CORRELATIONS BETWEEN EVOKED POTENTIALS AND MAGNETIC RESONANCE IMAGING IN MULTIPLE SCLEROSIS

Thesis submitted

by

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for the degree of

Doctor of Philosophy

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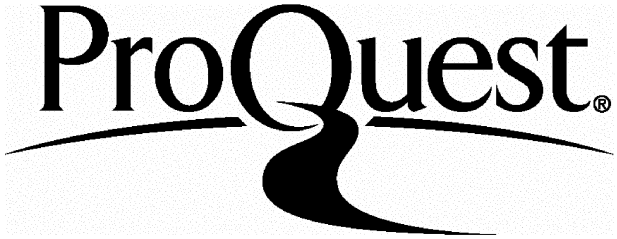

ABSTRACT

This thesis describes correlations between evoked potentials (EPs), magnetic resonance imaging (MRI) and clinical abnormalities in multiple sclerosis (MS).

In 31 patients with a cervical cord syndrome, MRI lesions occupying the left or right posterior quadrant of the cervical cord were significantly associated with abnormal somatosensory evoked potentials (SEPs) from the left or right median nerve, respectively. No association was found between brain MRI and SEP abnormalities. MRI and SEPs were only weakly correlated with clinical deficits, except in four cases who had a well localised lesion involving the posterior columns.

Brain MRI and hemifield visual evoked potentials (VEPs) were obtained in 15 MS patients with homonymous hemianopia. In each case studied, MRI revealed the presence of large postchiasmal abnormalities which decreased in size in coincidence with visual recovery. VEPs consistent with postchiasmal pathology were recorded in only five cases; latency increase was less frequent than amplitude reduction, which resolved with improvement in the field defect.

Among 21 patients with a clinically isolated optic neuritis, the amplitude of the cognitive event-related potentials was significantly attenuated and the performance on psychometric tests assessing relevant cognitive functions significantly poorer in cases with extensive brain MRI abnormalities as compared to those showing fewer lesions.

In 11 patients with acute optic neuritis, leakage of Gadolinium-DTPA within the optic nerve lesions was associated with reduction of the VEP amplitude and visual acuity. One month later, the absence of leakage was paralleled by a significant improvement of the VEP amplitude and recovery of the visual acuity. Since gadolinium leakage probably indicates inflammation, the resolution of the latter seems to be an important factor in the recovery from acute optic neuritis.

These findings illustrate how the study of the correlation between EP, MRI and clinical abnormalities may improve our understanding of the pathophysiology of MS.

ACKNOWLEDGEMENTS

I am very grateful to Dr. Steve Jones, my supervisor, for guiding me through the research presented in this thesis. He has been conscientious, patient and caring.

I am indebted to the NMR Research Group at the Institute of Neurology, and in particular to Dr. David Miller, Dr. Gordon Plant and Dr. Bryan Youl, for providing the MRI and clinical data. I also thank Dr. Anthony Feinstein of the Neuropsychiatry Department at the National Hospital, for providing the neuropsychological data.

I am grateful to Dr. Martin Halliday for welcoming me in his Unit at the National Hospital, and to my colleagues Mrs. Pamela Almaz, Mr. Idris Roberts, Mr. Jack Pitman, Ms. Fatima Shawkat and Dr. Anthony Towell for their help and support. In particular, I would like to thank Dr. Geoff Barrett for helping me to analyse the cognitive evoked potentials included in the study.

I am grateful to the Multiple Sclerosis Society of Great Britain and Northern Ireland for providing financial support.

Finally, I thank my family and friends for their constant encouragement and, in particular, my mother who has suffered as much as me during the writing of this work.

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LIST OF ABBREVIATIONS

BAEPs	brainstem auditory evoked potentials
BBB	blood-brain-barrier
CNS	central nervous system
CSF	cerebral spinal fluid
CREAE	chronic relapsing experimental allergic encephalomyelitis
CT	computerised tomography
EPs	evoked potentials
ERPs	event-related potentials
Gd-DTPA	Gadolinium-diethylene triamine pentacetic acid
IQ	intelligence quotient
IR	inversion recovery
lg_{10}	decimal logarithm
LGN	lateral geniculate nucleus
MANOVA	multivariate analysis of variance
MR	magnetic resonance
MRI	magnetic resonance imaging
MS	multiple sclerosis
p	probability
PASAT	paced auditory serial addition test
PVSAT	paced visual serial addition test
RT	mean reaction time
RTSD	within subjects variability of the reaction time
SD	standard deviations
SDMT	symbol-digit modalities test
SE	spin echo

SEPs	somatosensory evoked potentials
STIR	short time inversion recovery
VEPs	visual evoked potentials

CHAPTER 1

INTRODUCTION

1.1 AIMS OF THE STUDY

Evoked potentials (EPs) and magnetic resonance imaging (MRI) are useful techniques in the diagnosis and investigation of multiple sclerosis (MS). The former point out abnormalities of conduction in the central sensory pathways due to the presence of plaques (Chiappa, 1990), while the latter illustrates the development of lesions by highlighting changes in the density and behaviour of mobile protons (Ormerod et al., 1986b).

The role of EPs and MRI in the diagnosis of MS has been exhaustively dealt with in previous studies (for review see Matthews, 1991). In the main, the usefulness of these techniques lies in the ability of revealing clinically silent abnormalities, thus providing evidence of spatial dissemination which is one of the essential elements in the clinical diagnosis. In doing so MRI is more effective than single EP techniques (Paty et al., 1988), mainly due to the fact that the latter test only specific structures within the sensory pathways.

The present study was designed to examine the degree of correlation between EP and MRI abnormalities in MS and elucidate how these relate to clinical deficits. In particular, some specific questions were addressed. Are areas of altered MRI signal in sensory pathways always associated with abnormalities of the sensory conduction, and vice versa? Areas of altered MRI signal commonly found in the

cerebral hemispheres of MS patients seldom give rise to clinical deficits detectable on routine neurological examination. What, therefore, are the morphological and electrophysiological features of symptomatic brain MRI lesions? In the early stages of MS, does the extent of brain MRI abnormalities correlate with cognitive impairment? On MRI, the use of contrast agent makes it possible to distinguish acute from chronic MS lesions (Miller et. al., 1988d). Is the pattern of associated electrophysiological abnormalities different between the two stages of lesion development?

A clarification of these questions may provide us with some insights into the pathophysiology of MS and help us to understand the complex relationship between lesions, physiological abnormalities and clinical deficits.

1.2 SENSORY EVOKED POTENTIALS

1.2.1 GENERAL FEATURES

The application of appropriate stimuli to sense organs or artificial electrical stimuli to a peripheral nerve trunk produces electrical activity in associated structures of the nervous system which can be detected by electrodes on the skin adjacent to the activated regions. Evaluation of the amplitude, latency, waveform and distribution of

these potentials gives information regarding impulse transmission in axons and synaptic relays of the activated pathway.

Dawson (1947) was the first to record cortically generated potentials from the human scalp following electrical stimuli applied to a peripheral nerve trunk. Superimposition of waveforms recorded after successive stimuli made it possible to distinguish the stimulus-related responses from the background activity. Later, Dawson (1954) described the use of an averaging device, which carried out summation of successive responses, thus improving the signal-to-noise ratio. In the following years, the technique became widely used in the investigation of various neurological diseases, MS in particular (Halliday, 1982a).

The ability of EPs to reveal lesions which are "clinically silent" is particular useful in the early stages of MS, when the clinical picture may be attributable to only one lesion and the diagnosis is, therefore, uncertain.

1.2.2 STUDIES IN MULTIPLE SCLEROSIS

1.2.2.1 Somatosensory evoked potentials

The first studies of somatosensory evoked potentials (SEPs) in MS described abnormalities of the cortical potentials following stimulation of the median nerve. The series

published by Halliday and Wakefield (1963) included two patients with MS. Both had impaired joint position sense in the hands but preserved pain and temperature sensation. Cortical responses were bilaterally delayed, as compared with neurologically normal controls, and the amplitude was smaller from the more affected arm. It was suggested that cortical SEPs reflect activation of the posterior column pathways, but are independent of the spinothalamic tracts. These findings were confirmed by Baker et al. (1968) and Namerow (1968) in two series of 91 and 40 cases, respectively, with definite MS. They recorded abnormal SEPs in 84% and 94% of patients with a proprioceptive sensory loss in the tested arm and in 50% and 43% of those without such a deficit. The characteristic abnormality was absence of the cortical component N20 (a negative-going potential with a latency of approximately 20 ms), with broadening and delay of the subsequent positivity. In 14/17 patients, Desmedt and Nöel (1973) recorded delayed cortical responses with normal peripheral potential at wrist and axilla. This suggested that the slowing of conduction responsible for the abnormality of the cortical response was confined to the central segment of the somatosensory pathways.

One of the consequences of demyelination is an impaired ability of the axons to conduct a high frequency of impulses, due to an increase of the refractory period of transmission (McDonald, 1963; McDonald and Sears, 1970). Sclabassi et al. (1974) provided evidence of this deficit

in humans with MS by recording cortical responses to repeated stimulation of the median nerve. The potentials recorded from the scalp consisted of an oscillation of the same frequency as the stimulus, superimposed on the waveform of the SEP following the initial stimulus. In normal subjects, this oscillation could be seen at stimulus frequencies up to 100 Hz, whereas in MS patients this limit was reduced and appeared inversely correlated with the severity of the proprioceptive deficit in the tested arm.

Since the cervical spinal cord is one of the commonest sites in which MS plaques occur, it is of interest to examine the alterations of the cervical SEP. This potential, named N13 or N14, proves to be comparable to or even more sensitive than the cortical one. In a large series including 126 patients with established or suspected MS (Small et al., 1978) abnormalities of N14 and N20 were detected in 48% and 36% of waveforms, respectively. The association of an abnormal N14 with a normal N20 was nine times more frequent than the converse. Another difference concerned the type of abnormality: N14 was mainly attenuated or distorted but rarely delayed, whereas N20 was more frequently delayed than attenuated. The differences between N14 and N20 components may be partly accounted for by the fact that N14 shows a highly stereotyped waveform in the normal population, while the appearance and amplitude of N20 vary a great deal. It follows that amplitude abnormalities of the N14 can be easily detected, whereas minor waveform al-

terations of the N20 may be missed. The frequent coexistence of an abnormal N14 with a normal N20 could alternatively be due to some amplification of the disrupted afferent volley in the thalamus and cortex (Eisen et al., 1979), since it is known that cortical SEPs of normal or near normal amplitude may be recorded even when the afferent volley is greatly attenuated. However, this mechanism does not appear to operate in some patients, as described by Eisen et al. (1982). Another factor is that cervical and cortical potentials are due to partially independent pathways, namely the collateral branches of the primary sensory neuron which enter the grey matter of the cervical cord or turn rostrally into the posterior columns. Dorsal horn synaptic potentials associated with the former branch make a major contribution to N14 at low cervical level, so that the N14 may be affected by a central cord lesion which leaves N20 intact (Jones, 1982a).

Some patients with MS experience exacerbation of pre-existing symptoms or development of new ones following a hot bath or physical exertion. This phenomenon has been attributed to an increased lability to heat in demyelinated fibres, such that temperatures not far beyond the normal range induce conduction block. Matthews et al. (1979) provided indirect evidence of conduction block in the somatosensory pathways after heating. They recorded cervical and cortical SEPs in 14 MS patients before and after raising the body temperature by about 1°C. Heating

shortened the latency of N14 and N20, a phenomenon almost entirely due to increase of the conduction velocity in the peripheral nervous system. In addition, it doubled the incidence of undetectable N14 (16% to 38%) and reduced the amplitude of nearly all the detectable ones. The latter changes occurred mainly in patients who experienced concurrent exacerbation of symptoms.

The measurement of the cervico-cortical conduction time (N14 to N20) may reveal minor delays in the supraspinal somatosensory pathways. This parameter should be more sensitive than the absolute latency of N20, because it is independent of the arm length and varies relatively little with the body stature (Nai-Shin Chu, 1986). Ganes et al. (1980) detected a prolonged cervico-cortical conduction time in 23% of patients with certain or suspected diagnosis of MS, whose responses did not show any definite abnormality in absolute terms. When the evaluation of this parameter was added to that of the absolute SEP latency, the yield of abnormalities increased from 45% to 68%. Eisen and Odusote (1980) recorded an abnormal left-right difference of the cervico-cortical latency interval in 36/77 patients. This abnormality was the only one detected in 11 cases (14%), eight of whom were classified as suspected MS.

Anziska et al. (1978) recorded scalp near- and far-field potentials (generated in the sensory cortex and the sub-cortical sensory pathways, respectively), in 26 patients with established MS. Abnormalities were found in

25 cases (96%), among whom 12 had normal sensory examination. Garcia Larrea and Mauguière (1988) examined the incidence of amplitude and latency abnormalities of the far-field potential P14 (generated in the lower brainstem), in a series of 122 probable or definite MS cases. The P14 amplitude was expressed by its ratio with the amplitude of P9 (generated in the brachial plexus), which had a less skewed distribution than the absolute amplitude. The P14 latency was expressed by the P9-P14 inter-peak separation. Abnormal SEPs were recorded in 62 cases (51%) and in more than 95% of these P14 was attenuated and/or delayed on at least one side. In 12 cases (9.8%), the amplitude of the P14 was reduced, while all the other components were within normal limits.

Trojaborg and Petersen (1979) carried out a study of cortical SEPs to stimulation of the median and common peroneal nerves in 50 patients with established or suspected MS. They recorded absent or delayed potentials in 74% and 61% of responses from legs and arms, respectively. The higher incidence of abnormalities following lower limb stimulation was ascribed to the greater likelihood of detecting a lesion in a longer tract of the somatosensory system.

Before techniques for recording cervical SEP were in widespread use, Dorfman et al. (1978) developed an indirect method of measuring the spinal conduction velocity, which was based on the assumption that SEPs from the lower and

upper limbs are transmitted in parallel pathways from the cervical region to the cortex, conducting with the same velocity. This may be true in normal subjects, but in MS the two systems can be affected to a differing extent, so that a wrong estimation of the spinal conduction velocity below the cervical cord may result (Eisen and Nudleman, 1979). Thus, a more reliable technique for measuring the spinal and supraspinal conduction velocity was based on the direct measurement of the spino-cortical inter-peak latency. Using this method, Rossini et al. (1985) recorded a slowed cauda equina-vertex conduction velocity in 17/68 legs (25%) of patients with definite or suspected MS, following stimulation of the common peroneal nerve.

In the same paper, Rossini et al. (1985) suggested an alternative technique to detect subtle abnormalities of the cortical SEP. They recorded the cortical response to stimulation of the common peroneal nerve, using high-pass digital filtering. This method revealed high frequency wavelets overlapping the descending limb of the first major potential, which were difficult to perceive when conventional open band-pass filtering was used. These subcomponents were absent in one patient with suspected MS and had an increased interpeak latency interval in another. In both cases, the response recorded with standard filtering appeared normal.

In the past decade, several studies have focused on the diagnostic role of SEPs in MS. In various investigations, abnormalities were recorded in more than 50% of cases, the incidence being higher in definite than uncertain MS cases and in recordings from the lower than upper limbs. In the series published by Khoshbin and Hallett (1981), the overall yield was 69% (86% in definite and 58% in uncertain MS cases), abnormalities from lower and upper limbs being detected in 76% and 47% of cases, respectively. Abnormal SEPs were detected in 67% of patients who had no sensory deficits. Comparable figures were produced by Bartel et al. (1983). They recorded abnormal SEPs in 61% of patients: 88% in definite, 67% in probable and 51% in possible cases, classified according to the McAlpine's criteria (McAlpine, 1972). Abnormalities were detected in 51% of those who had otherwise intact somatosensory functions. Rossini et al. (1985) reported abnormal SEPs in 88% of patients (94% definite, 68% probable and 55% possible MS cases). In this series, median nerve responses were abnormal in 46% of patients whose arms were clinically unaffected. The incidence of clinically silent SEP abnormalities in the very early stages of MS has been little investigated, but appears to be very low: 9% in patients with an isolated brainstem episode (Hume and Waxman, 1988) and 7% in cases with previous isolated optic neuritis (Jones, 1982b). In the same paper, Jones (1982b) pointed out that the alterations of the SEPs in MS follow a characteristic

pattern: the peripheral nerve component (N9) is preserved, the cervical potential is usually attenuated or fragmented and the cortical response is more commonly delayed.

In a serial study, lasting 18 months, Davis et al. (1985) failed to find any strong correlation between SEP and somatosensory changes. On first examination, SEPs were abnormal in 11/12 definite MS cases, three of whom had no sensory deficits. On subsequent tests, eight patients developed deficits of vibration and proprioceptive sensation and in only three of these SEPs deteriorated. In one, the N13/P14 components became undetectable and in another they showed a more prolonged latency; in the third patient N20, previously delayed, was no longer identifiable. In another patient, the latency of the N13/P14 returned to normal in coincidence with the disappearance of the sensory deficit. In three patients SEPs improved despite worsening of the sensory impairment. In most cases improvement or deterioration of SEP components was not paralleled by appropriate sensory changes. It was concluded that SEP recording is not a reliable indicator of disease activity, as judged on clinical grounds.

Few studies have addressed the question as to whether SEP abnormalities are directly associated with the presence of MS lesions in the somatosensory system. To date, such a correlation has been demonstrated in one report by Matthews and Esiri (1979). In a MS patient who died seven months after SEPs were recorded, the absence of the N13 and N20

from the left median nerve was associated with the finding at autopsy of a plaque in the left side of the cervical cord, extending from C3 to T1 segments. The lesion occupied mainly the lateral column and had extensions involving the root entry zone and the lateral fibres of the posterior column at C3/C4 and C8/T1. In a more recent investigation (Eisen et al., 1987), recording of cortical SEPs and brain MRI were performed in 200 clinically probable or possible MS cases. In 117 patients (58.5%) brain MRI revealed 527 lesions; about half of these involved the somatosensory pathways, mainly the thalamo-cortical radiations. About half of patients (51%) showed SEP abnormalities, the most frequent of these being waveform distortion. A significant association was found between either normal or abnormal SEP and MRI findings. The distortion of the SEP morphology was believed to be produced by MRI lesions in the mid-periventricular areas, which interfered with the discharge in thalamo-cortical circuits.

In the last decade, MRI has proved more sensitive than SEPs in revealing brain abnormalities in patients with MS (Gebarski et al., 1985). However, SEP recording is still a valid tool for the investigation of this disease. It reveals abnormalities of conduction in spinal and supraspinal somatosensory pathways in more than 60% of patients and in about half of those who show no evidence of proprioceptive sensory deficits in the tested limb. In ad-

dition to the advantage of low cost, SEPs are able to detect lesions at caudal levels of the spinal cord where imaging is more difficult (see also paragraph 1.4.2).

1.2.2.2 Visual evoked potentials

Halliday et al. (1972) recorded visual evoked potentials (VEPs) in 19 patients with unilateral optic neuritis, using two types of stimuli: a black and white chequerboard pattern-reversal and an unstructured flash. The responses to pattern-reversal stimulation were significantly delayed in 18 affected eyes and in two clinically unaffected ones. The mean VEP amplitude was reduced by half and the mean latency increased by about 30% when comparing symptomatic with asymptomatic eyes. No comparable increase in latency was found in the flash responses. These were greatly attenuated in two patients only, who were in the acute stage of the attack and had a markedly reduced visual acuity. This abnormality, however, recovered quickly. Thus, flash stimulation was abandoned in following investigations because of its low sensitivity in detecting optic nerve pathology. In a subsequent paper, Halliday et al. (1973a) described the evolution of the VEP abnormalities following an attack of optic neuritis. In typical cases, the amplitude decreased in coincidence with the drastic reduction of the visual acuity, while the latency of any residual potential was increased. During the recovery

phase, the amplitude became larger with improvement of vision, often reaching virtually normal values, whereas the latency remained prolonged. Thus, there was a dissociation between VEP amplitude and latency and a response of increased latency but preserved waveform was considered to be a typical sign of a previous attack of optic neuritis.

Subsequent studies aimed to assess the sensitivity of VEPs in revealing optic nerve pathology in MS. Halliday et al. (1973b) recorded delayed responses in 49/51 patients (96%). Of these, 24 had a history of optic neuritis and 25 were visually asymptomatic. Eleven patients out of the 51 underwent examination of the fundi, colour vision and visual fields and in four of them a delayed VEP was the only sign of optic nerve pathology. In succeeding investigations, the incidence of VEP abnormalities in MS was lower than that reported by Halliday et al. (Asselman et al., 1975; Mastaglia et al., 1976; Matthews et al., 1977; Trojaborg and Petersen, 1979). The overall yield varied from 50% to 72% and increased with the certainty of diagnosis: 20% to 38% in possible, 33% to 83% in probable and 75% to 96% in definite MS cases. Abnormalities confirmed optic nerve disease in 83% to 100% of patients with history of optic neuritis and revealed clinically silent lesions in 47% to 70%. Asselman et al. (1975) recorded delayed responses in 70% of eyes with normal or slightly impaired visual acuity and in 44% of those with normal or marginally

affected colour vision; overall, 28% of eyes with no symptoms or signs of optic nerve involvement had delayed VEPs.

VEP abnormalities were also reported in 46% (Asselman et al., 1975) or 50% (Hennerici et al., 1977) of patients with an isolated brainstem syndrome and in 25% (Asselman et al., 1975) or 10% (Blumhardt et al., 1982a) of patients with acute remitting spinal cord syndrome. Some studies focused on the slowly progressive spastic paraparesis of the middle age, which shows no signs of involvement outside the spinal cord but has been found to develop spatial and temporal dissemination of neurological deficits in 20% of cases during a follow up period of five to 10 years (Marshall, 1955). The incidence of abnormal VEPs in this condition showed a marked variability between studies: 5/22 cases (Asselman et al., 1975), 19/25 (Bynke et al., 1977) and 7/9 (Matthews et al., 1977). Blumhardt et al. (1982a) reported abnormal VEPs in 12/36 (33%) patients with chronic relapsing and in 23/64 (36%) cases with chronic progressive spastic paraparesis. The incidence showed a threefold increase in recordings performed between three and six years from the onset of symptoms as compared with less than three years, suggesting that at this time in the course of the disease dissemination outside the spinal cord occurred.

After an episode of acute optic neuritis, the full-field VEPs may show some characteristic waveform alterations, which are consistent with a more marked involvement

of the macular than paramacular fibres. One of these abnormalities is the so called "pseudo" delay (Halliday, 1982b). In this situation, the response from the central part of the visual field, P100, is greatly reduced and masked by the potential arising from the peripheral part of the field. The latter terminates with a positivity peaking at about 135 ms (P135), which can sometimes be mistaken for a delayed P100. P100 and P135 can be discriminated by stimulating the left and right half-field. In hemifield responses, P100 and P135 can be shown to project predominantly to opposite sides of the scalp, the P100 ipsilateral and the P135 contralateral to the stimulated half field (Blumhardt et al., 1978). Another morphological abnormality of the full-field VEP is a "w-shaped" waveform, which usually results from superimposition of the P135 on a partially attenuated P100 (Blumhardt, 1987).

Recording of VEPs has been used to elucidate the mechanism of Uhthoff's symptom, which is a temporary impairment of vision following physical exercise or a hot bath. Persson and Sachs (1980) studied seven MS patients with Uhthoff's symptom before and after exercise. The VEP amplitude decreased in coincidence with reduction of the visual acuity and subsequently increased with improvement of vision. This suggested evidence that a reversible conduction block occurred during exercise.

In an attempt to ascertain whether VEPs are a useful technique for monitoring disease activity, Matthews and Small (1979) carried out serial recordings in two groups of patients with definite or probable MS for a) 18 and b) one to 40 months. In three patients of the former group, the VEP latency increased following a mild visual relapse and thereafter remained more prolonged than before. In the latter group, there was a reasonable correlation between changes of the visual acuity and VEP latency. A deterioration or improvement of the visual acuity was accompanied by a prolongation or shortening of the VEP latency, respectively, in 24/39 eyes (61%). In nine of these, the latency returned to normal values. The VEP was unchanged in 37/58 eyes (64%) in which the visual acuity was stable. Thus, there was a certain degree of correlation between visual and VEP changes occurring during the course of the disease.

Despite the fact that at autopsy plaques are often found in the postchiasmal pathways and especially in the optic radiations, in the literature there are few reports of VEP abnormalities consistent with retrochiasmal demyelination. In the series published by Onofrj et al. (1982), concerning patients with homonymous hemianopic defects of different origin, two had MS. In these, on full and left or right half field stimulation the P100 was attenuated at scalp electrodes ipsilateral to the defective hemifield. In an MS patient with a right homonymous hemianopia, Halliday (1982c) reported an attenuation of the

P100 to a full field stimulus in the channels ipsilateral to the defective hemifields, the abnormal response distribution being similar for both eyes. This type of distribution, characteristic of unilateral retro-chiasmal pathology, was called "uncrossed asymmetry". In another patient, who had no visual symptoms (Halliday, 1982c), the left homonymous hemifield responses were significantly attenuated as compared to the right homonymous hemifield components. In a detailed examination of the visual fields, a desaturation to red colour was found in the left homonymous half-fields. In one investigation of 32 patients with lesions of the posterior visual pathways (Blumhardt et al., 1982b), VEPs were recorded in two MS patients within a few days of the onset of homonymous hemianopia. Responses from the affected hemifields were absent in one case and markedly attenuated in the other.

It had been earlier on established that during the recovery phase of acute optic neuritis the amplitude of the VEP increases, paralleling the improvement of vision, while its latency remains prolonged (Halliday et al., 1973a, see above). Subsequent studies have shown that the VEP latency shortens during the weeks or months following the attack. The reported incidence of improvement is 32% during four weeks follow up (Diener and Scheibler, 1980), 26% during 14 weeks (De Weerd and Jonkman, 1982), 14% during 12 months (Confraveux et al., 1982), 24% during 18 months (Matthews and Small, 1979) and 39% during 46 months (Hely et al.,

1984). Full normalisation of the VEP latency has been reported in less than 10% of eyes, during a follow up period not exceeding 18 months (Matthews and Small, 1979; De Weerd and Jonkman, 1982). The improvement of the VEP latency after acute optic neuritis appears to be more consistent in childhood (Kriss et al., 1988). Changes of the VEP amplitude are controversial: in one investigation a deterioration of this parameter was detected during 18 months follow-up (Matthews and Small, 1979), while in another no significant overall change was recorded during 14 to 28 months (Carroll et al., 1984). For a more detailed description of these studies see paragraph 5.2.1.

After the introduction of MRI in the investigation of MS, studies have been carried out to compare the sensitivity of this technique with that of VEP recording in detecting demyelinating optic nerve lesions. In the report by Miller et al. (1988b) on 37 patients who had experienced an attack of acute optic neuritis, VEPs were abnormal in 100% of symptomatic and 27% of asymptomatic eyes, whereas MRI showed a optic nerve lesion in 84% of affected and 20% of unaffected optic nerves. This demonstrates that, using current imaging methods, VEP recording is more sensitive than MRI in revealing demyelinating optic nerve lesions (see also paragraph 1.4.2).

1.2.2.3 Brainstem auditory evoked potentials

Robinson and Rudge (1975) produced a first preliminary report of brainstem auditory evoked potentials (BAEPs) in MS. In 30 patients, 27 definite and three with probable diagnosis of MS, they examined potentials occurring within 10 ms of a binaural click stimulus. Of these, wave V (believed by them to be generated in the region of the inferior colliculus) was the best defined so that it was chosen to classify records. Abnormalities were recorded in 22 cases (73%), 12 of whom had no brainstem deficits. Amplitude attenuation was encountered more often than latency increase (16 and 10 cases, respectively) and was the only abnormality in the asymptomatic cases. In a following study, Robinson and Rudge (1977) examined 88 patients with definite MS. In 57 cases (65%) the amplitude and latency of the wave V were beyond the 95% confidence limits constructed for the normal population. Abnormalities occurred in 82% and 76% of patients who had definite or probable clinical evidence of a brainstem lesion and in 51% of those whose brainstem functions otherwise appeared normal. Recording of middle latency components (between 10 and 60 msec) added an additional 12% of abnormalities to the whole group of patients. Similar results were obtained by Stockard et al. (1977), using monaural stimulation. In this study, normal limits were based on the evaluation of the I-III, I-V and III-V inter-component latency separations as

well as the amplitude of wave V, although delays were considered a more reliable sign of abnormality than waveform attenuation. Abnormalities were found in 65/100 patients and in 45 consisted of components with increased latency with or without reduced amplitude. When patients were divided into definite, probable and possible diagnostic categories, the incidence of abnormal BAEPs was 93%, 77% and 35% respectively. Only the definite cases had unequivocal clinical evidence of a brainstem lesion. In a more comprehensive study, Robinson and Rudge (1980) compared BAEPs between definite or uncertain MS cases, patients with isolated neurological syndromes compatible with demyelination, patients with a single acute non-diagnosed episode and subjects with brainstem or disseminated disorder different from demyelination. The latter included vascular, compressive, inflammatory or degenerative disease and Arnold-Chiari malformation. Early and middle latency components were analysed. Abnormal responses were recorded in 56/96 MS cases, in 9/18 patients with progressive spastic paraparesis, in 4/4 patients with bilateral retrobulbar neuritis, in 9/27 patients with an isolated non-diagnosed neurological episode and in 26/100 patients with disorders different from demyelination. Changes of the middle latency responses were detected only in the MS group, in whom these increased the total yield of abnormalities. Thus, recording of middle latency components added significant power to the test. Among MS cases, abnormal BAEPs were strongly as-

sociated with clinical signs of a brainstem lesion. A high incidence of abnormal responses (70% or more) was detected in patients showing brainstem dysfunctions, despite the fact that in some of them the diagnosis of MS was uncertain. By contrast, in patients not showing brainstem disorders the incidence of abnormal responses decreased by about 50% from definite to probable or possible cases.

A serial study on 27 MS cases was carried out in order to investigate the relationship between BAEP abnormalities and clinical changes (Robinson and Rudge, 1978). During a follow up period ranging from nine to 30 months, 16 patients experienced relapses and remissions, not always involving the brainstem, while 11 showed a stable clinical course. In 10 of the latter group, amplitude and latency of the BAEPs were remarkably constant between consecutive recordings and in only one did the latency become abnormal. By contrast, BAEPs showed "fluctuations", i.e. deterioration, improvement or normalisation, in 8/16 patients with unstable clinical course. The changes were usually unrelated to the timing or type of symptoms and in only one case was an abnormality detected in coincidence with a relapse involving the brainstem. The authors suggested that the instability of the BAEPs could be due to a general effect of activity of the disease on conduction in demyelinated fibres.

Kjaer (1980a) pointed out that the incidence of abnormal BAEPs increased with illness duration and degree of disability, as one would expect. In this series of 121 definite or suspected MS cases, patients with duration of symptoms of about 20 years had a significantly higher incidence of abnormalities than those who had been ill for about two years. Also, among definite cases, the occurrence of abnormalities was almost twice as frequent in patients with moderate or severe disability as compared with those with mild clinical involvement.

Recent studies focused on the clinical and MRI correlates of BAEP abnormalities. In one investigation (Baum et al., 1988), BAEPs were abnormal in 19/43 (44%) definite MS cases and were significantly correlated with the presence of brainstem dysfunctions. Areas of altered signal in the medulla, pons and mid-brain were detected in 60.5% of patients. In 71% of cases showing both BAEP and MRI abnormalities, the level of the MRI lesion corresponded to that suggested by the BAEP findings. Thus, there was a close correlation between BAEP and MRI findings. The conclusions of van der Poel et al. (1988) were different. They studied 40 patients, of whom 28 were classified as definite MS and 12 had an isolated brainstem syndrome compatible with demyelination. BAEPs were abnormal in 21/28 definite MS cases (75%) but in only one patient with an isolated brainstem lesion. Wave V was affected in every abnormal waveform. MRI was performed in 20 cases only and showed a

variety of lesions in the medulla, pons and mid-brain in 9/9 MS cases and 5/11 (45%) patients with an isolated brainstem lesion. Although areas of increased signal at pontine level were detected in all patients with abnormal BAEPs, there was no clear pattern of correlation between alteration of single BAEP components and location of MRI lesions. Often, MRI and BAEP abnormalities were not commensurate with each other in the sense that large MRI lesions were sometimes associated with minimal or no BAEP abnormalities and, less frequently, BAEPs were found abnormal in the absence of an associated MRI lesion. Since this investigation was carried out with the same scanner as the one currently in use, there was considered to be a little prospect for further correlation studies.

