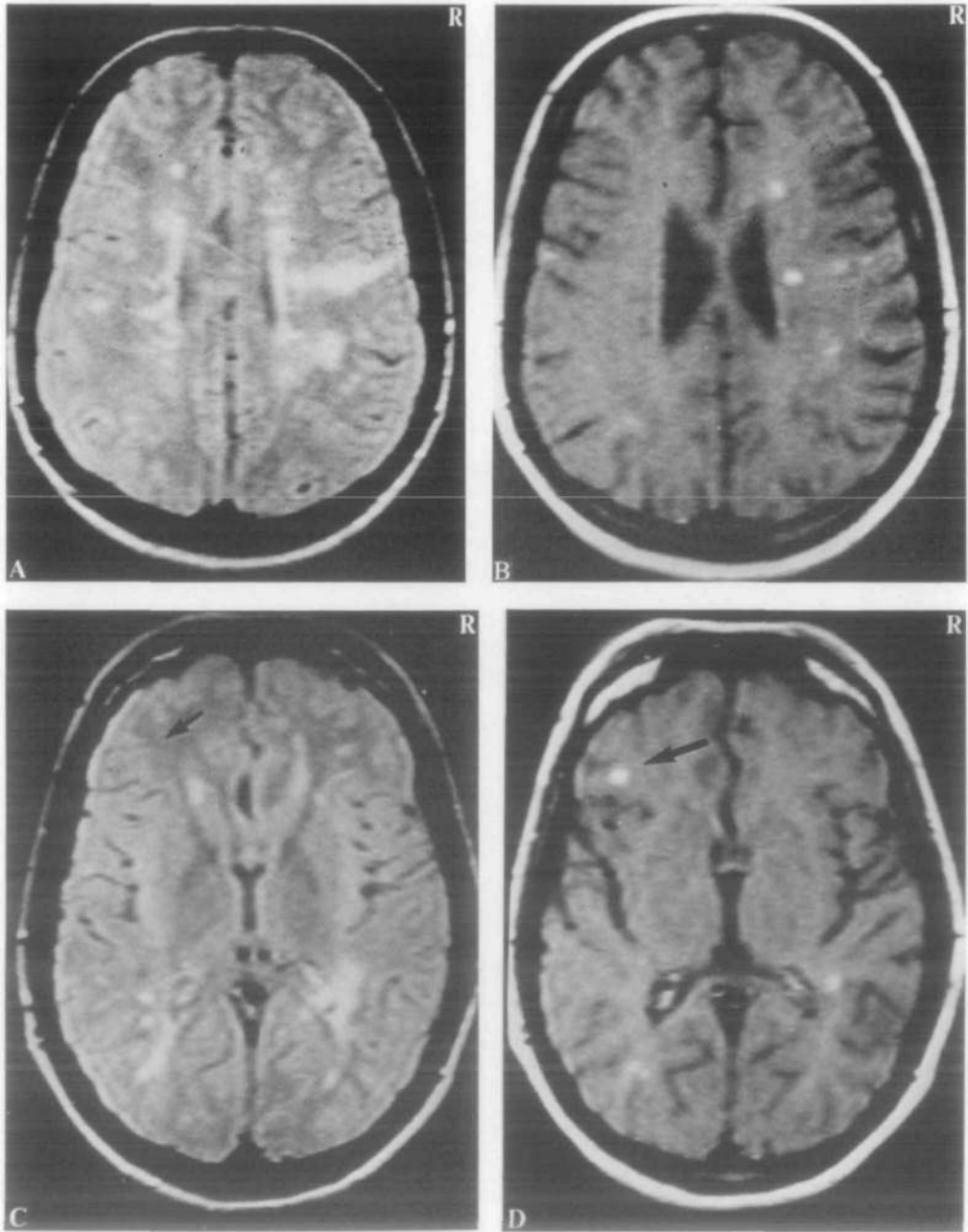


FIG. 1A-D.

