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Cortical lesions in multiple sclerosis

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Summary

Although previous studies have shown that the lesions of multiple sclerosis may involve the cerebral cortex, there is little published research on the prevalence and distribution of such lesions. Using neuropathological techniques and MRI, a series of studies has been undertaken in order to assess this, in particular to identify their relationship to cortical veins. A serial MRI study showed that the use of gadolinium proffered an increase in cortical lesion detection of 140% and showed that 26% of active lesions arose within or adjacent to the cortex. In a post-mortem study, MRI under-reported lesions subsequently analysed neuropathologically, particularly those arising within the cortex. In a further 12 cases examined, 478 cortical lesions were identified, of which 372 also involved the subcortical white matter. Seven different lesion types were identified; the majority arose within the territory of the principal cortical veins, whilst the remaining quarter arose within the territory of the small branch or superficial veins. Small cortical lesions are common in multiple sclerosis and are under-reported by MRI. Investigation of the cortical venous supply shows how such lesions may arise, and why the majority also involve the underlying white matter.

Keywords: multiple sclerosis; cortical lesions; neuropathology; MRI

Introduction

The lesions of multiple sclerosis typically arise within the optic nerves, spinal cord, brainstem and the periventricular white matter of the cerebral hemispheres. These are readily detected *in vivo* by means of MRI which has greatly improved diagnostic accuracy in this disorder and through research which has increased understanding of the pathophysiology of the disease. Recent MRI studies using the paramagnetic agent gadolinium, which, by virtue of enhancement of the process of longitudinal relaxation, shows up lesions associated with inflammation and breakdown of the blood–brain barrier (Kermode *et al*., 1990), have shown that lesions also arise within grey matter structures, particularly the cortex. Using conventional MRI sequences cortical lesions are less likely to be visible on T_2-weighted images than those in white matter; this is in part due to grey matter lesions having longer relaxation times than those of normal white matter which results in poor contrast resolution between grey matter and lesions in the cortex compared with lesions and white matter. Partial volume effects with surrounding CSF outside the cortex also play a role, but it is likely that differences in the cellular density of cortical lesions compared with white matter lesions may be most important; high cellular density may not allow a sufficient expansion of the extracellular space to allow an increase in relaxation times in cortical lesions, as is seen in those arising in white matter.

It is known that lesions may involve the cortex, although there is little research published which has set out to identify their nature and pathogenesis, and their clinical significance. Brownell and Hughes (1962) in a series of 32 cases found that 26% of all hemisphere lesions were found outside the white matter, with 17% at the leucocortical junction, 4% in the central grey matter and 5% within the cortex itself. Lumsden (1970) in his study of 60 cases found that 93% of cases showed involvement of the cortex to a varying degree with some cases showing only a few cortical lesions, whilst in one case there were 465 gyral plaques. In 10 of the cases, 290 lesions (59% of all hemisphere lesions) were seen to involve the cortex. Both studies showed that lesions involving the cortex were sited predominately at the leucocortical junction.

The vascular supply of the cerebral cortex is made up of branches of cerebral arteries which form a network within the pia before penetrating the cortex to supply it and the underlying white matter (Graham, 1992). Studies have shown that the cortex may be divided into four cortical vascular regions (De Reuck, 1972; Duvernoy *et al*., 1981). The first region lies within the molecular layer (layer I) of the cortex; Ia is devoid of capillaries and crossed by arterial and venous trunks, Ib contains a vascular network whose vessels run perpendicular to the cortical surface. These vessels also

supply layer II, the external granular layer. The second cortical vascular region lies within the superficial pyramidal layer (IIIa and IIIb) and is made up of palisades of vessels running perpendicular to the cortical surface. The third region is the most densely vascularized part of the cortex and lies within the deep pyramidal layer (layer IIIc), the internal granular layer (layer IV) and part of the ganglionic layer (layer Va), forming a dense meshwork of venous branches. The fourth region lies within the deep cortical structures (layers Vb and VI) and is less densely packed with vessels but continuous with the deep, long branching principal veins which pass through these layers parallel to the cortical surface. Studying cortical vessels following injection of Indian ink and gelatin and low viscosity resin, Duvernoy and co-workers were able to distinguish six different types of cortical artery and five types of cortical vein (Duvernoy *et al*., 1981) (Figs 1–7, this paper). The principal vein (V_5) passes through the cortex to the white matter. Its territory forms a conical shape whose base lies at the leucocortical junction. The largest purely intracortical vein (V_4) drains all six cortical layers, and V_3–V_1 drain progressively more superficial regions of the cortex.

We have undertaken a series of studies using neuropathological techniques and MRI which set out to assess (i) the frequency with which cortical lesions arise *in vivo* by means of T_1-weighted MRI and the sensitivity with which they are detected by MRI by means of a comparison with neuropathological examination; (ii) the characteristics of cortical lesions in a series of post-mortem specimens and their relationship to other white matter lesions subjacent to the cortex; and (iii) how cortical lesions arise using knowledge about the venous supply of this region of the hemisphere. A greater understanding of the nature of cortical lesions may allow an increase in understanding of the involvement of the cortex in the pathogenesis of cognitive and other deficits in multiple sclerosis.

Methods

In vivo MRI study

Twenty-five patients (mean age 31.7 ± 6.6 years) with clinically definite multiple sclerosis (Poser *et al*., 1983) attending the Neurological Outpatient Department of the Academic Hospital of the Free University of Amsterdam underwent serial MRI examinations at monthly intervals. Seventeen had relapsing–remitting multiple sclerosis and eight had a secondary progressive course. The median disease duration was 6 (range 1–24) years, the median EDSS (expanded disability status scale) was 3.0 (range 1.0–6.0). Imaging was undertaken on a 0.6 Tesla system with a standard head coil and a multi-slice spin echo technique, giving rise to T_2-weighted images [TR (repetition time) 2755 ms, TE (echo time) 60 and 120 ms] with two excitations, and gadolinium enhanced T_1-weighted images (TR 400 ms, TE 28 ms, four excitations). The slice thickness was 5 mm (gap 1.25 mm) and the in-plane resolution was 1 × 1.3 mm. The performance of the scanner was stable throughout the study period. The number and location of enhancing lesions were noted by F.B. and P.R.A., and also whether or not enhancing lesions showed any accompanying change in signal intensity on T_2-weighted images.