1.2.2.4 Multiple sensory evoked potential techniques

SEPs, VEPs and BAEPs show different sensitivities in revealing lesions in the central sensory pathways. This can mostly be explained according to the different length of the pathways concerned and the tendency of the MS plaques to develop in some areas more frequently than in others. In many studies, the incidence of VEP and SEP abnormalities was similar; in some investigations VEPs proved to be more sensitive than SEPs, whereas in others the opposite was found. In a series of 29 definite and suspected MS cases, Kjaer (1980b) recorded abnormal VEPs in 62% and abnormal

SEPs in 55%. In another series of 220 patients, Javidan et al. (1986) recorded abnormal VEPs in 84% of definite, 55% probable and 39% of possible MS cases, whereas the incidence of abnormal SEPs was 79%, 65% and 26%, respectively. In an investigation of 123 patients with established or possible MS, Bartel et al. (1983) detected abnormal VEPs in 58% of cases and abnormal SEPs in 61%. The incidence of BAEP abnormalities is consistently lower than that of VEPs or SEPs, especially in cases in whom the diagnosis of MS is uncertain. In the above quoted studies, the incidence of BAEP abnormalities was 52% (Kjaer, 1980), 48% (Bartel et al., 1983) and 66%, 39% and 17% in definite, probable and possible cases (Javidan et al., 1986). All investigators agreed that the combined use of VEPs, SEPs and BAEPs is very useful for diagnostic purposes, as it increases the overall yield of abnormalities.

Some studies have considered the relative prognostic value of VEPs, SEPs and BAEPs, that is their sensitivity in detecting abnormalities in the very early stages of MS and how this predicts the subsequent course of the disease. Deltenre et al. (1982) studied 133 cases during a four-year follow-up. In this period, 44 patients developed clinically definite MS, 27 were found to have another neurological disease and 62 still had an uncertain diagnosis at final examination. EPs had revealed one or more clinically silent lesion in 81.8% of patients of the first group (VEPs being more often affected than SEPs and BAEPs), in 18.5% of cases

of the second and in 19.4% of subjects of the third. EPs had been normal in only one patient (2.2%) who developed definite MS, in 35% of subjects who were found to have another neurological disease and in 34% of cases who remained undiagnosed at the end of the study period. The findings of Matthews et al. (1982) were similar. They studied 71 patients during a variable follow-up period not exceeding 38 months. Of 49 initially probable or possible MS cases, 24 were re-classified as definite MS. EPs had revealed clinically silent lesions in 13 of these (54%), while false negative results were obtained in eight cases (33%). In three patients progressing to definite MS, EP findings had only confirmed sensory deficits which were apparent on clinical examination. In 21 patients the diagnostic category was unchanged: EPs had revealed asymptomatic lesions in two of these (10%), had been normal in 17 (81%) and had confirmed clinical deficits in two others. Two out of the 49 patients were not followed-up and two others progressed from "possible" to "probable" category. In the latter, EPs had not shown sub-clinical abnormalities. In a third category of 22 patients with a single acute non-diagnosed neurological episode, EPs had revealed sub-clinical lesions in one out of four patients who then developed definite MS, but had been normal in four who progressed to the probable or possible category. EPs had also been abnormal in 3/14 acute non-diagnosed patients who did not show any change in the clinical picture during the

study period. Hume and Waxman (1988) studied 204 patients during a period not exceeding 33 months. EPs had revealed clinically silent lesions in 65% of patients who developed definite MS, in 42% of those who progressed to a less uncertain diagnostic category, in 14% of patients whose diagnostic category was unchanged. The incidence of normal responses was 10% in the first group, 37% in the second and 75% in the third. These findings demonstrate that sensory EP techniques have a predictive value in the diagnosis of MS suspects, when the clinical picture is uncertain. Because of the occurrence of false negatives, however, the absence of EP abnormalities at this stage does not exclude the diagnosis of MS. The fact that subclinical EP abnormalities can be recorded in patients who subsequently develop another neurological disease (19% in the series by Deltenre et al., 1982) underlines that EP findings are not specific to MS and, therefore, must be interpreted "in the whole clinical context".

In the majority of patients with active MS, EPs show a trend to worsen with time, despite the fact that symptoms and signs may improve. Walsh et al. (1982) recorded median nerve SEPs and VEPs in 56 patients with definite MS at the beginning and end of a 30 months follow up study. At the beginning of the investigation, VEPs were abnormal in 84% of cases, the cervical SEP in 49% and the cortical SEP in 52%. At the end of the follow up period, none of the responses showed improvement, components being either un-

changed or more abnormal. This trend was found in patients whose clinical condition had improved, worsened or shown no significant change during the study period. The EP evolution was thought to reflect the progressive dissemination of the disease, which was not always reflected in the clinical picture.

In recent years, some studies have compared the relative sensitivity of MRI and VEPs, SEPs and BAEPs in the investigation of MS. It is now well established that, in general terms, MRI is more sensitive than EPs and this difference is greater in the early stages of the disease. In the series published by Cutler et al. (1985), MRI revealed abnormalities in 16/19 (84%) definite MS cases and in 5/8 (63%) probable ones. Sensory EPs were abnormal in 13/19 (68%) and 1/8 (13%), respectively. In another study of 30 patients with suspected MS (Gebarski et al., 1985), MRI showed abnormalities in 26 cases (87%) and EPs in 13 (43%). In two out of the four cases with no MRI lesions, EPs were either normal or showed doubtful abnormalities. However, in another investigation of 23 suspected MS cases (Giesser et al., 1987), EPs were found to be abnormal in 18 patients and MRI in 15. In 19/23 cases MRI and EPs were either both abnormal or both normal, whereas in four cases in whom MRI showed no lesions EPs were abnormal.

Thus, EP techniques are still useful in the investigation of MS, as they may reveal abnormalities when MRI fails to do so. This happens especially in areas of the CNS which

are relatively inaccessible to MRI, such as the thoracic and lumbar spinal cord and the optic nerves (see also paragraph 1.4.2.).

1.3 COGNITION AND EVENT-RELATED POTENTIALS IN MS

The first observations on cognitive impairment in MS were made by Charcot (1877) and Gowers (1892-1893), who pointed out the presence of memory deficits in some patients. Reports on cognitive disturbances in MS have been relatively few for many years and only in the last decade or so has the introduction of neuropsychological investigation made possible a systematic assessment of cognitive functions in MS patients. It has become clear that cognitive disturbances occur more frequently than was previously believed. Deficits are usually mild or moderate and, for this reason, may be overlooked on routine neurological examination. Memory is frequently affected. Recall of verbal or non-verbal material is often impaired and this has been attributed to defective ability of encoding (Beatty et al., 1988) or retaining acquired information (Rao, 1986). Recognition memory appears to be affected only in advanced cases (Rao, 1986) as is memory for remote events (Beatty et al., 1988). Defective ability to solve problems has also been reported (Rao, 1986). Processing of new information may be slowed (Beatty et al., 1989), especially if this is presented at a fast rate (Litvan et al., 1988). The perfor-

mance of tasks requiring sustained attention may be impaired, as suggested by a prolongation of the reaction time after presentation of auditory or visual stimuli (Elsass and Zeeberg, 1983; Jennekens-Schinkel et al., 1988a and b). Despite these deficits, the global intellectual state is well preserved in the majority of cases.

The pattern of cognitive dysfunction in MS was defined by Rao (1986) as "sub-cortical dementia", because of its similarity to that encountered in pathologies of sub-cortical structures (e.g. Parkinson's or Hungtinton's disease). The distinct pattern of "cortical dementia" is characterised by a more severe deterioration of the intellectual state, with aphasia, agnosia and acalculia. Recently, however, language deficits, involving verbal fluency and naming skills, have been detected in patients with definite diagnosis of MS (Beatty et al., 1989). The authors suggested that MS has features of both sub-cortical and cortical dementias, which is consistent with the hypothesis that disseminated demyelination in the cerebral white matter affects sub-cortical as well as cortical functions.

Cognitive impairment seems to begin early in the course of MS. Deficits of memory and abstracting ability have been detected in patients with clinically isolated optic neuritis or MS of recent onset (Lyon-Caen, 1986). Deterioration of auditory and visual attention has been recorded in patients with optic neuritis, a brainstem or

spinal cord syndrome (Callanan et al., 1989). There is no agreement as to whether the severity of cognitive deficits increases with disease duration or the degree of neurological disability. Such a correlation has been suggested by some authors (Huber et al., 1987; van der Burg et al., 1987), but not found by others (Rao et al., 1984). These discrepancies are partly related to methodological difficulties which hamper the interpretation of cognitive deficits, associated with the presence of primary sensory-motor deficits and effect of affective disorders or psychoactive drugs on test performance (Rao, 1986).

Attempts have been made to correlate the degree of cognitive impairment with the extent of brain pathology, detected on MRI. It was found that in patients with definite or suspected MS, cognitively impaired cases had more disseminated brain abnormalities on MRI than unaffected cases (Franklin et al., 1988; Callanan et al., 1989). The severity of cognitive dysfunctions was found to be related to the exent of atrophy of the corpus callosum (Huber et al., 1987; Rao et al., 1989a), the total brain lesion area and the degree of cerebral atrophy (Rao et al., 1989b). In the latter study, the total lesion area was directly correlated with the severity of deficits of recent memory and conceptual reasoning, while the size of the corpus callosum was inversely correlated with the degree of impairment of sustained attention and speed of information processing.

Cognitive functions can be investigated by means of electrophysiological tests. The ability of attending to and discriminating among stimuli is assessed in target detection tasks. In the "oddball" paradigm, subjects may be presented with tones of different pitch (auditory modality) or with various written characters displayed on a screen (visual modality) and are required to press a hand-held button on hearing or viewing a previously designated target stimulus. This occurs relatively infrequently and is interspersed with non-target stimuli. The brain potentials associated with the performance of this task, cognitive event-related potentials or ERPs, are dominated by a large positivity, occurring some 300 ms after stimulus presentation (P300 or P3). P3 is believed to be associated with the ability to discriminate among stimuli and decision making as to whether to respond or not (Pritchard, 1981). It is preceded by smaller negative and positive potentials, which probably reflect both sensory and cognitive aspects of the oddball task. The reaction time, which can also be measured during the performance of the oddball task, is the time separating the presentation of target stimuli and the execution of the response (i.e. button press), and is dependent on both cognitive and motor skills.

A P3 of prolonged latency and/or reduced amplitude has been recorded in a variety of conditions, including Alzheimer's dementia (Pfefferbaum et al., 1984; Neshige et al., 1988) and Parkinson's (Hansch et al., 1982) or

Hungtington's disease (Homberg et al., 1986). Goodin and Aminoff (1986) suggested that cortical and sub-cortical dementia can be differentiated from one another electrophysiologically, as in the former only P3 was abnormal, whereas in the latter the earlier components were also affected.

Abnormalities of the cognitive ERPs in MS have been assessed by Newton et al. (1989). They studied 23 patients with definite MS and one with isolated optic neuritis, using an oddball paradigm in both the auditory and the visual modality. Abnormalities of the ERP components were encountered in 13 (56.5%), MS cases only, and involved mainly the P3. The reaction time was prolonged in 11 patients, two of whom had a normal ERP waveform. Eight patients with abnormal ERPs and/or reaction time showed evidence of intellectual deterioration and/or memory deficits on neuropsychological investigation, while in five these faculties were unaffected. Thus, electrophysiological evidence of cognitive impairment was demonstrated in the majority of established MS cases. The finding of abnormal ERPs in subjects performing within the normal range on neuropsychological tests suggested that recording of cognitive ERPs may have a complementary role in the cognitive assessment of MS patients. In the same investigation, patients with ERP abnormalities had a longer disease duration, a greater degree of neurological disability and more disseminated brain lesions on MRI than patients with normal

responses. However, between the two groups there was no significant difference in the pattern of lesion distribution. It was concluded that ERP abnormalities were correlated with the degree of dissemination of the disease, as suggested by neurological examination and brain MRI. Similar results were obtained by Honig et al. (1992) in 31 patients with definite MS. In this study, the P3 latency increased and the amplitude decreased with the extent of brain MRI lesions, the degree of cognitive impairment, assessed by the Kurtzke cerebral function scale, and the duration of the disease. The latter correlation was unrelated to age effects. P3 parameters were weakly correlated with the degree of neurological disability, measured by the expanded disability status scale, according with the fact that the latter reflects mainly spinal cord pathology. These results reinforced the hypothesis that in MS, ERP abnormalities are correlated with the dissemination of plaques in the cerebral white matter, which interferes with cognitive functions by producing "cortical deafferentation and disconnection". The conclusions of Giesser et al. (1992) were in apparent disagreement with this observation. They studied 12 patients with definite diagnosis of MS, 6 of whom were clinically demented. The latter showed a prolonged N1 and P2 latency and an increased N1-P3 latency interval as compared to non-demented cases. Since patients in both groups had brain MRI lesions (11/12 cases), it was

concluded that ERP abnormalities were associated with cognitive decline but not with the presence of white matter lesions.

1.4 MAGNETIC RESONANCE IMAGING

1.4.1 GENERAL PRINCIPLES

MRI exploits the property of hydrogen ions (protons) to resonate under certain conditions. When placed in a magnetic field, they tend to align themselves with the direction of that field. If then another magnetic field is applied (i.e. radio-frequency pulse), they are displaced and, in this state, absorb energy. Once the effect of the pulse has ended, they tend to return to their equilibrium position and re-emit the absorbed energy as electromagnetic radiations. The rate of this motion depends on the physical properties of the surrounding water, which are expressed by the time constants T_1 and T_2. Thus, the magnitude of the returned MRI signal depends on the density of hydrogen ions, T_1 and T_2. The former varies little between biological tissues, whereas the latter two time constants vary markedly between tissues. During the formation of an image, sequences of radio-frequency pulses are manipulated so as to enhance the contribution from T_1 or T_2. In this way, contrast between tissues is produced.

1.4.2 MRI STUDIES IN MULTIPLE SCLEROSIS

Young et al. (1981) first reported MRI findings in MS. In 10 patients with definite or probable diagnosis, they detected a total of 131 lesions. Most of these were located in the cerebral hemispheres, mainly close to the lateral margin of the lateral ventricles and corresponding to the characteristic distribution of plaques in pathological studies. A few lesions were also seen in the brainstem and cerebellum. The abnormalities showed an irregular morphology and asymmetrical distribution. CT scan revealed only 19 periventricular lesions, which corresponded to the largest areas of altered signal seen on MRI. In following studies of 10 (Lukes et al., 1983) and 42 (Runge et al., 1984) patients with definite MS, multiple abnormalities in the periventricular white matter were found in 100% of cases. In no more than 30% lesions were seen in the cerebellum (Lukes et al., 1983) or in the brainstem (Runge et al., 1984). CT scans appeared abnormal only in patients who showed extensive MRI changes and did not detect any lesion outside the cerebral hemispheres. It was suggested that T_2-weighted sequences were effective in pointing out white matter abnormalities in the cerebellar and cerebral hemispheres (Lukes et al., 1983), whereas T_1-weighted techniques appeared more suitable to the investigation of the brainstem (Runge et al., 1984). The first report of spinal cord imaging in MS was produced by Maravilla et al. (1984).

Using a T_2-weighted sequence, they found abnormalities in the upper cervical cord of 10/21 patients (48%) with a definite diagnosis, all of whom also had brain lesions. It was pointed out that there are some difficulties in imaging the cord, related to the size of the receiver coil, affecting the signal-to-noise ratio, and the artefacts produced by the cardiac and respiratory movements.

Ormerod et al. (1987) studied 144 patients with clinically definite or probable MS, classified according to the criteria of Poser et al. (1983). One hundred and fourty-two cases (99%) showed lesions in the white matter surrounding the lateral ventricles, the areas close to the body, trigone and occipital horns being most frequently involved (more than 80% of cases). White matter abnormalities separated from the lateral ventricles were also seen in 90% of patients. Lesions in the brainstem and cerebellum were less common (68% and 49%, respectively), especially in the cases diagnosed as clinically probable. The lesions showed variable size and shape and their outline was almost invariably irregular. During the period of the study, 6 patients died and their brains underwent pathological examination. In each abnormal slice, plaques were seen in areas corresponding to those of the MRI abnormalities. At histological examination, lesions showed varying degrees of myelin loss and astrocytic gliosis. The axons were usually spared, but were severely reduced in number when the loss

of myelin was extensive. The findings were in keeping with previous pathological and MRI observations (Stewart et al., 1984).

Soon it became clear that the MRI changes are characteristic of but not specific to MS, as similar patterns can occur in other conditions. Among these there are cerebrovascular or inflammatory diseases and advanced age. Ormerod et al. (1984 and 1987) pointed out that a single focal hemisphere lesion with a smooth outline is characteristic of cerebrovascular disease, whereas multiple periventricular abnormalities with an irregular outline are frequent findings in MS.

Brant-Zawadzki et al. (1985) studied 5 demented patients, aged 65 to 70 years, and two control groups comprising 9 and 5 healthy subjects, aged 74 to 81 years and 59 to 66 years, respectively. Brain MRI abnormalities were present in all cases of the first group, in six of the second and in two of the third. Demented patients and older healthy subjects had more extensive abnormalities than younger healthy individuals. In another series of 151 patients older than 50 years (Gerard and Weisbergh, 1986), the incidence of periventricular foci of high signal intensity was 31% in individuals with risk factors for cerebrovascular disease, 56% in subjects with cerebrovascular symptoms and 79% of cases in whom both these features were present. The MRI abnormalities were interpreted as foci of infarction or demyelination with gliosis, both con-

ditions in which the water proton density increases. A reduction of the cerebral perfusion, which worsens with age and in the presence of cerebrovascular disease, was thought to be responsible for these lesions. Fazekas et al. (1988) pointed out some MRI features which made possible a distinction between MS and old age. In the latter, the changes usually showed smaller size (6 mm or less), appeared infrequently in the periventricular regions and were rarely seen outside the cerebral hemispheres. The authors suggested that the presence of at least two of these features led to the correct diagnosis with 100% confidence. Unfortunately, it is widely known that borderline cases do often occur, in which the pictures appear less characteristic and, therefore, the interpretation is more difficult.

Some inflammatory diseases can produce brain MRI changes which are indistinguishable from MS. In most cases these conditions present with specific systemic features which lead to the correct diagnosis, but sometimes they manifest isolated neurological syndromes compatible with MS. In 10 patients with vasculitis some characteristic MRI features were identified (Miller et al., 1987a) periventricular abnormalities were usually milder than in MS, whereas discrete hemisphere lesions were more extensive and could be found in the absence of periventricular lesions. Furthermore, changes suggestive of vascular dysfunction, such as focal abnormalities in the territory of a major cerebral artery, multiple cortical lesions or areas

of cortical atrophy, were common. Another condition not easily distinguishable from MS is acute disseminated encephalomyelitis. In 8/10 patients with this disease, Kesserling et al. (1990) pointed out a characteristic distribution of white matter abnormalities. Five cases had extensive and symmetrical changes in the cerebral and cerebellar hemispheres, which involved the basal ganglia in one. In three other patients, there were multiple discrete cerebral lesions with only minor periventricular abnormalities. Areas of altered signal in periventricular white matter were reported in 14/21 (67%) patients with neurosarcoidosis (Miller et al., 1988a); six out of the 14 were younger than 50 years. In each abnormal case, the pictures were indistinguishable from those seen in MS.

MRI is very sensitive in detecting disseminated brain abnormalities in patients with an isolated neurological syndrome of the types with which MS often presents. Periventricular white matter changes were seen in 50% of patients with optic neuritis (Jacobs et al., 1986), in 74% of those with an acute or chronic brainstem syndrome (Ormerod et al., 1986a) and in 75% of those with an acute or chronic non-compressive spinal cord syndrome (Miller et al., 1987b). The morphology, distribution and extent of these lesions were highly suggestive of MS plaques. However, to make the diagnosis of MS it is necessary to prove "temporal dissemination" of these abnormalities. This could be achieved in 2 ways: either by identifying lesions

of different age in the same image or by detecting new lesions in longitudinal studies. In a serial study, Ormerod et al. (1986a) measured the T_1 and T_2 relaxation times of brain abnormalities detected in patients with a clinically isolated acute or chronic brainstem syndrome. These values were higher in acute lesions and, in subsequent scans, were seen to fall towards those measured in chronic lesions. In a later investigation, however, the measurement of T_1 and T_2 did not prove effective in discriminating lesion age (Miller et al., 1988d). Miller et al. (1988c) carried out a prospective study in 53 patients with clinically isolated optic neuritis. Within a mean follow up period of 12 months, MS developed in 56% of patients who had shown multiple brain abnormalities at presentation and in 16% of those without such a finding. Clinical relapses in fact occurred only in the former group. This suggested that the disseminated brain abnormalities, seen at the beginning of the study, were probably demyelinating lesions.

Paty et al. (1988) compared the diagnostic usefulness of MRI with that of evoked potentials in 200 suspected cases of MS. Brain images strongly suggestive of MS were obtained in 66% of patients presenting with an isolated optic neuritis and in 60% of those showing a chronic progressive myelopathy. In the former group, abnormal SEPs were recorded in 34% and in the latter abnormal VEPs were obtained in 54%. During a follow up period not exceeding one year, 19 patients developed clinically definite MS and in

18 of these MRI had shown brain changes characteristic of MS. It was concluded that MRI was more sensitive than evoked potentials in detecting disseminated cerebral lesions, especially in the early stages of MS.

However, recording of evoked potentials is very useful in testing areas of the CNS less accessible to MRI, such as the thoracic and lumbar segments of the spinal cord and the optic nerve. In patients with a clinically isolated, non-compressive spinal cord syndrome involving the thoracic or lumbar segments, Miller et al. (1987b) reported abnormal posterior tibial nerve SEPs in 67% of cases but an altered spinal cord MRI signal in only 28%. The small size of the cord, artefacts produced by cardiac and respiratory movements, the distance of the cord from the surface coil and the size of the latter were thought to be factors responsible for the failure of MRI to detect intrinsic spinal cord lesions in the majority of cases. Similarly, MRI is less sensitive than VEPs in detecting demyelinating optic nerve lesions (Miller et al., 1988b, see also paragraph 1.2.2.2). The low resolution of the scanner in relation to the size of the optic nerve and the poor capability of imaging its intracranial segment were thought to be responsible for the limited sensitivity of MRI.

In order to clarify the nature of the MRI abnormalities, quantitative methods have been developed in which pathological changes were correlated with the value of T_1 and T_2 and their relaxation characteristics. Three types

of lesions were studied in the brains of cats: vasogenic and cytotoxic oedema (Barnes et al., 1987) and astrocytic gliosis (Barnes et al., 1988). Oedema consists of accumulation of water in the extracellular space. When the lesion is vasogenic, there is a brief initial phase of high protein density, due to extravasation of plasma proteins which are subsequently removed. If the lesion is cytotoxic, the protein content is relatively low throughout. Astrocytic gliosis is characterised by high density of astrocytic processes in the damaged zones. In these 3 instances, T_2-weighted images showed areas of increased signal, which corresponded accurately with the presence of lesions but made a distinction among them impossible. However, the MR parameters did successfully distinguish between lesion types. In the first study (Barnes et al., 1987), one day after the induction of vasogenic oedema, T_1 and T_2 were increased above their pre-morbid values in approximately the same proportion. Three days after the induction of vasogenic oedema and throughout the duration of cytotoxic oedema, however, the increment of T_2 was about double than that of T_1, in correspondence of a low protein density in the accumulated water. The T_1 relaxation was always monoexponential, whereas the T_2 relaxation was biexponential, comprising a short-T_2 and a long-T_2 component. The mean relaxation time of the short-T_2 component did not show any marked difference between normal appearing and oedematous white matter, whereas that of the long-T_2 com-

ponent was considerably increased in the oedematous tissue. Thus, these components were likely to correspond with intracellular and extracellular compartments of water, respectively. In case of gliosis (Barnes et al., 1988), only T_1 was increased in the damaged as compared to normal white matter, whereas T_2 did not show any noticeable change. The T_1 and T_2 relaxations were monoexponential, which suggested no expansion of the extracellular compartment of water at the site of the lesions. These results supported previous observations that the tissue changes associated with demyelination are responsible for the generation of an abnormal MRI signal. Demyelination "per se" plays a limited role (Bottomley, 1984). A more recent study focused on the features of old MS lesions (Barnes et al., 1991). In one case of long-standing MS, electromicroscopic examination revealed expansion of the extracellular space in most lesions, showing a great variability among plaques, which was attributed to differing degrees of axonal loss. MR parameters were computed in 53 lesions of 16 patients with long-standing MS (mean duration=15.6 years). In all these lesions T_1 and T_2 were increased as compared to the normal appearing white matter, although their increment showed a marked variability among abnormalities. In 28/53 (53%) lesions the T_2 relaxation was biexponential, which was consistent with expansion of the extracellular space.

A very interesting application of MRI in the past few years has been the study of the natural history of individual MS lesions, which has important implications in understanding the pathogenesis of the disease. Grossman et al. (1986) studied 15 patients with definite MS, before and after intravenous injection of the contrast agent gadolinium diethylenetriamine pentacetic acid (Gd-DTPA), which is a marker for the breakdown of the blood-brain-barrier (BBB). Post-contrast T_1-weighted images showed enhancement in 12 cases, all of whom also had lesions visible in non-contrast studies. Nine out of the 12 were judged to have active disease, as they had shown change in neurological deficits within 4 weeks prior to the study, and in these the recent neurological deficits could be correlated with areas of enhancement. Leakage of contrast was also present but "less prominent" in three out of the six patients with a clinically stable course. It was concluded that Gd-DTPA enhancement was a distinguishing feature between active and inactive lesions. In another study (Isaac et al., 1988), seven patients with relapsing and remitting MS were followed-up monthly for six months. Overall, 17/36 (47%) of T_2-weighted images showed signs of activity. These included the appearance of 18 new lesions, enlargement of 10 pre-existing lesions and shrinkage of seven, five of which eventually disappeared. All these active changes were asymptomatic. A serial study of 10 clinically definite MS cases was performed to assess the dura-

tion of Gd-DTPA enhancement (Miller et al., 1988d). At the first examination, a total of 56 enhancing lesions was detected in eight patients, all of whom experienced a clinical relapse at the time of scanning. Most abnormalities were asymptomatic, although in six cases zones of enhancement corresponded to the lesion responsible for the clinical deficit. One month later, enhancement had disappeared in about two thirds of the pre-existing lesions and was detected in all 12 new ones. Six months after the first scan, enhancement had disappeared in all pre-existing lesions and was present in 8/15 new ones. It was concluded that reversible Gd-DTPA enhancement was a consistent feature of new MRI abnormalities, lasting mostly less than one month.

In a dynamic study, different patterns of Gd-DTPA enhancement were described (Kermode et al., 1990b). In eight patients with clinically definite MS, brain scans were obtained before and after administration of contrast, the latter being repeated several times at four minute intervals. Initially, small lesions appeared to enhance homogeneously, whereas large ones showed a honeycomb or ring-like appearance. Four to 20 minutes later, these were filled in and, at about five hours from contrast administration, the area of enhancement corresponded to that of the lesion seen in the initial pre-contrast scan. At this stage, enhancement was more marked in the central than the peripheral area, consistent with a diffusion of the

contrast from the margin of the lesions inwards. After several months, the extent of the region of altered signal in non-contrast scans had decreased, to approach that of the area of initial enhancement. In four patients, Gd-DTPA enhancement was observed before the appearance of a corresponding lesion in pre-contrast scans and, in one case, even before the appearance of an appropriate clinical deficit (Kermode et al., 1990a). Thus, leakage of contrast was the first detectable sign of a lesion in vivo.

The pathological significance of Gd-DTPA enhancement was investigated in another study (Hawkins et al., 1990). In chronic relapsing experimental allergic encephalomyelitis (CREAE) in guinea-pigs, areas of enhancement corresponded with sites of perivascular inflammation. In these, leakage of markers for BBB breakdown was increased. Since CREAE and MS show similar histological and MRI changes, it was concluded that enhancement was likely to indicate inflammation in MS too. How do these vascular abnormalities relate to demyelination? Since in experimental demyelination, unaccompanied by inflammation, breakdown of BBB cannot be observed, it is likely that "Gd-DTPA enhancement reflects inflammation and not demyelination per se" (Hawkins et al., 1990). Furthermore, vascular abnormalities have been reported in the retina of patients with acute optic neuritis (Lightman et al., 1987). Since the

retina lacks myelin, it has been suggested that vascular changes are to a certain extent independent of demyelination (for review see McDonald and Barnes, 1989).

The study of disease activity has led to the acknowledgement of some distinctive MRI features underlying different patterns of clinical course (Thompson et al., 1990). In this report, 29 MS patients were scanned, 16 with secondary progressive and 13 with primary progressive disease. The degree of neurological disability was mild or moderate in the former and severe in the latter. Secondary progressive cases showed larger lesions and more extensive enhancement than the primary progressive group. Also, in follow up after six months, the former group developed a greater number of new lesions, most of which enhanced, whereas the latter showed fewer new lesions, none of which enhanced. These observations suggested the possibility of different pathogenesis for secondary progressive and primary progressive MS.

In conclusion, MRI studies have provided with several new insights into the pathophysiology of MS. Recordings of EPs in the same patients adds a further dimension and is potentially able to establish a closer connection between tissue changes and consequences for nerve function.

CHAPTER

2

CORRELATION OF SEP ABNORMALITIES WITH BRAIN AND CERVICAL CORD MRI

2.1 INTRODUCTION

One of the unanswered questions in the pathophysiology of multiple sclerosis is whether plaques are inevitably associated with abnormalities of nerve conduction, and vice versa. To date, there has been only one report which demonstrates such an association (Matthews and Esiri, 1979). In a patient with MS but intact proprioceptive sensation, the N13 and N20 components were undetectable following stimulation of the left median nerve. This finding correlated with the presence of a plaque on the left side of the cervical cord, found at autopsy seven months after SEP recording. The lesion occupied the lateral column and the lateral fibres of the posterior column from C3 to T1 levels.

The question of the relationship between pathological and physiological abnormalities of the somatosensory system in MS has been addressed in vivo by one previous investigation (Eisen et al., 1987). Recording of cortical SEPs and brain MRI were performed in 200 patients with clinically probable or possible MS. One hundred and seventeen patients (58.5%) showed disseminated MRI abnormalities suggestive of MS, with a total number of 527 lesions. About half of these appeared to involve the somatosensory pathways, the thalamo-cortical radiations being most affected. One hundred and two patients (51%) showed SEP abnormalities, which comprised mainly waveform distortion. There was a

significant association between either normal or abnormal SEP and MRI findings. The distortion of the SEP waveform was thought to be due to disseminated periventricular MRI lesions, which might have interfered with the discharge in thalamo-cortical radiations.

The aim of the present study was to investigate whether and to what extent SEP abnormalities are correlated with cervical cord and brain MRI lesions in patients presenting with a cervical cord syndrome. The relationship was also examined between SEP or MRI abnormalities and clinical deficits.

