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Pathological findings correlated with magnetic resonance imaging in subcortical arteriosclerotic encephalopathy (Binswanger's disease)

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SUMMARY Formalin-fixed brain slices from four cases of subcortical arteriosclerotic encephalopathy in which a firm diagnosis could be made both clinically and pathologically have been studied by magnetic resonance imaging (MRI). The slices were subsequently embedded in paraffin-wax or celloidin and sections were cut in the same plane as the MRI slices. There was a good correlation between the extent and severity of the abnormal MRI signal and the pathological changes. Areas of diffuse MRI abnormality corresponded with areas of axonal and myelin loss with gliosis, and small "lacune"-like lesions corresponded with lacunar infarcts histologically. Sparing of the subcortical U-fibres was seen histologically and on MRI. The abnormal signal probably originates from increased tissue water attributable to gliosis and an expanded extracellular space.

Subcortical arteriosclerotic encephalopathy (SAE) was originally described by Otto Binswanger in 1894 as "encephalitis subcorticalis chronica progressiva".[1] The disease most often affects hypertensive patients in the sixth or seventh decade of life.[2–6] There is usually a history of dementia, stroke and a stepwise deterioration with development of focal neurological signs, pyramidal and extrapyramidal.[4–7] The important pathological features of SAE are widespread degeneration of large areas of the deep hemisphere white matter with diffuse and patchy axonal and myelin loss with gliosis.[2–4 8 9] These changes are thought to arise from chronic ischaemia involving the white matter as a result of arteriosclerosis of small arteries and arterioles.[2–4 8]

Modern neuroimaging techniques have led to a renewed interest in SAE.[5 7 10–12] Magnetic resonance imaging (MRI) is superior to CT scanning in detecting white matter changes in vascular disease and multiple sclerosis (MS).[12–17] Scanning formalin-fixed post mortem brains shows that the areas of abnormal MRI signal in MS correspond with plaques histologically.[18–20] As no such correlation has been made in SAE, we have carried out a similar study on the brains of four patients in whom a clinical diagnosis of this disorder had been confirmed at necropsy.

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Material and method

In the Neuropathological Department of Maida Vale Hospital there were four cases in which the diagnosis of SAE had been established pathologically. Sufficient data were available from case notes to make a firm clinical diagnosis, and adequate material was available for MRI and correlative neuropathological study. These brains provide the basis for this report. They had been kept in formalin for one to 12 years. All had been sectioned previously but slices approximately 10 mm thick had been preserved in formalin. Slices from the cerebrum, cerebellum and brainstem were investigated by MRI using a 0·5 Tesla imager (Picker International). Hemisphere slices were studied using standard head gradient coils and 10 mm MRI slice thickness. The usual sequence was a Carr-Purcell-Meiboom-Gill multi-echo sequence (TR 2000, TE 40–320). Inversion Recovery sequences were also used (IR 2000/500/40 and STIR, Short Inversion Time IR 2000/100/40).[21] For slices of pons a smaller set of gradient coils was used and 5 mm MRI slice thickness scanned. Two control brain slices were scanned using STIR and multi-echo sequences from patients aged 62 and 66 years with a non neurological disease.

Table 1 *The main clinical features of the cases*

Case	Sex	Age at death (yrs)	Duration of illness (yrs)	Hypertension	Neurological features	Psychiatric features
1	M	47	2	Yes	Left hemiparesis Ataxic episode	Personality change Dementia
2	F	40	1	Yes	Right hemiplegia	Dementia
3	F	52	15	No	Falls Ataxic gait Extrapyramidal syndrome Left hemiparesis	Personality change Dementia
4	M	68	5	Yes	Minor strokes Ataxic gait Pseudobulbar palsy Spastic paraparesis	Paranoid ideas Dementia

The slices investigated with MRI were subsequently embedded in paraffin-wax and celloidin. Sections from these and numerous other previously embedded blocks were stained by the following methods: haematoxylin and eosin, Nissl's cresyl violet, elastic van Gieson, Heidenhain's myelin, Klüver-Barrera's luxol fast blue-cresyl violet, Bielschowsky's axon impregnation, Holzer's crystal violet for glial fibrils and Mallory's phosphotungstic acid haematoxylin. In cases 1, 2 and 3 smaller blocks from the cerebral cortex and white matter, thalamus and basal ganglia were also studied in serial sections. From each block 100 consecutive sections were stained with haematoxylin and eosin, elastic van Gieson, Mallory's phosphotungstic acid haematoxylin and luxol fast blue-cresyl violet methods.

