Journal of the Neurological Sciences, 1987, 77: 147–152
Elsevier

JNS 02759

Chronic periphlebitis retinae in multiple sclerosis
A histopathological study

Pamela J. Shaw, Nicholas M. Smith, Paul G. Ince and David Bates

Departments of Neurology and Pathology, University of Newcastle upon Tyne and the Royal Victoria Infirmary, Newcastle upon Tyne (U.K.)

(Received 4 March, 1986)
(Revised, received 23 July, 1986)
(Accepted 24 July, 1986)

SUMMARY

Retinal periphlebitis in multiple sclerosis is of particular interest in relation to our understanding of the pathogenesis of the demyelinating central nervous system plaques. Previous studies have largely been clinical, and there is little detailed histopathological information relating to this condition. We present the first detailed report in the neurological literature on the histological findings in chronic periphlebitis retinae associated with multiple sclerosis. The most significant abnormalities of the affected retinal veins were the presence of thick laminated collagen in the wall, associated with a scanty infiltration of plasma cells.

Key words: Multiple sclerosis; Periphlebitis retinae; Retinal histopathology

INTRODUCTION

The first description of the association of retinal venous sheathing (or periphlebitis retinae) and multiple sclerosis (MS) was by Ter Braak and Herwaarden in 1933. The association was confirmed in 1944 by Rucker, who described detailed ophthalmological findings in 34 patients with retinal venous sheathing, 21 of whom were subsequently diagnosed as having multiple sclerosis. The reported prevalence of periphlebitis retinae

Correspondence address: Dr. David Bates, Department of Neurology (Ward 6), Royal Victoria Infirmary, Newcastle upon Tyne NE1 4LP, U.K.

in multiple sclerosis has varied from 10 to 20%. (Rucker 1947; Wybar 1952; Haarr 1953; Scott 1961; Archembau et al. 1965; Bamford et al. 1978).

The clinical appearances of periphlebitis retinae vary according to the age of the lesion (Haarr 1963). During the active phase the involved retinal veins are often dilated, segmented and sheathed by cotton-wool like patches with ill-defined edges. These changes are usually found in the peripheral fundus at least two to three disc diameters from the optic disc. Chronic retinal periphlebitis is characterised by the presence of sharply defined narrow white lines along the veins.

The importance of retinal periphlebitis in MS is in increasing our understanding of the pathogenesis of demyelinating plaques in the central nervous system (CNS). Adams has suggested that perivenular inflammatory cell cuffing in the CNS may be the first event in plaque formation (Adams 1977). Other authors have also argued that the occurrence of periphlebitis retinae favours the hypothesis that vascular changes are the primary factor in the genesis of MS plaques (Fog 1965).

The purpose of this paper is to describe the histological appearances of multiple sclerosis-associated periphlebitis retinae in a patient who was observed to have the condition for 14 years.

CASE REPORT

W. R. was an 18-year-old apprentice electrician who presented in April 1971 with an 8-month history of weakness, stiffness and sensory disturbance first of the left and then of the right lower limb. These symptoms had fluctuated in severity, with at least two episodes of exacerbation.

On examination he had a spastic and ataxic gait and Romberg's sign was positive. In the left fundus perivenous sheathing was noted two disc diameters below the optic disc on the nasal side. There was impairment of cerebellar function and a spastic triparesis involving the left upper and both lower limbs. Proprioception and vibration sense were impaired in both lower limbs. The abdominal reflexes were absent and both plantar responses were extensor.

The clinical diagnosis of multiple sclerosis was supported by the finding of ten lymphocytes per microlitre and a total protein level of 1.09 g/l of which 22% was IgG, in the CSF. Visual evoked responses were grossly abnormal with delay, dispersion and poor resolution bilaterally. A myelogram was negative.

The patient's course was one of progressive deterioration. Two years after presentation he was virtually paraplegic and by 1984 he had no useful limb movement and profound dysarthria. In April 1985 he was admitted with a chest infection. He was anarthric and tetraplegic with wasted areflexic limbs. The optic discs were pale and the retinal venous sheathing was still present in the left eye. The patient's condition deteriorated and he died on the day after admission.