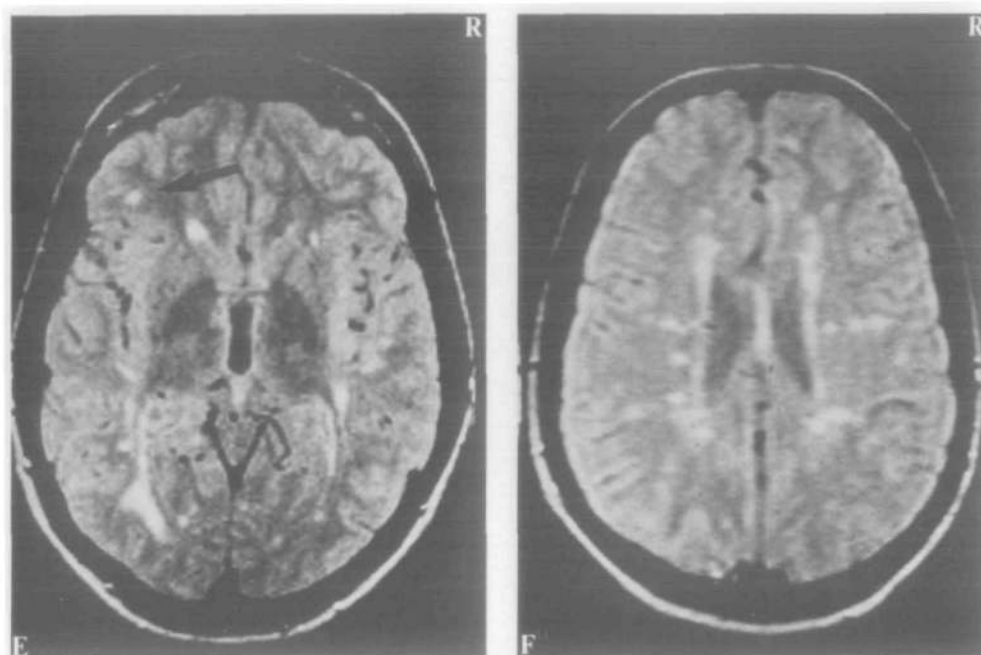


FIG. 1. A, unenhanced T₂ weighted MRI (SE_{2000/60}) showing a large lesion adjacent to the right precentral gyrus. B, T₁ weighted Gd-DTPA enhanced MRI (SE_{500/40}) several minutes later at the same level as fig. 1A showing several small areas of enhancement. C, unenhanced T₂ weighted MRI (SE_{2000/60}). No lesion is visible where arrowed. D, T₁ weighted Gd-DTPA enhanced MRI (SE_{500/40}) several minutes later at the same level as fig. 1C showing a brightly enhancing lesion. E, unenhanced T₂ weighted MRI (SE_{2000/60}) 10 days later at the same level as figs 1C and D. The lesion is now visible. F, unenhanced T₂ weighted MRI (SE_{2000/60}) 2 months later at the same level as fig. 1A showing shrinkage of the large prefrontal gyrus lesion.

(CREAE), a disease with pathological similarities to MS, enhancement with Gd-DTPA has been shown to correlate with the presence of active inflammation and occurs at the time of relapse (Hawkins *et al.*, 1990). Given the pathological parallels between the two conditions (Lassmann, 1983), it is probable that enhancement in MS is also occurring at sites of active inflammation. Furthermore, the pattern of Gd DTPA enhancement seen in acute and subacute lesions in MS (Kermode *et al.*, 1990) correlates well with the distribution of inflammation seen in pathological studies; small new lesions tend to enhance uniformly, corresponding with focal perivenular lesions, while larger older lesions show peripheral ring-like enhancement in keeping with the histological findings at postmortem of myelin breakdown products and inflammatory cells in the same distribution (Prineas and Connell, 1978). Our observations suggest that inflammation occurs very early in the evolution of the new lesion and is in keeping with the accumulating evidence that inflammation is an early and possibly the primary event in the development of new white matter change in MS.