Five to ten representative areas from the sections cut from the scanned blocks were examined and the degree of pathological change represented by myelin loss was graded as follows: 0 = none, 1 = slight, 2 = moderate and 3 = severe (assessed by TR). The signal intensity of the corresponding areas in the scans was graded in a similar fashion (assessed by C P H).

Results

The clinical details of the four cases and the neuropathological findings are summarised in tables 1 and 2 respectively. Case 3 is similar to previous reports of SAE unaccompanied by documented hypertension, when the neuropathological examination revealed typical histological changes.[4 8 22]

Pathology

The weight of the brains varied from 1120 to 1340 gm. There was some degree of greyish discolouration of the white matter in every case. Additionally the white matter always contained lacunae which were also found in the basal ganglia in all cases, in the pons in all cases, and in the internal capsule in case 3. Small, old cerebellar infarcts were present in two cases (1, 3). The large arterial branches showed moderate to severe macroscopic atherosclerotic change in all cases. The lateral and third ventricles were enlarged to a variable extent in every case.

Histology

The cortex was characteristically normal although scattered, old ischaemic scars were occasionally seen in case 3. In all cases there was extensive, more or less symmetrical white matter damage. In the areas affected there was significant myelin pallor and axonal loss accompanied by a variable degree of fibrillary gliosis. There was no evidence of true demyelination with relative preservation of axon continuity. Microcystic change was seen to involve the most severely affected areas of periventricular and deep hemisphere white matter. The changes in the hemisphere white matter were diffuse but always spared the subcortical U-fibres. The topographical distribution of the white matter abnormality was fronto-parieto-occipital in all cases, and slight temporal involvement was detected in cases 1 and 3. In three cases (2, 3 and 4) involvement of the corpus callosum was also seen in the form of thinning at various levels. The outline of the lateral ventricles frequently presented a ragged appearance as a result of intense gliosis in the periventricular area.

Lacunae were surrounded by dense layers of gliosis in the white matter, basal ganglia and pons. The lacunae of the hemisphere white matter tended to spare the U-fibres. In cases 1 and 2, large old cystic cavities densely lined by haemosiderin-containing

Table 2 *Neuropathological data of the cases*

Case	1	2	3	4
*Severity of change**				
White matter damage	3	3	3	2
Ischaemic lesions in the pontine base	3	3	2	1
Callosal involvement	0	3	2	2
Atherosclerosis of large arteries	3	2	3	2
Arteriosclerosis of small arteries	3	3	3	2
*Presence of pathological change***				
Lacunae	Y	Y	Y	Y
Microaneurysm formation	Y	N	Y	N
Scattered cortical scars	N	N	Y	N

*Severity of change: 0 = none, 1 = slight, 2 = moderate, 3 = severe.
**Presence of pathological change: Y = yes, N = no.

