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doi:10.1136/jnnp.51.2.260

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Perivascular iron deposition and other vascular damage in multiple sclerosis

C W M ADAMS

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SUMMARY Evidence of damage to cerebral vein walls was sought in 70 cases of multiple sclerosis. Seventy control cases were also examined. The multiple sclerosis cases showed venous intramural fibrinoid deposition (7%), recent haemorrhages (17%), old haemorrhages revealed by haemosiderin deposition (30%), thrombosis (6%) and thickened veins (19%). In all, 41% of all multiple sclerosis cases showed some evidence of vein damage. Occasional control cases showed haemosiderin deposition in the brain but, unlike the multiple sclerosis cases, these were diffuse and almost entirely related to coexistent cardiovascular or cerebrovascular disease. Haemosiderin deposition was common in the substantia nigra and other pigmented nuclei in all cases. It is concluded that the cerebral vein wall in multiple sclerosis is subject to chronic inflammatory damage, which promotes haemorrhage and increased permeability, and constitutes a form of vasculitis.

Involvement of the cerebral venous system in multiple sclerosis has been recognised for many years. In particular, plaques are centred on small veins or venules and extend outwards therefrom along branch veins as Dawson's fingers. The veins in acute cases are usually the site of a lymphocyte-plasma cell infiltrate, which varies in intensity between modest to moderately severe. Chronic cases show less perivascular infiltration, which is often absent in the inactive or "burnt-out" case. In some active acute cases of multiple sclerosis the vein walls themselves are heavily infiltrated with inflammatory cells, but without infiltration of the adventitia and perivascular tissues. Chronic plaques often contain vein walls thickened by collagen. Although these processes are non-specific, they do indicate that the vein wall is implicated in the inflammatory process, and is thereby damaged and thickened, partly analogous to the thickening in endarteritis obliterans in arteries passing through foci of chronic inflammation. Nevertheless, it could be held that the vein wall is merely acting as a conduit for inflammatory cells but, if so, it should return to normality after subsidence of inflammation.

The purpose of this study was to determine to what extent vein walls are damaged in multiple sclerosis, and whether such inflammatory damage constitutes a form of vasculitis.

Methods

Paraffin blocks were prepared or recut from brain samples from 70 cases of multiple sclerosis, 64 random control cases obtained at necropsy and six cases of cerebral infarction or haemorrhage. The stroke cases were taken as "positive controls" for the presence of haemosiderin derived from haemorrhage. The multiple sclerosis cases were obtained from the MRC multiple sclerosis tissue bank at Guy's Hospital and from the Department of Neuropathology, Runwell Hospital, Wickford, Essex. Blocks usually included central white matter, third, lateral and fourth ventricles, brainstem, pons, medulla and cerebellum. Approximately 350 areas of multiple sclerosis brain and 200 areas from the control brains were studied. Apart from routine stains, sections were stained with Perls' potassium ferrocyanide technique for haemosiderin (iron), a MSB-trichrome method, phosphotungstic acid-haematoxylin, luxol fast blue, solochrome or other myelin stain. Holzer's method and, sometimes, with anti-fibrin peroxidase.

Results

The results are summarised in the table, and represen-
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Table  Vein wall damage and iron deposition in multiple sclerosis and control brains*

<table>
<thead>
<tr>
<th></th>
<th>Multiple sclerosis</th>
<th>Controls</th>
<th>Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intramural fibrinoid</td>
<td>5 (7%)†</td>
<td>Nil</td>
<td></td>
</tr>
<tr>
<td>Recent haemorrhage</td>
<td>12 (17%)†</td>
<td>Nil</td>
<td>2 (100%)</td>
</tr>
<tr>
<td>Old haemorrhage (haemosiderin)</td>
<td>21 (30%)‡</td>
<td>4 (6.3%)§</td>
<td>4 (100%)</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>4 (6%)†</td>
<td>Nil</td>
<td></td>
</tr>
<tr>
<td>Collagenised thick veins</td>
<td>13 (19%)†</td>
<td>Nil</td>
<td></td>
</tr>
<tr>
<td>Total cases implicated</td>
<td>29 (41%)</td>
<td>10 (12.5%)</td>
<td></td>
</tr>
</tbody>
</table>

*Excluding changes in pigmented nuclei of brainstem; see text.
†No case associated with either cardiovascular or cerebrovascular disease.
‡Four of 21 multiple sclerosis cases containing haemosiderin had coexistent cardiovascular disease. Haemosiderin in multiple sclerosis brains was plaque-related in 20 of 21 cases.
§Three of four control cases containing haemosiderin had coexistent cardiovascular disease.

Active plaques were identified by the presence of a perivenular lymphocytic infiltration, an often irregular or shelving edge to the lesion and increased cellularity of the plaque or its edge. Chronic or subactive plaques showed trivial or absent lymphocytic infiltration, an often sharp edge, a much reduced cellular population and frequent thick-walled vessels.