The patients gave informed consent to participate in the MRI studies which were approved by the Ethics Committee of the Free University, Amsterdam.

Post-mortem MRI—neuropathology study

Two formalin fixed brains of patients from the multiple sclerosis brain bank of the Queen's University of Belfast Neuropathology Department from cases of clinically definite multiple sclerosis were examined. Coronal whole brain slices were cut at 1 cm thickness. Brain slices were scanned individually with a standard 7.5 inch surface receiver coil on

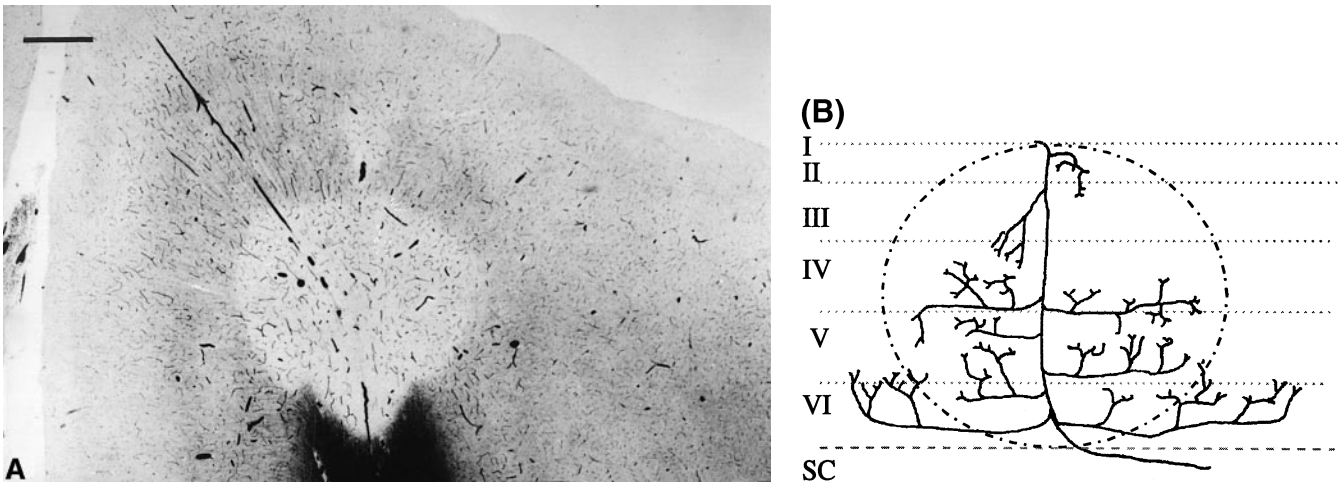
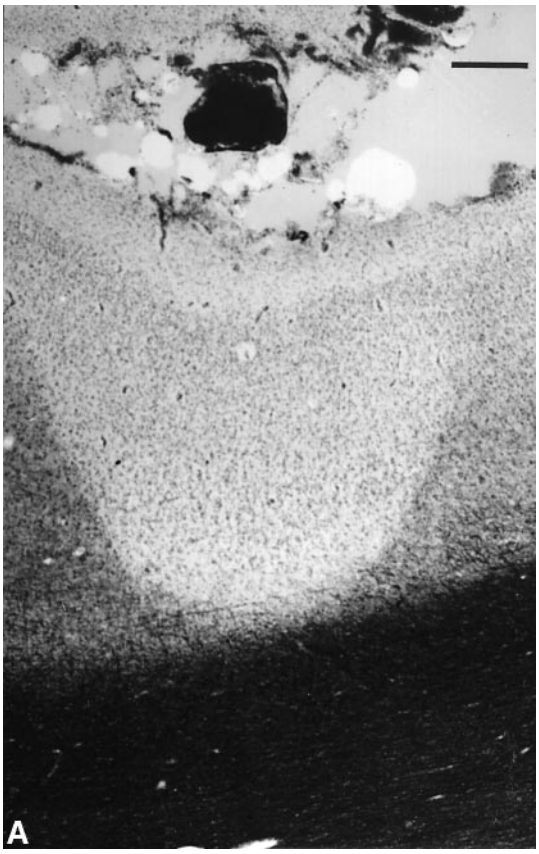


Fig. 1 (**A**) Cortical lesion type 1 is located in the deeper cortical laminae and subcortical white matter; Heidenhain's myelin, bar = 1.3 mm. (**B**) Such lesions may arise within the territory of the proximal branches of the principal cortical vein (V_5). [Here and in all the other captions, the proximal end of a cortical vein is near the capillary bed whilst the distal end denotes the point of joining a larger venous channel. The nomenclature recommended by Duvernoy *et al*. (1981) is used.]