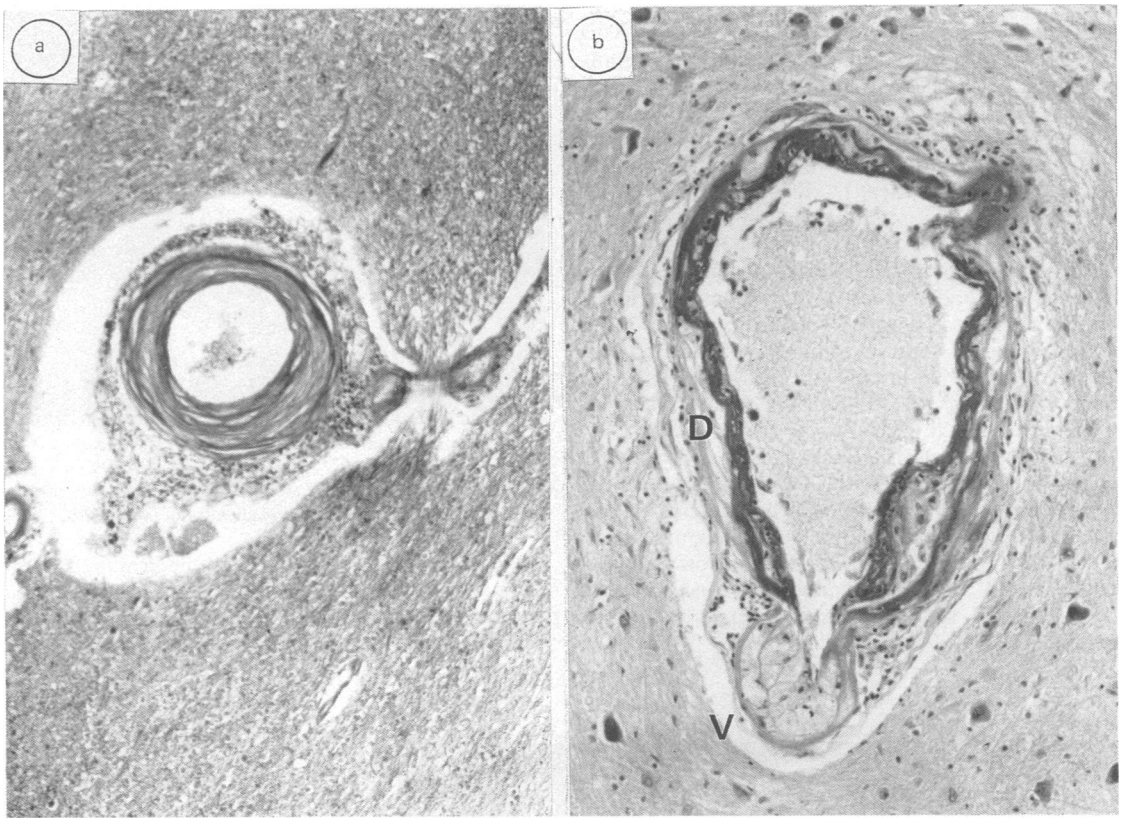

Fig 1 *a) Ateriosclerotic perforating artery from affected deep white matter (case 1). Elastic van Gieson, × 175.*

b) Arterial vessel (V) with microaneurysmal dilatation (D) (case 1). Haematoxylin and eosin, × 140.

macrophages were found, which occupied the right and the left putamen respectively. There was frequent brainstem damage which consisted of patchy or more widespread diffuse involvement of the white matter of the basis pontis with axonal and myelin loss, gliosis and lacunae. These changes were the result of both secondary long tract degeneration from involvement of descending tracts and direct damage to the pontine white matter. The atherosclerotic changes of the large arteries were moderate to severe in all cases. The small arteries presented significant thickening and fibrosis of the wall, and splitting of the internal elastic lamina (fig 1a). Prominant thickening of the arteriolar walls and hyalinosis were present in all cases. Distension of the perivascular space (état criblé of Vogt) was seen in the hemisphere white matter and basal ganglia in all cases.

Serial sections of cases 1, 2 and 3 revealed microaneurysm formation (fig 1b). There was occasional fibrinoid deposition in the walls of small arteries as well as of microaneurysms. In cases 1 and 3 a thrombosed microaneurysm or occluded disorganised small artery was found in association with lacunae.

In no case were amyloid, senile plaques or neurofibrillary tangles found. Thus, the pathological changes in all four cases were typical of SAE.[2-6 8 9]

Magnetic resonance imaging

The images obtained from the fixed brain slices which had been in formalin for up to 12 years were, not surprisingly, of poorer quality than those routinely obtained in vivo. Nevertheless, after trying a variety of sequences we identified three (see methods) which gave sufficiently good differentiation between grey and white matter, and between normal (fig 2) and pathological brain (figs 3–5) for us to obtain images which could be usefully compared with subsequent histological preparations in the same planes.

MRI reflected the distribution of the pathological changes. There was good agreement between the abnormal images and the corresponding histological sections with areas of abnormal signal affecting the

periventricular and deep white matter (fig 3a), although the outlines were not precisely the same. This difference is to be expected, since the MRI represents averaging of the signal over a slice 10 mm thick whereas the histological sections were 20 μm thick.