2.2 CASE MATERIAL

2.2.1 Patients

The patient group consisted of 31 subjects, 21 females and 10 males, aged 22 to 51 years (mean 33±9 years). Each patient presented with a cervical cord syndrome involving the sensory and/or motor pathways and 12 also showed additional disseminated neurological deficits. None, however, had any history or signs of additional spinal cord lesions. When the clinical picture, evoked potentials, MRI and cerebro-spinal fluid analysis for IgG oligoclonal bands were considered, 27 patients fulfilled the diagnostic criteria for MS established by Poser et al. (1983): clinically definite MS three cases; laboratory supported

definite MS 11 cases; clinically probable MS 13 cases. The other four patients did not show clinical or para-clinical evidence of involvement beyond the cervical spinal cord. In these cases, neurological examination and radiological findings made the possibility of a compressive, traumatic, degenerative or vascular pathology unlikely and the lesion was, therefore, considered compatible with demyelination. At the time of the study, the cervical cord syndromes had a duration of one to 139 months (mean 32 months) and appeared relapsing and remitting in 21 cases, progressive (i.e. duration longer than six months without exacerbations or remissions) in seven cases and acute (i.e. one episode lasting less than one month) in three cases.

2.2.2 Controls

Normal SEP limits were derived separately from 16 healthy males, aged 21 to 39 years (mean 33±4 years), and 15 healthy females, aged 18 to 37 years (mean 27±5 years).

2.3 METHODS

2.3.1 Somatosensory evoked potentials

Patients sat comfortably in an armchair in a semi-darkened room. The stimulus, a 200μs constant voltage square wave, was applied to the median nerve at either

wrist and the posterior tibial nerve at either ankle, with an intensity sufficient to produce a moderate twitch of the thenar and plantar muscles, respectively.

Silver/silver chloride disc recording electrodes were placed over the mid point of each clavicle, the spinal vertebrae C7 and C2, the anterior aspect of the neck on the midline above the thyroid cartilage ("supraglottal" location), the mastoid ipsilateral to the stimulated arm, the hand area of the sensory cortex on both sides (2 cm behind the vertex and 7 cm toward each tragus) and the foot area of the sensory cortex (2 cm behind the vertex). A common reference was located at Fz (International 10-20 system). Later, in off-line analysis, the supraglottal potential was subtracted from the low cervical one and the clavicle response contralateral to the stimulated arm was subtracted from the remaining channels, in order to obtain neck and scalp non-cephalic referred waveforms [Fig. 2.1].

The amplifier high frequency response was less than 3dB down at 5KHz and the time constant was 1 s. Four hundred sweeps were averaged in each run, which was repeated once or more in each limb. The averager epoch was 32 ms (8 sample points/ms), starting 3 ms after the stimulus pulse, in recordings from the median nerves, and 64 ms (4 sample points/ms), with a post-stimulus delay of 13 ms, in recordings from the posterior tibial nerves. When

a consistent cortical response could not by identified within this time, the averager epoch was doubled (64 ms and 128 ms, respectively).

The major components evoked from the upper limbs were N9 (clavicle), N13 (C7) and N20 (scalp) using Fz reference, and N13 (C7-supraglottal) and P14 (scalp-clavicle), using a non-cephalic reference. From the lower limbs the major potential was the P40 component on the scalp [Fig. 2.1]. The N9-N20 and N13-N20 interpeak latencies were measured, but only the former was considered in statistical evaluations as the N13 was very degraded in some cases and its latency difficult to determine.

The normal latency limits were defined by the mean + 2.5 standard deviations (SD) of the absolute latency and the N9-N13, N13-N20 and N9-N20 inter-peak latency intervals in the control groups. Latency differences between the two sides were determined by the mean ± 2.5 SD of the inter-side (left-right) latency differences. The normal amplitude limits were determined by the mean - 2.5 SD of $\log_{10}$ amplitude and $\log_{10}$ [P9/P14] amplitude ratio, the latter as suggested by Garcia Larrea and Mauguière (1988). Amplitude differences between the two sides were determined by the mean ± 2.5 SD of $\log_{10}$ [left/right] amplitude ratio. The amplitude values were transformed into their $\log_{10}$ as the latter show a less skewed distribution.

2.3.2 Magnetic resonance imaging

All patients were imaged on a Picker 0.5 Tesla superconducting scanner, within 10 days of the SEP recording. Brain and spinal cord pictures were interpreted by two neuro-radiologists, who were blind to clinical and electrophysiological findings. Abnormalities were defined by areas of increased signal in T_2-weighted sequences or areas of decreased signal in T_1-weighted sequences.

The brain was imaged using a 30 cm spherical receiver coil. A moderately T_2-weighted sequence ($SE_{2000/60}$) was performed in every case. When changes were equivocal, a more heavily T_2-weighted sequence ($SE_{2000/120}$) and/or a T_1-weighted sequence ($IR_{2000/40/500}$) was added. Contiguous slices of 5 or 10 mm thickness were obtained in the axial plane through the whole brain.

The cervical cord was imaged with a saddle-shaped receiver coil. Contiguous 5 mm thick sagittal slices through the cord were obtained in every case using T_1-weighted ($SE_{500/40}$) and T_2-weighted ($SE_{1500/80}$) sequences. Additional contiguous axial 5 mm slices were obtained through regions in which intrinsic areas of altered signal were suspected in sagittal images. Abnormalities were only accepted when identified in both sagittal and axial pictures. The longitudinal extent of a lesion between the cervicomedullary junction and C7 was defined in sagittal images. The transverse extent of a lesion was determined in axial

images, by dividing the cord into four quadrants: left anterior, left posterior, right anterior right and posterior. A lesion was said to be present in a given quadrant if it occupied the greater part of it. The resolution of the scanner did not allow the identification of individual tracts within the spinal cord. In correlating morphological with electrophysiological and clinical findings an assumption was made that lesions occupying the posterior quadrants probably affected the posterior columns, while lesions in the anterior quadrants were likely to involve the spinothalamic tracts.

2.3.3 Statistical analysis

The association between SEP and MRI abnormalities was assessed using the Fisher exact probability test. The degree of correlation between N9-N20 interpeak latency or P40 absolute latency and the longitudinal extent of the cervical cord lesions was analysed using the Spearman rank correlation test.

2.4 RESULTS

2.4.1 Clinical findings

The cervical cord syndrome was manifested by sensory and motor deficits in 24 patients, isolated sensory impairment in four and isolated motor impairment in three. The sensory symptoms included numbness and paraesthesiae. The sensory signs were considered to suggest a lesion in the posterior columns when there was an abnormality of joint-position sense, two-point discrimination or vibration sense, and the spinothalamic tracts when pain or temperature sensation was affected. The motor symptoms included weakness and sometimes stiffness, with difficulties in walking. The motor signs were typical of lesions in the pyramidal pathways (spasticity, brisk tendon reflexes, extensor plantar reflexes, either decrease or absence of the abdominal reflexes). In the majority of cases, the sensory and motor deficits were bilateral but distributed asymmetrically between the two sides. In seven patients there was clinical evidence of a lesion located in one side of the spinal cord: three of these presented with the Brown-Séquard syndrome and four with proprioceptive sensory loss in one hand, known as "the useless hand of Oppenheim". Three patients of the latter group had also uni- or bilateral motor deficits [Table 2.1]. Ten patients showed Lhermitte's sign and 10 had sphincter disturbances.

2.4.2 SEP abnormalities

SEPs were abnormal in 21/31 patients (67.7%). In the group comprising 27 MS cases, 18 showed abnormal median nerve components and eight of these also had abnormal responses from the posterior tibial nerve (in two patients the latter were not recorded). Among four cases with an isolated spinal cord lesion, three showed abnormal median nerve components and two of these also had abnormal posterior tibial nerve responses (in one the latter were not recorded).

Using a reference at Fz, abnormalities of N13 and/or N20 were detected in 19/31 cases (61.3%). P40 was affected in 10/28 patients (35.7%). In the supraglottal reference recordings, N13 was abnormal in 10/30 cases (33.3%), two of whom had normal Fz reference SEPs. With the clavicle reference, P14 was abnormal in 14/31 cases (45.2%) and was ill defined and so not interpretable in four. In the majority of the abnormal waveforms, N13 (Fz and supraglottal reference) showed a reduced amplitude, whereas N20, P14 and P40 had a prolonged latency. N20 was absent in two cases and P40 in another [Table 2.1 and Fig. 2.2a].

2.4.3 MRI abnormalities

Areas of altered signal in the cord and/or brain were detected in 28/31 patients (90.3%). In the MS group, 25/27 cases (92.6%) showed abnormalities which involved the cervical cord in 21 and the brain in 21. Three out of four patients with an isolated spinal cord lesion (75%) had abnormal MRI.

In the cervical cord, the MRI abnormalities were of various sizes, affecting one or both sides and extending from one to all cervical segments. In some cases the lesions were localised mainly anteriorly or posteriorly, whereas in others they involved both anterior and posterior regions. Similarly, in some patients the lesions were predominantly left- or right-sided, whereas in others they were bilateral. In five cases the lesions were associated with swelling and in three with atrophy of the spinal cord [Fig. 2.2b]. MRI abnormalities which it was assumed might possibly involve the somatosensory pathways at supraspinal level were observed in 20 patients. They were located unilaterally, bilaterally or centrally in the medulla (five cases), pons (five cases), internal capsule (three cases), sensory radiations (17 cases) and sensory cortex (one case). In 17 patients abnormalities were also present in the cervical cord [Table 2.1].

2.4.4. Correlation between SEPs AND MRI

In Fz reference recordings from the median nerve, there was a statistically significant correlation between abnormalities of N13 and/or N20 and the presence of a cervical cord lesion ($p=0.012$). This was confirmed when responses from the left or right arm were compared with lesions in the left or right side of the cord, respectively ($p=0.002$ and $p=0.018$), and when responses from either arm were compared with lesions in the posterior cervical cord ($p=0.013$). Conversely, no significant correlation was found comparing responses from the left or right arm with lesions in the right or left side of the cord, respectively, or between responses from either arm and lesions in the anterior cervical cord ($p>0.05$). No significant overall correlation was found comparing posterior tibial nerve and non-cephalic reference median nerve responses with cervical cord lesions ($p>0.05$) [Table 2.2].

Abnormalities of amplitude and latency of the N13 were assessed in relation to the levels of the cord lesions. In supraglottal reference recordings, the incidence of N13 abnormalities was greatest (100%) in patients with lesions at C6-C7 levels and decreased in relation to lesions at higher levels. Conversely, in Fz reference waveforms the occurrence of N13 abnormalities was unrelated to the level of the cord lesions [Table 2.3]. Cord lesions located at C6-C7 were significantly correlated with abnormalities of the

supraglottal reference N13 ($p=0.029$), but just failed to reach statistical significance with abnormalities of the Fz reference N13 ($p=0.06$). On the other hand, cord lesions located at C1 and/or the cervico-medullary junction were significantly associated with abnormalities of the Fz reference N13 and clavicle reference P14 ($p=0.01$ and $p=0.017$, respectively), whereas the supraglottal reference N13 showed no such correlation [Table 2.4].

The N9-N20 interpeak latency and the absolute latency of P40 were closely correlated with the longitudinal extent of the cervical cord lesions (i.e. number of levels involved) in the ipsilateral side of the cervical cord: left side $r=0.57$ and 0.58, respectively ($p<0.001$); right side $r=0.38$ and 0.41, respectively ($p<0.02$). For the tibial nerve SEP the relationship was approximately linear, equivalent to about 2 ms delay per level. However, since the standard deviations of the P40 latency were very large and only four patients showed cord lesions longer than two levels, this observation is of limited value [Fig. 2.3].

No significant correlation could be demonstrated between abnormalities of the SEPs from either side of the body and MRI lesions apparently involving the supraspinal somatosensory pathways.

2.4.5 Correlation between SEPs and cord syndromes

SEPs were abnormal in 17/24 patients with sensory and motor deficits, in 2/4 cases with only sensory and in 2/3 patients with only motor dysfunction. When SEP abnormalities were compared with sensory symptoms and signs, the latter showed a greater degree of correlation than the former, although in neither case was this statistically significant. Thirteen patients had sensory signs consistent with a lesion in the posterior columns and 13 patients in the spinothalamic tract. The same incidence of SEP abnormalities was observed in both groups (69%).

Using the Fisher test, no significant correlation could be demonstrated between SEPs from either side of the body and ipsilateral and contralateral sensory symptoms, posterior column signs or spinothalamic tract signs, neither was there any correlation when these factors were combined into the broader category "sensory involvement".

2.4.6 Correlation between MRI and cord syndromes

Cord MRI was abnormal in 24 patients, 18 showing sensory and motor deficits, four only sensory and two only motor dysfunctions. In some cases the cord lesion appeared smaller and in others larger than that suspected on clinical grounds. Ten patients had a MRI lesion apparently involving the posterior cord: nine of them showed sensory and

motor impairment and one only sensory abnormalities. Four patients with MRI lesions in the anterior cord showed both sensory (two posterior column and three spinothalamic tract) and motor deficits. Ten patients had lesions in the anterior and posterior cord: five of them showed sensory and motor, three only sensory and two only motor abnormalities.

The extent of the cord lesions was examined in relation to the distribution of sensory deficits. In 12 patients the cord MRI lesions and the sensory abnormalities were bilateral; eight patients had unilateral cord lesions and bilateral sensory impairment; one patient had a bilateral cord lesion and unilateral sensory involvement. When cord MRI was compared with sensory symptoms and signs separately, the latter showed a higher degree of correlation than the former, although in neither case was this statistically significant, nor was there any correlation when symptoms and signs were combined together. The upper level of the cord lesions as suggested by the neurological examination was in all but one case at or below the upper level of the cord lesion seen on MRI, although it was not possible to establish a definite level from clinical data in every case.

No significant correlation was found between the extent of cord MRI abnormalities and the distribution of clinical motor involvement. No significant correlation

could be demonstrated between sensory symptoms and/or signs on either side of the body and brain MRI lesions apparently involving the intracranial somatosensory pathways.

A close correlation between clinical, electrophysiological and morphological findings was found in 4 patients presenting with the "useless hand of Oppenheim" (Cases 11, 20, 22 and 30). In all these cases abnormal SEPs were recorded from the affected arm. The abnormality involved the N13 and N20 in Fz reference recordings and the P14 in clavicle reference waveforms. N13 obtained with supraglottal reference was normal in each case. P40 was abnormal from both sides in one patient (Case 22) and from the affected side in another (Case 30). In each case MRI showed a lesion in the side of the cord ipsilateral to the affected arm. This was located at C5 level (Case 20), C2-C3 level (Case 11) and the cervico-medullary junction (Cases 22 and 30). Three of these patients also had brain lesions in the medulla, pons and sensory radiations [Figs. 2.4a and b and 2.5a and b].

2.5 DISCUSSION

It was found that abnormalities of the N13 and/or N20 recorded following median nerve stimulation with an Fz reference were significantly correlated with the presence of MRI lesions in the posterior half of the spinal cord (and hence probably involving the posterior columns) or on

the side ipsilateral to the stimulus, but not in the anterior half or on the contralateral side. Abnormalities of the P40 were less well correlated with lesions in the posterior or ipsilateral hemicord. The N9-N20 interpeak latency and the P40 absolute latency were correlated with the length of the lesion in the ipsilateral hemicord, although the value of this observation was limited by the fact that only 4 patients had lesions longer than 2 levels. These results provide evidence that MRI abnormalities in the posterior half of the cervical spinal cord are with high probability associated with abnormalities of the somatosensory conduction. The finding that longer cord lesions tended to be associated with more prolonged SEP latencies suggests that demyelination was present in these lesions.

In previous studies on SEP findings in MS, the incidence of SEP abnormalities was higher from the lower than the upper limbs, in accordance with the fact that the investigation of a longer segment of the somatosensory pathways increased the chance of detecting lesions (Trojaborg and Petersen, 1979; Trojaborg et al., 1981; Khoshbin et al., 1981; Bartel et al., 1983; Rossini et al., 1985). In the present study, abnormalities were recorded in 61.3% of patients from the median nerve and in 35.7% of cases from the posterior tibial nerve. The probable explanation for this apparent discrepancy is that the sample selected for the present investigation is not representative of the en-

tire MS population. Patients were selected on the basis of a cervical cord syndrome, without evidence of a lesion in the thoracic and lumbar segments of the cord. At cervical level, the structures connected with the upper limbs occupy a bigger volume than those arising from the lower limbs. Thus, a lesion in the cervical cord is more likely to affect the upper than lower limbs. In our series, all the patients with an abnormal response from the posterior tibial nerve also had abnormal components from the median nerve, hence a cervical cord lesion could have been responsible for both abnormalities. Isolated changes of the lower limb SEPs might have occurred, due to cervical cord lesions affecting the gracile tract only, but were not included in this series.

Another result of this study was that MRI lesions at C6-C7 were correlated with abnormalities of the cervical N13 recorded to a supraglottal reference, whereas lesions at C1 or the cervico-medullary junction were associated with abnormalities of the scalp P14. These findings are in keeping with the view that the N13 recorded with this montage is generated by the interneurones of the grey matter of the cervical cord, where fibres of the median nerve enter the cord (Desmedt and Cheron, 1980). On the other hand, the P14 is a volume conducted event believed to be generated in the most rostral segments of the dorsal

columns and the medial lemniscal fibres just above the foramen magnum (Mauguière et al,. 1983; Mauguière and Ibanez, 1985).

With the methods used in the present study no evidence was found that MRI abnormalities in the supraspinal somatosensory pathways interfere with the sensory conduction. This is not surprising if we consider that the localisation of MRI lesions in intracranial structures can only be made with some approximation. Furthermore, in the patients of this study the majority of brain abnormalities (85%) lay in the periventricular areas, where the fibres arising from the somatosensory nuclei of the thalamus diverge in their projections to the sensory-motor cortex. Thus, the activated fibres might not have been affected by the MRI lesions or the proportion of involved fibres might have been insufficient to cause changes detectable by SEP recording. Finally, it may be a significant factor that demyelination is not a dominant component of an MRI lesion. Anatomical and radiological studies have shown that oedema and gliosis produce MRI abnormalities (Barnes et al., 1987; Barnes et al., 1988). Myelin "per se" contributes little to the generation of the MRI signal, because of its low content of mobile protons. The assumption that MRI lesions are not invariably associated with myelin loss throughout the whole volume of tissue may explain why sometimes normal

SEPs can be recorded in the presence of extensive areas of altered signal, e.g. Case 6 of this series [Fig. 2.6a and b].

In previous studies, abnormalities of the cortical SEPs have been related to the presence of MS lesions in the somatosensory radiations. Eisen et al. (1987) recorded a high incidence of scalp responses of distorted waveform in a group of 200 clinically possible or probable MS cases. They related this abnormality with the presence of a high number of MRI lesions in the mid-periventricular area, thus probably involving the thalamo-cortical radiations. That lesions at this level can alter the morphology of the cortical SEP had been previously suggested by Rossini et al. (1985). Using restrictive (high band-pass) digital filtering, they recorded high frequency sub-components contained in the latency range of the cortical response to common peroneal nerve stimulation. These wavelets were absent or delayed, respectively, in two patients with suspected MS who showed normal response using the conventional (open band-pass) digital filtering. Desynchronization of the afferent volley in thalamo-cortical circuits was thought to be responsible for this abnormality. The present study cannot confirm or refute these findings, although the absence of these wavelets may not be a reliable indicator of abnormality, as they are not always observed in the normal population.

In the full group of 31 patients there was a limited and non significant correlation between SEP abnormalities and sensory symptoms or signs on either side of the body. The same incidence of abnormalities (69%) was obtained in the presence of sensory signs implicating the posterior columns (two-point discrimination, joint position and vibration sense) or the spinothalamic tracts (pain and temperature sensation). This is in apparent disagreement with reports of a correlation between SEP abnormalities and posterior column sensory deficits, but not spino-thalamic impairment (Halliday and Wakefield 1963; Yu and Jones 1985). Recently, Restuccia and Mauguière (1991) showed that dissociated loss of pain and temperature sensation was significantly correlated with attenuation of the N13 recorded from the dorsum of the neck at C6 to an anterior cervical reference. In this montage, the activity generated in the grey matter of the cervical cord is believed to be to a large degree isolated from that produced in the posterior columns and supraspinal structures. The authors pointed out that in most previous studies N13 was recorded with a cephalic reference, in which activity generated in the posterior columns and supraspinal structures overlapped with the spinal potential, thus hampering a correct evaluation of the N13 amplitude. For this reason, isolated abnormalities of the N13 due to lesions of central cord structures, ie syringomyelia, might have been overlooked.

In the full group of 31 patients there was also no significant correlation between the location of MRI cord lesions in axial views and the pattern of sensory or motor impairment. There are a number of possible explanations for the failure of MRI to localise precisely spinal cord lesions. First, interpretation of the images is impaired by inhomogeneity of the surface receiver coil and CSF motion artefacts (Miller et al., 1987b). Also, the limit of resolution of the scanner makes it possible that small lesions were not seen. Furthermore, localisation of the lesion to a certain quadrant of the cord does not mean that a specific tract is involved by demyelination. Nevertheless, it was observed that the upper limit of the cord lesions in sagittal views was consistently at or above the level of the lesion deduced on clinical grounds. This suggests that MRI identifies pathological processes which may or may not be symptomatic, although without a precise anatomical-functional correlation.

A close correlation between MRI, SEPs and functional impairment was found in four cases who presented with the "useless hand of Oppenheim". This consists in a profound loss of joint position sense in one upper limb, largely sparing the lower limb, and has been generally been attributed to a lesion in the cuneate tract. Abnormal SEPs were recorded from the affected arm in all four patients and also from one or both lower limbs in two. In each case, MRI showed a lesion in the appropriate side of the cord,

located between C5 and the cervico-medullary junction. In this example, the clear correlation between electrophysiological MRI and clinical findings was probably due to the fact that the underlying lesion was well localised in the cervical cord. Similarly, a close correlation has been demonstrated in the optic nerve of patients with optic neuritis (Miller et al., 1988b) and in the brainstem of patients with deafness (Barrat et al., 1988). When a lesion is ill defined and/or involves areas apparently not crucial for any given function, the correlation between clinical, electrophysiological and MRI findings is weaker.

In conclusion in patients with a demyelinating cervical cord lesion, areas of altered MRI signal in the cervical cord are usually associated with appropriate abnormalities of the SEPs. Conversely, MRI lesions in the white matter of the cerebral hemispheres seem not to produce SEP abnormalities, using standard recording methods. In the present study, both SEP and MRI changes were only poorly correlated with the pattern of clinical deficits. This could be due to the approximation introduced by the evaluation of clinical findings, the fact that SEPs provide only an incomplete measure of conduction in somatosensory pathways and the likelihood that areas of altered MRI signal are not necessarily representative of or conterminous with an area of myelin damage.

TABLE 2.1: CLINICAL, SEP AND MRI FINDINGS

				Cord syndrome			
				Sensory		Motor	
No	Age	Sex	Diagnosis	Left	Right	Left	Right
1	27	F	CDMS	σ	σ	σΦ	σΦ
2	20	M	CDMS	σπ	σπ	σΦ	Φ
3	35	F	CDMS	σ	σ	σΦ	σΦ
4	33	F	LSDMS	σπα	σπα	Φ	Φ
5	38	M	LSDMS	σπ	σπ		
6	22	M	LSDMS	α	σα		
7	31	F	LSDMS	σ		σΦ	Φ
8	27	F	LSDMS	σα	σπα	Φ	Φ
9	28	F	LSDMS	σ	σ		
10	39	M	LSDMS	σα	σα	σΦ	
11	36	F	LSDMS	σπα	σ	Φ	
12	28	F	LSDMS	σ	σα	σ	
13	26	F	LSDMS	σ	σ	σΦ	Φ
14	36	F	LSDMS	σ		Φ	Φ
15	50	F	CPMS			σΦ	σΦ
16	49	F	CPMS	σ	σ	σΦ	Φ
17	40	F	CMPS			σΦ	Φ
18	36	M	CPMS	π	π	σΦ	σΦ
19	45	M	CPMS		α	σΦ	σΦ
20	26	F	CPMS	σ	σπ		
21	21	F	CPMS			σΦ	Φ
22	25	F	CPMS		σπ		σ
23	44	M	CPMS	σ	σ	σΦ	σ
24	48	F	CPMS	σ	σπα	σΦ	σΦ
25	20	M	CPMS	σπ	σπ	Φ	Φ
26	32	F	CPMS	α	σπ		σΦ
27	34	F	CPMS	σα	σα	Φ	Φ
28	38	F	ICL	σ	σ	Φ	Φ
29	38	M	ICL	σπα	σπα	σΦ	σΦ
30	39	F	ICL	σ	σπα	Φ	Φ
31	26	M	ICL	σα	σα	Φ	Φ

Table 2.1 continued /

TABLE 2.1 continued

Median Nerve

	Left						Right					
	N9		N13		N20		N9		N13		N20	
No	μV	ms	μV	ms	μV	ms	μV	ms	μV	ms	μV	ms
1	-18.8	9	-0.5	13	-1.0	25	-18.7	10	-1.8	13	-1.2	20
2	-5.4	10	-0.6	12	-0.2	27	-8.0	9	-1.2	**14**	-0.3	24
3	-7.3	10	-0.9	**14**	-0.5	23	-8.2	10	-1.2	13	-0.2	23
4	-16.2	10	-6.1	13	-1.9	18	-13.3	10	**-3.0**	**14**	-0.7	18
5	-5.8	10	-3.4	14	-1.1	20	-5.3	10	-3.5	14	-3.2	21
6	-10.3	11	-3.2	14	-2.2	21	-12.2	11	-2.4	14	-2.7	21
7	-5.8	11	-2.5	14	-1.7	20	-5.6	11	-1.9	14	-2.5	21
8	-8.6	9	-1.9	12	-1.6	18	-11.3	8	-0.4	16	-0.5	24
9	-11.2	9	-1.6	13	-0.9	18	-10.1	9	-1.9	**15**	-1.6	19
10	-6.1	10	-1.3	14	-1.7	20	-8.9	10	-1.5	15	-1.8	21
11	-12.1	10	-2.3	12	-1.0	22	-10.2	10	-3.3	12	-2.1	19
12	-13.4	9	-2.8	11	-0.6	17	-17.5	9	-1.8	11	-0.7	**20**
13	-14.3	9	-3.7	12	-2.5	18	-11.3	9	-4.3	12	-3.1	17
14	-16.1	9	-2.0	12	-2.5	18	-10.6	10	-1.9	12	-2.4	18
15	-8.3	11	-1.5	14	-1.3	20	-7.6	11	-1.9	16	-1.6	23
16	-4.1	10	-2.4	13	-1.9	19	-6.1	10	-2.3	13	-2.5	19
17	-6.8	10	-1.1	**13**	ABS	ABS	-6.3	10	-1.3	12	-0.6	37
18	-16.5	11	-2.8	14	-4.5	20	-20.8	11	-5.7	14	-2.6	20
19	-7.6	11	-2.3	14	-2.6	21	-3.4	11	-1.4	15	-2.7	21
20	-15.8	10	-3.6	14	-1.6	19	-13.4	10	**-1.7**	14	-0.5	19
21	-6.9	9	-1.9	12	-1.4	18	-5.4	7	-5.0	12	-0.8	18
22	-2.6	11	-1.9	13	-0.8	17	-2.7	11	-0.9	13	ABS	ABS
23	-4.8	12	-2.4	17	-1.2	23	-4.1	12	-2.5	15	-2.2	22
24	-13.5	9	-1.7	11	-0.9	22	-9.2	9	-2.4	**14**	-1.9	21
25	-4.0	10	-3.7	14	-2.0	22	-4.3	10	-1.8	14	-1.7	20
26	-8.2	9	-4.0	13	-2.4	18	-9.6	10	-3.8	13	-2.5	18
27	-5.7	9	-2.6	13	-0.8	19	-8.0	9	-3.4	13	-0.9	18
28	-11.9	9	-1.5	13	-0.9	24	-12.4	9	-0.6	13	-0.5	21
29	-5.9	8	-3.0	13	-1.6	18	-6.0	8	-1.9	13	-1.9	18
30	-8.6	10	-2.0	14	-2.5	18	-9.7	10	-0.8	14	-0.1	22
31	-3.7	10	-0.9	16	-0.7	23	-3.0	11	-1.9	17	-0.8	24

Table 2.1 continued /

TABLE 2.1 continued

	Median nerve								Tibial nerve			
	Left				Right				Left		Right	
	nN13		P14		nN13		P14		P40		P40	
No	μV	ms	μV	ms	μV	ms	μV	ms	μV	ms	μV	ms
1	0.8	13	0.8	15	1.6	13	1.9	15	0.2	35	0.7	49
2	0.6	11	0.5	11	2.2	11	0.9	11	0.2	49	0.3	54
3	0.3	14	0.7	15	1.1	13	2.0	18	0.1	43	0.8	66
4	2.6	13	6.5	13	1.8	14	2.6	14	6.5	42	5.0	41
5	1.9	14	3.0	14	2.6	14	2.2	14	0.9	38	1.1	39
6	1.8	14	2.5	14	2.3	14	1.3	14	1.7	43	1.3	43
7	1.0	15	2.7	14	1.0	14	1.9	14	0.4	41	0.4	42
8	1.5	12	2.9	13	1.6	12	2.1	16	1.0	49	1.8	49
9	0.4	13	1.8	13	1.1	15	1.4	15	1.6	40	0.9	41
10	0.9	14	1.3	14	0.6	13	1.5	15	2.7	44	2.1	43
11	1.6	12	1.6	15	1.5	12	2.3	12	1.5	39	3.8	38
12	1.8	12	1.1	13	2.3	11	3.4	10	4.2	37	2.9	37
13	2.4	12	2.4	13	1.6	12	2.3	12	2.2	42	1.3	40
14	2.1	12	2.3	12	1.5	11	2.1	13	1.0	37	1.6	39
15	0.6	14	0.9	14	0.4	16	1.1	16	0.2	60	0.4	62
16	1.5	13	2.9	13	1.5	13	2.2	14	0.6	42	1.1	41
17	0.5	13	NI	NI	1.0	13	NI	NI	0.7	52	0.5	48
18	2.0	14	2.9	14	2.4	14	3.1	14	4.9	41	4.1	40
19	0.5	14	1.3	17	0.4	15	1.5	17	0.2	48	0.2	43
20	1.4	13	2.0	13	1.1	13	1.8	14	1.7	39	1.7	39
21	NR	NR	2.1	12	NR	NR	NI	NI	1.5	40	1.3	41
22	4.1	14	1.8	15	3.8	13	1.3	15	1.0	46	0.4	45
23	1.8	13	1.4	17	1.6	13	0.6	15	1.0	49	0.7	46
24	1.4	12	NI	NI	0.4	12	2.6	16	NR	NR	NR	NR
25	0.6	14	1.6	14	2.5	13	1.6	14	NR	NR	NR	NR
26	2.5	13	1.3	13	1.9	12	1.8	13	0.8	35	0.9	36
27	1.0	13	2.6	13	3.0	12	2.1	12	3.0	44	4.2	41
28	2.8	13	1.8	12	3.0	13	2.3	13	ABS	ABS	0.6	45
29	1.0	12	0.8	13	0.9	12	0.8	13	0.4	38	0.4	37
30	2.3	13	2.8	13	1.3	13	1.4	14	2.8	42	1.8	45
31	1.3	15	NI	NI	2.8	16	NI	NI	NR	NR	NR	NR

Table 2.1 continued /

TABLE 2.1 continued

MRI lesions

	Cervical cord				Intracranial		
No	**A/P**	**L/R**	**Levels**	**SW/AT**	**L**	**C**	**R**
1	AP	R	2 3		Rad		Rad
2	AP	LR	2 3 4 5 6	AT	Rad	Med	
3	AP	LR	4 5 6	SW	Int cps		
					Rad		Rad
4	P	LR	2		Rad	Med	Rad
5	AP	LR	3		Pons		
					Rad		Rad
6	AP	LR	3				Int cps
					Rad		Rad
7					Rad		Int cps
8	P	LR	2 3 4 5				
9	AP	R	5 6		Rad	Med	
10	P	LR	3 5		Rad		
11	P	L	2 3			Med	Pons
12	P	R	1 2		Rad		
13	P	LR	3		Rad		Rad
14	AP	LR	4 5	SW			
15	AP	LR	1 2		Rad	Med	Rad
16					Rad		Rad
17	AP	LR	1 2 3 4				Pons
			5 6 7		Rad		Rad
18							
19					Rad		Rad
							Cor
20	P	R	5				Rad
21							
22	P	R	CMJ			Pons	
23	A	LR	CMJ				
24	P	LR	2 3	AT	Rad		Rad
25	P	LR	2	SW			
26	A	R	2 3	SW	Pons		
27							
28	AP	LR	2 3	AT			
29							
30	A	R	CMJ				
31	A	L	2 3	SW			

Table 2.1 continued /

TABLE 2.1 continued

Legend: CDMS = clinically definite MS;
LSDMS = laboratory supported definite MS;
CPMS = clinically probable MS;
ICL = isolated cord lesion; σ = sensory or motor symptoms; α = sensory signs implicating the spinothalamic tracts; π = sensory signs implicating the posterior columns; Φ = motor signs;
nN13 = N13 recorded with a supraglottal reference;
NI = not interpretable; NR = not recorded;
ABS = absent; A = anterior; P = posterior; L = left;
R = right; CMJ = cervico-medullary junction;
AT = atrophy; SW = swelling; C = centre;
Rad = radiations; Med = medulla;
Int cps = internal capsule; Cor = cortex;
abnormal values underlined;
underlined and bold = significant inter-side difference.