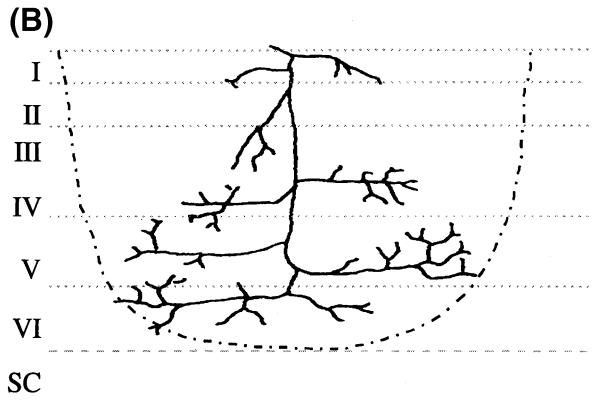
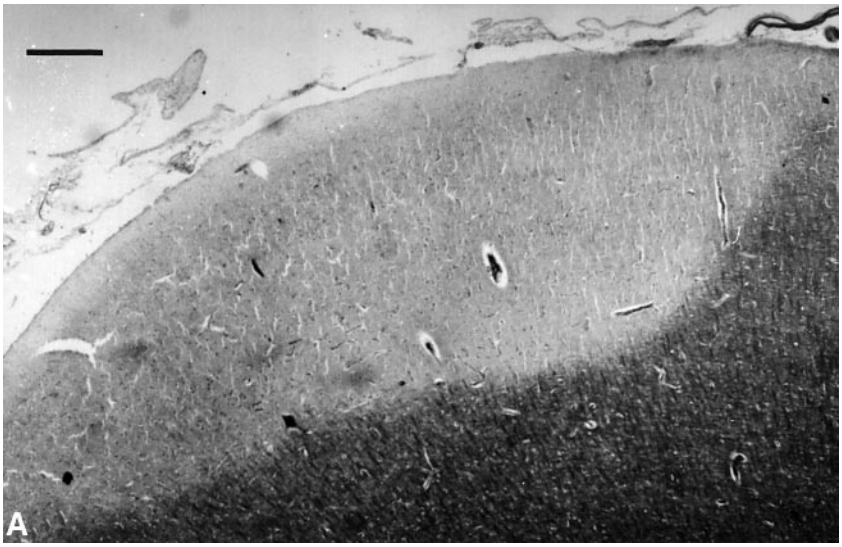


Fig. 2 (**A**) Type 2 lesions affect all cortical layers, but without involving the underlying subcortical white matter; luxol fast blue-cresyl violet; bar = 1.3 mm. (**B**) These lesions may arise within the territory of either V_4 or V_5 (without involving the proximal branch draining the subcortical white matter).



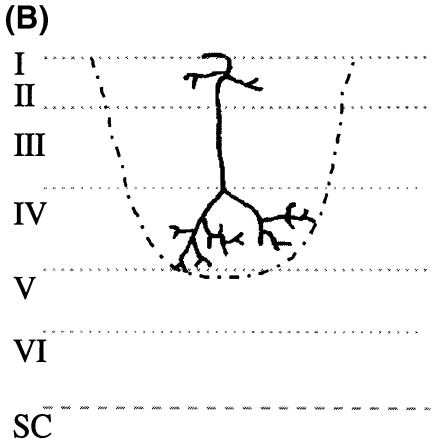


Fig. 3 (**A**) Type 3 lesions are usually extensive and located only in the superficial cortical layers; luxol fast blue-cresyl violet; bar = 2 mm. (**B**) These lesions may arise within the territory of a number of small superficial veins originating directly from the central vein of the gyrus (V_1–V_3), but may also affect the distal parts of V_4 and V_5.

the same 0.6 T system used in the *in vivo* study. A spin echo pulse sequence was employed (TR 2000 ms, TE 48 and 96 ms, two excitations) with a slice thickness of 5 mm and an in-plane resolution of 0.5×0.5 mm. The post-mortem images were analysed on a SUN Sparc2 workstation using home programmed software operating under

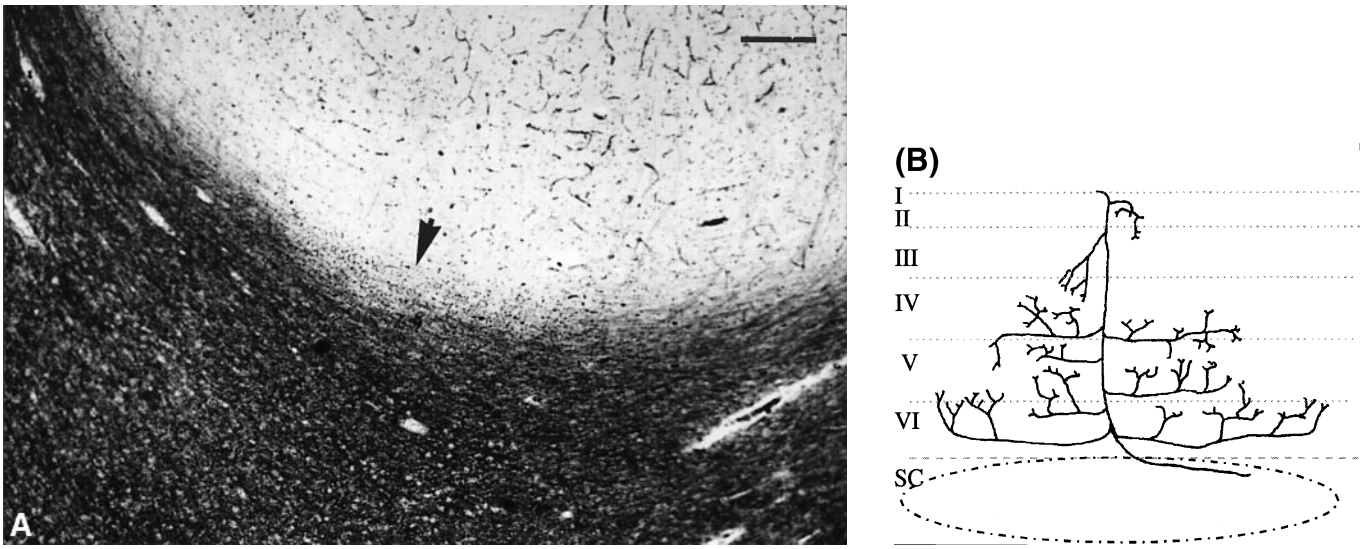


Fig. 4 (**A**) Type 4 lesions affect only the subcortical U-fibres; Heidenhain's myelin, bar = 0.8 mm. (**B**) This lesion may be related to the proximal end of the principal vein (V_5).