There was variable extension into the gyral white matter in hemisphere slices, but with characteristic sparing of the subcortical U-fibres (large arrowhead, figs 3a and 5a). Ventricular dilatation was a universal feature. It was not possible to assess adequately the presence or absence of callosal atrophy on one coronal slice. Small rounded areas of high signal ("lacune"-like lesions) were seen on MRI in the deep white matter of the temporo-parieto-occipital slice of case 1 (fig 4a) and in the putamen in case 2. Localised high signal involving the pons was seen in cases 1 and 2. The areas of abnormal signal were seen on proton density, T2-weighted (spin echo) and T1-weighted (inversion recovery) sequences. With multi-echo sequences changes were seen best with spin echo times, TE 80 and 120. STIR sequences (TI 100) showed changes more clearly than more conventional inversion recovery sequences (TI 500), but no major difference between the results of spin echo and inversion recovery sequences was discernible.

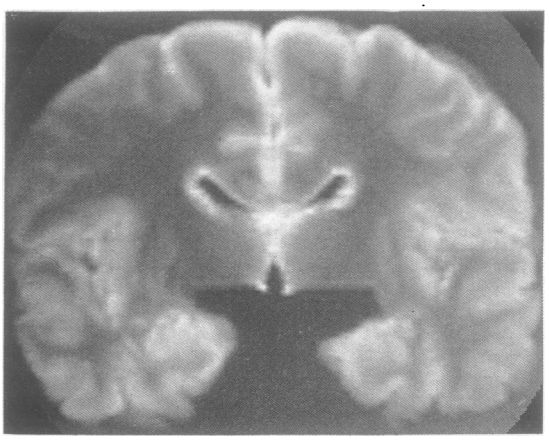

Fig 2 *Control brain slice from parieto-temporal area of a patient aged 62 years (STIR sequence, IR 2000/100/40). The localised high signal around the ventricles is commonly seen in vivo over the age of 50 in apparently normal individuals.*

Correlation between the pathological and MRI examinations are shown in table 3 and are illustrated in figures 3, 4 and 5. A control brain slice is shown for comparison (fig 2). One case is reported in detail.

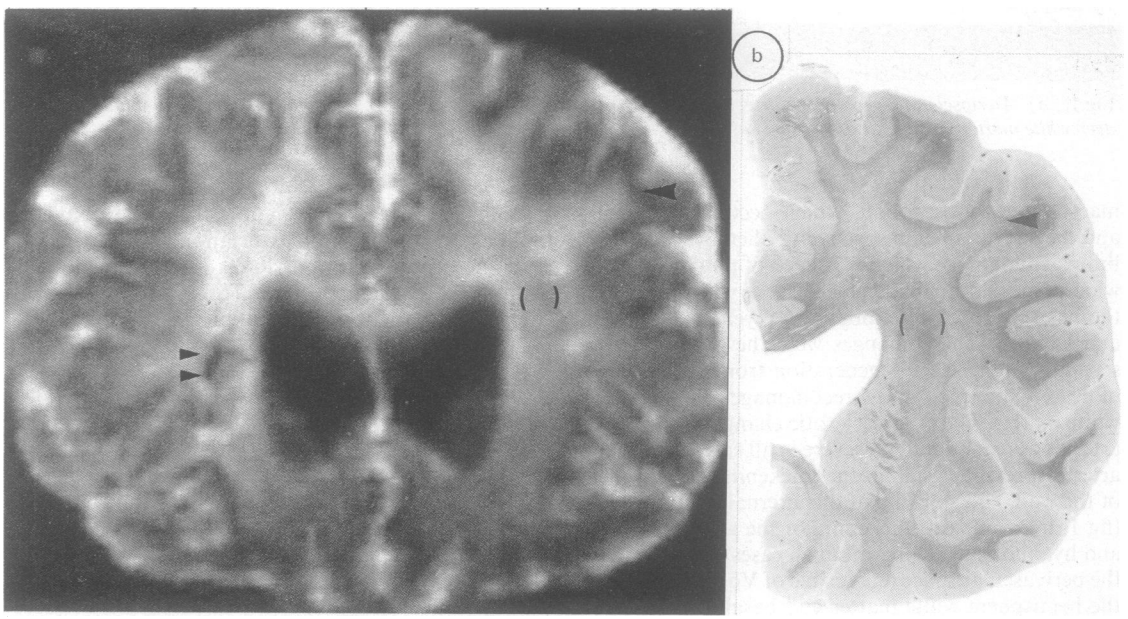

Fig 3 *Frontal slice (case 1) a) STIR sequence (IR 2000/100/40) showing abnormal high signal from the periventricular and deep white matter (brackets indicate area of overall relatively lower MRI signal; large arrowhead points to sparing of subcortical U-fibres and small arrowheads to cystic cavity in the right putamen). b) Corresponding histological slice showing extensive myelin loss (brackets indicate area of relative sparing of myelin and large arrowhead to relative sparing of U-fibres). Klüver-Barrera method, × 1·5.*

