
Although the perivenous localization of cellular cuffing and plaque formation in multiple sclerosis is well known, and vascular abnormalities of the retinal vessels detected by opthalmoscopy have also been reported, no one is yet clear on the frequency and significance of these findings. The aim is to document the presence of vascular changes and cells in the ocular media in a series of patients presenting with isolated optic neuritis, and to assess the significance of these findings for subsequent conversion to multiple sclerosis. Patients diagnosed with acute optic neuritis and without previous ocular disease or possible manifestations of multiple sclerosis are recruited from the Physicians’ Clinic at Moorfields Eye Hospital. Of the 50 participants (31 females and 19 males, aged 14–49 years), of whom 3 have had one previous episode of optic neuritis, none are treated and all but 1 make a spontaneous recovery, eventually achieving visual acuity in the affected eye of 6/9 or better. After routine neurological and ophthalmological examination, the pupils are dilated and fluorescein angiography performed.

The results are clear. Fourteen patients have an abnormal retina (Fig. 1): vascular sheathing (two), fluorescein leakage (six) or cells in the ocular media (two) as the only abnormality; combinations of vascular sheathing and fluorescein leakage (four); or cells also in the context of sheathing or fluorescein leakage (four). In 5 of these 14 patients, the changes are only seen in the eye contralateral to that showing acute optic neuritis.

Follow-up is at a mean of 3.5 years (ranging from 1 month to nearly 12 years). At this stage, 13 (28%) of 46 patients have developed clinically definite multiple sclerosis, using the recently described ‘Poser’ criteria. But conversion is more likely, and happens faster, in those with than those without retinal abnormalities (8 of 14 patients versus 5 of 32 patients, respectively). These proportions change to 8 of 13 versus 3 of 30 patients if the 3 individuals with a previous episode of optic neuritis are excluded. The relative risk for converting to multiple sclerosis in the presence of any retinal abnormality is 14.4.

Class I and Class II histocompatibility typing using serological methods (46 of 50 patients) confirms a previous study from Ian McDonald (1933–2006) and his team showing a frequency of HLA-DR2 that is intermediate between those seen in patients with multiple sclerosis and healthy individuals; and with the relative risk increased to 4.3 in the presence of HLA-DR2. Martin Halliday (1926–2008) carries out visual evoked potentials in 31 of 50 patients. In 10 with retinal abnormalities, all but 1 show an absent or delayed response (2 or 7, respectively) in the affected or contralateral eye. Of the 21 patients studied, who have normal ophthalmoscopic findings, the visual evoked potential is absent in 2, delayed in 14 and normal in 5. Neither these frequencies nor the mean latencies (119.56 ± 16.89 ms and 118.63 ± 18.80 ms for those with and without retinal abnormalities, respectively) differ between the groups.

Why have the authors observed a higher frequency of retinal abnormality than others? ‘Most neurologists have been reluctant to accept the observation, having failed to see it for themselves. Few however, are experienced in the systematic examination of the periphery of the retina and it should be emphasized that in only one of our patients were abnormalities visible at the posterior pole through the undilated pupil.’ The team from Moorfields Eye Hospital has studied patients with optic neuritis soon after presentation; and any suggestion that their observations are artefacts resulting from an aberrant light reflex is addressed by the objective evidence from abnormalities of fluorescein angiography. Based on the clinical features, supported by tissue typing and evoked potential data that are not dissimilar from previous series, that these cases are fully representative of acute isolated optic neuritis is not in doubt. Might they have sarcoidosis, in which retinal sheathing is more commonly seen? Certainly not; the absence of optic disc swelling or systemic symptoms and signs and the excellent spontaneous recovery seen in all but one patient would be most atypical. ‘While we cannot exclude the possibility that some had sarcoidosis, there is no evidence that they did.’

Everything suggests that the presence of retinal abnormalities, whenever these may have occurred with respect to the recent onset of optic neuritis, carries the same significance for subsequent clinical conversion as does clinical or laboratory evidence for a lesion outside the visual system; and the retinal vascular abnormalities indicate that the pathological process underling demyelination of the CNS is already active during this inaugural event. So what significance is provided by this window on the brain for the pathogenesis of multiple sclerosis? The retinal vessels and those of the CNS each have continuous endothelial tight junctions. The processes of Müller cells and astrocytes ensheath blood vessels in the retina and brain, respectively, and separate their endothelium from the basement membrane and pericytes. ‘In multiple sclerosis, perivascular cuffing is commonly observed in histological
sections of the brain and can be seen readily in the retina where it has been observed to correspond with segments of ophthalmoscopically observed sheathing. This suggests that the sheathing of retinal vessels is the visible clinical sign of perivascular lymphocytic infiltration and accompanying oedema that characterize the lesions of multiple sclerosis. Importantly, this cuffing is occurring in a region that is free of myelin and oligodendrocytes. Therefore, it cannot be secondary to demyelination that has already developed through some other mechanism. Rather, the primary events are occurring at the vascular endothelium. In assembling these arguments, the authors draw extensively on the observations of Professor Ingrid Allen using the collection of eyes from people with multiple sclerosis that she has assembled in Belfast, Northern Ireland. Analyses of that resource have appeared in several of Dame Ingrid’s authoritative accounts of the neuropathology of multiple sclerosis written in monographs and other reviews during and since the 1980s. Now, with Professor Allen as co-author, Ari Green and colleagues from San Francisco use that material to provide an updated and definitive neuropathological account of the eye in multiple sclerosis (see page 1591).

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