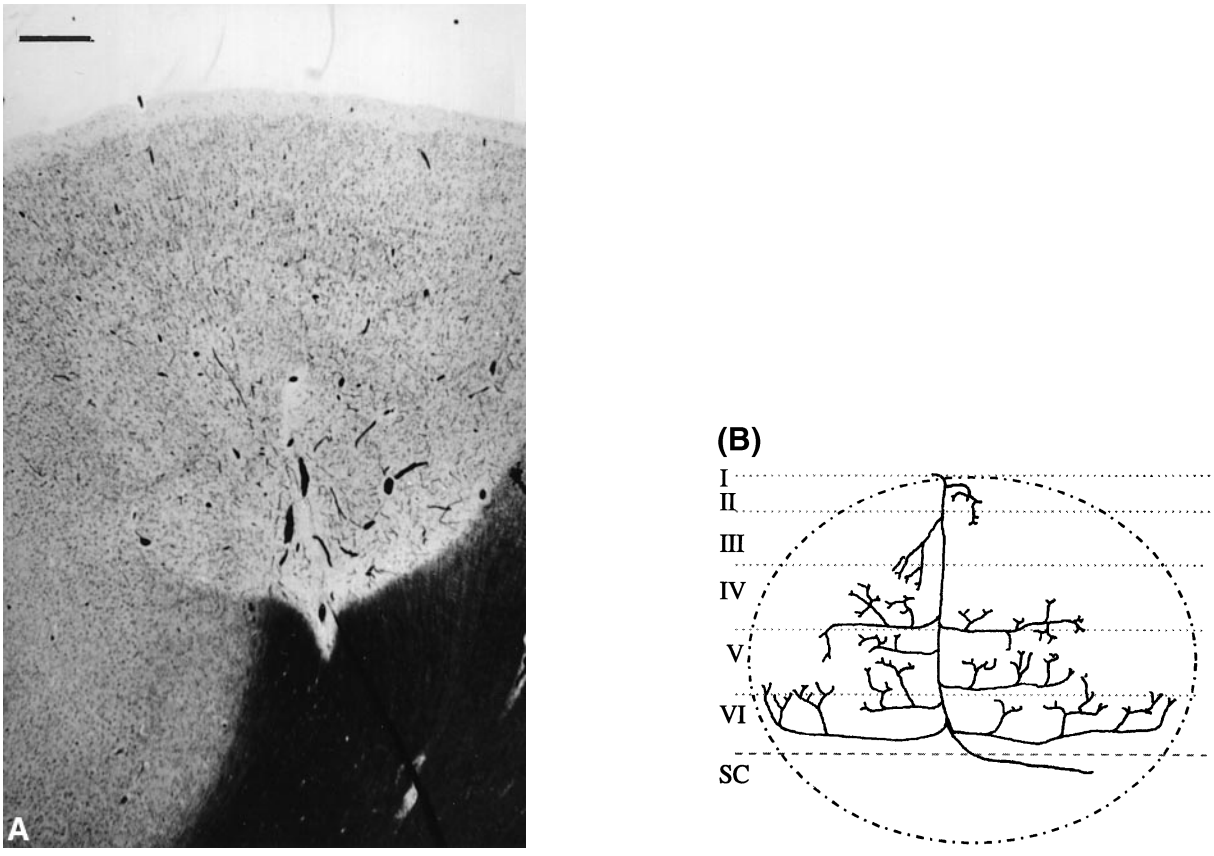


Fig. 5 (**A**) Type 5 lesion is a large cortical lesion affecting all cortical laminae and subcortical white matter; luxol fast blue-cresyl violet, bar = 1.3 mm. (**B**) The distribution of such lesions corresponds to the territory of a principal vein.

Openwindows^{TM}. Each lesion was identified on the T_2-weighted image, and the area of the lesion calculated using an interactively established signal intensity threshold. Lesions were classified as being cortical, juxtacortical (within the white matter subjacent to the cortex) or periventricular.