Perivascular inflammation or cuffing in macroscopically normal appearing white matter, which had previously been considered a rare finding, is now well documented (Adams, 1975; Allen and McKeown, 1979), and more recently the crucial observation of

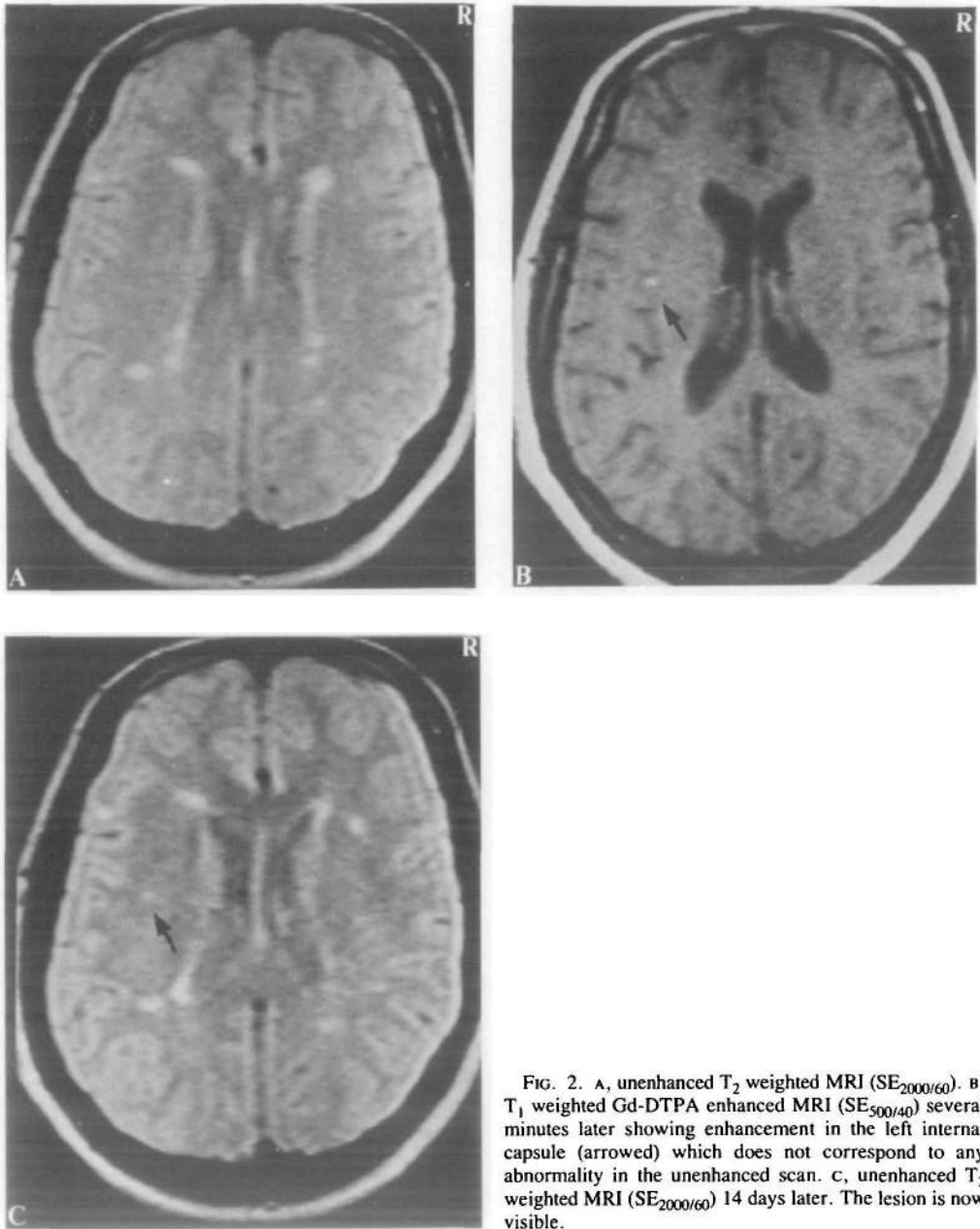


FIG. 2. A, unenhanced T_2 weighted MRI ($SE_{2000/60}$). B, T_1 weighted Gd-DTPA enhanced MRI ($SE_{500/40}$) several minutes later showing enhancement in the left internal capsule (arrowed) which does not correspond to any abnormality in the unenhanced scan. C, unenhanced T_2 weighted MRI ($SE_{2000/60}$) 14 days later. The lesion is now visible.