TABLE 2.2: ASSOCIATION BETWEEN MEDIAN SEP FINDINGS AND MRI LESIONS (Exact probability Fisher test)

		Median SEPs (Fz reference)		
		Both sides	**Left**	**Right**
Spinal	cord	0.012		
	Left		0.002	NS
	Right		NS	0.018
	Posterior	0.013		
	Anterior	NS		
Brain		NS		
	Left		NS	NS
	Right		NS	NS

TABLE 2.3: PERCENTAGE OF N13 ABNORMALITIES IN RELATION TO THE LEVELS OF CORD LESIONS

	N13 abnormalities	
	Supraglottal reference	**Fz reference**
Cord levels		
C6-C7 (4)	100% (4)	100% (4)
C5-C4 (8)	50% (4)	75% (6)
C3-C2 (17)	35% (6)	59% (10)
C1-CMJ (6)	33% (2)	100% (6)

Number of cases in parenthesis
CMJ = cervico-medullary junction

TABLE 2.4: ASSOCIATION BETWEEN N13 OR P14 ABNORMALITIES AND LEVELS OF THE CORD LESIONS (Exact probability Fisher test)

	N13	nN13	P14
Cord levels			
C1-CMJ	0.01	NS	0.017
C2-C3	NS	NS	NS
C4-C5	NS	NS	NS
C6-C7	NS	0.029	NS

N13 = Fz reference; nN13 = supraglottal reference; CMJ = cervico-medullary junction.

Fig. 2.1 Normal left median and posterior tibial nerve SEPs (29 year-old female). Upper and lower limb responses were recorded over the foot sensory cortical area (1), left and right hand sensory cortical areas (2 and 3), ipsilateral mastoid process (4), the spine at C2 (5) and C7 (6) levels, the anterior aspect of the neck on the midline above the thyroid cartilage, "supraglottal location", (7) and left and right clavicle (8 and 9) with Fz reference. The upper limb responses were also transformed off-line to non-cephalic reference: channels 2-8 referred to clavicle (9) and channel 6 referred to channel 7.

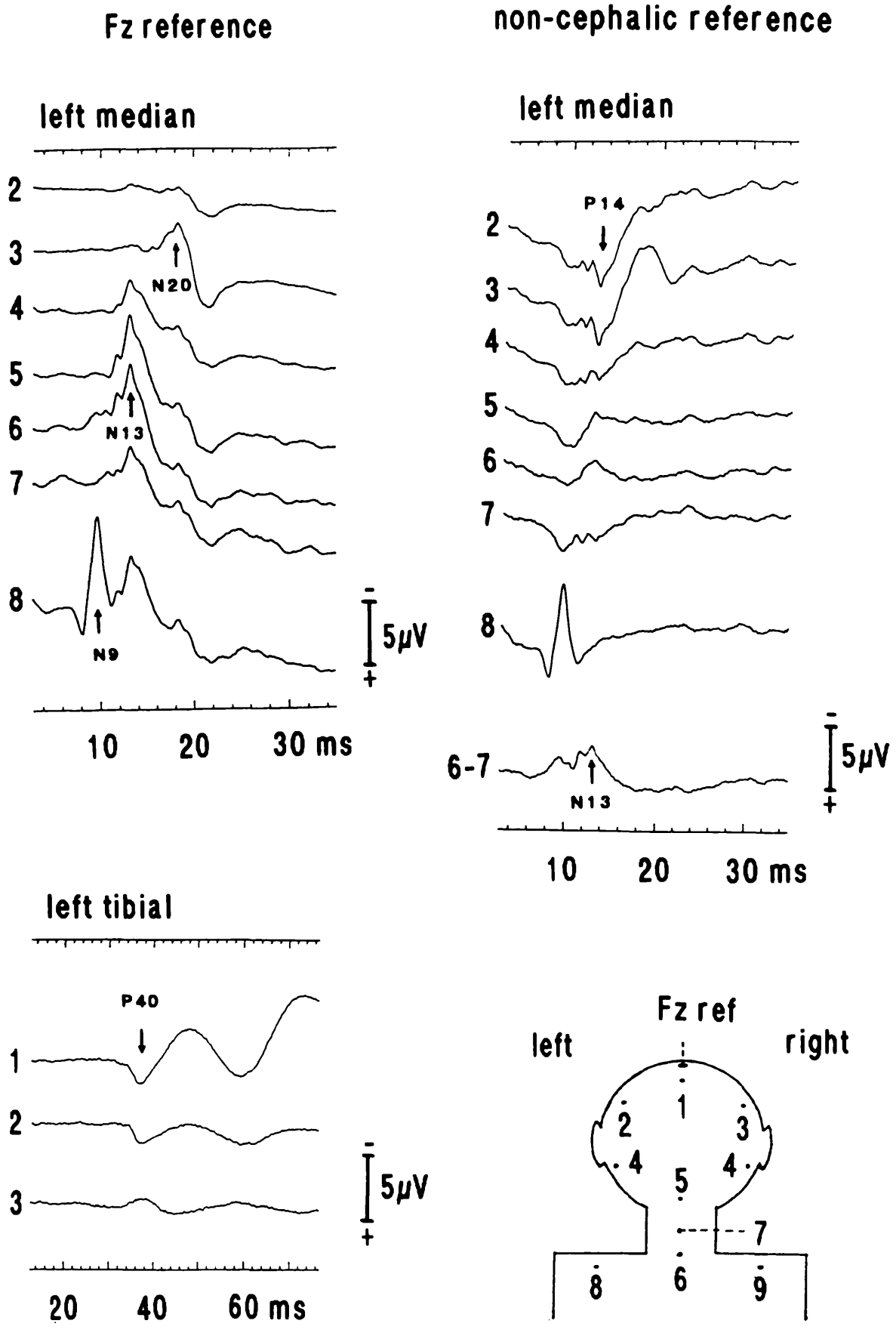

Fz reference
non-cephalic reference
left median
left median
P14
N20
N13
N9
2
3
4
5
6
7
8
5μV
10
20
30 ms
6-7
N13
5μV
10
20
30 ms
left tibial
P40
1
2
3
5μV
20
40
60 ms
Fz ref
left
right
1
2
3
4
4
5
7
8
6
9

Fig. 2.1

Fig. 2.2a **Case 28** (38 year-old female), median and posterior tibial nerve SEPs. In the Fz reference recordings, N20 is delayed bilaterally and N13 is degraded from the right arm. P40 is unidentifiable from the left posterior tibial nerve and degraded and delayed from the right. In the non-cephalic reference recordings (Fig. 2.2a continued), N13 is normal and P14, although not clearly identified, is within normal limits.

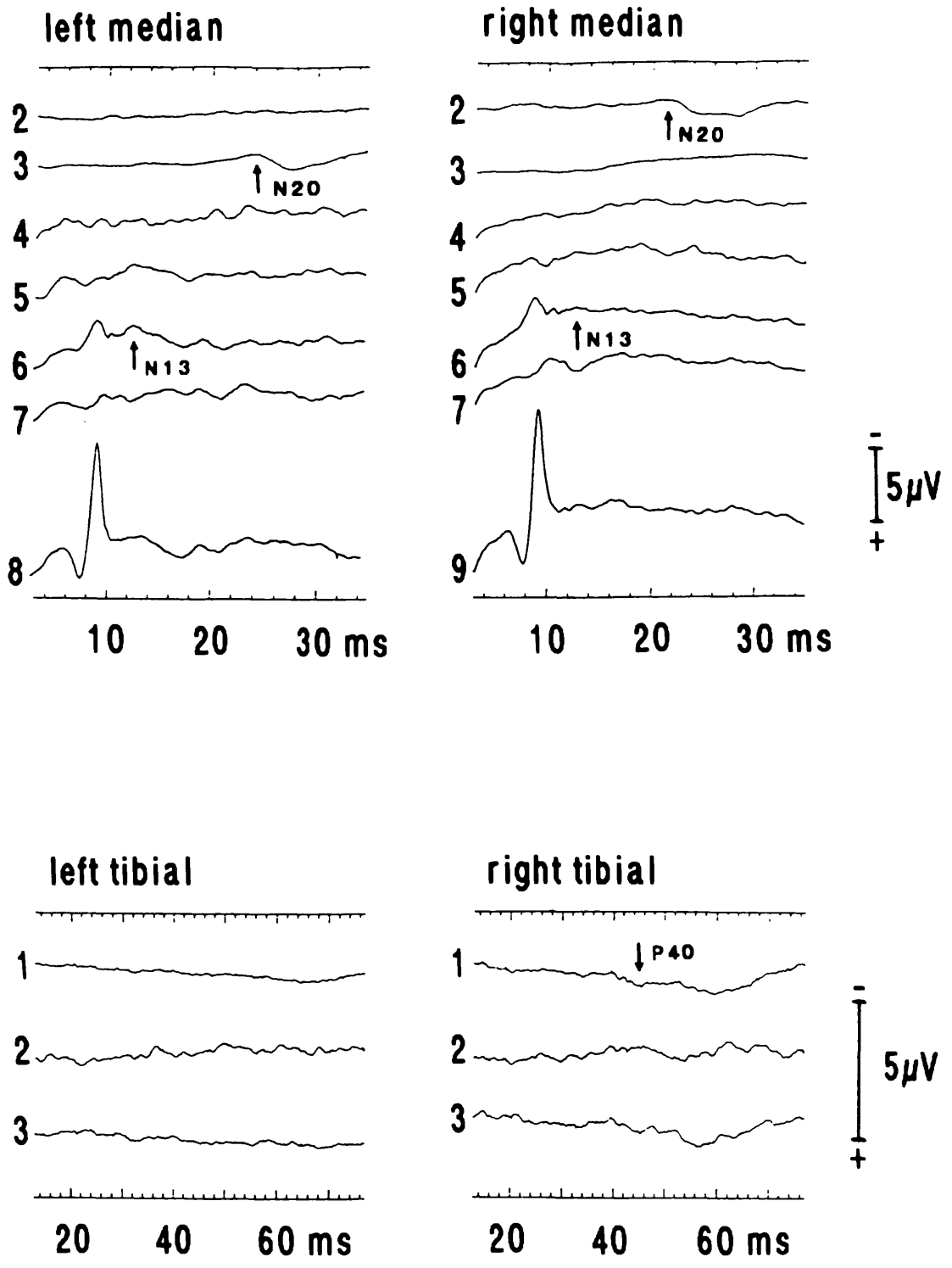
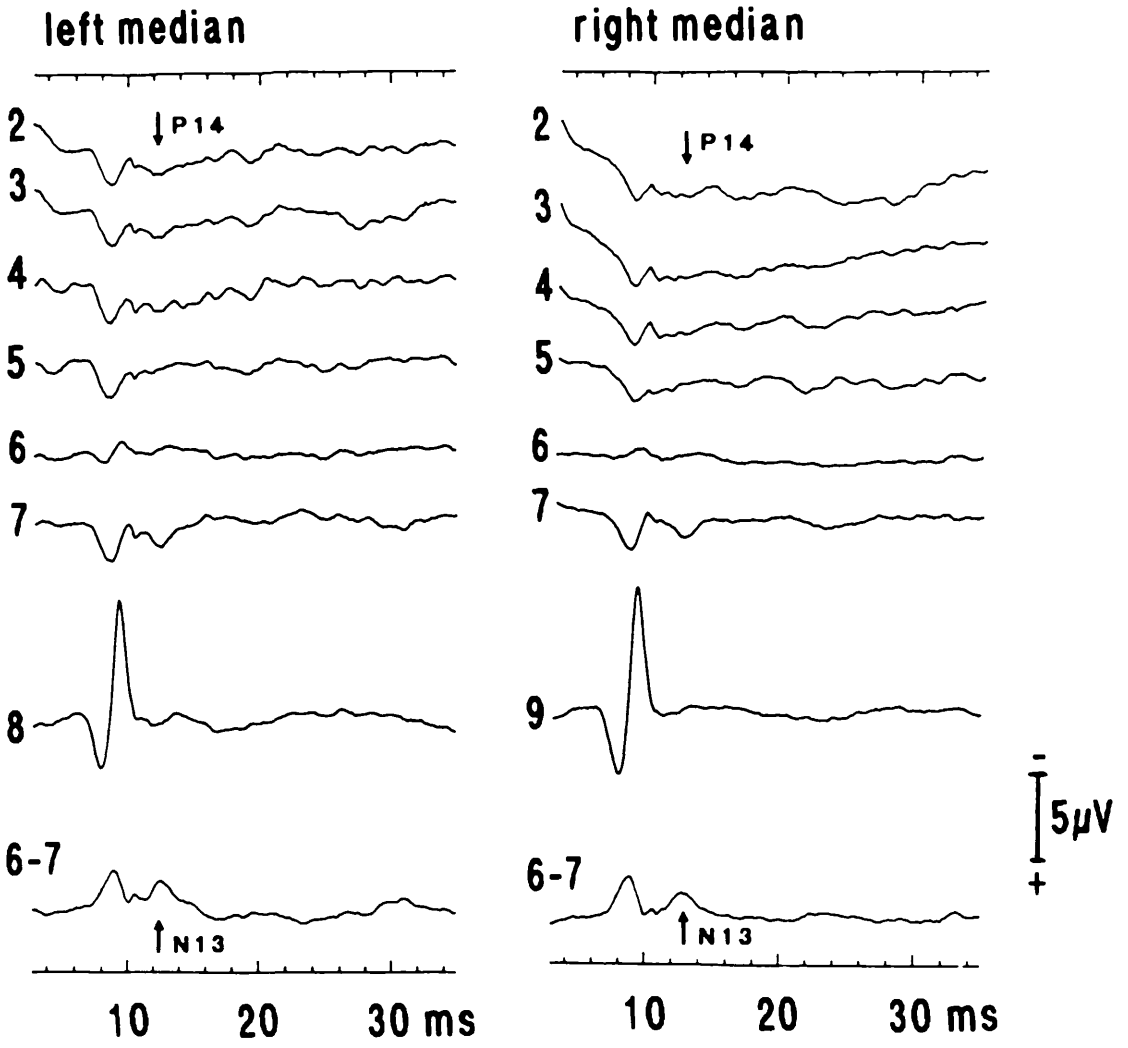

Fz reference
left median
right median
2
3
4
5
6
7
8
9
N20
N13
10
20
30 ms
5μV
left tibial
right tibial
1
2
3
P40
20
40
60 ms

Fig.2.2a

non-cephalic reference



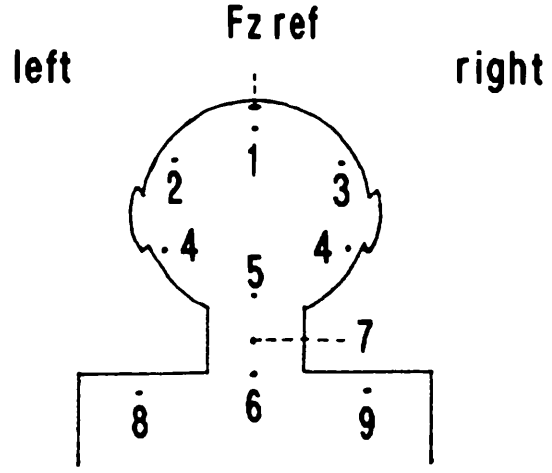


Fig.2.2a continued

Fig. 2.2b **Case 28**, cervical cord and brain MRI. The sagittal view of the cord (top left) shows an area of increased signal and marked atrophy at C2-C3 levels. The axial view of the cord (bottom left) displays antero-posterior flattening and increased signal throughout at the same level. In the brain image, axial view (top right), a lesion is visible in the left pre-central area.

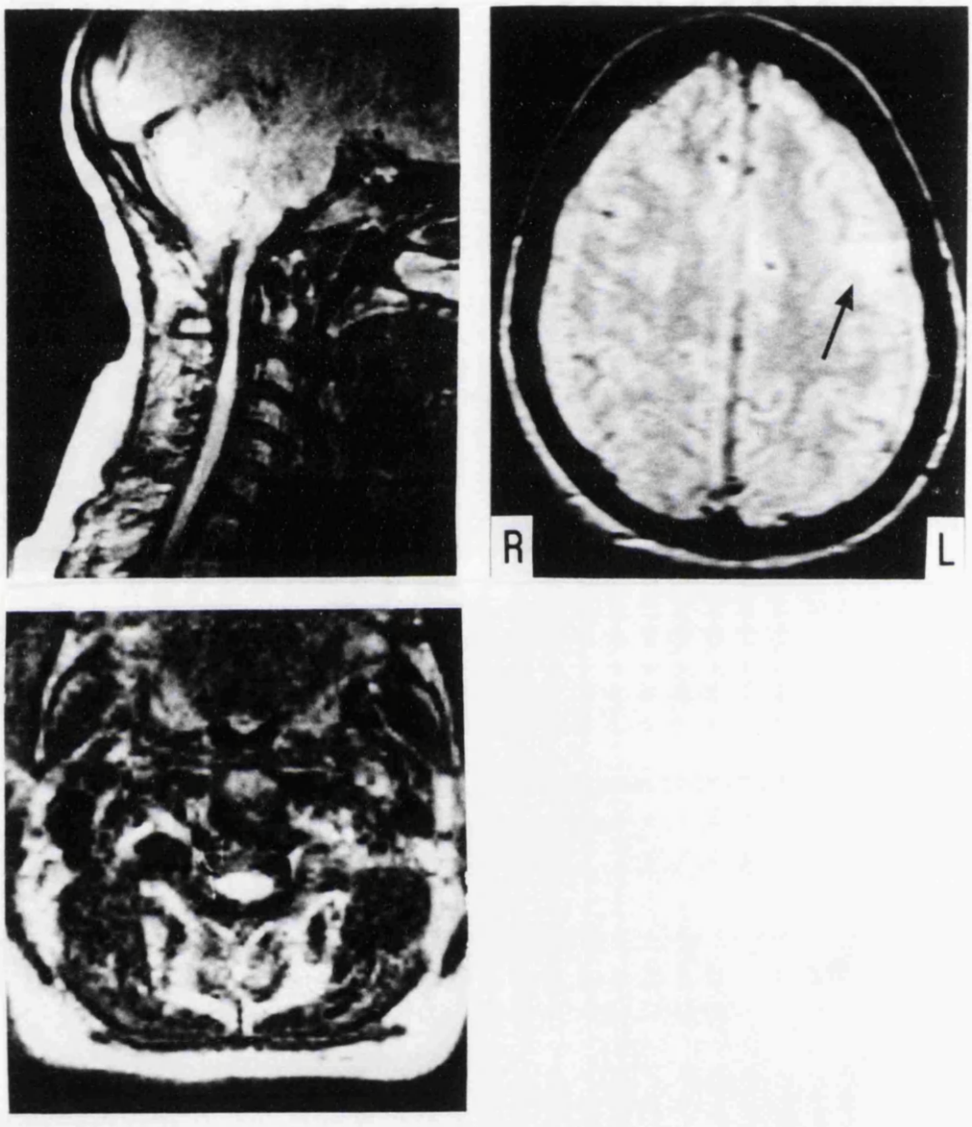
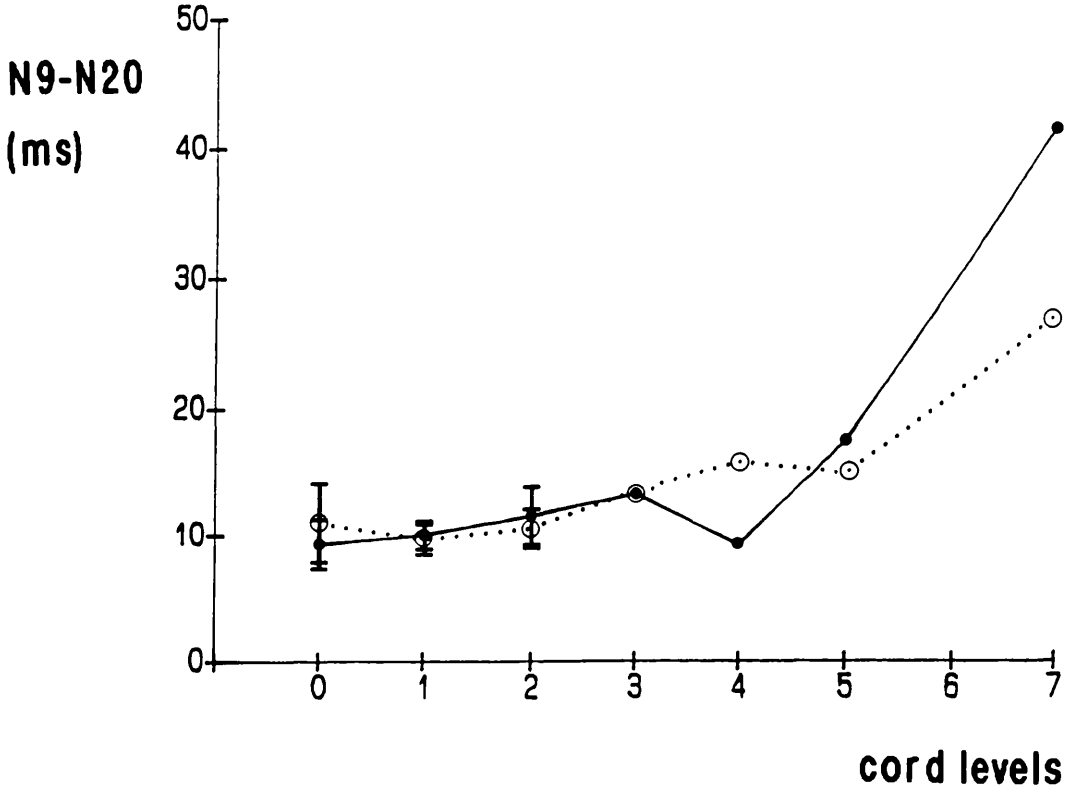


Fig.2.2b

Fig. 2.3. Variation of the N9-N20 interpeak latency (top) and P40 absolute latency (bottom) in relation to the longitudinal extent of the cord lesion on the ipsilateral side. Continuous line=left side; dotted line=right side. Filled and empty circles=mean latency values for left and right side, respectively; vertical lines=their standard deviations. Only 4 patients showed cord lesions extending beyond 2 levels.


N9-N20
(ms)
50
40
30
20
10
0
0
1
2
3
4
5
6
7
cord levels

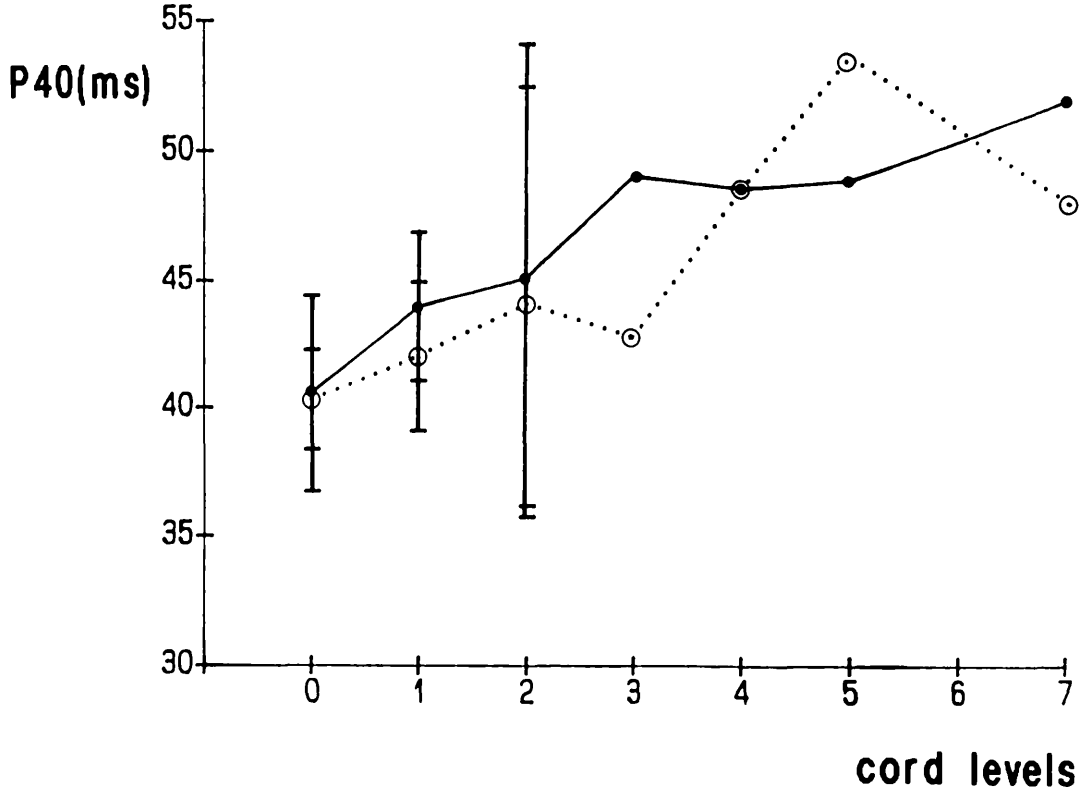

P40(ms)
55
50
45
40
35
30
0
1
2
3
4
5
6
7
cord levels

Fig.2.3

Fig. 2.4a **Case 11** (36 year-old female), median and posterior tibial nerve SEPs. In the Fz reference recordings, N20 is delayed and P40 attenuated on the left side. In the non-cephalic reference recordings (Fig. 2.4a continued), P14 is delayed from the left arm.

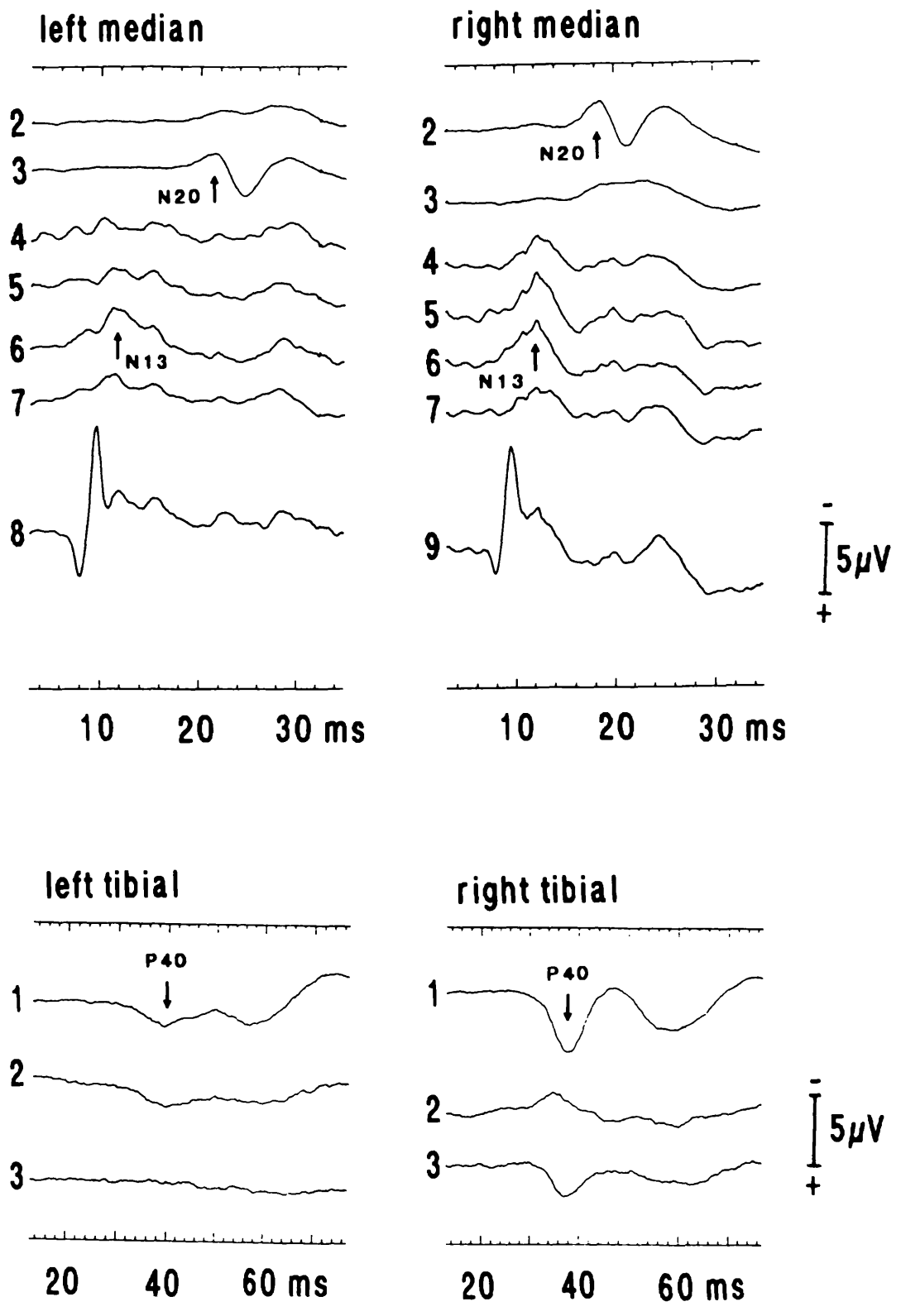
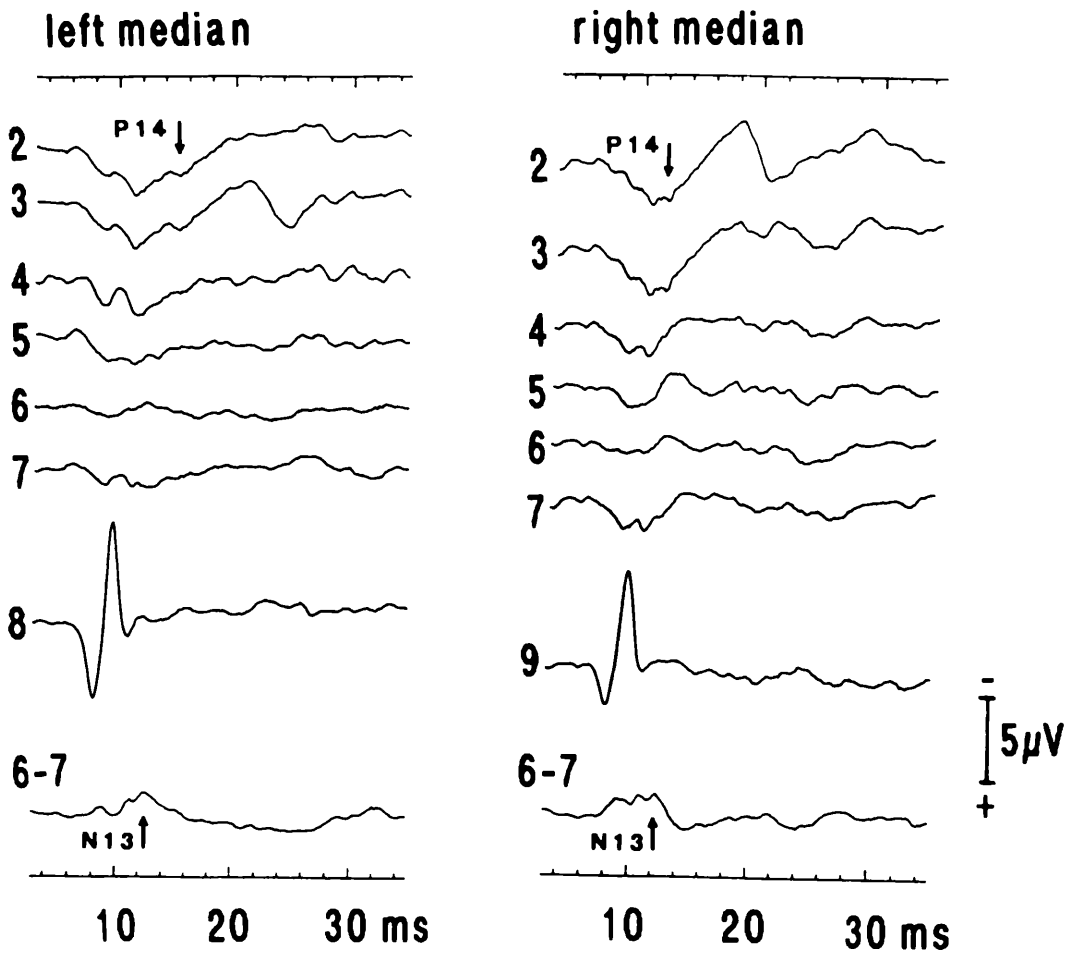

Fz reference
left median
right median
2
3
N20
4
5
6
N13
7
8
9
10
20
30 ms
5μV
left tibial
right tibial
P40
1
2
3
20
40
60 ms

Fig.2.4a

non-cephalic reference



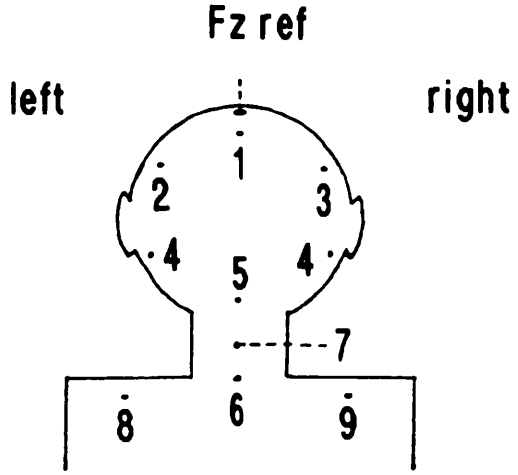


Fig.2.4a continued

Fig. 2.4b **Case 11**, cervical cord MRI. The sagittal view (top) shows an area of increased signal at C2-C3 levels. The axial view (bottom) displays an area of increased signal in the left posterior quadrant at the same level.