Post-mortem findings. Death was due to a combination of bronchopneumonia and recent pulmonary embolism to the lower lobe of the right lung.

The brain weighed 1400 g and was normal in external appearance. The brain stem was markedly atrophic, with a semitranslucent surface. Numerous plaques of multiple

sclerosis were present in the hemispheric white matter, the cerebellum, pons and medulla.

The spinal cord was atrophic and showed confluent demyelination of the lateral and posterior tracts.

The eyes. The retinae were examined in situ and the periphlebitic lesions identified. The abnormal veins showed mild focal dilatation and were outlined throughout the abnormal segment by regular white bands on either side of the vessel (Fig. 1). At each end of the lesion there was tapering of the vascular lumen and the perivenous sheath. Where tributary vessels entered the vein through the lesion, the perivenous tissue extended minimally along the tributary.

Histology of the eye. Paraffin sections were stained with haematoxylin and eosin and a range of special stains including phosphotungstic acid haematoxylin (PTAH) and immunoperoxidase studies for the following antigens: glial fibrillary acidic protein (GFAP); neurone-specific enolase; factor VIII related antigen; S-100 protein; immunoglobulin heavy chains and kappa and lambda light chains.

Light microscopy showed that the periphlebitic lesions affected the retinal veins only, the arterioles being normal in appearance. The venous endothelium was normal. The most significant abnormality of affected veins was the presence of thick, laminated hyalinisation of the wall as shown in Fig. 2. In the centre of the periphlebitic lesion the hyalinisation affected almost the whole circumference of the vein, with only a short

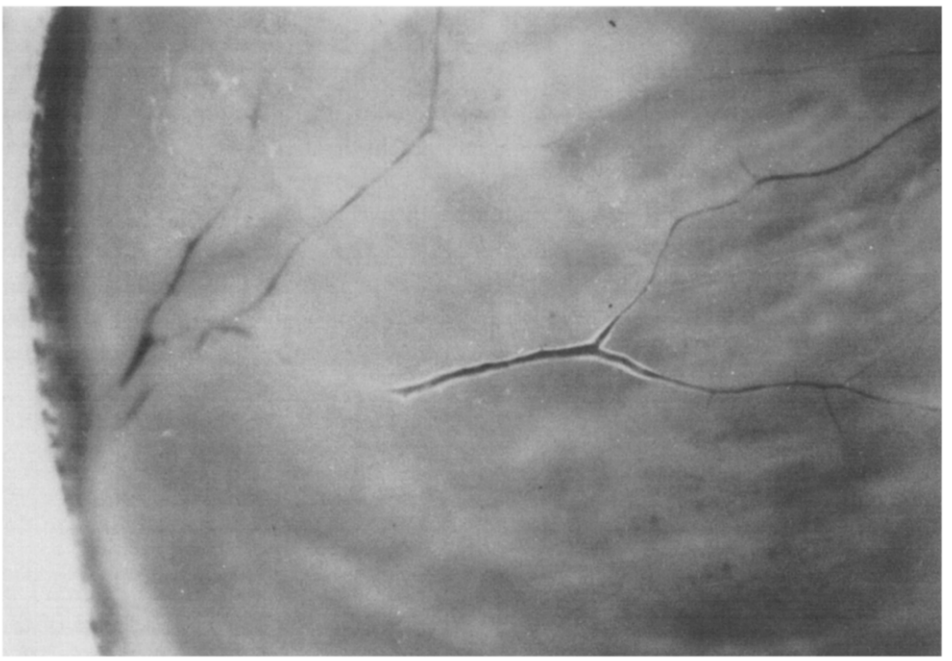

Fig. 1. Stereomicroscopical appearance of the retinal vessels in situ. The retinal vein branch shows dilatation over the affected segment. Stereomicrograph, × 10.