inflammatory infiltrate confined to the vessel wall of venules in the brain with normal surrounding tissue has been made (Adams *et al.*, 1985). This latter observation is further supported by findings in the retina of patients with optic neuritis and MS (Rucker, 1944). In this area which is free of myelin, venous sheathing has been detected in up to 25%

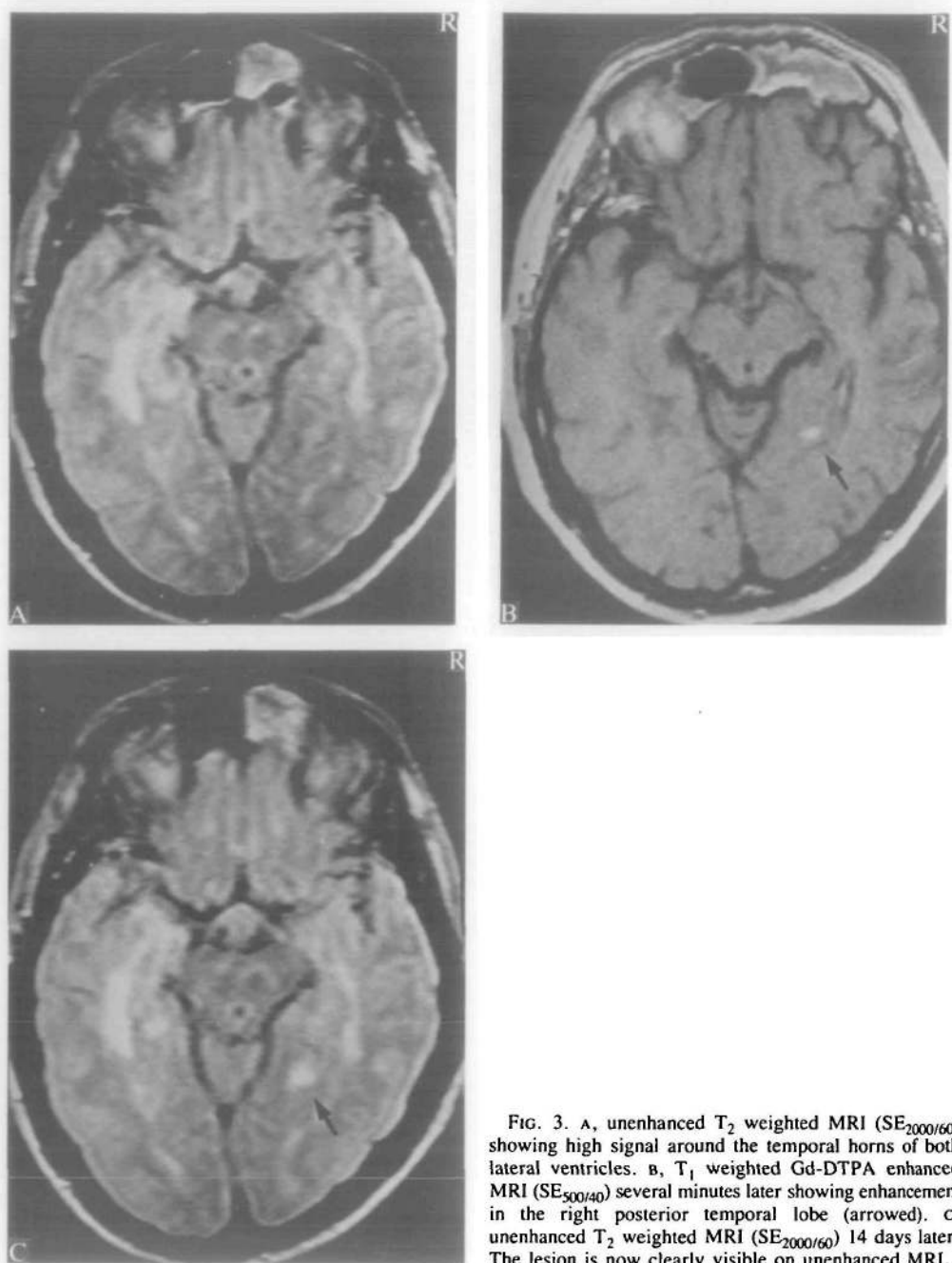


FIG. 3. A, unenhanced T₂ weighted MRI (SE_{2000/60}) showing high signal around the temporal horns of both lateral ventricles. B, T₁ weighted Gd-DTPA enhanced MRI (SE_{500/40}) several minutes later showing enhancement in the right posterior temporal lobe (arrowed). C, unenhanced T₂ weighted MRI (SE_{2000/60}) 14 days later. The lesion is now clearly visible on unenhanced MRI.

of patients when studied appropriately (Lightman *et al.*, 1987; Graham *et al.*, 1989); these appearances are frequently accompanied by leakage on fluorescein angiography. Histologically, the sheathing corresponds with perivenular infiltration with mononuclear