The individual slices of one of the brains were recorded

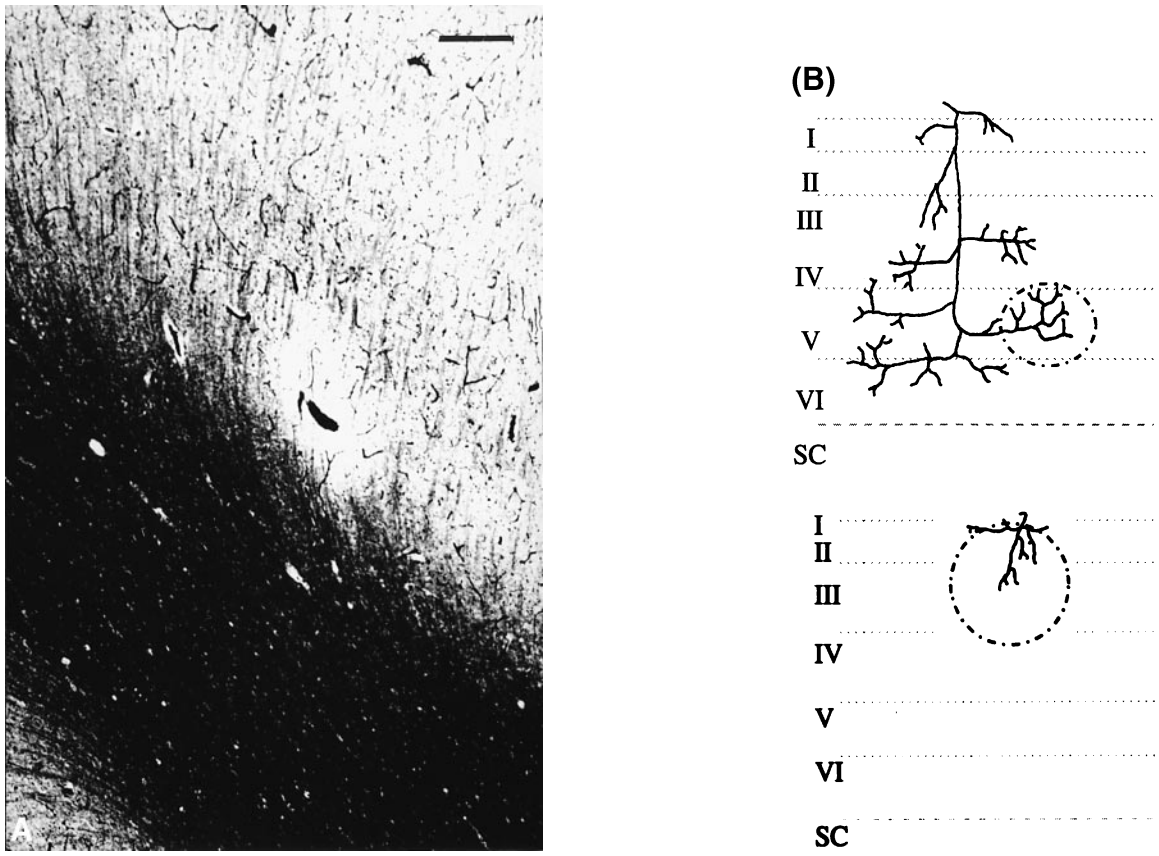


Fig. 6 (**A**) Type 6 lesions are small and occur in any part of the cortical ribbon; Heidenhain's myelin, bar = 0.8 mm. (**B**) This lesion type may arise within the territory of the small branches of the larger perforating venous channels (V_4 and V_5), but may be within the territory of V_1–V_3.

as a binary image using a Leitz TAS Plus image analyser, then carefully dissected into tissue blocks for paraffin-embedded histological investigation. Each block was labelled and recorded on a hard copy binary map for subsequent two-dimensional reconstruction. Blocks were processed and embedded in paraffin wax and 5 μm sections were stained with luxol fast blue, and counterstained with haematoxylin and eosin. Each section was examined on a Leitz orthoplan microscope using a ×10 planapo bright field objective, and lesions were manually mapped on to the appropriate binary image. Individual lesions on each slice were recorded as white matter, cortical or juxtacortical.

Neuropathological study

Previously cut hemisphere sections from 12 brains held at the Neuropathology Department of the Institute of Neurology of patients who had suffered from multiple sclerosis were studied. The medical notes had been scrutinized by one of us (D.K.) in order to verify the diagnosis on clinical grounds. The material had been fixed in buffered formalin and embedded in celloidin or paraffin wax. Large whole brain sections in the coronal plane or smaller regions in which cortex was included, which had been stained with haematoxylin and eosin, luxol fast blue–cresyl violet, Heidenhain's myelin stain and phosphotungstic acid haematoxylin, were viewed.

Cortical lesions were defined as sharply demarcated demyelinated areas with relative preservation of both axons and neurons with or without an accompanying inflammatory cell infiltration. These were identified and counted by TR and DK. It soon became clear that cortical lesions showed a distinctive pattern, shown in Figs 1–7. Each lesion was typed according to this pattern. An assessment of the extent of infiltration of mononuclear inflammatory cells and the degree of cellularity both within and at the edge of each lesion in which there was white matter involvement was attempted according to methods previously published (Revesz *et al.*, 1994). This was not possible in the case of lesions which involved cortex only owing to their normal high cellular background.

Results

In vivo MRI study

A total of 172 scans was performed (median per patient 5, range 1–14). Two hundred and fifty-eight enhancing lesions were seen (median per patient 2, range 0–8). There were 41 enhancing cortical lesions (Fig. 8A) (median per patient 0,