Five active cases of multiple sclerosis (7% of the total) showed fibrin (fibrinoid) within the vein wall (fig 1), while recent haemorrhages (fig 2) were found in 12 cases (17%). Two of these haemorrhages were older and brown pigment was seen within attendant macrophages. Haemosiderin, revealed with Perls' method, was seen in plaques or within 2 mm of the plaque edge in 21 cases (30%). It sometimes lay in ill-defined pallisades at the plaque edge (fig 3), sometimes within microglia and, most commonly, lay within vein walls (figs 2–3).

In active cases, haemosiderin was sometimes found in areas of intense oedema and myelin pallor, often associated with marked perivenular lymphocytic cuffing. Only one case of multiple sclerosis showed haemosiderin with no relation to plaques, edges of plaques or areas of oedema and myelin pallor: there was no generalised vascular disease in this case.

In four chronic cases of multiple sclerosis (6%),

![Fig 1 Venule at edge of plaque of active multiple sclerosis, showing fibrinoid (arrows) stained red in vein wall. Left: blue filter. Right: red filter. MSB-trichrome. Bar = 20 μm.](https://jnnp.bmj.com)
Fig 2  Venous haemorrhages within chronic multiple sclerosis plaques. Haemosiderin (iron) deposition in wall of venule at right; indicating present and previous episodes of haemorrhage. Limits of haemorrhages indicated by arrows. H and E and Perl's ferrocyanide. Bar = 20 μm.

Fig 3  Haemosiderin (iron deposition) in wall of small venule in chronic multiple sclerosis plaque (left), and at edge of active multiple sclerosis plaque (right). Iron indicated by arrows. Perl's ferrocyanide, red filter. Bar = 12 μm.
there were venous thrombi or encrustations presumed to have arisen by organisation of thrombi (fig 4). In one case thrombosis was accompanied by local haemorrhage, but neither this nor other thrombotic cases appeared to be early lesions. Chronic lesions in 13 cases (19%) contained thick-walled veins, whose whole thickness was uniformly collagenised (fig 4).

The findings in the control and stroke cases are summarised in the table. The ten control and stroke cases that showed parenchymal or perivascular haemosiderin (apart from iron in the pigmented brain-stem nuclei, see below), suffered from cerebrovascular disease (six), coronary heart disease and hypertension (two), congestive heart failure (one), and neoplasia (one). The cerebrovascular cases (infarction or haemorrhage) showed massive iron deposition around the lesions, and served as positive controls. One cerebrovascular case showed subpial haemosiderin deposition10 11 and this was presumed to result from previous subarachnoid haemorrhage. Some sections showed artefactual staining with ferrocyanide, either in the form of focal fine vesiculate staining or as coarse granules scattered over the surface of the section.

All but three of the 33 control cases, where there was good sampling of the pigmented brain stem nuclei, showed moderate amounts of haemosiderin deposition in the substantia nigra, olive or areas immediately adjacent to these nuclei.

No control case showed intramural deposition of fibrinoid. With the obvious exception of the six cerebrovascular accident cases, the control cases showed no recent haemorrhages or thromboses.

Discussion

The observations reported here indicate that veins in or around multiple sclerosis plaques suffer more damage than would be expected by simple involvement in an acute inflammatory episode. This damage is seen as occasional deposits of fibrin or fibrinoid within the vein wall (6% of cases), frequent recent haemorrhages (17%), or residual haemosiderin as evidence of past haemorrhage (30%) in direct relationship to plaques, and occasional thromboses within plaque veins (6%). Such thromboses, however, do not appear to be associated with early plaques, in accord with Dow and Bergland12 and with Zimmerman and Netsky.13

Capillary haemorrhages have been described in multiple sclerosis14 15 and occasional venous hae-
The results reported here reinforce the view that damage to the vein wall is an important aspect of the pathology of the multiple sclerosis plaque. The vasculitis caused is different from and of a more modest nature than that, for example, in systemic lupus or polyarteritis nodosa but is, nevertheless, enough to cause haemorrhage, and structural and permeability changes in the vessel wall.

The term proposed by Lendrum for a wide range of vasculitic disorders is plasmatic vasculosclerosis, and the damage to the vein wall in multiple sclerosis could be regarded as causing a minor degree of such plasmatic vasculosclerosis.

Inflammatory and reparative changes in the vein wall might be exacerbated by pulsations or surges in intracranial venous pressure and may result in increased permeability of the multiple sclerosis plaque, as shown at necropsy, by immunohistochemistry and by brain scan.

The author is grateful to the Medical Research Council for a grant to aid this work and to the staff of the MRC Neuropathology Laboratory, Runwell Hospital, Wickford, Essex for help and providing some of the multiple sclerosis and control material used. The technical help of Mr Stefan Buk is gratefully acknowledged.

References

14 Siemerling E, Raeeke E. Beitrag zur Klinik und Pathologie der...
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