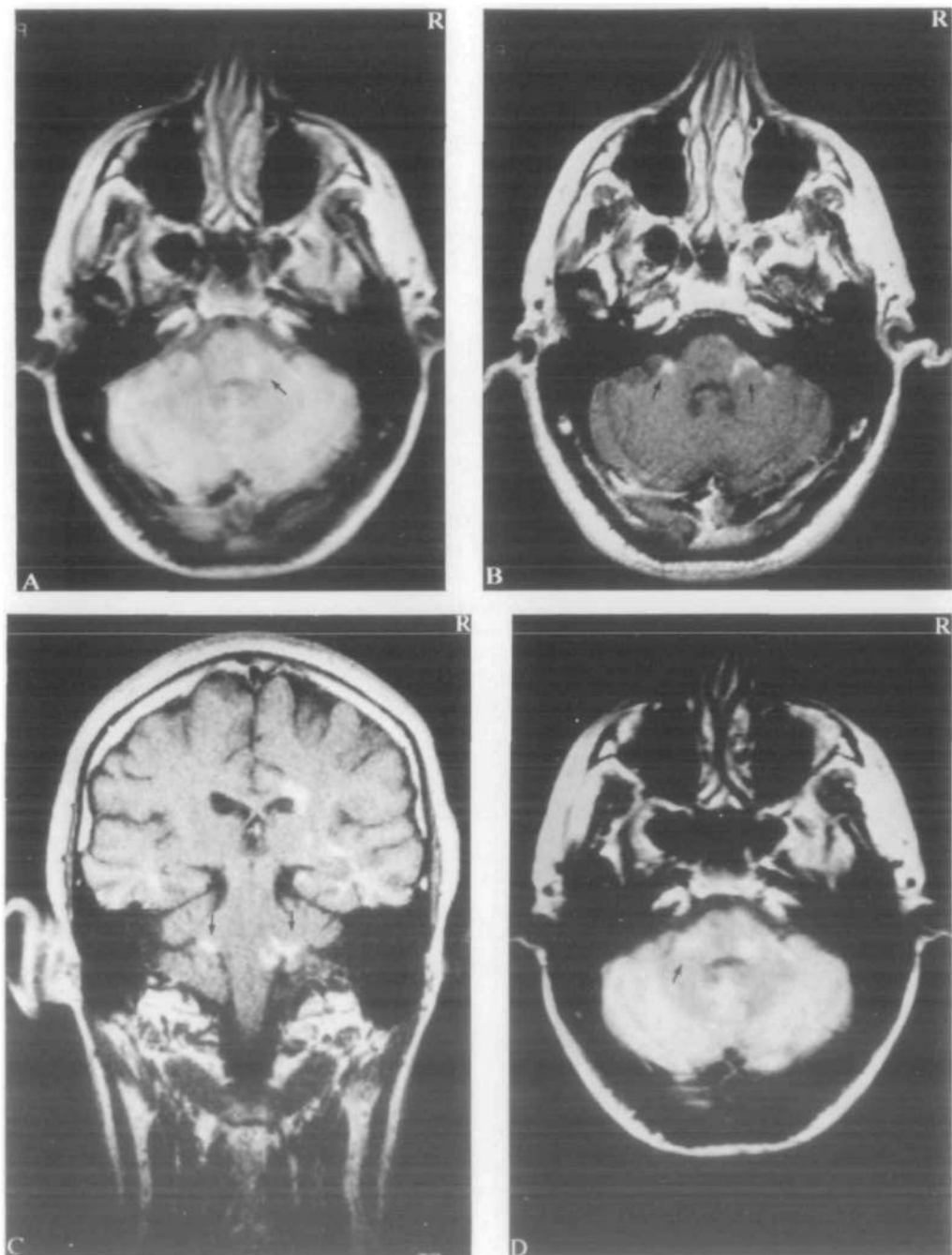


FIG. 4. A, unenhanced T₂ weighted MRI (SE_{2000/40}) showing a lesion in the right pons (arrowed) which extends to the root entry zone of the right acoustic nerve. B, T₁ weighted Gd-DTPA enhanced MRI (SE_{500/40}) several minutes later showing enhancement (arrowed) in both the right and left root entry zones of the eighth nerve. C, coronal T₁ weighted Gd-DTPA enhanced MRI (SE_{500/40}) taken immediately after B, also demonstrating the bilateral enhancement (arrowed). D, unenhanced T₂ weighted MRI (SE_{2000/40}) 1 month later which clearly shows a lesion in the left root entry zone.

cells (Fog, 1965) which is in fact quite common in the retina at postmortem (Klintworth, 1982; Arnold *et al.*, 1984) and occurs in the absence of inflammation in the subjacent retinal tissue (Ingrid Allen, personal communication). In summary, the detection of inflammation restricted to blood vessels with normal surrounding tissue suggests that this is a primary event in MS and not a secondary phenomenon.

The clinicopathological paradox

The second question these observations raise is that of the relationship between MRI abnormalities and clinical deficit. Several facts require explanation: MRI lesions are sometimes associated with clinical deficit and sometimes not, and a substantial functional deterioration may occur in the absence of relevant new lesions on MRI.