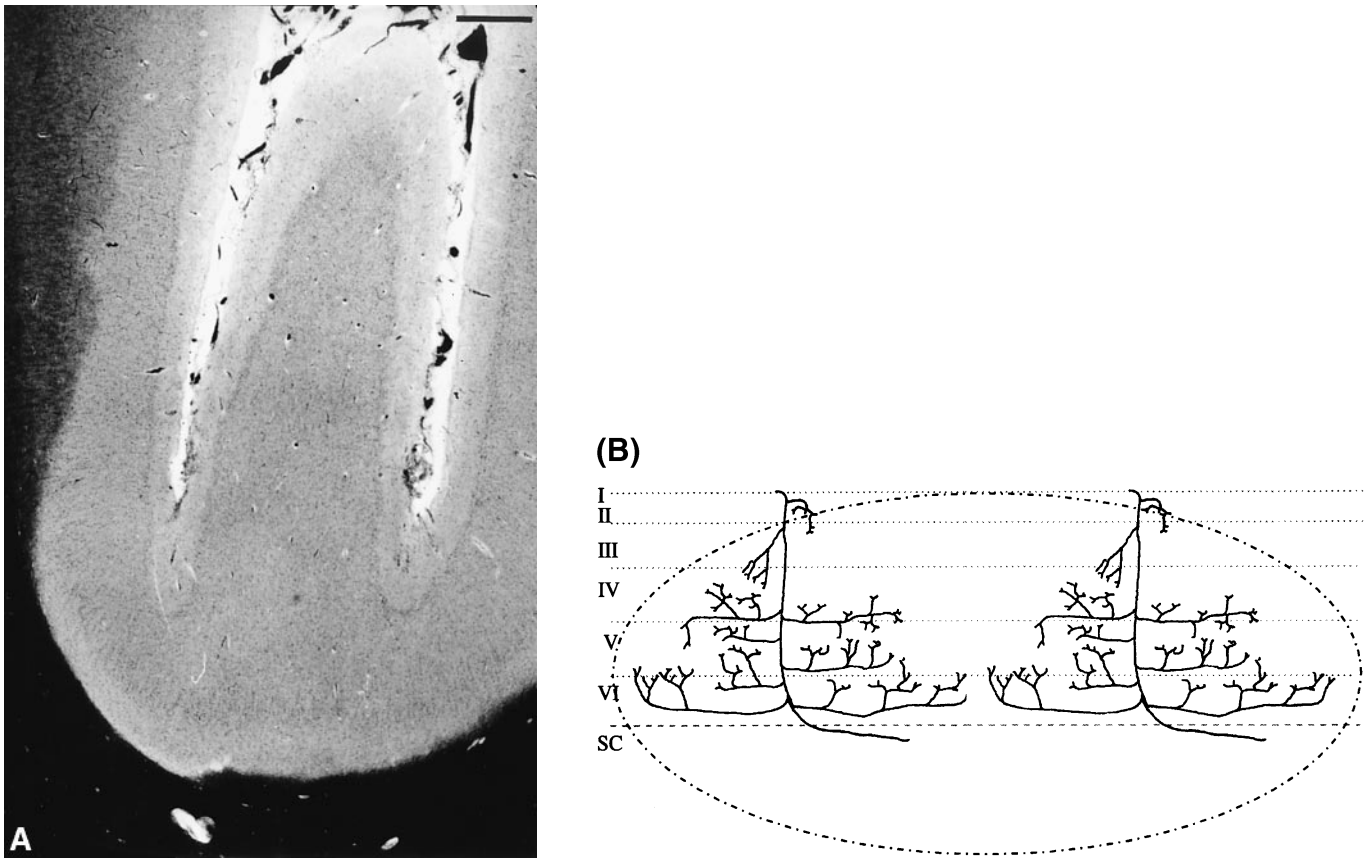


Fig. 7 (**A**) Lesion type 7 is the largest cortical lesion affecting both banks of a gyrus with or without involvement of the subcortical white matter; Heidenhain's myelin, bar = 2 mm. (**B**) Such a lesion may arise within the territory of a series of V_4 and V_5 (principal) veins, most likely affecting the larger collecting central vein of the gyrus.

range 0–15), of which 29 (70%) were seen on the corresponding T_2-weighted image (Fig. 8B). Twenty-seven enhancing lesions were seen adjacent to the cortex, of which 24 (89%) were seen on the T_2-weighted scans. One hundred and ninety enhancing lesions were seen elsewhere in the white matter, of which 187 (98%) were seen on corresponding T_2-weighted scans. The difference between lesion count using gadolinium and that using T_2-weighted images was significant ($\chi^2 = 41.16$, $P < 0.001$).

Post-mortem MRI—neuropathology study

The post-mortem images, having improved signal-to-noise ratio (owing to the use of a surface coil) and an absence of motion artefact, showed higher resolution. Both brains showed characteristic high signal intensity lesions most marked in the periventricular regions and centrum semi-ovale, but also in the cortices (Fig. 9A). Case I showed 66 white matter lesions, of which 8 (12%) were adjacent to the cortex. In case II, 134 white matter lesions were seen, of which 58 (43%) were juxtacortical and 2 (1.5%) were purely intracortical.

Histological examination of case II revealed 328 lesions, of which 14 (4.3%) were cortical, 108 were juxtacortical (32.9%) and 206 elsewhere in the white matter (62.8%) (Fig. 9B).

Neuropathological study

An average of 4 (range 2–6) coronal slices was inspected per brain. A total of 478 cortical lesions was identified. Three hundred and seventy-two (76%) showed involvement of the subcortical white matter, 106 (24%) arose exclusively within the cortex. Lesion type 1 accounted for the majority (210 lesions, 44%) of lesions (Fig. 10). Lesions occurred with equal frequency within gyri and within sulcal cortex, although sulcal lesions when present showed a tendency to arise at the deepest point of the sulcus. Neither the distribution nor the microscopic features of these lesions suggested an ischaemic aetiology.

Portions of lesion involving the cortex showed a tendency not to be inflamed, although since the cortex is in general a much more cellular structure it is more difficult to assess this accurately without recourse to modern immunohistochemical preparations. Similarly it was difficult to judge axon or neuronal loss within the intracortical part of the lesion.

Those parts of the lesion within the white matter were no different to those arising elsewhere within the white matter;