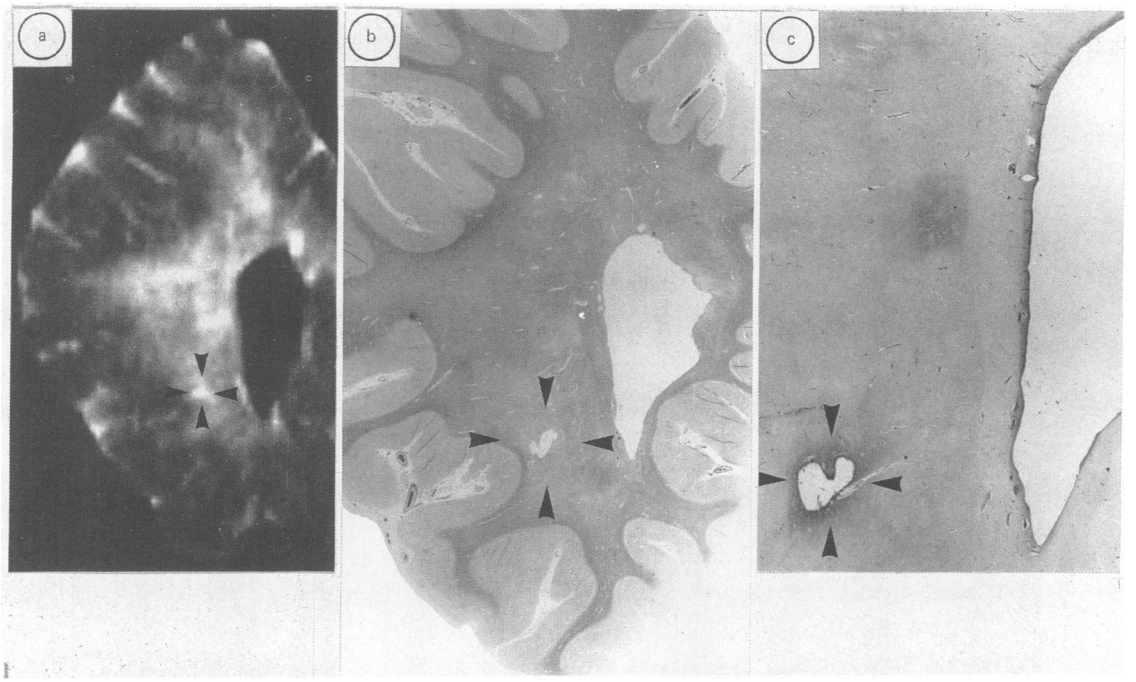

Fig 4 *Temporo-parieto-occipital slice (case 1) a) Spin echo sequence (SE 2000/80) showing periventricular high signal and a "lacune" like lesion (arrowheads). b) Higher magnification view of the corresponding histological slice showing extensive myelin loss, and a lacunar infarct (arrowheads). Heidenhain's myelin, × 1·5. c) Histological section showing intense gliosis around the lacune (arrowheads). Holzer's glial fibril method, × 3·7.*

CASE 1 (brain in formalin for 12 years)
This male patient had died at the age of 47. He was known to have had poorly controlled hypertension for five years. At the age of 45 he suffered a stroke with left hemiparesis and over the subsequent two years his condition gradually deteriorated. A progressive change in personality was noted by his relatives. Three weeks before his final admission to hospital, by which time he was markedly demented, he suffered an episode of worsening ataxia over three weeks associated with failure to take his hypertensive medication. On admission he was restless and hyper-