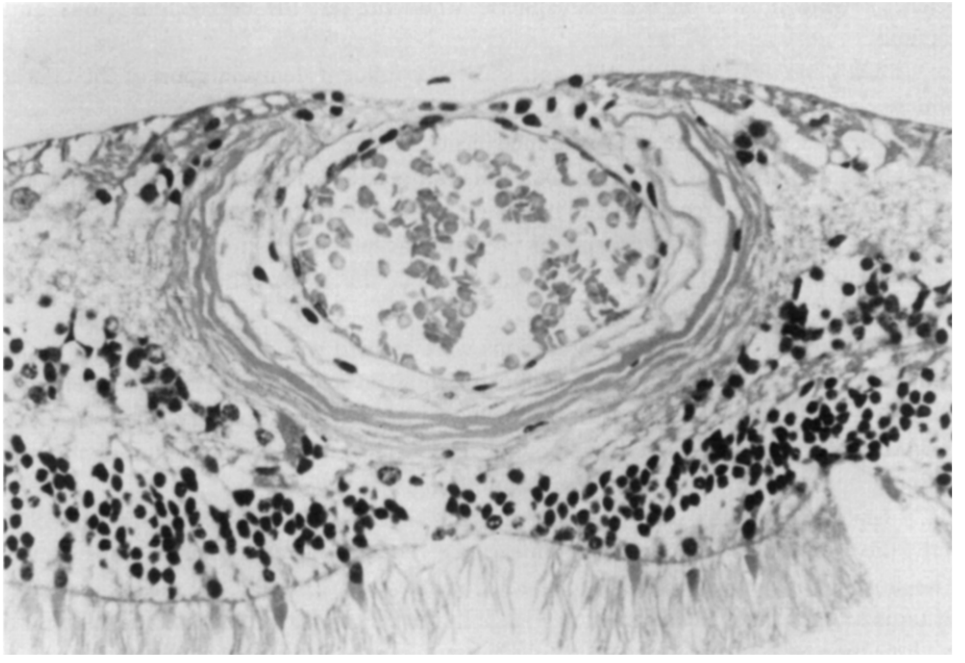

Fig. 2. Periphlebitis retinae lesion. The vessel lumen is greatly dilated. Concentric lamellae of hyaline material have replaced the normal 'lacy' perivenous connective tissue. A few plasma cells occupy a subendothelial position. The hyalinised tissue fails to surround the vitreous aspect of the vessel. H&E, × 25 obj.

segment of non-hyalinised vessel wall over the superficial (vitreous) aspect. At the tapered margins of the lesion there was only patchy hyalinisation of the vessel wall. Cellular infiltration was scanty with only occasional plasma cells and few other inflammatory cells. The plasma cells stained exclusively with IgG kappa. There was no glial proliferation in the vicinity of the lesion. Stains for glial cytoplasmic processes (PTAH, Ipx GFAP) suggested some distortion of the normal glial – vascular relationship. Dendritic glial processes were present between the laminated bands of hyaline material. The hyaline material was not stained by any of the antisera studied, but trichrome staining suggested that it was composed of laminated collagen.

Electron microscopy confirmed the above findings. The vessel wall was predominantly composed of collagen fibrils showing a rather disorganised pattern of deposition (Fig. 3).

DISCUSSION

Our case provides the first detailed report in the neurological literature of the histopathological findings in chronic periphlebitis retinae associated with MS. In 1965 Fog briefly described the pathological findings in a patient with MS and periphlebitis. Histologically the changes were compatible with the acute form of periphlebitis retinae.