In order to try to resolve the paradox presented by these dissociations between clinical deficit and pathological activity we must first consider what MRI abnormalities represent. In essence, they indicate the presence of regions in which there are changes in the amount of water and its physicochemical state. In practical terms this comes to changes in intracellular water (i.e., changes in the amount of cytoplasm per unit volume), and in extracellular water (i.e., oedema). The latter has a varying content of protein depending on the type of pathological process present and the stage of its evolution, and will have correspondingly different MRI signals at different times (Barnes *et al.*, 1987a, Larsson *et al.*, 1988). With present clinical MRI technology normal myelin and myelin breakdown products are not directly visualized, though the presence of breakdown products may be suspected (Kermode *et al.*, 1989). Thus the MRI changes chiefly reflect alterations in tissue elements other than the nerve fibres, interference with the function of which is necessary for the development of a clinical deficit. Nevertheless, in CREAE the development of enhancement usually does correspond with areas of myelin damage (Hawkins *et al.*, 1990). A good correlation between MRI abnormality and functional loss is therefore to be expected when lesions occur in regions where there is a concentration of all the nerve fibres essential to a particular function. A good example is provided by Case 4 with deafness and corresponding lesions at the eighth cranial nerve root entry zones, and by optic neuritis where 84% of symptomatic optic nerves show MRI changes (Miller *et al.*, 1988b). Why then are such extensive lesions so often seen in the cerebral hemispheres with little clinical deficit? A number of factors are involved.