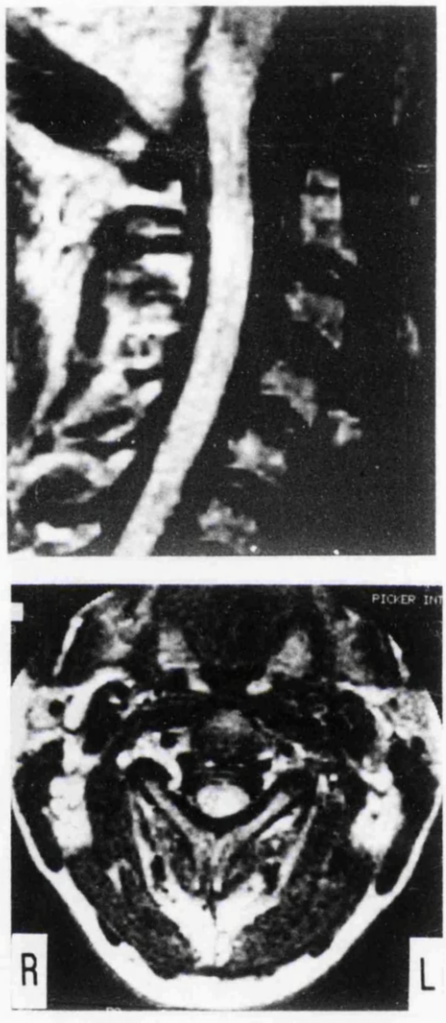


Fig.2.4b

Fig. 2.5a **Case 20** (26 year-old female), median and posterior tibial nerve SEPs. In the Fz reference recordings, N13 and N20 are attenuated from the right arm. In the non-cephalic reference recordings (Fig. 2.5a continued), N13 and P14, although ill defined, are within normal limits.

Fz reference

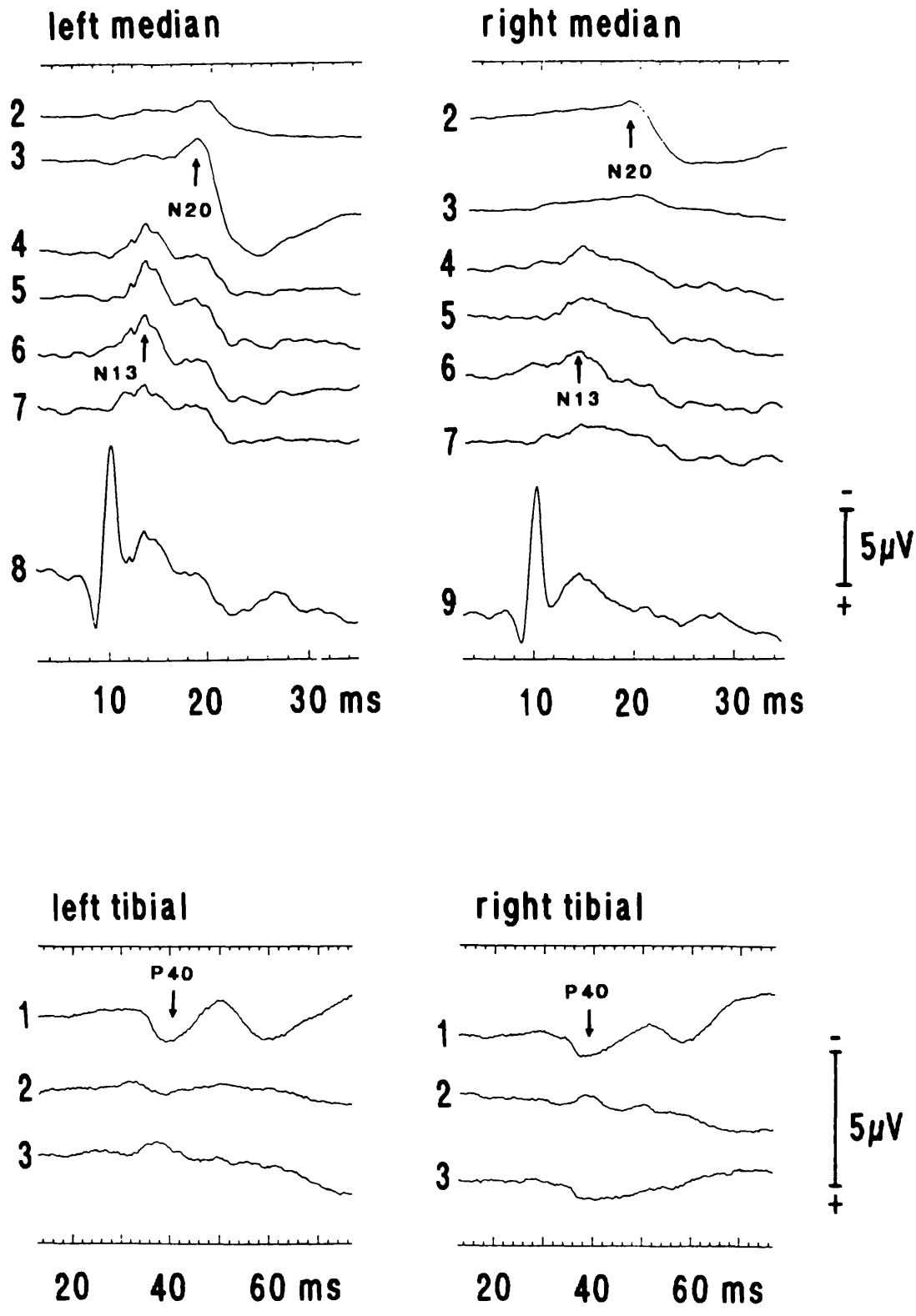
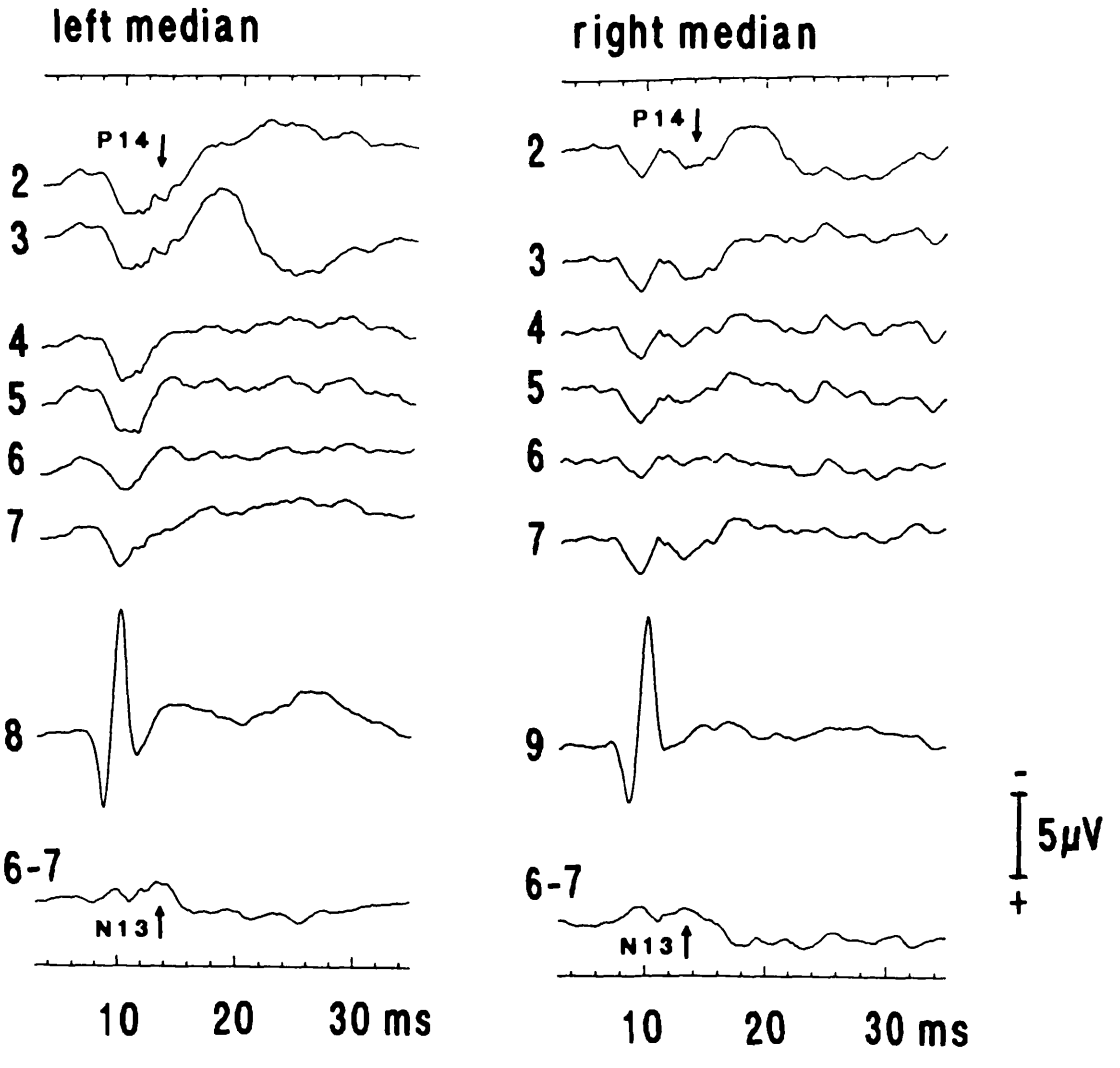


Fig.2.5a

non-cephalic reference



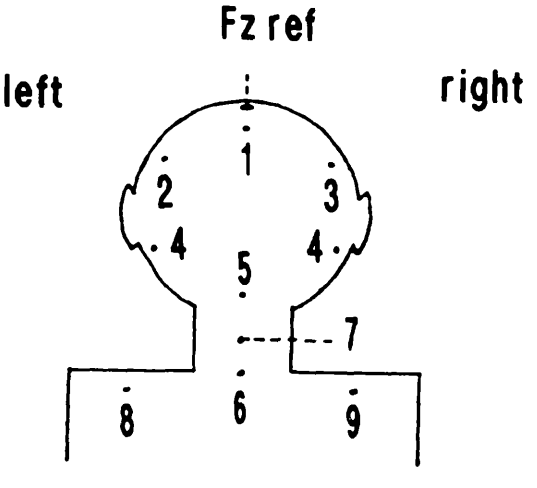


Fig.2.5acontinued

Fig. 2.5b **Case 20**, cervical cord and brain MRI. The sagittal view of the cord (top left) shows an area of increased signal at C5 level. The axial view of the cord (bottom left) displays an area of increased signal in the right posterior quadrant at the same level. In the brain images, axial views (top and bottom right), areas of increased signal are visible in the white matter of the right hemisphere.

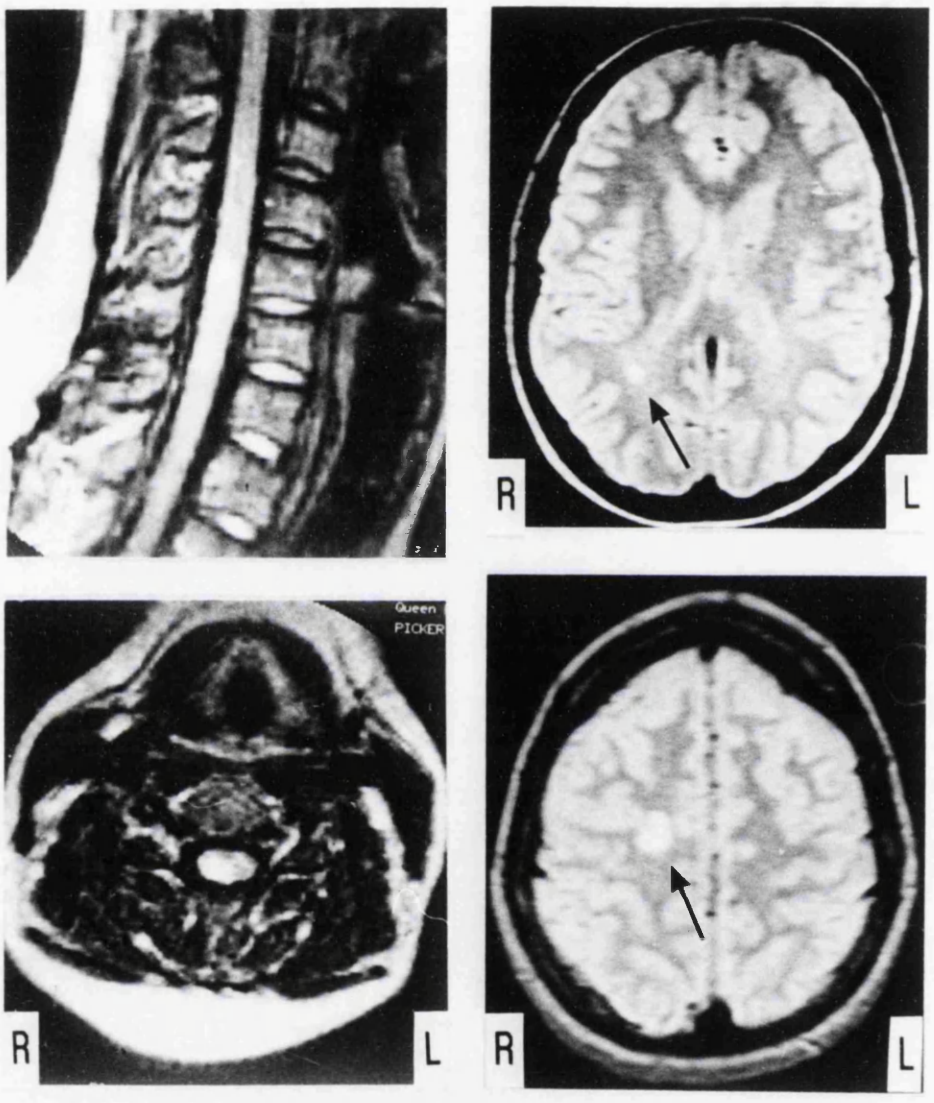


Fig.2.5b

Fig. 2.6a Case 6 (22 year-old male), median and posterior tibial nerve SEPs. Normal responses in both Fz and non-cephalic reference recordings (Fig. 2.6a continued).

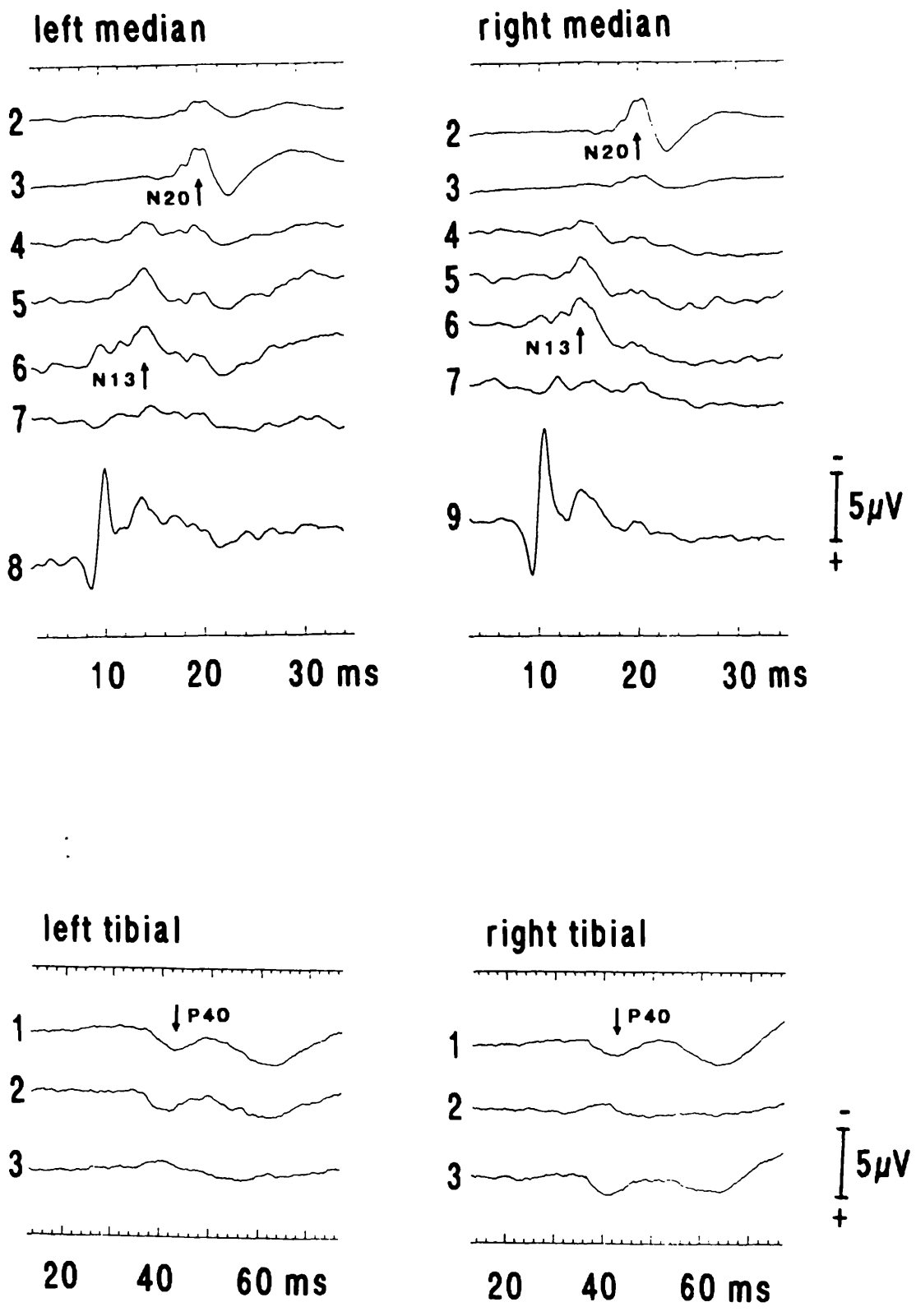
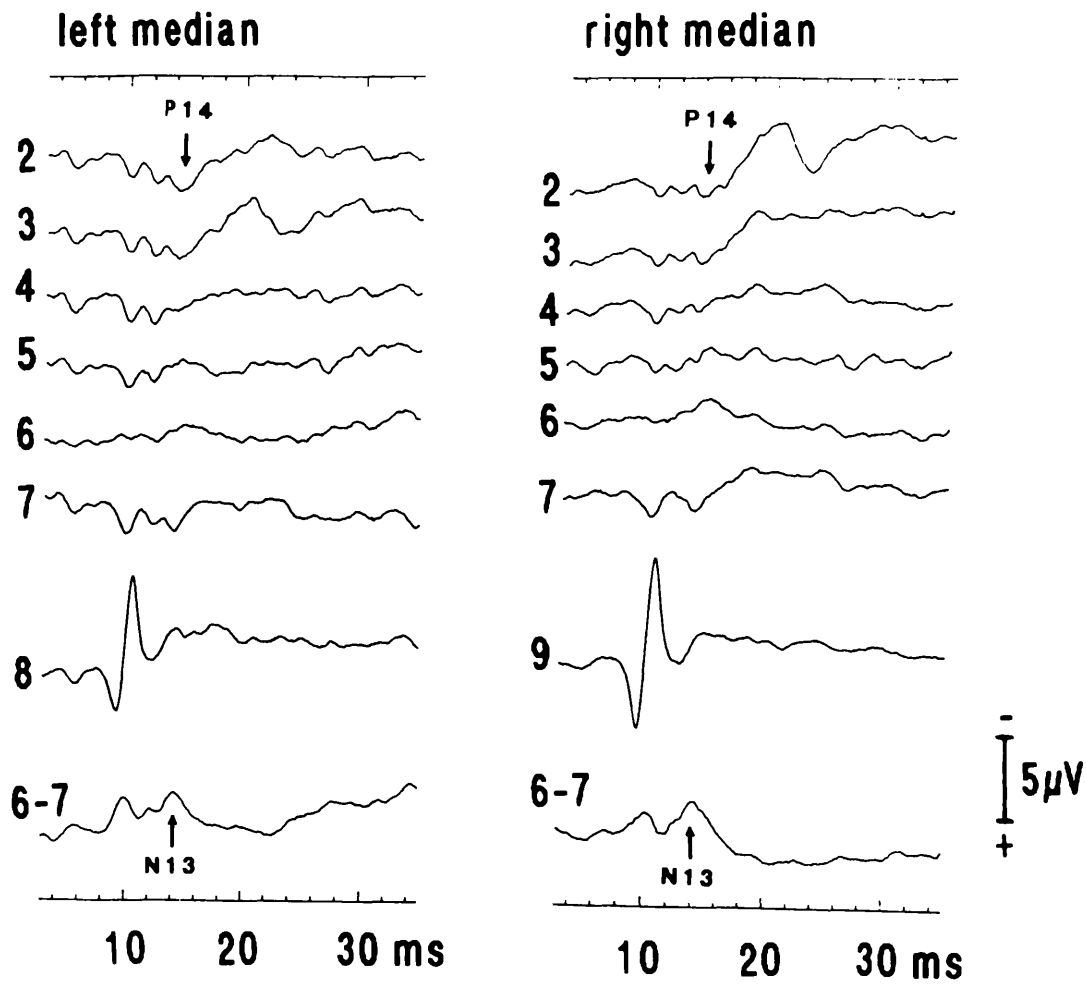

Fz reference
left median
right median
2
3
N20
4
5
6
N13
7
8
9
5μV
10
20
30 ms
left tibial
right tibial
1
P40
2
3
20
40
60 ms

Fig.2.6a

non-cephalic reference



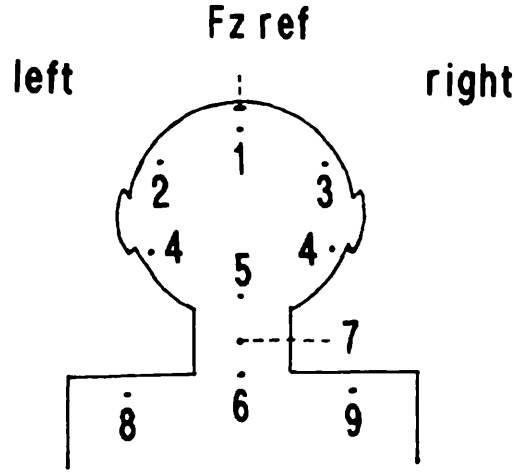


Fig.2.6acontinued

Fig. 2.6b **Case 6**, cervical cord MRI. The sagittal view (top) shows an area of increased signal at C3 level. The axial view (bottom) displays an area of increased signal which involves the whole cross-section of the cord at the same level.

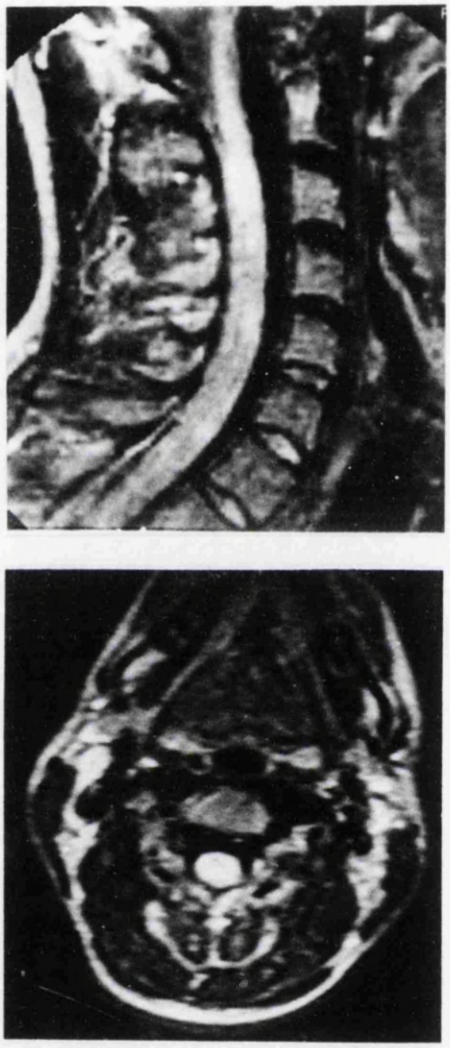


Fig.2.6b

CHAPTER

3

MRI AND VEP FINDINGS IN MS PATIENTS WITH SYMPTOMATIC RETROCHIASMAL LESIONS

3.1 INTRODUCTION

MS lesions have often been discovered at autopsy in the retrochiasmal visual pathways, in particular the optic radiations. Lehoczky (1954) studied 20 MS cases and found that 85% of these had lesions in the optic radiations. In 22 cases Brownell and Hughes (1962) found that 40% of the total number of plaques in the cerebral white matter were periventricular and the areas around the posterior horns of the lateral ventricles were almost always involved.

Similar observations have been made in vivo using MRI. Ormerod et al. (1987) detected periventricular abnormalities in 142/144 patients with clinically definite or probable MS. The areas around the occipital horns of the lateral ventricles were the second most frequently affected (in 83% of cases) after the regions around the trigone and body (96% of cases). More recently in a study of patients with a clinically isolated optic neuritis, Hornabrook et al. (1992) reported MRI abnormalities in the optic radiations in 20/28 cases.

Despite these findings, clinical evidence of involvement of the retrochiasmal visual pathways has rarely been reported in MS. Traquair (1925) pointed out that occasionally retrobulbar neuritis invades the postchiasmal pathways. Subsequently, other authors stressed the rarity of homonymous hemianopic defects in MS (Chamlin and Davidoff, 1954). The incidence in published series was very

low, 5/365 cases (Boldt et al., 1963) or 8/215 (Kurtzke et al., 1968). Patterson and Heron (1980) failed to find any homonymous hemianopic defect in their group of 49 patients with MS or isolated optic neuritis. Rosenblatt et al. (1987) described two MS cases with right homonymous hemianopia and MRI lesions in the left optic tract-chiasm junction and left optic radiations, respectively.

Electrophysiological evidence of postchiasmal pathology, documented by VEP recording, is also rare in MS. In 2 patients with homonymous hemianopic defects, Onofrj et al. (1982) detected an attenuation of the VEP on the midline and at scalp electrodes ipsilateral to the defective half-fields, on both full and hemifield stimulation. Halliday (1982c) described 2 cases with VEP abnormalities suggestive of postchiasmal involvement. In one of these, who had a right homonymous hemianopia, the full field response from either eye was attenuated at the right sided scalp electrodes. The other patient showed degraded and delayed responses from the left homonymous half fields and desaturation to red in those hemifields. In two patients, Blumhardt et al. (1982b) reported attenuated and absent homonymous hemifield responses, respectively, recorded within days of the onset of visual blurring in those hemifields. In 2 patients showing a right postchiasmal lesion on MRI, Sartucci et al. (1989) detected an attenuation of the full field response on the left side of the scalp to stimulation of either eye.

In the present study, 15 MS patients showing homonymous hemianopic defects underwent brain MRI and recording of full and hemifield visual evoked potentials. The object of the investigation was that the examination of the morphological and electrophysiological features of symptomatic retrochiasmal lesions might help to elucidate why homonymous hemifield defects are rare in MS despite the frequent pathological involvement of postchiasmal pathways.

3.2 CASE MATERIAL

3.2.1 Patients

The patient group comprised 15 subjects, 7 males and 8 females aged 20 to 50 years (mean 34±8 years), with clinically definite MS (Poser et al., 1983). They all presented with visual symptoms in the left or right hemifields of both eyes and showed homonymous visual field defects on neuro-ophthalmological examination.

3.2.2 Controls

Normal limits of VEP amplitude and latency were obtained separately from 16 healthy females, aged 20 to 48 years (mean 33±10 years) and 12 healthy males, aged 26 to 50 years (mean 37±9 years).

3.3 METHODS

3.3.1 Goldmann perimetry

Goldmann perimetry was performed as soon as possible after the patient noticed visual symptoms, usually within three weeks, and repeated after a mean of approximately six months (range one to 12 months). Fields were assessed by the measurement of isopters to the target I4e and, where time permitted, to additional targets. The extent of the defects was recorded to both dynamic and static stimulation. At follow-up, the hemianopic field defect was judged to have resolved if there were no longer significant differences between the isopters obtained in both nasal hemifields and both temporal hemifields. If the field defect had not recovered at the second visit, the patients were re-examined at longer intervals. In one patient (Case 14) visual field examination was not possible in the left eye, because of pre-existing severe left optic neuropathy.

3.3.2 Magnetic resonance imaging

Images were obtained as soon as possible after the onset of the visual symptoms, always within three weeks, in 13 patients. T_2-weighted images were obtained in a Picker 0.5 Tesla superconducting scanner, using $SE_{2000/60}$ sequences. Contiguous slices of 5 mm thickness were obtained through

the brain in the axial plane. One patient (Case 8) was imaged in a 0.26 Tesla machine. In another patient (Case 7) Gadolinium-DTPA enhancement was employed, using an additional T_1-weighted sequence ($SE_{500/40}$). Scans were assessed by a neuroradiologist who was unaware of the perimetric findings. Abnormalities localised in the retrochiasmal pathways were noted. In 11 patients CT studies had been carried out at the onset of the visual symptoms as part of the routine investigation prior to recruitment for the study.