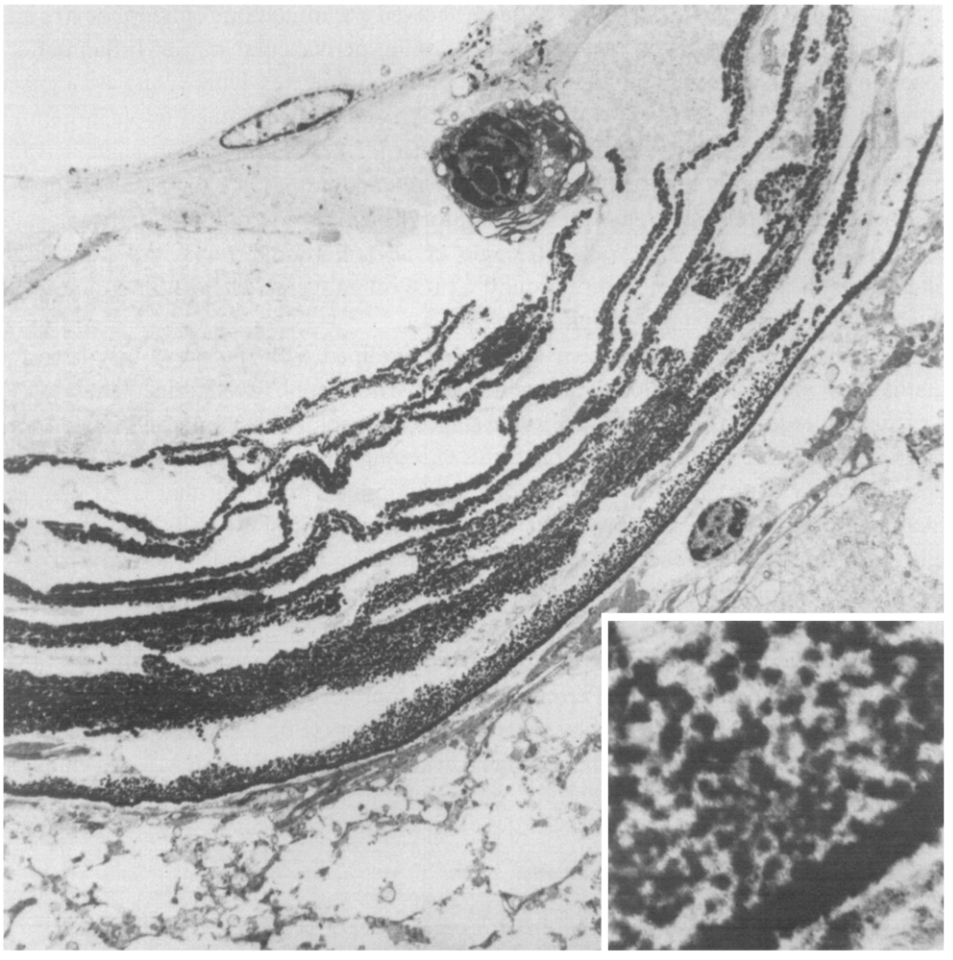

Fig. 3. Electron-micrographic appearance of the vessel wall. A normal endothelial cell is present at the upper left. A plasma cell is conspicuous in the subendothelial zone. The irregular concentric bands of granular collagenous tissue are clearly visible within the basement membrane. EM, × 2200. *Inset*: Unpolymerised tropocollagen fibrils within the hyaline tissue. EM, × 17850.

There was infiltration of the walls of veins by lymphocytes and plasma cells as well as perivascular cellular infiltration and reactive changes in the adjacent vitreous. Arnold et al. reported on the pathological findings relating to the eyes from 47 autopsy cases of multiple sclerosis (Arnold et al. 1984). They found evidence of retinal periphlebitis in four cases in which the histological findings were similar to those reported by Fog. Immunoperoxidase studies showed abnormal permeability of vessels in areas both with and without periphlebitis indicating that the vascular changes may be more widespread than detected clinically. No chronic periphlebitic lesions were identified in this study. In 1985 Engell et al. reported the findings in two cases of multiple sclerosis associated retinal periphlebitis, one of whom was the same patient described by Fog. Microscopic

examination of the eyes of these two patients showed accumulations of lymphocytes and plasma cells in the walls of veins and surrounding perivascular tissue. Inflammatory reaction was also present in the vitreous, with lymphocytes lying along condensed vitreous strands. Some vessel walls appeared fibrosed and contained fewer inflammatory cells. There was no evidence of gliosis with PTAH staining. Toussaint in 1983 published a histopathological description of the retinal findings in two patients with MS and periphlebitis retinae. He found inflammatory lesions with nodular lympho-plasmacytic accumulations in the walls of single or several retinal veins and perivenous alterations of an undefined nature around all the retinal veins, ensheathing them from their papillary origin to the periphery.