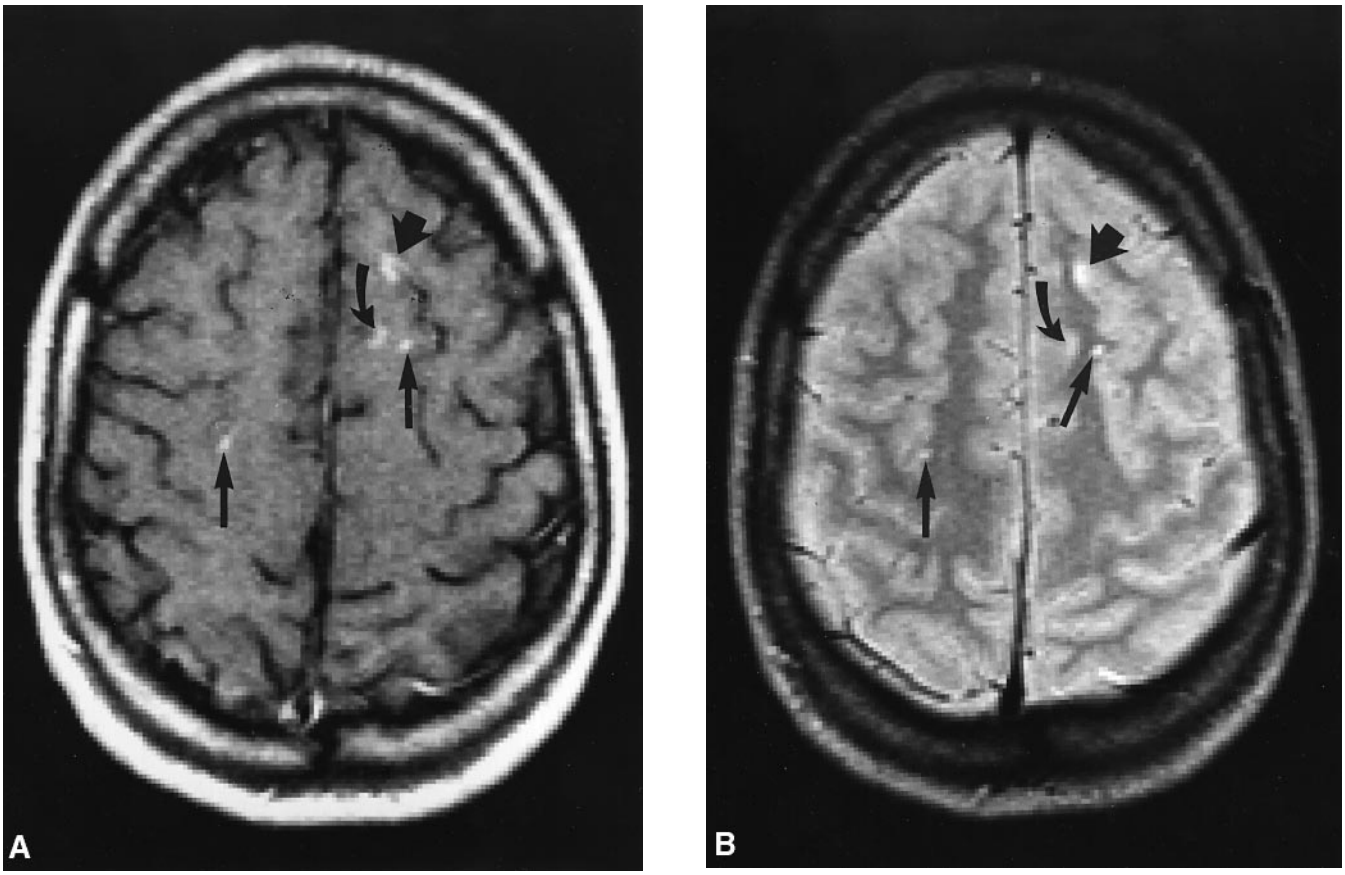


Fig. 8 (**A**) T_1-weighted MR image (TR 400 ms; TE 28 ms) following gadolinium and (**B**) corresponding T_2-weighted MR image (TR 2755 ms; TE 60 ms). There are four enhancing lesions in **A**. Two smaller lesions (straight arrows) lie in subcortical white matter, two others are juxtacortical (short arrow) and intracortical (curved arrow). Note that the juxtacortical and intracortical lesions are less visible.

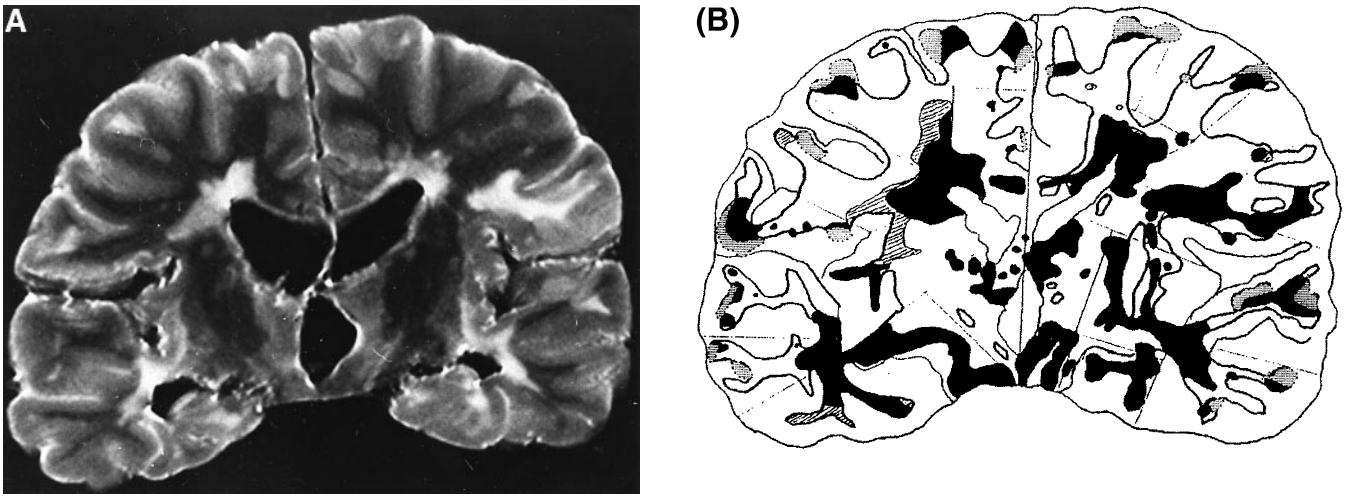


Fig. 9 (**A**) T_2-weighted MRI scan (TR 2000 ms; TE 96 ms) of slice 6 of post-mortem case II showing periventricular white matter and cortical lesions. (**B**) Histological examination of slice 6 reveals a larger number of multiple sclerosis lesions, including cortical plaques, than does MRI.

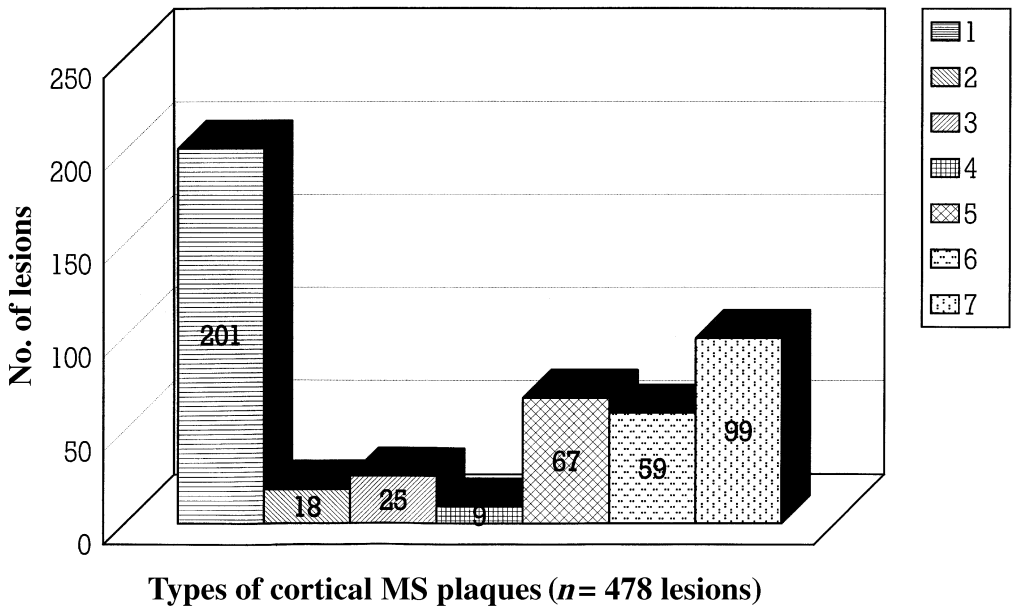


Fig. 10 Histogram showing the distribution of cortical lesions (n = 478) according to the classification in Figs 1–7.