Follow-up images were obtained after careful repositioning in 5 patients to document eventual changes of the lesions thought to be responsible for the visual field defects.

3.3.3 Visual evoked potentials

Pattern reversal VEPs were recorded in 13 patients within six weeks of the onset of the visual symptoms; eight cases were then followed-up after four to 77 months. In two additional patients (Cases 6 and 15) only a follow up recording was carried out four and five months, respectively, after the onset of the visual symptoms.

Full and hemifield responses were recorded in a darkened room. The patient sat comfortably one metre away from a translucent circular screen, the radius of which subtended 16° at the eye. Onto the screen a slide of black

and white chequerboard pattern was back-projected by means of a rotatable mirror placed at an angle of approximately 45° to the projector lens. The subtense of each check was 50' and the brightness levels were 227 and 8.2 cd/m^2 for white and black checks, respectively. The reversal was effected every 505 ms by an angular movement of the mirror, which produced rapid (10 ms) horizontal displacement of the pattern through one square width. The fixation point was provided by a bright spot in the centre of the screen. During stimulation of the left or right hemifield, the vertical right or left half of the screen was masked, respectively.

Five silver/silver chloride disc recording electrodes were placed in a horizontal chain across the occipital area, on the midline 5 cm above the inion and 5 and 10 cm to either side. Three additional electrodes were located on the midline 2.5 cm above the inion, at the inion and 5 cm below it. A common reference electrode was placed 12 cm above the nasion [Fig. 3.1].

The amplifier high frequency response was less than 3 dB down at 5 KHz and the time constant was 1 s. The averaging window was 320 ms and the sampling interval 1.25 ms. Two hundred sweeps were averaged in each run, which was repeated at least twice in either eye. The full field stimulus evoked a triphasic negative-positive-negative complex, whose positive peak occurred at about 100 ms in normal subjects (P100). On hemifield stimulation, the P100 and

preceding and following negative potentials were present at midline scalp electrodes and at locations ipsilateral to the stimulated hemifield, while a complex of opposite polarity was recorded on the contralateral side [Fig. 3.1]. Since the present study was concerned with postchiasmal lesions, only hemifield responses were analysed. Measurements of the P100 amplitude and latency were taken from the electrode location 5 cm ipsilateral to the stimulated half field.

The normal latency limit was defined by the mean + 2.5 standard deviations (SD) of the absolute latency in the control groups. Normal limits of monocular hemifield latency asymmetry were defined by the mean ± 2.5 SD of the interfield latency difference (left-right) in either eye. Normal limits of monocular hemifield amplitude asymmetry were defined by the mean ± 2.5 SD of $\log_{10}$ [left/right] amplitude ratio in either eye. Normal limits values were as follows. Absolute latency: 114 ms, females, and 126 ms, males. Monocular hemifield latency asymmetry: -11 ms and 9 ms, females; -10 ms and 10 ms, males. Monocular hemifield amplitude asymmetry: 0.4 and 2.1, females; 0.4 and 2.6, males.

3.3.4 Statistical analysis

Responses from affected and unaffected hemifields in the same patients were compared using the paired t-test (two tailed probability). The terms "affected" and "unaffected" are used throughout to describe the fields in which defects due to postchiasmal lesion were evident.

3.4 RESULTS

3.4.1 Visual field defects

a) Acute findings

All 15 patients presented with visual symptoms in homonymous hemifields. In addition, four patients had hemiparesis, another clinical feature which is uncommon in MS (Cases 6, 7, 11 and 14), and one also had dysphasia (Case 14).

On Goldmann perimetry, three patients had a macular splitting homonymous hemianopia (Cases 5, 7 and 12) and two had dense partial homonymous hemianopia (8 and 11) when first seen. Two patients showed a general depression of the hemifield (Cases 2 and 14) with a macular splitting hemianopia to I4e but statokinetic dissociation to larger targets. Seven patients (Cases 1, 3, 4, 6, 9, 10 and 15) had homonymous scotomata, often showing some incongruity

between the two eyes and statokinetic dissociation to larger targets (Cases 4 and 9). The remaining patient (Case 13) displayed an incomplete left homonymous lower quadrantic field defect on perimetry and phosphenes within the left homonymous hemifields [Table 3.1].

b) Follow-up

All patients except Cases 3, 7, 11 and 12 showed a complete recovery of their visual deficits during the follow-up period. Recovery had occurred within three months of the onset of visual symptoms in all except Cases 6 and 14 (four months), Case 4 (six months) and Case 13 (12 months). Only two patients did not show any improvement: Case 7 had persisting macular splitting homonymous hemianopia at six months and Case 11 had a defect which remained unchanged for at least seven years in four examinations. Cases 3 and 12 showed an incomplete recovery at nine and 18 months, respectively [Table 3.1].

3.4.2 MRI abnormalities

a) First scan

Thirteen patients had multiple areas of altered signal on brain MRI and in many cases there was more than one abnormality involving the visual pathways. It was not dif-

ficult to identify the lesion probably responsible for the field defect because of its location, its change in size on subsequent examination or both. In one patient (Case 7) MRI was carried out with Gadolinium-DTPA and the lesion thought to cause the field defect enhanced, indicating breakdown of the blood-brain-barrier (BBB). In six cases the MRI abnormality was in the region of the optic tract and the lateral geniculate nucleus (LGN); in two it involved the posterior limb of the internal capsule and in six it was located more posteriorly in the optic radiations, involving the white matter of either the temporal or the occipital lobes. In two patients (Cases 1 and 11) MRI was not performed during the phase of acute visual impairment. In Case 11 a contemporary CT study revealed a large retrochiasmal lesion in the left optic radiations, which showed ring enhancement. Case 1 had no visible retrochiasmal abnormality on CT, but was included in our series because of the adequacy of VEP and perimetry data [Table 3.1].

In addition, CT was carried out during the acute phase in Cases 3, 6, 7, 8, 10, 12, 13, 14 and 15. A postchiasmal lesion thought to be responsible for the visual impairment was visible in all but three patients (Cases 3, 10 and 15), and showed ring enhancement in three (Cases 8, 11 and 14).

b) Follow-up

Follow up MRI was performed in Cases 5, 7, 13, 14 and 15. In all of these the postchiasmal lesion was visibly smaller as compared to the initial scan.

3.4.3. VEP abnormalities

a) First recording

In 13 patients VEPs were recorded within six weeks of the onset of the visual symptoms and in all but one (Case 13) a homonymous hemianopic defect was detected by Goldmann perimetry. The defect consistently involved all or part of the central 15° of the visual field.

Five patients (38.5%) showed a significant asymmetry between left and right half field responses from either eye, consistent with a post-chiasmal lesion. In every case the asymmetry corresponded to the side of the homonymous visual field defect. The responses from the affected homonymous hemifields were absent in three patients (Cases 1, 7 and 12) and delayed in another (Case 10) [Figs. 3.2a and 3.3a]. In the remaining patient (Case 5) the response from the defective hemifield was absent from the left eye and delayed from the right eye. In all these patients the full field responses were within normal limits in terms of amplitude and latency [Table 3.2].

An additional six patients out of the 13 (46.2%) had abnormal full or half field responses from one or both eyes (delayed, reduced or absent), but without a significant asymmetry between heteronymous hemifield components in each eye and, therefore, not indicative of a post-chiasmal lesion (Cases 2, 4, 8, 9, 11 and 14). These findings were suggestive of unilateral or bilateral optic neuropathy. Two patients (15.4%) had normal VEPs (Cases 3 and 13) [Table 3.2].

At the time of the visual field defect, there was no significant mean amplitude difference between non-hemianopic and hemianopic hemifield VEPs in either eye. The mean latency of hemianopic hemifield responses was significantly increased in the left eye ($p<0.01$), but not in the right eye [Table 3.3].

b) Follow-up

One or more VEP recording was performed in 8 patients at various time intervals during a follow up period ranging from 4 to 77 months [Table 3.2].

Three of these patients (Cases 7, 10, and 12) had shown VEP abnormalities consistent with a post-chiasmal lesion at the first examination. The responses from the affected hemifields had returned to within normal limits in Case 12, but remained undetectable in Case 7. A latency asymmetry between responses affected and unaffected

homonymous hemifields was still recorded in Case 10 [Fig. 3.3b]. In Case 7 and 12, the amplitude of the half- field VEPs appeared to be related to the extent of the hemianopic defect: responses were unchanged when the corresponding visual field defect showed no improvement (Case 7) [Fig.3.2b], but reappeared when partial recovery of the visual field defect was detected (Case 12).

Of the remaining five patients, Case 9 developed an amplitude asymmetry between hemifield responses from the right eye in the expected direction according to the original field defect which, however, had recovered clinically in both eyes by the time the follow up VEP was recorded. In Cases 2 and 8 the latency of the left eye right half-field response had returned to within normal limits. Cases 3 and 11 showed no change in comparison with the first recording.

In Cases 6 and 15 VEPs were recorded at 4 and 5 months, respectively, from the onset of the visual symptoms, when the homonymous field defect had fully recovered. They showed delayed responses from both eyes consistent with bilateral optic neuropathy but no evidence of homonymous hemifield abnormalities.

No specific relationship was found between the changes of the VEPs at follow up and the location of the lesions in the post-chiasmal pathways.

3.4.4 Case histories

Case 5. A 42 year-old man known to have had symptoms of MS since the age of 25 presented with blurred vision in both eyes. Two weeks following the onset of this symptom, Goldmann perimetry revealed a complete, macular splitting, right homonymous hemianopia. MRI showed a discrete lesion in the region of the left optic tract/LGN and multiple periventricular and discrete white matter lesions. The right hemifield VEP was absent in the left eye and showed a significantly increased latency (18 ms) as compared to the left half-field response in the right eye.

Three months later Goldmann fields were within normal limits. One year later, the lesion responsible was still visible on MRI but much smaller.

Case 7. A 38 year-old woman known to have MS noticed "gaps" in her left field of vision. A few days later she developed a left hemiparesis, while the visual loss progressed over a further week. Three weeks following the onset of visual symptoms Goldmann perimetry revealed a macular splitting left homonymous hemianopia. There was also a left hemiparesis, emotional lability and impaired memory.

CT showed a large low density lesion, exerting moderate mass effect and involving the whole of the right internal capsule. On MRI a very large lesion was confirmed

in the region of the right lentiform nucleus; several small foci of gadolinium enhancement were observed within it in an enhanced scan carried out in the same session. Non-enhancing lesions in the white matter of the left parietal and both temporal lobes were also present. At this time, VEPs were absent from the left homonymous hemifields, but normal from the right homonymous hemifields [Fig.3.2a].

Four months later there was no change in the field defect nor in the VEPs. On MRI, however, the presumed causative lesion was much smaller [Fig. 3.2b]. After six months there was still no change in the field defect.

Case 12. A 29 year-old man suddenly noticed impaired vision to his left. A week later Goldmann perimetry revealed a macular splitting left homonymous hemianopia. VEPs were absent from the left homonymous hemifields, but normal from the right homonymous hemifields. CT showed a low density lesion in the right posterior parietal and occipital regions with moderate mass effect. MRI confirmed a large right occipito-parietal lesion extending from the cerebral grey matter to the occipital horn of the lateral ventricle. Other lesions were present in the cerebral white matter and in the brain stem.

The subjective visual disturbance resolved in six weeks. At eight weeks, however, a lower quadrantic defect remained and even at 18 months a partial left lower

homonymous quadrantic defect was detected to I4e, with marked statokinetic dissociation to III4e. After 11 months follow up, VEPs had returned to normal.

Case 13. A 27 year-old woman noticed shimmering in her left field of vision, of abrupt onset becoming more intense over 15 minutes and subsiding after one hour. Six days later this symptom recurred and on this occasion she noticed partial but persistent loss of vision to her left. Two weeks after the initial episode, Goldmann perimetry revealed an incomplete left lower quadrantic field defect using targets I2e and I4e. CT revealed a circumscribed subcortical lesion in the right occipital region. MRI showed multiple lesions in the deep white matter of both cerebral hemispheres, the largest of which occupied the right occipital region. VEPs were normal.

Twelve weeks later the field defect had resolved totally and on MRI the right occipital lesion was smaller.

Case 14. At the age of 17 this patient had an acute brainstem disturbance and bilateral optic neuritis. He made a good recovery from the former, but the visual acuity in the left eye remained at counting fingers with a dense central scotoma. During the following 10 years he had a number of further clinical episodes of MS and at the age of 37 he developed a progressive dominant hemisphere syndrome characterised by seizures, memory impairment, difficulty

with word finding and writing. In addition, he noticed that his vision was worse. CT revealed a low density lesion in the left temporoparietal region, showing ring enhancement. In the right eye Goldmann perimetry pointed out a complete hemianopia to I4e and statokinetic dissociation to II4e and III4e throughout the right hemifield. MRI showed an extensive abnormality in the white matter of the left temporal, parietal and occipital lobes. VEPs were normal from the right eye [Fig.3.4].

Four months later the field defect had recovered. Follow up MRI showed a little reduction of the lesion, which did not enhance with Gadolinium-DTPA although previously it had shown contrast enhancement on CT.

3.5 DISCUSSION

In this study it was proposed to address the question why homonymous hemianopic defects are rare in MS despite the high incidence of lesions in the postchiasmal pathways documented at autopsy or on MRI. To this purpose, the morphological and electrophysiological features of symptomatic retrochiasmal lesions were examined in a group of 15 patients with MS.

A postchiasmal abnormality was identified on MRI in all but one patient on the side contralateral to the homonymous hemianopic defect. The most striking feature of these abnormalities was their large size, in fact they were

also detected on 7/11 CT studies. Eight lesions were placed in the optic tract, lateral geniculate nucleus or posterior limb of the internal capsule, whereas 5 occupied the optic radiations. Size and location of the lesions suggest that a large number of postchiasmal fibres was likely to have been involved in every case. The size of the lesions probably accounts for the association of the homonymous hemianopic defect with hemiparesis (4 cases) or dysphasia (one case), deficits which are unusual in MS. At the time of the homonymous field defect, contrast enhancement was detected in 3/7 CT studies and in the one MRI investigation in which Gadolinium-DTPA was used; at follow up, decrease in lesion size was noted in 5/5 cases, 3 of whom showed also a total recovery of the visual field defect. Leakage of contrast agent is indicative of damage to the BBB and inflammation within MS lesions (Hawkins et al., 1990), while shrinkage of MRI abnormalities, which has been reported in MS, is usually attributed to partial resolution of oedema within the lesions (Kermode et al., 1990b). Thus, at the time of the homonymous field defect the postchiasmal lesions of the present study probably contained a certain amount of inflammation and oedema which then resolved producing a recovery of the visual deficit. This phenomenon may explain the good prognosis of the homonymous field defects (13/15 cases), and such clinical evolution can partly account for the rarity of homonymous field defects in MS reported in

previous investigations (Traquair, 1925; Chamlin and Davidoff, 1954; Boldt et al., 1963; Kurtzke et al., 1968; Patterson and Heron, 1980; Rosenblatt et al., 1987).

There was a low incidence of abnormalities of hemifield VEPs consistent with a postchiasmal lesion (38.5% of cases). Various factors can explain this result. First, the coexistence of optic neuropathy, which can mask alterations of the VEP waveform due to retrochiasmal pathology (6 cases in this study). Furthermore, in the normal population there is a large intra-individual interhemispheric variability in the exposure of the primary visual cortex and, in particular, the macular area on the convexity of the occipital pole (Polyak, 1957; Brindley, 1972; Stensaas et al., 1974). This affects the amplitude of the P100 evoked from monocular heteronymous hemifields, with the consequence that the limits of normal amplitude asymmetry must be wide. Thus, partial homonymous hemianopic defects are not always detectable, as they produce a degree of amplitude asymmetry which may not be beyond normal limits. The interaction between the "premorbid" amplitude asymmetry and the side of the pathology is also important: the amplitude asymmetry can be either obscured or enhanced depending on whether these factors "operate in the opposite or the same direction" (Blumhardt, 1987). Another factor is that upper and lower quadrants of the visual field contribute to differing extents in the generation of the pattern reversal VEP. In a series of 50 normal subjects,

Blumhardt and Halliday (1979) noticed that the P100 recorded from the lower quadrants was usually larger than that evoked from the upper quadrants. Thus, the likelihood of detecting a significant amplitude asymmetry of hemifield VEPs depends on whether defects are mainly located in upper or lower quadrants. Finally, only defects affecting the central part of the visual fields are likely to cause significant abnormalities of hemifield VEPs for the following reason. In the visual cortex, the central region of the visual field is more strongly represented than the peripheral area (Brindley, 1973; Reivich et al., 1981). During the recording of pattern reversal responses with standard methods only the central 0-16° of the visual field were stimulated, and a large proportion of the response (particularly the P100) comes from stimulation of the central 0-6° (Blumhardt et al., 1989). Consequently, defects mainly affecting the peripheral visual fields are likely to cause only minor alterations of the VEP waveform, which would not be sufficient to put it beyond normal limits.

In only two cases of this study was the latency of responses from hemianopic hemifields increased. However, the mean latency difference between responses from hemianopic and non-hemianopic hemifields was 10 ms in the left eye and 9 ms in the right eye, which reached the 5% significance level in the latter but not in the former. The low incidence of delayed responses from defective

hemifields is in agreement with previous findings of postchiasmal lesions of either demyelinating or non-demyelinating origin (Onofrj et al., 1982; Celesia et al., 1983; Blumhardt et al., 1982b). All patients in the present series had homonymous hemianopic defects, which suggest block of conduction in a certain number of fibres subserving the affected hemifields. Thus, one might expect that responses from these hemifields to show a reduced amplitude rather than an increased latency. On the other hand, the rarity of heteronymous hemifield latency asymmetries generally reported in MS is surprising, taking into account the frequent presence of demyelinating lesions in the postchiasmal pathways documented at autopsy (Lehoczky, 1954; Brownell and Hughes, 1962). One explanation may be that in the postchiasmal pathways the fibres subserving two homonymous halves of the visual field are dispersed in a progressively larger volume from the chiasm to the optic radiations. Thus, whereas a wide region of oedema may block conduction in a large proportion of fibres, a small plaque of demyelination within the oedematous area may affect an insufficient number of fibres to cause detectable delays of hemifield VEPs. In this respect, it is of interest that in the present series 4/5 patients with a significant latency asymmetry between monocular hemifield responses showed on MRI a lesion in the region of the optic tract and LGN, where fibres are concentrated in a relatively small volume.

Full field VEPs are of limited usefulness in the assessment of retrochiasmal pathology. In this circumstance, the full field response should show an asymmetry which has the same direction on stimulation of either eye ("uncrossed", Halliday, 1982c). A fairly large degree of uncrossed asymmetry, however, occurs in the normal population, mainly due to the anatomical factors described above. Thus, only very marked asymmetries can be considered suggestive of postchiasmal pathology, whereas more limited asymmetries, like those produced by partial homonymous hemianopic defects, are of difficult interpretation unless hemifield responses are evaluated (Blumhardt, 1987).

The rarity of clinical evidence of postchiasmal as compared to prechiasmal lesions could be due to differences in the anatomy of different parts of the visual system and their relationship to the lesions. In this respect, three factors should be taken into consideration. First, the proportion of nerve fibres damaged by a lesion of a certain size. In the optic nerve, the fibres are concentrated in a relatively small volume whereas in the optic radiations they occupy a wider area, more so posteriorly. Thus, a lesion of a given size may affect most of the fibres in the optic nerve, but a much smaller proportion of fibres in the optic radiations. The orientation of the lesion with respect to the fibres may also be important in determining the likelihood of conduction block (which is mainly responsible for the acute clinical deficit), as the more inter-

nodes which are damaged the higher is likely to be the risk. Since MS lesions tend to be oriented along venules and not fibre tracts, a lesion of given size may have relatively little effect posteriorly where venules follow a curvilinear course but a greater effect in the optic nerve where venules are in parallel with the nerve fibres. Finally, oedema may have a different effect at different sites. In the optic nerve, fibrous septa limit the possibility of expansion (though swelling of the nerve can occur), with the consequence that the pressure associated with oedema is more concentrated on the nerve fibres. Conversely, in the cerebral hemispheres oedema can spread widely around the fibres, reducing the pressure on the latter. A similar argument could be applied concerning the diffusion of cytokines released during inflammation but, at present, little is known about their effect on nerve conduction.

In conclusion, it has been demonstrated that in MS homonymous hemifield defects are usually associated with the presence of particularly large MRI abnormalities in the optic radiations. Smaller areas of increased signal are located preferentially in the optic tract, lateral geniculate nucleus or posterior limb of the internal capsule. Even amongst these cases, significant asymmetries of amplitude and/or latency of hemifield VEPs are relatively rare. Con-

sequently, VEPs are of much less value in detecting this type of pathology compared with lesions in the anterior visual pathways.

TABLE 3.1: VISUAL FIELDS AND LOCATION OF THE POST-CHIASMAL LESION

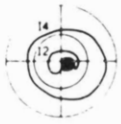
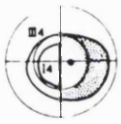
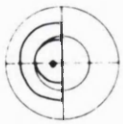
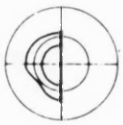
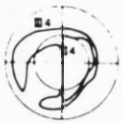
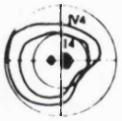
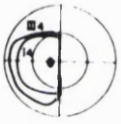
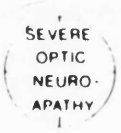
Case	Goldmann perimetry: First examination Left	Goldmann perimetry: First examination Right	Follow-up	MRI lesion
1 M 40			Full recovery within 4 weeks	Not performed
2 F 33			Full recovery within 8 weeks	Left LGN
3 M 40			Partial recovery at 9 months	Left OT and LGN
4 F 50			Full recovery within 6 months	Right OT and LGN
5 M 41			Full recovery within 12 weeks	Left OT and LGN
6 M 31			Full recovery within 16 weeks	Right OT
7 F 38			No change at 6 months	Right OT*
8 F 23			Full recovery within 12 weeks	Left IC (posterior limb)

Table 3.1 continued /

TABLE 3.1 continued

Case	Goldmann perimetry: First examination Left	Goldmann perimetry: First examination Right	Follow-up	MRI lesion
9 F 24			Full recovery within 12 weeks	Left IC (posterior limb)
10 M 32			Full recovery within 8 weeks	Left OR
11 F 40			No change at 7 years	Left OR
12 M 30			Partial recovery at 18 months	Right OR
13 F 20			Full recovery within 12 months	Right OR
14 M 37			Full recovery within 4 months	Left OR
15 F 33			Full recovery within 12 weeks	Left OR

Legend:

LGN = lateral geniculate nucleus
OT = optic tract
IC = internal capsule
OR = optic radiations
* = Gd-DTPA enhancement

TABLE 3.2: VEP MEASUREMENTS

First recording

Case	Homonymous hemianopia	Left eye				Right eye			
		LHF		RHF		LHF		RHF	
		μV	ms	μV	ms	μV	ms	μV	ms
1	right	4.0	104	abs	abs	2.5	104	abs	abs
2	right	4.4	100	6.6	**115**	5.0	101	9.2	108
3	right	4.0	100	2.9	99	2.2	96	3.1	94
4	left	abs	abs	abs	abs	abs	abs	abs	abs
5	right	2.0	122	abs	abs	2.0	123	5.0	141
6	right	NR	NR	NR	NR	NR	NR	NR	NR
7	left	abs	abs	5.2	111	abs	abs	3.7	114
8	right	4.3	104	5.9	**116**	5.3	106	3.5	114
9	right	3.0	124	5.0	124	4.0	113	5.0	125
10	right	5.1	115	2.6	146	7.0	116	2.9	134
11	right	7.0	105	**3.0**	113	9.0	107	5.0	116
12	left	abs	abs	4.0	104	abs	abs	4.0	102
13	left	2.3	111	1.6	111	3.2	112	4.9	114
14	right	abs	abs	abs	abs	5.0	96	3.4	104
15	right	NR	NR	NR	NR	NR	NR	NR	NR

Follow up

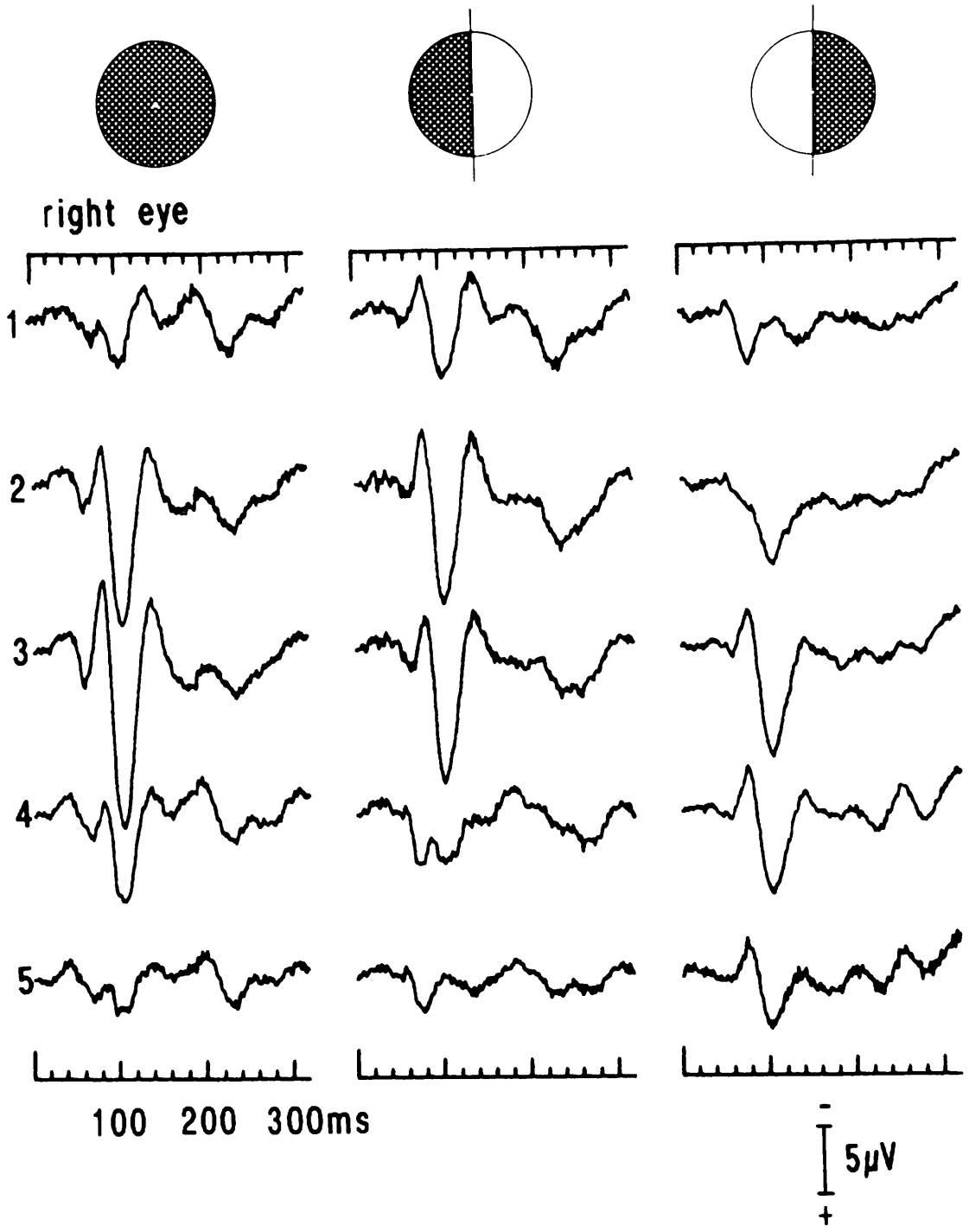
Case	Duration (months)								
2	4	5.8	99	8.8	110	6.8	106	7.1	111
3	6	3.5	99	1.9	95	4.2	105	2.5	104
6	4	2.6	135	4.0	135	2.9	123	2.0	135
7	4	abs	abs	4.7	110	abs	abs	7.3	110
8	16	8.5	101	11.2	106	9.1	103	9.5	108
9	4	3.4	123	4.8	123	7.0	116	**1.6**	123
10	8	5.5	115	7.3	131	6.6	118	3.3	129
11	77	7.2	110	**1.4**	115	5.1	113	2.5	119
12	11	4.9	110	4.6	109	5.0	113	4.6	109
15	5	7.0	143	6.6	141	2.9	111	2.6	120

Legend: LHF = left half field; RHF = right half field; abs = absent; abnormal values underlined; underlined and bold = significant monocular; interfield asymmetry; NR = not recorded.

TABLE 3.3: COMPARISON OF THE MEAN±SD AMPLITUDE (μV) AND LATENCY (ms) OF THE P100 BETWEEN HEMIANOPIC AND NON-HEMIANOPIC HEMIFIELD VEPs

	Left eye (N=7)		Right eye (N=9)	
	μV	ms	μV	ms
Hemianopic hemifields	4.0±1.8	118±14.5	4.5±2.0	117±14.7
Non-hemianopic hemifields	4.2±1.7	108±8.8	4.9±2.2	108±9.2
t	0.2	2.1	0.5	4.1
p	NS	NS	NS	<0.01

Fig. 3.1 Normal pattern reversal EPs to a 0-16° full and half field chequerboard stimulus (28 year-old male). The full field response consists of a triphasic negative-positive-negative complex, which shows a fairly symmetric distribution across the scalp 5 cm above the inion. The positive peak of this complex (P100) displays the largest amplitude on the midline. On hemifield stimulation, P100 and preceding and following negative potentials are recorded on the midline and at scalp electrodes ipsilateral to the stimulated half-field, while a smaller complex of opposite polarity is recorded on the contralateral side.



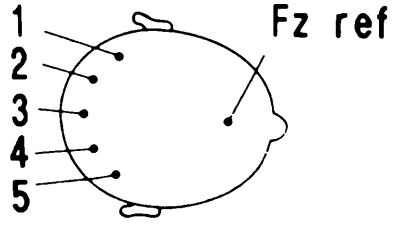


Fig.3.1

Fig 3.2a **Case 7** (38 year-old female). Top: full and hemifield VEPs. On full and left- half field stimulation, the P100 is not identifiable at the left sided electrodes in either eye. Note the similarity of the response from the full and right half field. Bottom left: Goldmann perimetry, showing a macular splitting left homonymous hemianopia. Bottom right: brain MRI, axial view. A very large area of increased signal is visible in the region of the right optic tract at temporo-parietal level.

