Disseminated lesions at presentation in patients with optic neuritis

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SUMMARY Thirty five adults and two children with clinically isolated optic neuritis were examined by magnetic resonance imaging (MRI) to determine the presence of disseminated lesions within the brain at presentation and to compare these findings with the results of evoked potential studies. Of the adult patients, 61% showed lesions on the scans whereas the evoked potentials suggested the presence of lesions outside the visual system in 30%. MRI is a sensitive method for the demonstration of clinically unsuspected lesions in patients with uncomplicated optic neuritis.

Optic neuritis is a common presenting feature of multiple sclerosis, although not every patient with it ultimately develops the clinically expressed disseminated disease.1 The diagnosis of multiple sclerosis still depends on the demonstration of abnormalities attributable to lesions at multiple, necessarily separate, sites in the central nervous system.2 For this reason it is of considerable interest to determine the frequency with which patients suffering from optic neuritis have evidence of additional lesions at presentation. Because of the remarkable sensitivity of magnetic resonance imaging (MRI) in detecting cerebral lesions in multiple sclerosis,3 we have used it in a systematic investigation of patients presenting with isolated acute optic neuritis. We have compared the incidence of MRI evidence of abnormalities outside the optic nerve with that derived from evoked potentials.

Patients

The investigation was approved by The Ethics Committee of The National Hospitals and conformed to the guide lines of The National Radiological Protection Board. The diagnosis of optic neuritis was made on standard criteria,4 patients with medical conditions known to be associated with optic neuropathy4 being excluded. Patients were also excluded if there had been a previous episode of neurological disturbance, or if additional neurological signs other than those referable to the symptomatic eye were present. Most patients had been referred to the Physicians Clinic at The Moorfields Eye Hospital, and the remainder to The National Hospitals, Queen Square and Maida Vale. We investigated 35 adult patients aged 16 to 47 years, (mean 32). Of these, 28 had presented with acute unilateral optic neuritis and three with acute simultaneous bilateral optic neuritis. In addition, we scanned four adults with acute bilateral sequential optic neuritis (aged 29, 31, 40, 40 yr) and two children, one aged 7 yr with bilateral consecutive optic neuritis, and the other aged 18 yr who had had an attack of bilateral simultaneous optic neuritis at the age of 13.

The MRI examination was carried out as soon as possible after the onset of optic neuritis. In the adults the interval ranged from 2 weeks to 44 weeks, mean 9 weeks. The child with consecutive optic neuritis was scanned 4 weeks after the onset of the second attack the first having occurred 24 weeks previously. The child with bilateral simultaneous optic neuritis was scanned 5 years after the episode.

Investigations

MRI imaging

We used a Picker proton NMR imager initially at 0·25 Tesla and subsequently at 0·5 Tesla. At least two sequences were used in each patient, spin-echo (SE) and inversion recovery (IR), using a multi-slice imaging technique for the whole brain with a slice thickness of 10 mm and distance of 12 mm between the centre of adjacent slices. In later examinations further SE sequences with different pulse intervals were used to increase the chance of detection of lesions which may not have been clearly visualised on one sequence. Images of calculated relaxation time constants (T1 and T2) were reconstructed in some patients and measurements of T1 and T2 were made. The scans were reported "blind" by four independent assessors and only those unanimously considered to be abnormal were categorised as such. The total number of
lesions in each patient and their distribution were recorded. The scans of the patients were compared with scans from 37 apparently healthy individuals aged 19 to 62 (mean 38) years.

**Evoked potentials**
Visual (VEP), auditory (AEP), and somatosensory (SEP) evoked potentials were carried out on the majority of patients using methods previously described. The examinations were often performed on the same day as the MRI, and always within the same week.

**Other investigations**
The routine assessment included radiographs of skull, optic foramina and sinuses, a full blood count and ESR, determination of blood urea and glucose, and serological examination for syphilis. Lumbar puncture was not performed.

**Results**
Twenty-one of the 35 adults had clinically unsuspected lesions in the brain demonstrated by MRI. Resolution of the optic nerve is not satisfactory at present and no unequivocal lesions were detected there. VEPs however were abnormal in all affected eyes and in four of the clinically unaffected eyes in the 28 patients in whom the examination was performed.

Of the 28 patients with acute unilateral optic neuritis, 17 had abnormalities on the cerebral scans. Sixteen patients had periventricular changes either alone or in combination with other lesions within the white matter of the cerebral hemispheres or in the brain stem (four patients) or cerebellum (three patients). A typical example is shown in the figure. The most common site for the periventricular abnormalities was around or above the bodies of the lateral ventricles. Lesions were often seen in relation to the trigones which were occasionally the only site of periventricular changes. In one patient there was a single lesion within the white matter separate from the ventricles with no associated periventricular changes.

Fifteen of the 17 patients with abnormal scans had all three sets of evoked potentials recorded. In six there were abnormalities suggesting the presence of lesions outside the visual pathways. Nine of the 11 patients with normal scans were fully assessed electrophysiologically and in none were additional abnormalities found. We did not attempt a detailed correlation of the location of the abnormalities demonstrated by MRI with the evoked potential abnormalities.