In the first place, it must be remembered that many of the most obvious MRI lesions in MS occur in the periventricular regions, damage to which is not currently recognizable by neurological examination though there is an association (but not necessarily a causal connection) with cognitive deficit (Callanan *et al.*, 1989; Rao *et al.*, 1989). Secondly, the possibility of dissociation between nerve fibre damage and oedema has already been mentioned. This is clearly demonstrated in the first case (figs 1A, B, F) in which a very extensive area of abnormal signal corresponded to a smaller zone of enhancement; over the subsequent 2 months the lesion shrank to an area only slightly greater than that of the original area of enhancement. It is difficult to think of a pathological change other than oedema which could resolve so rapidly and completely in 2 months. This interpretation is supported by the biexponential T_2 magnetization decay curves recorded from such areas (D. Barnes, unpublished observations). While it is likely that oedema contributes to physiological and clinical deficit in regions where the tissue is not free

to expand (e.g., the optic nerve in the optic canal; Miller *et al.*, 1988*b*) the frequent lack of symptoms in patients with extensive oedema, not only in MS but with cerebral tumour, suggests that other factors appearing with a similar time course are more important. Demyelination is one of these, and the products of inflammatory cells might also contribute.

A further complicating factor that will influence the clinical expression of MS lesions is their orientation which is to the veins, which do not necessarily correspond to the direction of nerve fibres. Thus fibres in any particular pathway may traverse some lesions in their long axis, and others at right angles, and others obliquely. The extent of the myelin damage (which ultimately determines the severity of the conduction defects) will be very different in the different orientations. The difficulties are further increased by the fact that lesions are often irregular in outline so that different parts of a pathway at a single level may be damaged to differing extents: a clinical deficit will appear only when conduction in a critical proportion of the fibres is blocked. It must also be remembered that many regions of white matter contain a number of different pathways, so that the extent to which fibres subserving a particular function are damaged will be unpredictable from MRI images.

Finally, in chronic lesions the MRI changes correspond with a persisting increase in tissue water, predominantly extracellular, although gliosis is also present (Barnes *et al.*, 1987*a, b*). Again, there is not a necessary and direct relationship between these nonneural changes and axonal function which may have been restored to a varying extent by the compensatory process of remyelination or acquisition of the capacity to conduct in persistently demyelinated fibres (McDonald, 1986).

It is now appropriate to consider the explanation of the converse problem: the presence of significant clinical deficit with minimal MRI abnormality. This discrepancy is highlighted by the extensive lesions seen in benign MS when compared with primary progressive MS (Thompson *et al.*, 1989*b*). An obvious possibility is that many lesions large enough to produce conduction block (paranodal demyelination alone may be sufficient) are beyond the resolution of the present imager. Another possibility is that there is more wallerian-type degeneration in the chronic progressive cases. This process can be initiated by a small focal lesion and the modest gliosis which follows tract degeneration is not likely to change the MRI signal. Finally, especially in MS presenting as progressive spastic paraplegia, it is probable that many of the lesions producing disability are in the spinal cord where imaging is still less satisfactory than in the brain.

With this discussion in mind it is instructive to return to Case 4. Deafness in the right ear was established at presentation, and corresponded with an obvious MRI abnormality in the unenhanced scan at the entry of the eighth nerve to the brainstem. This lesion did enhance, and from animal studies (Hawkins *et al.*, 1990) it is likely that demyelination was present in association with the established and still active inflammation. There was no clinical deficit in the left ear at the time of presentation, though the evoked potential was already abnormal indicating that some nerve fibre damage had taken place; subclinical electrical abnormalities are a commonplace finding in demyelinating disease (Halliday, 1982). A faint area of abnormal signal was present on the unenhanced scan, and there was strong enhancement with gadolinium-DTPA indicating that blood-brain barrier was defective. We interpret these observations as indicating that inflammation was present, producing a small amount of oedema (compatible with the unenhanced images) but that

demyelination was still limited. Two weeks later there was a marked abnormality on the unenhanced scan which still enhanced strongly, making it likely (from experimental studies) that there would be more extensive demyelination, accounting for the deafness which was now present.

In summary, far from being surprised by the variable relationship between the numbers and extent of MRI abnormalities and clinical features, we should expect them. The occurrence of a breakdown in the blood-brain barrier before other MRI evidence of a lesion, or before the development of symptoms in an appropriately sited lesion, provides strong evidence that this vascular change is a very early event in the development of the new lesion.

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