Table 3 *Correlation of MRI and histological results*

Case	*Site*	*Method*	*Area investigated*									
			A	*B*	*C*	*D*	*E*	*F*	*G*	*H*	*I*	*J*
1	Hemisphere (frontal)	MRI	3	2	2	3	3	2	1	—	—	—
		Pathology	3	3	2	3	3	3	1	—	—	—
	Hemisphere (temporo-parieto-occipital)	MRI	3	2	1	3	3	2	2	3	0	0
		Pathology	2	3	2	3	3	3	2	3	2	2
	Pons	MRI	0	0	2	1	2	1	1	1	0	0
		Pathology	0	0	2	2	2	2	0	0	0	0
2	Hemisphere	MRI	3	3	1	1	3	0	0	0	1	—
		Pathology	3	3	1	1	1	0	0	1	0	—
	Pons	MRI	1	0	1	0	1	2	1	2	1	1
		Pathology	0	0	2	0	1	2	1	2	1	0
3	Hemisphere	MRI	0	0	3	2	3	0	1	1	0	1
		Pathology	1	1	3	2	3	0	1	1	0	0
	Pons	MRI	0	0	0	0	0	0	0	0	0	0
		Pathology	0	0	0	0	0	0	0	0	0	1
4	Hemisphere	MRI	3	1	3	0	2	1	1	0	3	—
		Pathology	3	3	3	0	3	2	0	0	2	—
	Pons	MRI	0	0	0	0	0	0	1	0	1	0
		Pathology	0	0	0	0	0	0	1	0	0	0

Areas were chosen where the MRI and pathological changes were graded independently: 0 = none, 1 = slight, 2 = moderate, 3 = severe.

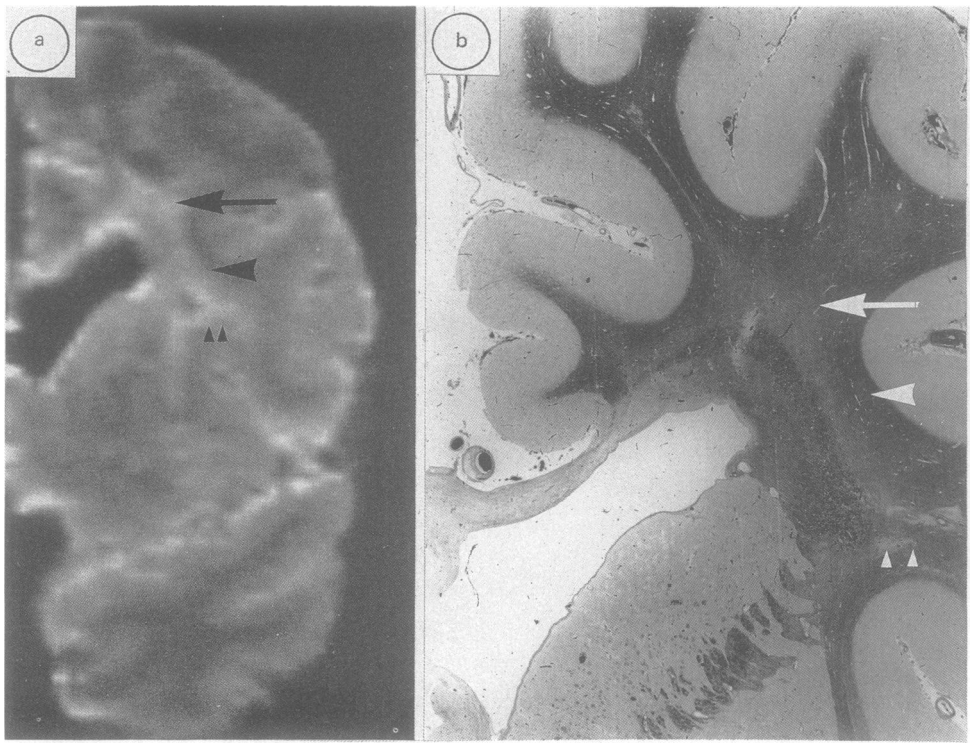

Fig 5 *Fronto-temporal slice (case 3) a) Spin echo sequence (SE 2000/80) showing periventricular high signal (arrow) and sparing of subcortical U-fibres (arrowhead). Small arrowheads indicate an area of patchy subcortical myelin loss. b) Higher magnification view of the corresponding hemisphere slice showing myelin loss (arrow) and sparing of subcortical U-fibres (arrowhead). Heidenhain's myelin, × 5.*

tensive (220/145 mm Hg). There was hypertonia of his left side with a left extensor plantar response. He later developed a flaccid hemiplegia first on the left and then on the right followed by coma. He died after 5 days.

Two hemisphere slices originating from the frontal lobe and the temporo-partieto-occipital region were studied. The frontal slice was taken through the rostrum of the corpus callosum (fig 3) and the temporo-parieto-occipital slice through the trigone (fig 4).