Two of the three adult patients with simultaneous bilateral optic neuritis had abnormal scans. One of the latter patients had had an abnormal SEP; the other was not assessed electrophysiologically. Three of the four patients with bilateral consecutive optic neuritis had abnormal scans. These three patients had a full evoked potential examination. In only one was
there evidence of abnormalities outside the visual pathways. Both children had normal scans. SEP and AEP were recorded only in the older patient, 5 years after the episode of optic neuritis; they were normal.

In no patient with a normal scan did the evoked potentials suggest the presence of clinically unsuspected cerebral lesions.

In six patients with acute unilateral optic neuritis follow up scans have been performed 6 months after the first examination. In one patient the second scan showed the presence of two new lesions in the cerebellum. This patient had experienced a week-long episode of sensory disturbance affecting the left arm and leg three weeks prior to follow-up. Of the remaining five, four initially had abnormal scans and of these, one showed some resolution of the scan appearance and three showed additional lesions. In the remaining patient the scan had initially been normal and remained so.

In the control group three patients had abnormal scans. Two had a few small isolated lesions in the hemispheres and one had extensive periventricular changes indistinguishable from those seen in multiple sclerosis. This apparently healthy volunteer gave no history of previous neurological illness in response to a general screening questionnaire, but the circumstances of recruitment precluded a detailed neurological assessment. The occasional finding of abnormalities in normal individuals is in keeping with the unsuspected discovery of evidence of multiple sclerosis at necropsy with a frequency at least as high as that of the clinical prevalence of the disease.6

Discussion

The incidence of additional lesions in the adult patients presenting with their first episode of optic neuritis (unilateral and bilateral simultaneous optic neuritis) was 19/31 (61%). The MRI scans revealed abnormalities in a substantially higher proportion of patients than that obtained from evoked potentials either in our study (8/27, 30%) or in previously reported series.7,8 On the other hand, VEPs were very much more sensitive than MRI in detecting abnormalities in the optic nerve itself.

The incidence of 61% for additional lesions in adults is similar to that for the incidence of multiple sclerosis after optic neuritis in the United Kingdom and it may be tempting to diagnose multiple sclerosis in the patients with multiple lesions. Because of the personal implications of a diagnosis of multiple sclerosis it cannot be emphasised too strongly that it is premature to do so. The frequency with which apparently isolated optic neuritis is the sole symptomatic expression of a more widespread but nevertheless monophasic pathological process (an acute disseminated encephalomyelitis) is unknown. There is clinical evidence that it can occur with bilateral optic neuritis in childhood9 following which multiple sclerosis is rare even after lengthy follow-up.10 The patient who had evidence of a new cerebellar lesion in the second scan 6 months after the first and who had had an additional episode of sensory disturbance is clearly likely to have multiple sclerosis. A diagnosis of multiple sclerosis might be possible at presentation if it were feasible to determine the age of lesions from the MRI characteristics: the presence of the lesions of different ages would provide good circumstantial evidence of a disease process of some duration. At present this is not possible, but current experimental work suggests that is may be. Following acute cold lesions of the cerebral cortex the pattern of increase in T1 and T2 is different in the acute oedematous phase from that in the chronic phase (D Barnes, WI McDonald, P Tofts, G Johnson and D Landon, unpublished). Comparison of T1 and T2 values for chronic brain stem lesions in patients with multiple sclerosis with those for acute lesion suggests that similar changes occur in human disease (IEC Omerod and P Rudge, unpublished). It seems likely that oedema is important in determining the changes in MRI signal in the acute lesion. The origin of the abnormal signal in chronic lesions is uncertain, but may be related to an increase in water content and therefore proton density as a result of the replacement of myelin by astrocytic processes12 and sclerosis. It is also conceivable that the signal might be modified by changes in the macromolecular environment provided within the glial cells.

A number of factors are already known to influence the risk for developing multiple sclerosis after optic neuritis, including recurrence,11,12 the presence of HLA DR211 (the actual association observed was with a locally defined antigen BT 101, which is equivalent to DR2 but with some cross-reaction with DRw1 and DRw6) and winter onset in HLA DR2 positive individuals,11 age and sex12 and the presence of oligoclonal bands in the CSF.13 The presence of the first three in combination increases the risk nearly 12 fold.11 Determination of the prognostic significance of the presence of multiple lesions at MRI at presentation, and with and without the presence of other risk factors, requires further investigation including serial scanning, and long-term follow-up.

The distribution of the additional lesions is of some interest. The periventricular changes and the distribution of cerebral lesions are similar to those in multiple sclerosis12. The predilection for the posterior white matter and in particular involvement of the optic radiation is interesting in relation to the delayed VEPs so characteristic of optic neuritis.14 The origin of the delays seen in demyelinating disease is still not fully...
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understood. The present observations suggest that in some patients there may be a contribution from slowing of conduction in posterior parts of the visual pathways as well as in the optic nerve itself.

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