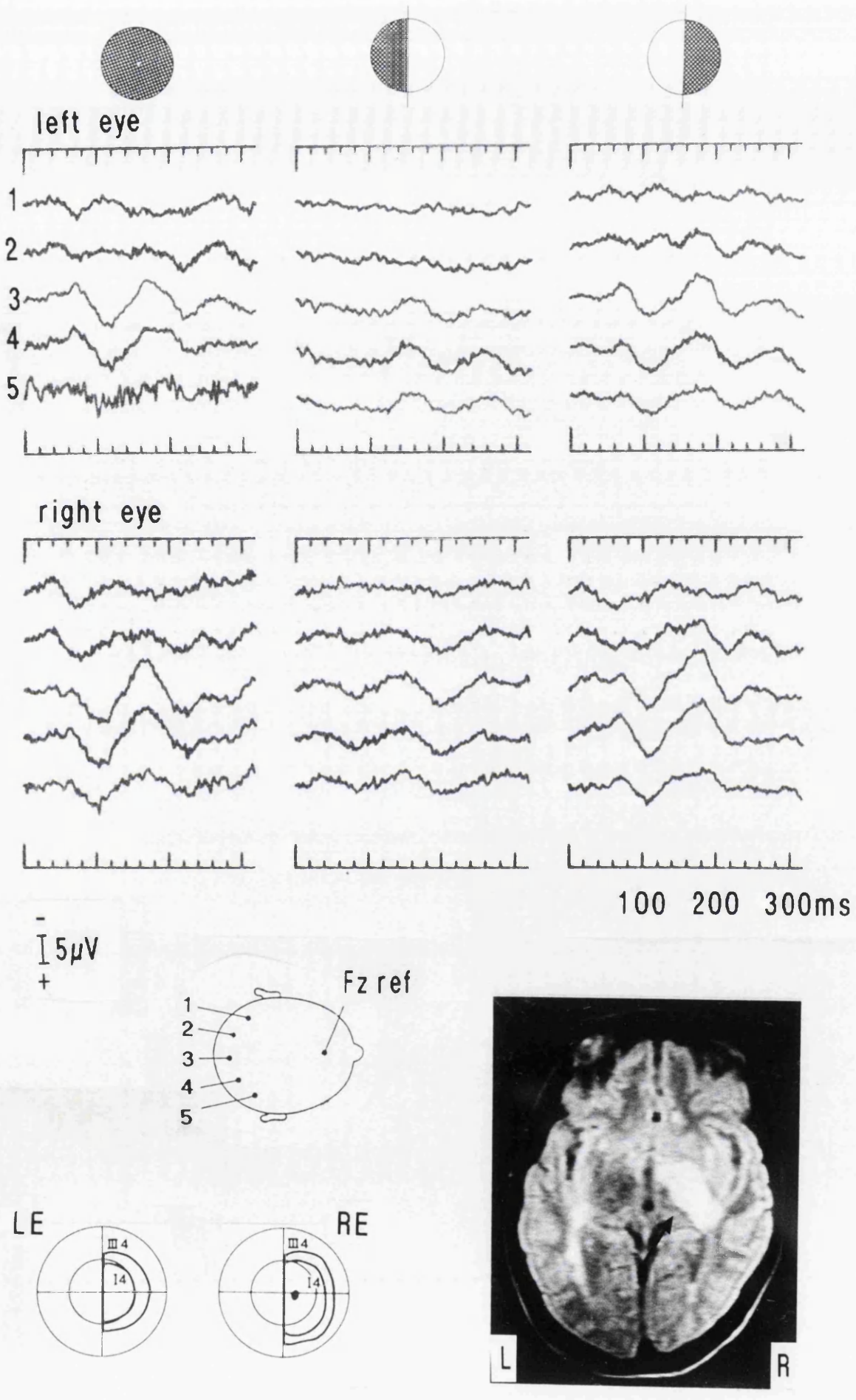

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Fig.3.2a

Fig. 3.2b Case 7, follow-up after four months, persistent total left homonymous hemianopia. Top: full and half field VEPs not showing any significant change since the first recording. Bottom: brain MRI, axial view. The area of increased signal in the region of the right optic tract displays a marked reduction as compared to the first scan.

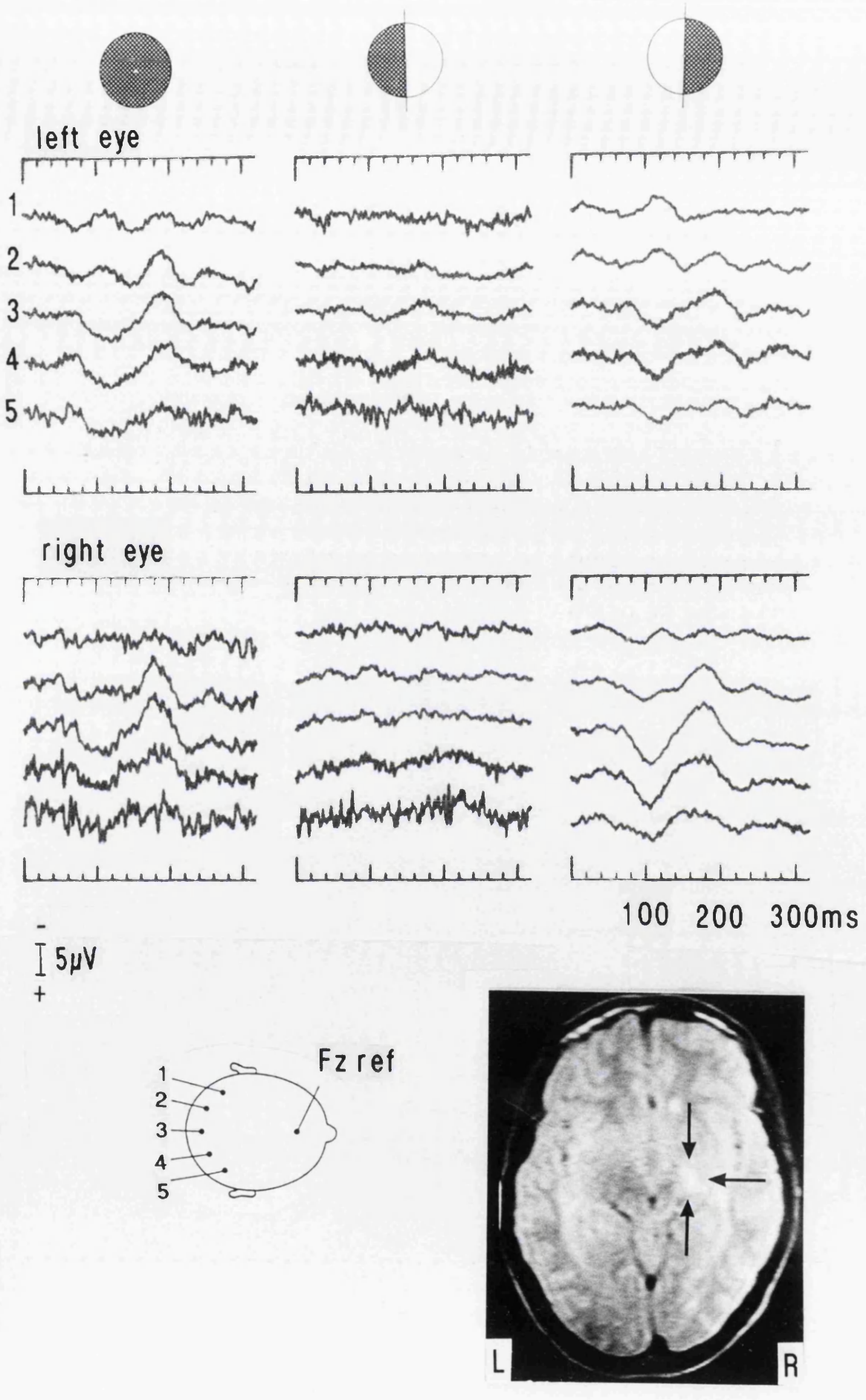

Fig.3.2b

Fig. 3.3a **Case 10** (31 year-old male). Top: full and hemifield VEPs. On full field stimulation, the P100 is not identifiable at the right sided channels in either eye. On half field stimulation, the right homonymous hemifield responses are attenuated and significantly delayed as compared to the left homonymous hemifield components. Bottom left: Goldmann perimetry, showing right homonymous scotomata to I4e target. Bottom right: brain MRI, axial view. An area of increased signal is visible in the left occipital lobe occupying the optic radiations.

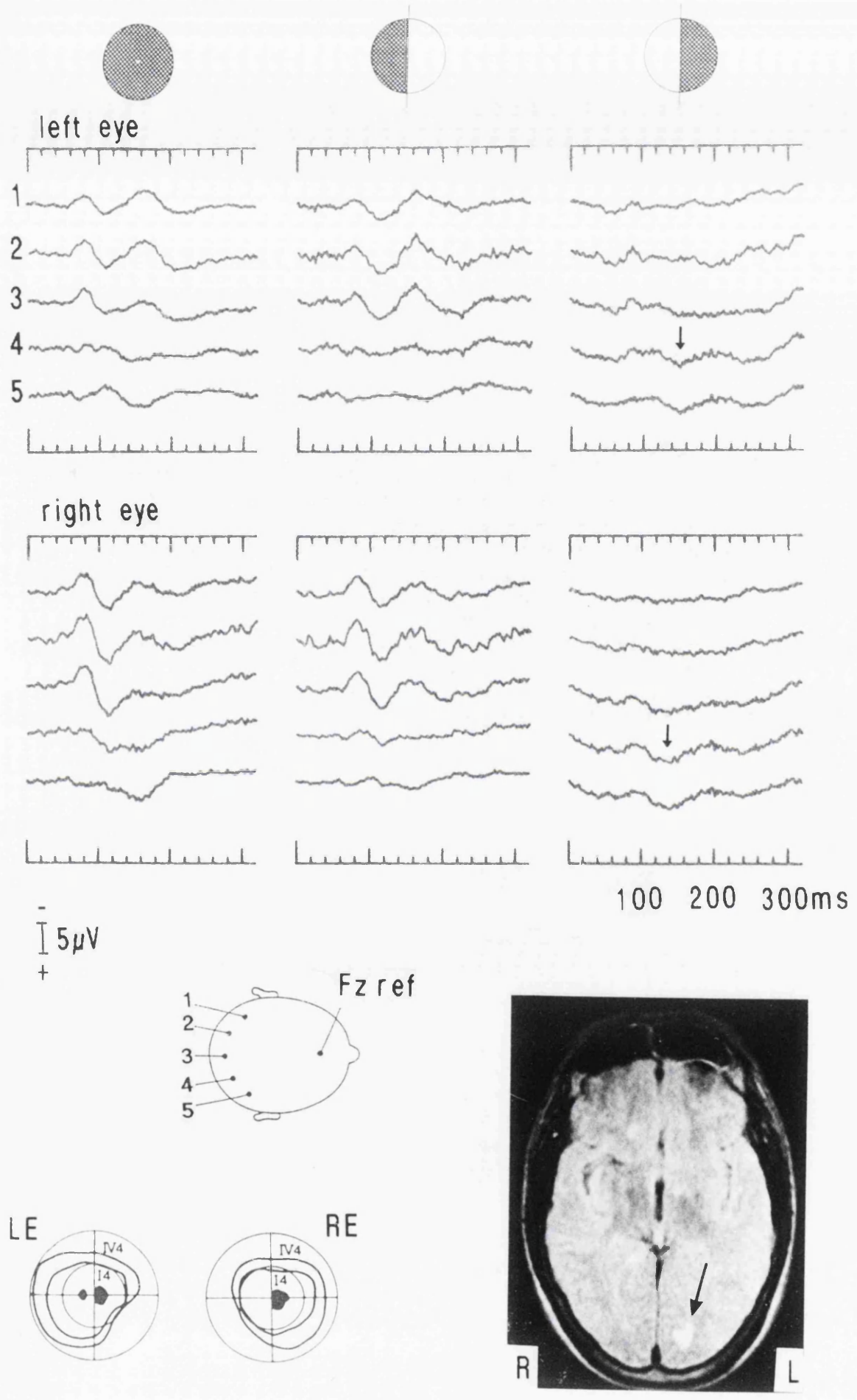
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Fig.3.3a

Fig. 3.3b **Case 10**, follow-up after eight months, full recovery of the visual field defect. Full and hemifield VEPs. The full field components show a fairly symmetric distribution across the scalp. The amplitude of the right homonymous half-field responses has increased since the first recording, but their latency is still significantly delayed as compared to that of the left homonymous hemifield components. There was no follow up MRI.

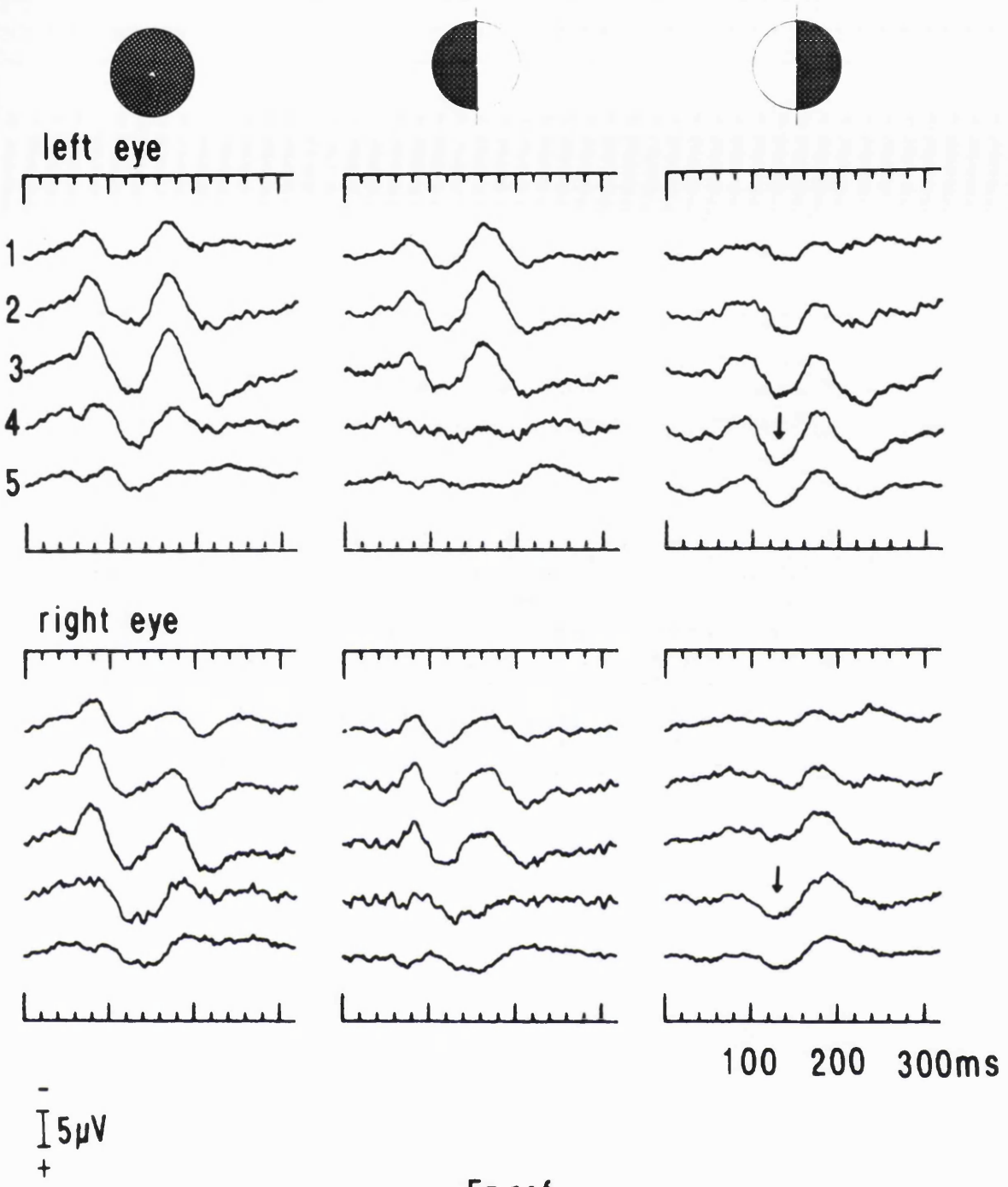
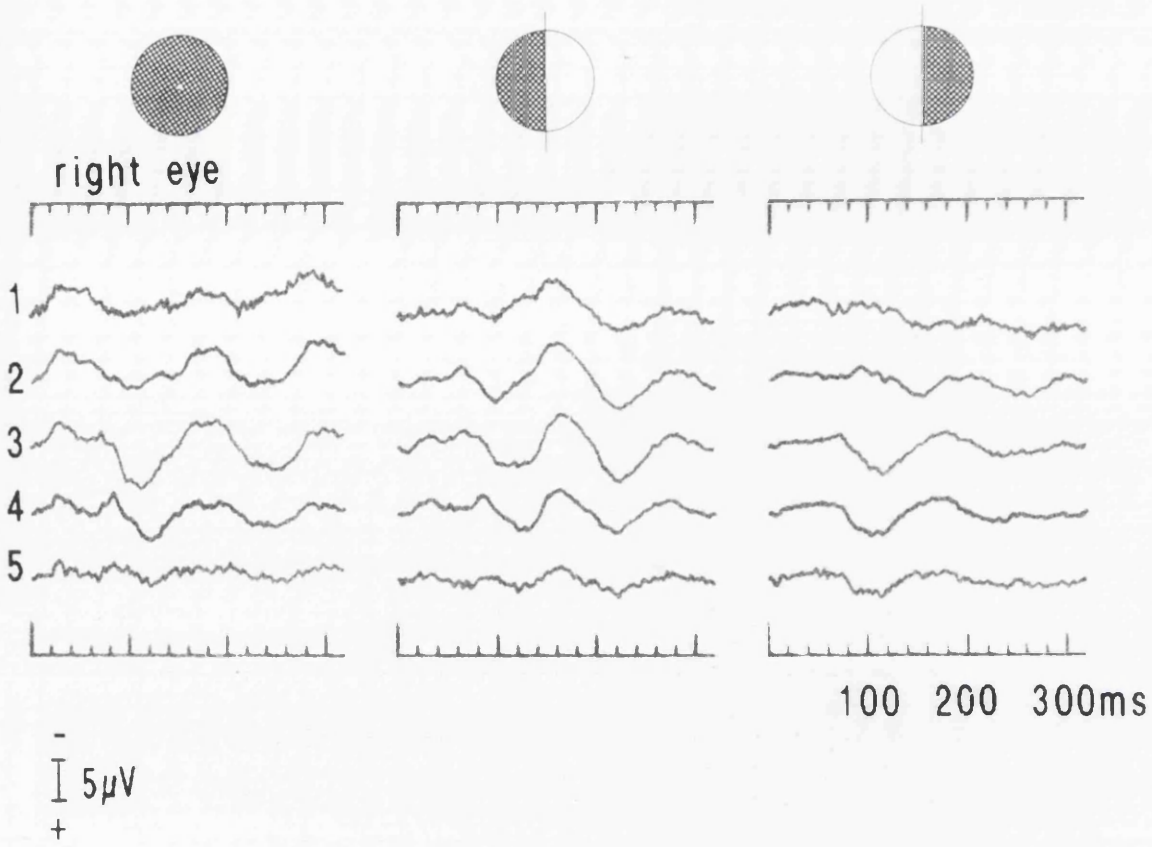


Fig.3.3b

Fig. 3.4 **Case 14** (37 year-old male). Top: normal full and hemifield VEPs recorded from the right eye. The left eye responses are not shown since they were absent, due to severe left optic neuropathy. Bottom left: Goldmann perimetry of the right eye showing macular splitting right hemianopia to I4e target and statokinetic dissociation to larger targets (shaded area) in the right hemifield. Bottom right: brain MRI, axial views. A very large lesion is visible in the left hemisphere, extending from the temporal (left) to the parietal and occipital lobes (right).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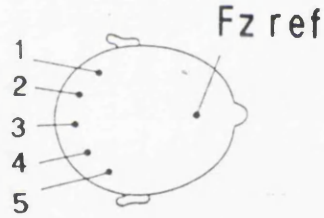
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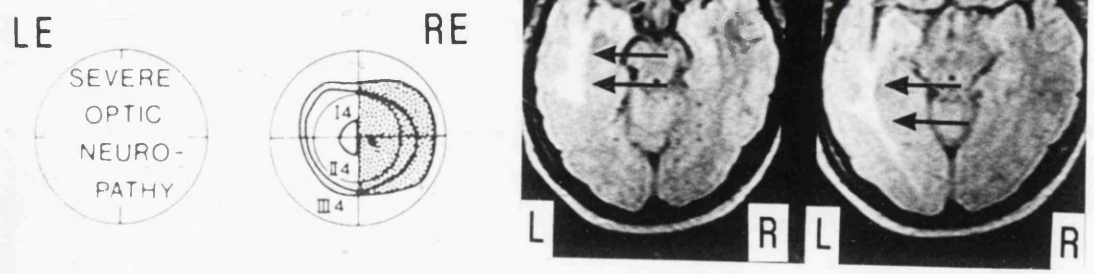
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Fig. 3.4

CHAPTER

4

COGNITIVE EVENT-RELATED POTENTIALS IN PATIENTS WITH CLINICALLY ISOLATED OPTIC NEURITIS

4.1 INTRODUCTION

It has long been known that cognitive deficits occur in multiple sclerosis (Charcot, 1877, Gowers, 1892-1893). However, only recently has the use of psychometric investigation made possible a systematic assessment of such disturbances. An impaired ability to acquire and retain verbal and visuo-spatial information has been detected in patients with a diagnosis of definite MS (Beatty et al., 1988; Rao, 1986) and a slowing in the processing of new information has also been reported (Litvan et al., 1988; Beatty et al., 1989). Tasks requiring sustained attention may be impaired (Elsass and Zeeberg, 1983; Jennekens-Schinkel et al., 1988a and b). Language skills and memory for remote events seem to be affected only in cases with general cognitive decline, assessed for example by the Mini Mental State Examination (Beatty et al., 1988). A certain degree of cognitive impairment has also been detected in patients with probable or suspected MS. Lyon-Caen et al. (1986) found memory deficits in 8/10 patients with probable MS and in 6/9 patients with clinically isolated optic neuritis. Callanan et al. (1989) studied 48 patients with isolated optic neuritis, a brainstem or a spinal cord syndrome. The IQ and visual and auditory attention were impaired in these patients as compared to controls. Attempts have been made to correlate the degree of cognitive deterioration with the extent of brain pathology seen on MRI. The severity of cog-

nitive deficits has been found to be correlated with the size and number of white matter lesions (Franklin et al., 1988; Callanan et al., 1989), the degree of cerebral atrophy and atrophy of the corpus callosum (Huber et al., 1987; Rao et al., 1989).

In electrophysiological investigation, the act of attending, discerning and responding to stimuli is associated with the generation of brain potentials. In the 3-stimulus "oddball" paradigm, subjects are required to discriminate among 3 stimuli of a single modality (usually auditory or visual), which differ along a single dimension (i.e. pitch), and are instructed to press a button when they recognise a pre-defined target stimulus. This occurs relatively infrequently and is randomly mixed with infrequent and frequent non-target stimuli. Correct identification of infrequent stimuli is associated with the generation of a large positive potential peaking at about 300 ms (P300 or P3), which is best recorded from the central and parietal regions of the scalp. In the auditory modality of the test, P3 is preceded by negative and positive potentials (N1, P2 and N2) which show largest amplitude at frontal and central scalp locations.

Abnormalities of the cognitive ERPs have been assessed in patients with definite MS. Newton et al. (1989) recorded abnormal responses in 13/23 patients, five of whom had no evidence of memory deficits or intellectual deterioration on neuropsychological investigation. Reaction time measures

were increased in 11 patients, two of whom had normal ERP waveforms. Cases with abnormal ERPs had a significantly longer disease duration, a higher degree of neurological disability, measured by the expanded disability status scale, and more extensive white matter lesions on brain MRI than patients with normal responses. Thus, it was concluded that neurophysiological evidence of cognitive decline was related to the degree of dissemination of the disease, as suggested by MRI and neurological parameters. Honig et al. (1992) confirmed these observation in a study of 31 definite MS cases. The amplitude of the P3 component decreased and its latency increased with the extent of abnormalities on brain MRI, the degree of cognitive impairment, measured by the Kurtzke cerebral function scale, and the duration of the disease. Giesser et al. (1992) studied 12 MS patients, six of whom were demented. The N1, P2 and P3 latency and the N1-P3 latency interval were significantly prolonged in demented as compared to non demented cases. Since patients in both groups (11/12) had brain MRI lesions, the authors concluded that the abnormal ERPs were related to cognitive impairment but not to the presence of disseminated brain MRI lesions, although no estimate was made of the volume of the latter.

In the present study, neuropsychological investigations, recording of cognitive ERPs and brain MRI were performed in 21 patients with a clinically isolated unilateral optic neuritis. In the U.K. it has been estimated that 75%

of patients presenting with clinically isolated optic neuritis eventually develop MS within 15 years following the attack (Francis et al. 1987); it was therefore assumed that most of the cases included in the present investigation were in the early stages of MS. The purpose of the study was to assess the incidence of ERP abnormalities and investigate whether neurophysiological and neuropsychological deficits were related with the dissemination of demyelination in the cerebral tissue, as suggested by MRI.

4.2 CASE MATERIAL

4.2.1 Patients

The patient group consisted of 21 subjects, 11 females and 10 males, aged 19 to 44 years (mean 31±8 years), presenting with a clinically isolated unilateral optic neuritis, which was diagnosed according to standard clinical criteria (Compston et al. 1978). The time elapsed from onset of visual blurring ranged from seven to 35 days (mean 15±8 days). At the time of the present study, the visual acuity had returned to normal (6/9 or better on Snellen Chart) in 11 affected eyes. Ophthalmological and investigative examinations did not show evidence of intra-ocular or retinal pathology; the general and neurological examinations were normal and the history did not suggest the oc-

currence of any significant neurological, cognitive or affective disturbance. None of the patients was on corticosteroid treatment.

4.2.2.Controls

a) Psychometry

The control data were obtained from 36 healthy subjects, matched with the patients for age range, years of education and premorbid IQ.

b) ERPs and reaction time

The control data were derived from 21 healthy subjects, age and sex-matched with the patients.

4.3 METHODS

4.3.1 Psychometric examination

Twenty patients underwent computerised psychometric testing on the same day as MRI and electrophysiological investigations. The tests, designed to detect deficits in attention and speed of intellectual functioning, included the symbol-digit modality test (SDMT) (Smith 1968) and the paced serial addition test (Gronwall and Sampson 1974), in

both visual (PVSAT) and auditory (PASAT) modalities (4 and 2 second stimuli in each test). SDMT and PVSAT were performed using both eyes.

4.3.2 Event-related potentials

Patients were required to perform an auditory 3-stimulus target detection task. In each run, three tones of different pitch were delivered through headphones: a 2 kHz (P=0.15), a 1 kHz (P=0.15) and a 1.5 kHz (P=0.70) tone, which were designated target, infrequent non-target and frequent non-target stimuli, respectively. The patients were asked to press a hand-held button as soon as possible after hearing the target tone. The tones were 50 ms in duration with rise and fall times of 10 ms and the inter-stimulus interval was 1.2 s. Stimuli were presented in a pseudo-random order from predetermined tables, until either a total of 25 artefact-free trials to target stimuli had been averaged or a total of 200 stimuli had been delivered. Two such runs were presented and, when an excess of eye movement artefacts reduced the number of accepted target trials below 50 (see below), an additional run was given. A practice run was performed before recording, in order to ensure that subjects responded correctly and were able to distinguish between the tones.

Three silver/silver chloride disc recording electrodes were placed on the scalp at Fz, Cz and Pz (International 10-20 System) and referred to linked electrodes fixed to the earlobes. Eye movements were monitored by a recording electrode located on the outer canthus of the right eye with reference to a second electrode on the glabella [Fig. 4.1]. Trials were rejected when the eye movement channel recorded potential changes exceeding 100 μV during the recording epoch.

The amplifier high frequency cut-off was less than 3 dB down at 5 kHz and the time constant was 3 s. The recording epoch was 960 ms, beginning 120 ms before presentation of the stimulus, with a sampling interval of 3.75 ms per ordinate. Only sweeps associated with correct performance were included in average.

Averaged waveforms for correctly identified target, infrequent non-target and frequent non-target stimuli were filtered digitally with a high frequency cut-off at 30 Hz before cursoring or plotting. Components were identified according to their polarity, latency and distribution over the scalp. Amplitude and latency were measured in averaged waveforms to both target and infrequent non-target stimuli. N1 was identified as a negative potential in the latency range of 75 to 145 ms, P2 and N2 were recognised as the most pronounced positive and negative component, respectively, after N1 but before P3 which, in turn, was defined as the most prominent positive response occurring after 270

ms [Fig. 4.1]. P3 was identifiable in all the control subjects; N1, however, was not identifiable in one subject at Pz during presentation of target stimuli. In the target condition, P2 and N2 were not detected in one subject at any scalp location and in another at Pz. In the infrequent non-target condition, P2 and N2 were absent in one subject at all scalp locations (see Fig. 4.1), at Cz and Pz in another and at Pz in a third. In addition, in both target and non-target conditions P2 and N2 were doubtfully present at one or more scalp locations in about 20% of subjects, in whom these components appeared as inflections on the descending limb of N1. Such features are in agreement with the common finding that in the normal population N1 is not always recorded at Pz and that P2 and N2 may be absent or very small at one or more scalp locations. It was therefore decided to analyse the amplitude and latency of the N1 and P3 only.

The amplitude of N1 was measured on the descending limb to P2 or the point of inflection corresponding to P2. The amplitude of P3 was measured from N2 or the point of inflection corresponding to N2. When P2 or N2 were not identifiable, the peak-to-peak measures N1-P2 and N2-P3 were not made. In the patient group, the absence of N1 at Pz and of P2 and/or N2 at Fz, Cz or Pz was not considered abnormal. The amplitude of N1 and P3 were not measured with respect to the mean activity occurring during the pre-stimulus baseline period, as is often done, for the follow-

ing reasons. The amplitude of evoked potentials frequently has a skewed distribution. When using the criterion mean ± SD to define normal limits, it is therefore necessary to transform the amplitude into another measurement whose distribution corresponds to a Gaussian curve. Logarithmic transformation usually results in a distribution which is not significantly skewed but requires that all amplitudes have positive sign or, at least, the same sign (in the latter case the absolute value is considered). In the present series, when measured from the pre-stimulus baseline some N1 amplitudes were positive and some P3 amplitudes were negative, due to a drift of the waveform below and above the baseline, respectively. It was therefore decided to measure the amplitude of N1 with respect to P2 and P3 with respect to N2, thereby yielding values which were always of the same sign and could therefore be transformed into the corresponding logarithms. Given the high degree of variability of the ERP waveform in the normal population, a criterion of mean ± 3.0 SD was chosen as the cut-off point between normal and abnormal amplitude or latency values.

The response performance was assessed by the mean reaction time to target stimuli (RT), the within subject variability of reaction time (RTSD) and the percentage of correct responses to target presentation (% hits).

The normal latency limit of ERPs and reaction time measures was defined by the mean + 3.0 SD of the absolute latency of N1, P3, RT and RTSD in the control group. The normal limit of N1-P2 and N2-P3 amplitudes was defined by the mean - 3.0 SD of $\log_{10}$ amplitude in the control group.

4.3.3. Magnetic Resonance Imaging

The brain was imaged on a Picker 0.5 Tesla superconducting scanner, using a T_2-weighted ($SE_{2000/60}$) sequence. In each subject 24 contiguous slices of 5 mm thickness were obtained throughout in the axial plane. Images were examined separately by two neuro-radiologists blind to neuropsychological and ERP data, who then reached agreement as to the number of lesions in each slice. Abnormalities were defined as areas of increased signal in the cerebral matter. The location of the lesions was not established precisely in relation to specific brain structures. The total lesion area was estimated using an interactive computer-based method which is described in detail elsewhere (Feinstein et al., 1992). In brief, the area in pixels (1 pixel = 3 mm^2) occupied by a single lesion was measured in each of the 24 brain slices obtained in every subject; the individual lesion areas were then summed to give the total lesion area.

4.3.4 Statistical analysis

Comparisons concerning scores on psychometric testing and reaction time measures were made using the Mann-Whitney U test (two tailed probability), in which correction for ties was computed when necessary. The association between brain MRI lesions and ERP abnormalities was determined by the Fisher exact probability test. The variance of ERPs across the 2 subgroups of cases showing a larger or smaller total lesion area (see paragraph 4.4.5 below) was assessed using repeated measures MANOVA, in which presentation of target or non target stimuli and site of recording were considered as within-subject factors. Probabilities were computed for F modified by the Greenhouse and Giesser correction to prevent the acceptance of too many false positive results (Keselman and Rogan 1980). The independent t-test (two tailed probability) was then conducted to identify factors contributing most prominently to the significant effects. The degree of correlation between ERPs, psychometric scores and total lesion area was computed using the Spearman rank correlation test.

4.4 RESULTS

4.4.1 Psychometric findings

On average, patients performed less well than controls in all tests. Mean score differences were significant in PVSAT 2 ($p<0.05$), but were not significant in the remaining tests [Table 4.1].

4.4.2 ERP abnormalities

Twelve out of 21 patients (57.1%) showed ERP abnormalities which involved: N1 latency in two patients, P3 latency in three, N1-P2 amplitude in two and N2-P3 amplitude in six. Abnormal responses were recorded to target stimuli alone in eight patients, to non-target stimuli in three and to both types of stimuli in one.