The areas of abnormality on the MRI broadly corresponded with the areas of visible abnormality on the cut surface of the brain. Stained sections showed that the areas of high signal corresponded with areas of intense gliosis in regions of severe axonal and myelin loss. Histologically there were scattered circumscribed areas of relatively better preserved myelin. This was obvious, for example, on the frontal slice where occipito-frontal fascicles were better myelinated, which corresponded to an area of relatively lower signal in a region of abnormally high signal on MRI (brackets, fig 3a). A large circumscribed area of low signal was seen to involve the right putamen corresponding to a large cyst at histology, as a result of past haemorrhage (small arrowheads, fig 3a). The lumen of the cyst was exposed on the cut surface of the brain slice and was empty of fluid. This would account for the cyst appearing as an area of low signal rather than high signal on MRI. The "lacune"-like lesion seen on the MRI of the temporo-parieto-occipital slice (arrowheads, fig 4a) corresponded with a small cystic region surrounded by intense gliosis (arrowheads, figs 4b and 4c) thus providing direct confirmation that such images in the appropriate clinical setting correspond with small, old infarcts. The lacunar infarct was deep within the brain slice at MRI and was thought to contain fluid, which would account for the area of abnormal high signal from the lacune on MRI as would be expected in vivo.

In the rostral pons there was atrophy with axonal and myelin loss of the fascicles of the corticospinal tract on the right side, with accompanying gliosis. This corresponded with abnormal signal on MRI.

Discussion

This study shows that areas of abnormal signal seen on the MRI images of post-mortem brain in patients with SAE correspond with the characteristic lesions histologically. This conclusion applies both to the diffuse changes in the white matter and the focal "lacune"-like changes. Similar MRI changes are seen *in vivo* and it is reasonable to conclude that in a similar setting their pathological basis is the same.[18]

The distribution of MRI changes in SAE and advanced MS may be indistinguishable (at least with MRI sequences commonly used at present), although in less severe cases of MS ventricular dilatation and periventricular white matter changes are not usually so extensive.[18] Focal lesions occur in both diseases, being attributable to lacunar infarcts in SAE and small plaques in MS.

It is striking how similar the MRI changes are in two diseases which have such different pathogeneses. Much confusion has been generated in the literature by loose reference to SAE as a demyelinating disease. It is not. While densitometry[23] would give more precise data about the degree of axonal and myelin loss in the two diseases, it is quite clear from the use of routine histological methods in our cases and in others in the literature that there is a more or less equal loss of axons and myelin in SAE,[3 4] in contrast to the characteristic lesion of MS in which the axons are relatively spared.[24] It is true that in advanced or unusually severe cases of MS axonal loss may be extensive with possible disappearance of neurones and ventricular dilatation.[25] Such late changes may help to account for the similarity of the MRI changes in these circumstances to those of SAE.

The pathological feature common to both SAE and MS, early and late, is astrocytic gliosis. Experimental work has provided evidence that abnormal MRI signals are generated from increased water content of the gliotic tissue.[26] "Pure" gliosis following an experimental cold lesion led to a prolongation of relaxation time, T1, and a minor change in T2.[26] It seems that gliosis alone, however, is inadequate to account for the intensity of the abnormal signals seen in MS which probably reflect the concomitant presence of increased extracellular water (Barnes D, unpublished results). Although formalin-fixed material examined by light microscopy provides an inadequate basis for commenting on small changes in the size of the extracellular space, the MRI changes in our patients with SAE were so marked that an increase in free tissue water is probable. This increase, together with the microcystic change and the gliosis, probably accounts for the high signals seen on MRI.

The histological finding of areas of relatively better preserved myelin within some lesions corresponded with areas of relatively lower signal within areas of abnormally high signal on the scans. This may provide the basis for the heterogeneous appearance of the white matter on MRI in patients with SAE during life.[18]

Sparing of the U-fibres is characteristic of SAE.[8 27] The blood supply to the subcortical U fibres is from small branches of the cortical vascular tree which may remain intact when there is ischaemia of the deep central white matter, which is believed to be the basis of SAE.[27 28] Sparing of the U-fibres might provide a helpful distinguishing feature from MS in which the lesions do not respect this subdivision, presumably because of their primarily perivenular orientation.[29]

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