200 lesions (53.7%) showed evidence of inflammation, 160 showed a cellular infiltrate (43%), 76 lesions showed edge activity (20.4%).

Comparison of the characteristics of cortical lesions with those of cortical veins seen in Duvernoy's study shows clearly that the majority of lesions arise within the territory of the principal vein V_5—types 1, 4 and 5 (277 lesions, 57.9%); the central vein of the gyrus—type 7 (99 lesions, 20.7%); or V_4—types 2 and 6 (77 lesions, 16.1%). Type 6 may also reflect involvement of small branch veins (2.5%) and type 3 superficial veins (V_1 and V_2) alone or proximal segments of V_4 and V_5 (3.6%).

Discussion

This multifaceted study set out to investigate the prevalence and characteristics of cortical lesions in multiple sclerosis. The MRI data provide important information; it is clear that T_2-weighted images cannot show cortical lesions well; reasons for this have been noted in the introduction. Even when high resolution images of post-mortem specimens are examined, the numbers of cortical lesions identified are considerably less than when the section is examined histologically. There is some evidence that the use of the alternative imaging sequence FLAIR (fast fluid-attenuated inversion recovery) may improve lesion detection within the cortex (Rovaris *et al*., 1997). This is because in this sequence CSF has zero signal, and grey matter and white matter have similar signal intensities, whereas the contrast between a T_2-weighted image of a lesion and that of normal appearing cerebral tissue is much greater. Clearly, lesions smaller than the resolution of the MRI system will only be seen on a subsequent histological examination, and in addition MRI lesions may appear confluent when clearly distinct histopathologically. This explains the large disparity between the number of white matter lesions recorded using the different methods, although it should be noted that fixation alters the distribution of water within tissue, with the result that relaxation times may change, which may in turn affect contrast (Nagano *et al*., 1987).

The data from the serial study confirm previous reports that the use of gadolinium greatly increases the number of new cortical lesions seen (Barkhof, 1992; Miller *et al*., 1993; Barkhof *et al*., 1997). The use of gadolinium in our series proffered an increase in lesion visibility of 140%.

We have shown that the majority of lesions are likely to arise within the juxtacortical white matter and cortex. Such lesions appear histologically to be no different to those arising elsewhere within the white matter. Others clearly arise within the cortex itself—types 2, 3, 6 and 7 (24% of lesions). Particularly prevalent was type 7 which arose within the cortical ribbon around the central vein of the gyrus.

Using knowledge of cortical venous architecture acquired by de Reuck (1972) and Duvernoy *et al*. (1981), we have been able to show that there is a clear relationship between the site and characteristics of cortical lesions and the five different types of cortical vein, just as Dawson's 'fingers' arise adjacent to veins in periventricular white matter. Large lesions which occupy the majority of the cortex with extensive subcortical involvement and predominately subcortical lesions are likely to arise as a result of involvement of the principal vein (V_5). Large type 7 lesions which pass around gyri are likely to reflect involvement of the central vein of the gyrus or a series of principal veins lying perpendicular to the gyral surface. Smaller intracortical lesions, such as types 3 or 6, may arise as a result of involvement of small branch veins or V_1 and V_2 (Figs 1 and 3).

Turning now to the clinical relevance of these lesions,

truly cortical clinical syndromes are rare; dysphasia, dyscalculia and cortical sensory loss were reported by McAlpine (1972). Kahana *et al*. (1971) and Poser (1978) found the incidence of aphasia to be 1% in their series. Alexia with agraphia (Day *et al*., 1987) and palinopsia (Jacome, 1985) have also been recorded. In those cases in which imaging has been reported it is clear that large subcortical lesions have been implicated. Seizures are also uncommon but series cite an incidence of 1–4% (Drake and MacKay, 1961; Matthews 1962, 1991). Early neuropathological studies identified an association between seizures and subcortical lesions (Drake and MacKay, 1961) and this has subsequently been shown *in vivo* in series with MRI (Ghezzi *et al*., 1990; Thompson *et al*., 1994; Truyen *et al*., 1996).

Dysfunction of cognitive skills arises in 50% of patients (Ron *et al*., 1991); the commonest psychometric deficits are impairments of visual and verbal memory, naming ability and attention skills (Beatty *et al*., 1989; Rao *et al*., 1989; Ron *et al*., 1991) with a relative preservation of high level visuospatial and language functions. It is possible that the large number of plaques which arise in the subcortical white matter may well be responsible for the form of cognitive deficits known to arise in multiple sclerosis; however, studies have shown that there is no clear relationship between the site or extent of such MRI lesions and the nature and severity of cognitive impairment (Huber *et al*., 1987; Franklin *et al*., 1989; Rao *et al*., 1989; Ron *et al*., 1991; Foong *et al*., 1997), although one group of investigators (Damian *et al*., 1994) found an association between the number of subcortical lesions and cognitive impairment. No relationship has been found between the incidence or severity of cortical atrophy or ventricular size and cognitive impairments, but other studies have shown a relationship between atrophy of the corpus callosum and cognitive impairments (Huber *et al*., 1987; Rao *et al*., 1989; Pozzilli *et al*., 1991), an idea put forward by R. O. Barnard over 20 years ago (Barnard and Triggs, 1974). Lesions in the subcortical white matter may also provoke clinical deficits, but our studies suggest that cortical and subcortical lesions may not occur with sufficient frequency to render them clinically important.

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