If the findings of the present study are combined with the previously reported histological studies (Fog 1965; Toussaint 1983; Arnold et al. 1984; Engell et al. 1985), a picture emerges of the active and chronic stages of periphlebitis retinae associated with multiple sclerosis. In the active phase the vascular changes resemble those around vessels in the acute phase of CNS plaque formation. In many chronic CNS plaques, blood vessels have thick collagenous walls (Weller 1985). Few cells are present in chronic plaques and those found usually consist of an occasional reactive astrocyte, lymphocyte or plasma cell. These appearances are similar to the findings we describe in this case of chronic periphlebitis retinae. Such histological similarity between the vascular changes in CNS plaques and retinal periphlebitic lesions suggests that they may have a common pathogenesis. Periphlebitis may therefore be an initial event in plaque formation, as has been suggested by several other authors (Fog 1965; Engell et al. 1984). If this is the case periphlebitis retinae may represent the basic lesion of MS in a clinically visible site.

REFERENCES

Adams, C.W.M. (1977) Pathology of multiple sclerosis: progression of the lesion, *Brit. Med. Bull.*, 33: 15–20.

Archembau, P., R. Hollenhorst and C.W. Rucker (1965) Posterior uveitis as a manifestation of multiple sclerosis, *Proc. Mayo Clin.*, 40: 544–551.

Arnold, A.C., J.S. Pepose, R.S. Hepler and R.Y. Foos (1984) Retinal periphlebitis and retinitis in multiple sclerosis, Part 1 (Pathologic characteristics), *Ophthalmology*, 91: 255–262.

Bamford, C.R., J.P. Ganley, W.A. Sibley and J.F. Laguna (1978) Uveitis, perivenous sheathing and multiple sclerosis, *Neurology*, 28: 119–124.

Engell, T., O.A. Jenson and L. Klinken (1985) Periphlebitis retinae in multiple sclerosis. A histopathological study of two cases, *Acta Ophthalmol.*, 63: 83–88.

Fog, T. (1965) The topography of plaques in multiple sclerosis, *Acta Neurol. Scand.*, 41 (Suppl. 15): 154–156.

Haarr, M. (1953) Periphlebitis retinae in association with multiple sclerosis, *Acta Psychiat. Scand.*, 28: 175–190.

Haarr, M. (1963) Retinal periphlebitis in multiple sclerosis, *Acta Neurol. Scand.*, 39 (Suppl. 4): 270–272.

Rucker, C.W. (1944) Sheathing of the retinal veins in multiple sclerosis, *Proc. Mayo Clin.*, 19: 176–178.

Rucker, C.W. (1947) Retinopathy of multiple sclerosis, *Trans. Amer. Ophthal. Soc.*, 45: 564–570.

Scott, G.I. (1961) Ophthalmic aspects of demyelinating diseases, *Proc. Roy. Soc. Med.*, 54: 38–42.

Ter Braak, J.G. and A. Herwaarden (1933) Ophthalmo-encephalomyelitis, *Klin. Monatsbl. Augenheilk.*, 91: 316–343.

Toussaint, D. (1983) Perivenous sheathing in multiple sclerosis, *Bull. Soc. Belge Ophthalmol.*, 208: 369–374.

Weller, R.O. (1985) Pathology of multiple sclerosis. In: W.B. Matthews, E.D. Acheson, J.R. Batchelor and R.O. Weller (Eds.), *McAlpine's Multiple Sclerosis*, Churchill Livingstone, Edinburgh, London, Melbourne, New York, pp. 301–343.

Wybar, K.C. (1952) The ocular manifestations of disseminated sclerosis, *Proc. Roy. Soc. Med.*, 45: 315–320.