For target stimuli, N1 latency was increased in Case 14 at Fz, Cz and Pz and in Case 18 at Pz; P3 latency was increased in Case 17 at Cz and Pz. In the same condition, the N2-P3 amplitude was reduced in six patients: in Case 3 at Fz and Cz, in Case 7 at Fz, Cz and Pz, in Cases 8, 17 and 21 at Cz and Pz, and in Case 20 at Fz and Cz. For infrequent non-target stimuli, P3 latency was increased in Cases 2 and 17 at Fz, Cz and Pz and in Case 12 at Cz and Pz; the N1-P2 amplitude was reduced in Case 10 at Pz and N1 was absent in Case 9 at Fz [Table 4.2 and Fig. 4.2].

4.4.3 Response performance

The RT was above normal limits in Case 17 and the RTSD was increased in Cases 12, 17 and 20. The percentage of correct responses to target presentation was above 90% in all but one patient (Case 17), in whom this was reduced to 36.2% [Table 4.2].

The mean RT was not significantly different between the patient and control groups, whereas the RTSD was significantly increased in patients as compared to controls ($p<0.01$) [Table 4.3].

4.4.4 MRI abnormalities

Disseminated areas of increased MRI signal were seen in 14/21 patients (67%) and appeared mainly distributed in parietal and occipital regions. In these 14 patients the total lesion area varied from 22 to 746 pixels (mean 182.7±205.6 pixels) [Table 4.2 and Fig 4.2].

4.4.5 Correlation between ERPs and MRI

ERPs were abnormal in 4/7 cases with normal MRI and in 8/14 cases with disseminated brain lesions. Thus, the association between the presence of MRI and ERP abnormalities was not significant ($p>0.05$, Fisher test) [Figs. 4.3 and 4.4].

In analysing the effect of the total lesion area on ERP components, patients were divided into 2 subgroups: cases with a total lesion area equal to or smaller than 35 pixels (subgroup 1 N=12) and cases with a total lesion area equal to or larger than 93 pixels (subgroup 2 N=9). This subdivision was chosen for the following reasons: it split the total number of patients approximately into half; the smallest lesion area in subgroup 2 was more than twice the largest lesion area in subgroup 1.

In MANOVA, the patient subgroup and site of recording each had a significant effect on N2-P3 amplitude ($F=4.98$ $p=0.039$ and $F=9.37$ $p=0.001$, respectively), whereas there was no effect of stimulus condition (infrequent target/non-target) on N2-P3 amplitude ($F=0.88$ $p>0.05$). The interaction of subgroup by site of recording was significant ($F=4.1$ $p=0.026$), but the interactions of subgroup by condition and subgroup by condition by site of recording were not significant ($F=0.06$ and $F=0.29$, respectively, $p>0.05$). Subgroup had no significant effect on N1 or P3 latency ($F=0.00$ and $F=1.24$, respectively, $p>0.05$), nor on N1-P2 amplitude ($F=2.33$ $p>0.05$). In both target and infrequent non-target conditions, the mean N2-P3 amplitude at Fz, Cz and Pz was numerically smaller in subgroup 2 as compared to subgroup 1. Differences between the 2 subgroups increased from Fz to Pz and reached the 5% significance level for both conditions at Pz only [Table 4.4]. The mean

RT and the RTSD were numerically greater in subgroup 2 as compared to subgroup 1, although differences were not statistically significant [Table 4.5].

In summary, the total lesion area had an effect on the N2-P3 amplitude, which was reduced in patients with more extensive brain MRI abnormalities. This effect varied with the site of recording and was stronger in the posterior (Cz and Pz) than anterior locations [Fig. 4.5]. The total lesion area had no demonstrable effect on response performance.

In cases showing brain MRI abnormalities, the total lesion area was inversely correlated with the N2-P3 amplitude at all scalp locations in the target condition and at Cz and Pz in the non-target condition. Target: Fz $r=-0.61$ $p<0.05$, Cz $r=-0.77$ $p<0.01$, Pz $r=-0.59$ $p<0.05$; non-target: Cz $r=-0.74$ and Pz $r=-0.70$, $p<0.01$. The total lesion area was also inversely correlated with the N1-P2 amplitude at Fz in the non-target condition only, $r=-0.88$ $p<0.001$. The total lesion area was not significantly correlated with the N1-P2 amplitude at any scalp locations following target stimuli or the N1-P2 amplitude at Cz and Pz following non-target stimuli, nor with the N1 or P3 latency in either condition.

4.4.6 Correlation between psychometry and MRI

On average, subgroup 2 performed less well than subgroup 1 in each test. Mean score differences were significant in PASAT 2 ($p<0.05$) and SDMT ($p<0.01$) only [Table 4.6]. In cases showing brain MRI lesions, there was not significant correlation between the total lesion area and the scores on any psychometric tests.

4.4.7 Correlation between psychometry and ERPs

No significant correlation was found between the scores on any psychometric tests and ERP values.

4.5 DISCUSSION

The auditory modality of the 3-stimulus oddball paradigm elicits a complex scalp waveform which includes a number of potentials, chiefly N1, P2, N2 and P3. It was preferred to measure the amplitude and latency of N1 and P3 only, as in the control group these were recorded more consistently than P2 and N2.

ERP abnormalities were detected in 12/21 patients (57.1%), four of whom had normal MRI. Among the 12 patients there were 14 abnormal responses, eight in the target and six in the non-target condition. P3 was found to be abnormal in 10 waveforms: in two the P3 latency was increased,

in six the N2-P3 amplitude was reduced and in two the P3 latency was increased and the N2-P3 amplitude reduced. Thus, a reduced N2-P3 amplitude was the most frequent abnormality of the P3 component, 8/10 responses (80%). N1 was abnormal in four waveforms, in all of which P3 was within normal limits: in one N1 was unidentifiable, in another the N1 latency was increased, in another the N1-P2 amplitude was reduced and the remaining the N1 latency was increased and N1-P2 amplitude reduced. Reaction time measures were prolonged in four patients, all of whom had abnormal ERPs, and the patients as a group showed a larger within-subject variability of the reaction time as compared to the controls.

In the oddball paradigm, the P3 potential is believed to be generated by the act of stimulus evaluation (Pritchard, 1981), although its peak often occurs later than the reaction time. P3 latency is directly related to the difficulty of the task (i.e. the latency increases when stimuli are less easily discriminable) and its amplitude is inversely related to the subjective probability of the target stimulus (i.e. the less expected the target stimulus the larger the amplitude, Donchin, 1981). The N1, P2 and N2 components are probably associated with both sensory and cognitive aspects of the oddball task. Specifically, at least six different brain processes have been indicated as occurring during the latency range of N1. These include activation of the auditory system, the act of selective

auditory attention, stimulus processing and formation of a memory of the stimulus (Näätänen and Picton, 1987). P2 is enhanced by the act of attention (Picton and Hillyard, 1974) and N2 appears to be related to discrimination between stimuli, its amplitude being larger as discrimination becomes more difficult (Fitzgerald and Picton, 1983). Thus, in more than half of the patients in the present study electrophysiological evidence was obtained of cognitive impairment probably related to the ability to discriminate among stimuli, although not sufficient to cause a marked deterioration in response performance.

In the present study BAEPs were not recorded, thus it could be argued that the presence of demyelination in the primary auditory pathways might have produced ERPs of reduced amplitude or increased latency. This seems unlikely for the following reasons. First, the N1 potential, which is believed to be related to both sensory and cognitive aspects of the oddball task, was well defined and of normal latency in all but four patients of the present series; this suggests that the afferent volley did not undergo any marked disruption in the brainstem or at any other subcortical level. Second, the increase in latency of the BAEPs in MS is typically of the order of few milliseconds, whereas the delays of the ERPs are usually much longer. In this study, the latency of N1 was increased by 15 to 34 ms above the normal limit; the latency of P3 was prolonged by between 15 and 157 ms above the normal limit in four cases.

Thus, most of the ERP abnormalities were probably due to brain pathology, although the present data do not allow the exclusion of a contribution from a brainstem lesion.

The incidence of ERP abnormalities (57.1%) is similar to that reported previously (56.5%) in a study of patients with established MS (Newton et al., 1989). The low incidence of increased reaction time measures in the present investigation (19%) as compared to the previous one (48%) is not surprising, since the reaction time depends on the efficiency of motor as well as cognitive skills, the former also being affected by the extent of motor disability in patients with established MS.

The other main finding of the present study was that the extent of brain MRI lesions was related to abnormalities of the ERP waveform and to scores on psychometric tests: the N2-P3 amplitude was reduced and the performance on PASAT 2 and SDMT poorer in the subgroup of patients with a larger lesion area. In addition, in 14 cases showing brain MRI lesions the total lesion area was inversely correlated with the N2-P3 amplitude at all scalp locations for both target and infrequent non-target stimuli and with the N1-P2 amplitude at Fz in the non-target condition only. Using T_2-weighted sequences, areas of altered MRI signal are produced by the increase in density of intracellular and extracellular water which accompanies the development of demyelinating lesions. Thus, the dissemination of demyelination in the cerebral matter, as suggested by MRI,

was associated with an attenuated N2-P3 potential and an impaired performance on tests of auditory attention and speed of information processing. The agreement between MRI and the results of the neurophysiological or neuropsychological investigations is understandable, since the PASAT2 and SDMT reveal deficits of skills which may be relevant to correct performance of an oddball task.

In previous investigations a correlation was found between the extent of brain MRI lesions and the degree of neuropsychological and neurophysiological abnormalities in suspected and definite MS cases. In a series of 48 cases with clinically isolated optic neuritis, a brainstem or a spinal cord syndrome, Callanan et al. (1989) found that the size and number of brain MRI lesions was correlated with the performance in tests of auditory attention and abstracting ability. In the group studied by Newton et al. (1989), patients with abnormal ERPs had a mean total size of brain MRI lesions almost twice that of cases with normal ERPs. Honig et al. (1992) found a significant correlation between decrease of the P3 amplitude or increase of its latency, extent of brain MRI abnormalities and degree of cognitive impairment. These findings support the hypothesis that the dissemination of demyelination in the cerebral white matter may produce disconnection between centres of cognitive functions. The findings of Giesser et al. (1992), however, are in apparent disagreement with this view. In their study of 12 established MS cases, the P3 latency was

increased in demented as compared to non-demented patients, despite the fact that brain MRI lesions were present in the latter as well as in the former group. In that investigation the authors did not measure the total area of the brain MRI lesions; thus, it cannot be ruled out that the subgroup of cases with an increased P3 latency might have had more extensive brain MRI abnormalities than the other subgroup. However, in individual cases the finding of a normal ERP waveform in the presence of brain MRI lesions is not rare. In the present series, six patients showed normal ERPs but brain lesions on MRI; conversely, four patients had abnormal waveforms but no brain MRI lesions. These discrepancies might be explained by the fact that small plaques of demyelination, insufficient to produce ERP abnormalities, may appear on MRI as large areas of altered signal which extend beyond the loss of myelin. Alternatively, other lesions may produce ERP abnormalities without causing detectable alteration of the MRI signal because of their size or location. Furthermore, since in the patients of the present series optic neuritis had occurred within about a month prior to the study, it is possible that other factors associated with the presence of an active demyelinating lesion might have affected the ERP waveform in the absence of structural lesions. Thus, the finding that extensive brain MRI lesions are associated with a deterioration of the ERP waveform may not apply in every single case.

In their investigation, Giesser et al. (1992) found that the P3 latency was inversely correlated with the performance on psychometric tests assessing mainly memory skills, whereas the present study failed to demonstrate any relationship between ERP measures and scores on tests of auditory and visual attention and speed of information processing.

In conclusion, in patients with a clinically isolated optic neuritis of recent onset it is possible to detect abnormalities of the cognitive ERPs. Cognitive impairment, manifested by a deterioration of the ERP waveform and a poorer performance on tests of relevant cognitive functions, is related to the dissemination of demyelination in the cerebral tissue, as suggested by MRI.

TABLE 4.1. MEAN PSYCHOMETRIC SCORES: COMPARISON BETWEEN THE PATIENT AND CONTROL GROUPS

	PASAT 4	PASAT 2	PVSAT 4	PVSAT 2	SDMT
Patients (N=20)	2.8	9.5	2.1	7.6	12.8
Controls (N=36)	2.3	7.9	1.4	4.8	11.8
U	332.5	301.5	333.5	238.0	250.5
p	NS	NS	NS	<0.05	NS

Scores: PASAT and PVSAT = number of errors;
SDMT = milliseconds

TABLE 4.2: LESION AREA, RESPONSE PERFORMANCE AND ERPs

No	Sex	Age	Pixels	RT (ms)	RTSD (ms)	%HITS
1	F	25	34	395	116	100
2	M	32	185	561	94	98
3	M	44	0	431	120	100
4	F	28	34	400	81	100
5	F	25	35	472	133	91
6	M	30	22	369	81	100
7	M	33	231	316	74	94
8	M	37	488	412	95	100
9	F	19	132	464	78	100
10	F	31	35	332	67	100
11	M	41	746	462	120	97
12	F	42	0	569	167	94
13	F	39	0	422	136	97
14	F	19	0	373	111	100
15	M	26	148	322	126	100
16	M	26	0	528	120	96
17	F	43	262	696	274	36
18	M	34	93	551	136	100
19	F	30	0	419	90	96
20	M	21	0	425	143	100
21	M	34	113	461	95	100

continued /

TABLE 4.2 continued

Target

	Fz				Cz				Pz			
No	N1	P3	N1-P2	N2-P3	N1	P3	N1-P2	N2-P3	N1	P3	N1-P2	N2-P3
1	101	338	9	6	98	341	7	14	79	364	15	20
2	83	386	7	3	98	386	8	7	98	371	7	12
3	116	345	8	1	113	353	9	4	124	368	9	15
4	116	341	4	14	120	345	8	19	124	356	9	18
5	86	390	3	9	86	386	9	11	abs	424	3	18
6	101	315	4	11	86	319	6	19	86	353	8	16
7	98	345	5	2	98	349	4	3	113	349	4	5
8	90	315	9	2	83	341	12	4	71	386	13	5
9	105	338	3	15	83	319	8	14	83	345	7	16
10	94	296	4	7	94	296	4	9	94	315	2	11
11	94	319	12	4	90	330	12	7	94	405	7	11
12	86	446	10	7	86	450	11	9	86	450	5	11
13	86	401	10	2	86	401	13	5	86	383	9	9
14	176	326	12	10	173	371	12	16	169	375	7	18
15	105	293	3	10	98	293	3	12	94	405	2	14
16	109	371	8	5	109	364	8	5	109	371	6	6
17	124	435	8	7	124	518	9	3	128	514	6	4
18	124	386	7	4	128	386	5	5	150	413	2	8
19	86	345	9	10	86	341	14	14	79	345	12	15
20	86	270	4	1	86	278	6	4	83	289	5	7
21	94	274	6	2	90	26	8	1	90	300	9	5

continued /

TABLE 4.2 continued

Non-target

	Fz				Cz				Pz			
No	N1	P3	N1-P2	N2-P3	N1	P3	N1-P2	N2-P3	N1	P3	N1-P2	N2-P3
1	94	326	9	14	90	326	16	12	83	308	10	8
2	94	398	11	6	94	401	10	6	86	401	7	7
3	109	326	9	14	94	323	12	15	86	323	8	7
4	131	341	7	14	113	330	12	17	94	345	10	12
5	75	315	2	10	90	311	12	9	105	315	5	9
6	83	326	6	10	90	296	12	15	94	308	11	13
7	98	338	11	2	98	379	13	2	94	364	8	4
8	94	375	12	6	90	349	20	5	86	348	15	3
9	abs	338	NR	14	90	289	12	11	90	308	10	15
10	98	337	5	23	98	333	6	32	98	341	3	25
11	98	289	13	7	94	315	14	5	98	304	8	6
12	90	323	13	5	86	398	17	3	86	409	12	7
13	86	304	15	8	86	315	18	6	90	319	9	9
14	143	323	8	10	83	285	14	10	75	270	4	13
15	105	345	9	4	101	349	12	4	109	364	8	3
16	98	326	7	8	105	285	9	9	116	296	7	10
17	98	548	10	16	98	551	13	11	98	551	8	6
18	116	308	7	9	109	311	6	13	116	296	3	11
19	101	341	11	11	86	341	18	11	83	341	13	13
20	124	318	4	8	86	293	8	9	83	308	5	11
21	86	326	9	12	90	319	17	11	90	308	7	10

Legend: N1 and P3 = ms; N1-P2 and N2-P3 = μV;
NR = not measured because of absent P2

TABLE 4.3 MEAN±SD OF RT AND RTSD (ms): COMPARISON BETWEEN THE PATIENT AND CONTROL GROUPS

	RT	RTSD
Patients (N=21)	447±93.4	86±18.3
Controls (N=19)	420±68.0	117±44.5
U	156	96
p	NS	<0.01

TABLE 4.4 MEAN±SD OF N2-P3 AMPLITUDE (μV): COMPARISON BETWEEN SUBGROUPS 1 AND 2

	Target			Non-target		
	Fz	Cz	Pz	Fz	Cz	Pz
Subgroup 1 (N=12)	6.4± 4.0	9.9± 6.0	14.1± 3.9	10.9± 5.1	12.5± 7.4	11.8± 4.6
Subgroup 2 (N-9)	5.7± 4.8	6.8± 4.3	9.9± 4.2	8.6± 5.2	7.2± 3.9	7.4± 3.8
t	0.8	2.0	2.3	1.0	2.1	2.4
p	NS	NS	<0.05	NS	NS	<0.05

TABLE 4.5 MEAN±SD OF RT AND RTSD (ms): COMPARISON BETWEEN SUBGROUPS 1 AND 2

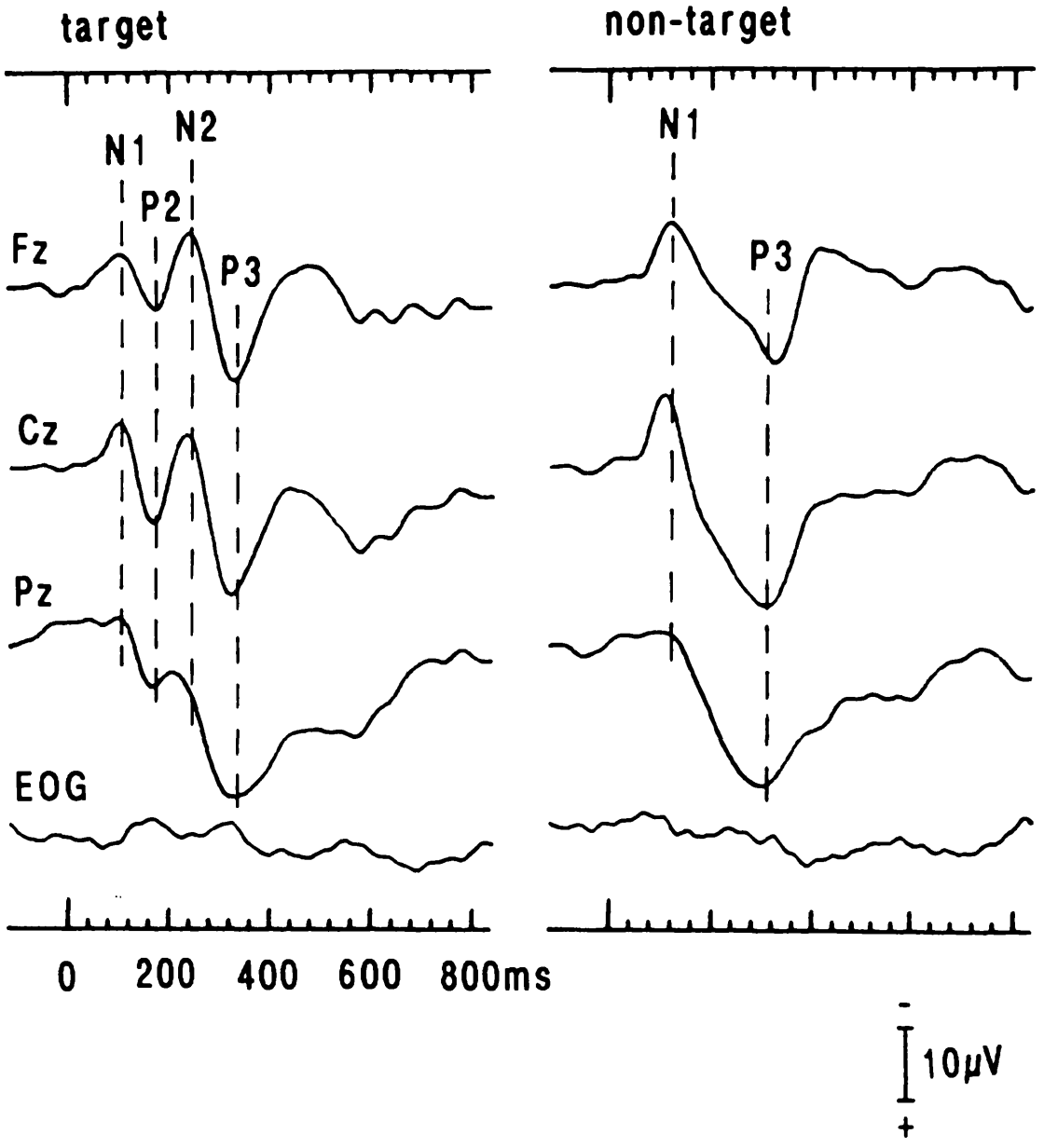
	RT	RTSD
Subgroup 1 (N=12)	428±67.1	114±29.5
Subgroup 2 (N=9)	472±119.9	121±61.0
U	42	51
p	NS	NS

TABLE 4.6 MEAN±SD OF PSYCHOMETRIC SCORES: COMPARISON BETWEEN SUBGROUPS 1 AND 2

	PASAT 4	PASAT 2	PVSAT 4	PVSAT 2	SDMT
Subgroup 1 (N=12)	2.2	7.8	1.5	7.6	12.0
Subgroup 2 (N=9)	3.8	12.0	3.0	9.4	13.9
U	38	28	40	32	13.0
p	NS	<0.05	NS	NS	<0.01

Scores: PASAT and PVSAT = number of errors; SDMT = ms

Fig.4.1 Normal cognitive ERPs recorded with a 3-stimulus oddball paradigm, auditory modality (25 year-old female). Note that in the non-target condition the N2 and P2 components are not identifiable at any scalp locations, as can sometimes be seen in normal subjects.


target
non-target
N1
N2
P2
P3
Fz
Cz
Pz
EOG
0 200 400 600 800ms
10μV
-
+

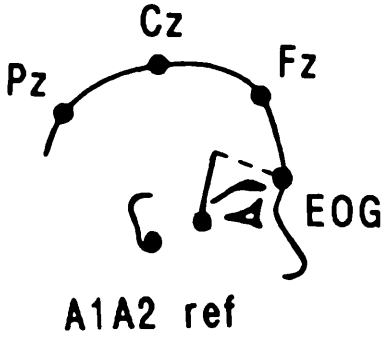

Cz
Pz
Fz
EOG
A1A2 ref

Fig.4.1

Fig. 4.2 **Case 17**. Top: cognitive ERPs. In the target condition, P3 is delayed at Cz and Pz and N2-P3 is degraded at Pz. In the non-target condition, the P3 is delayed at Fz, Cz and Pz. Bottom: brain MRI, axial views. Areas of increased signal are visible in the parietal lobes (left) and in the left occipital lobe, near the trigone (right).

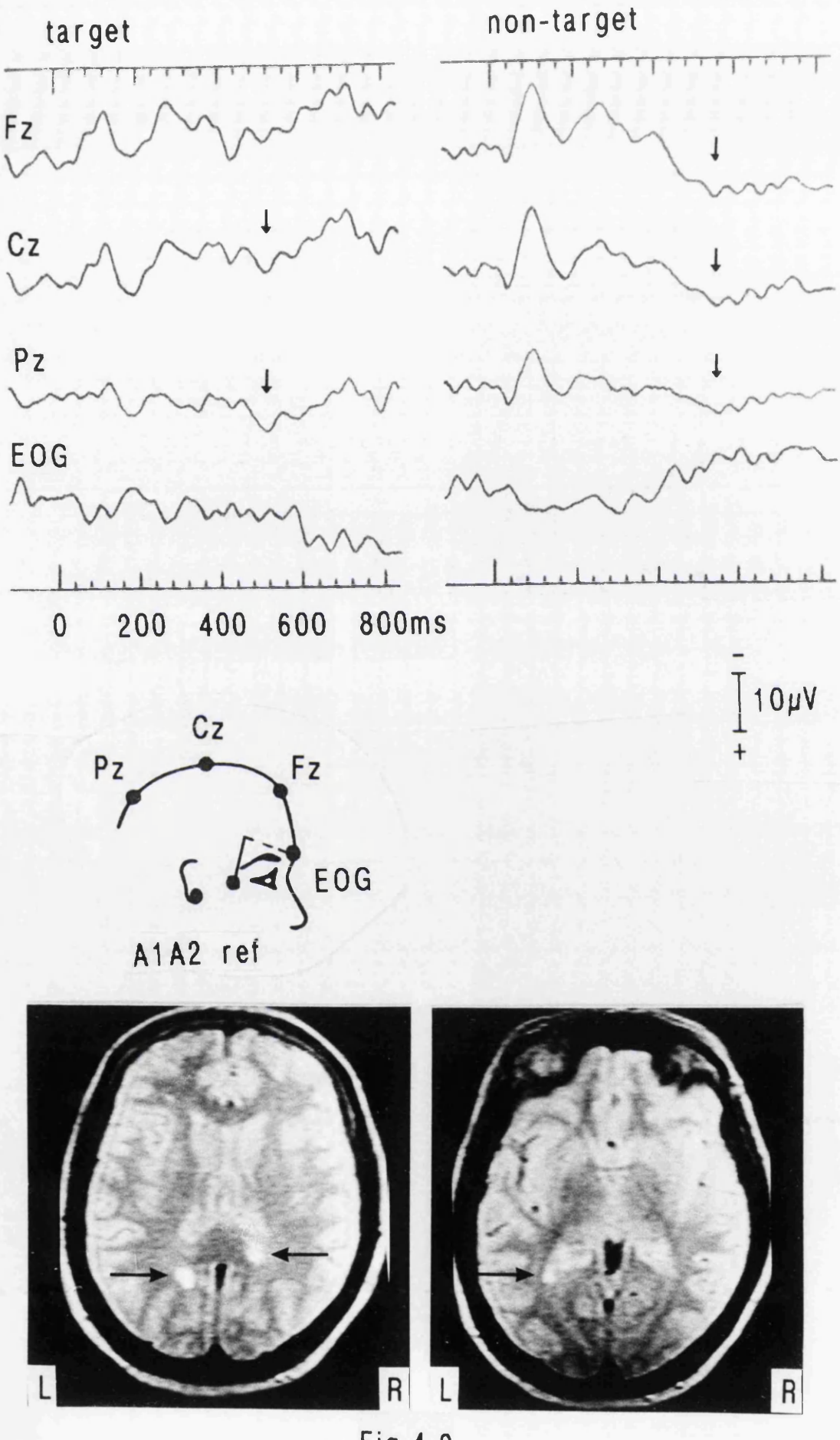
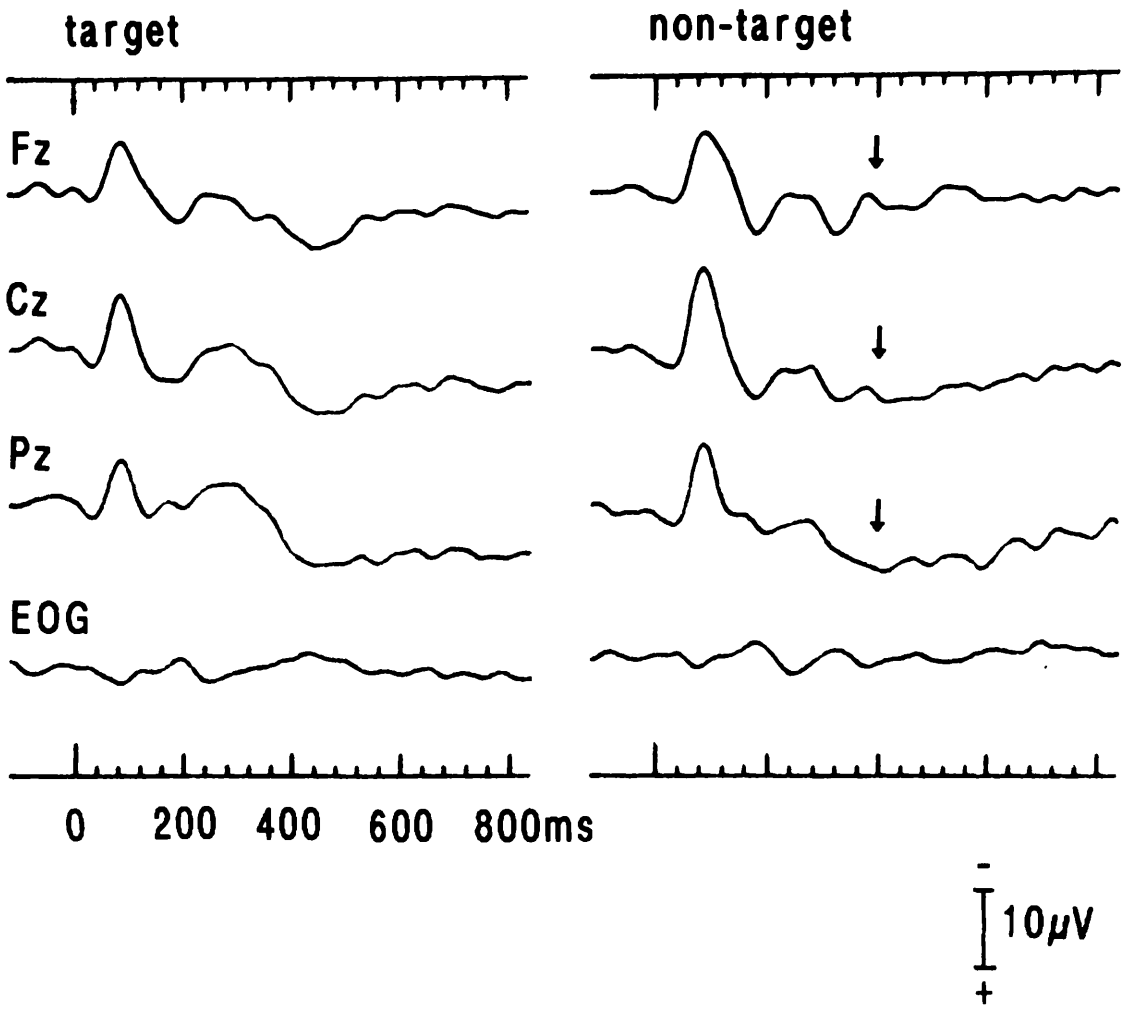

target
non-target
Fz
Cz
Pz
EOG
0 200 400 600 800ms
10μV
Cz
Pz
Fz
EOG
A1A2 ref
L
R
L
R

Fig.4.2

Fig. 4.3 **Case 12** (42 year-old female), cognitive ERPs. The responses to target stimuli are within normal limits. In the non-target condition, N2-P3 is degraded at Fz and Cz and P3 is delayed at Pz. Note that the P3 latency is usually shorter in the non-target than target condition. There were no detectable lesions on brain MRI.


target
non-target
Fz
Cz
Pz
EOG
0 200 400 600 800ms
10μV
-
+

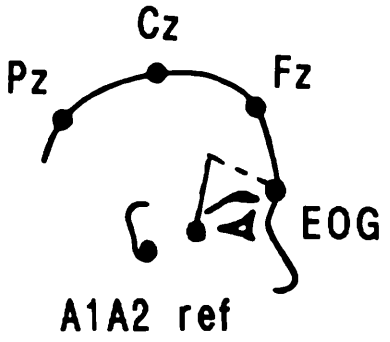
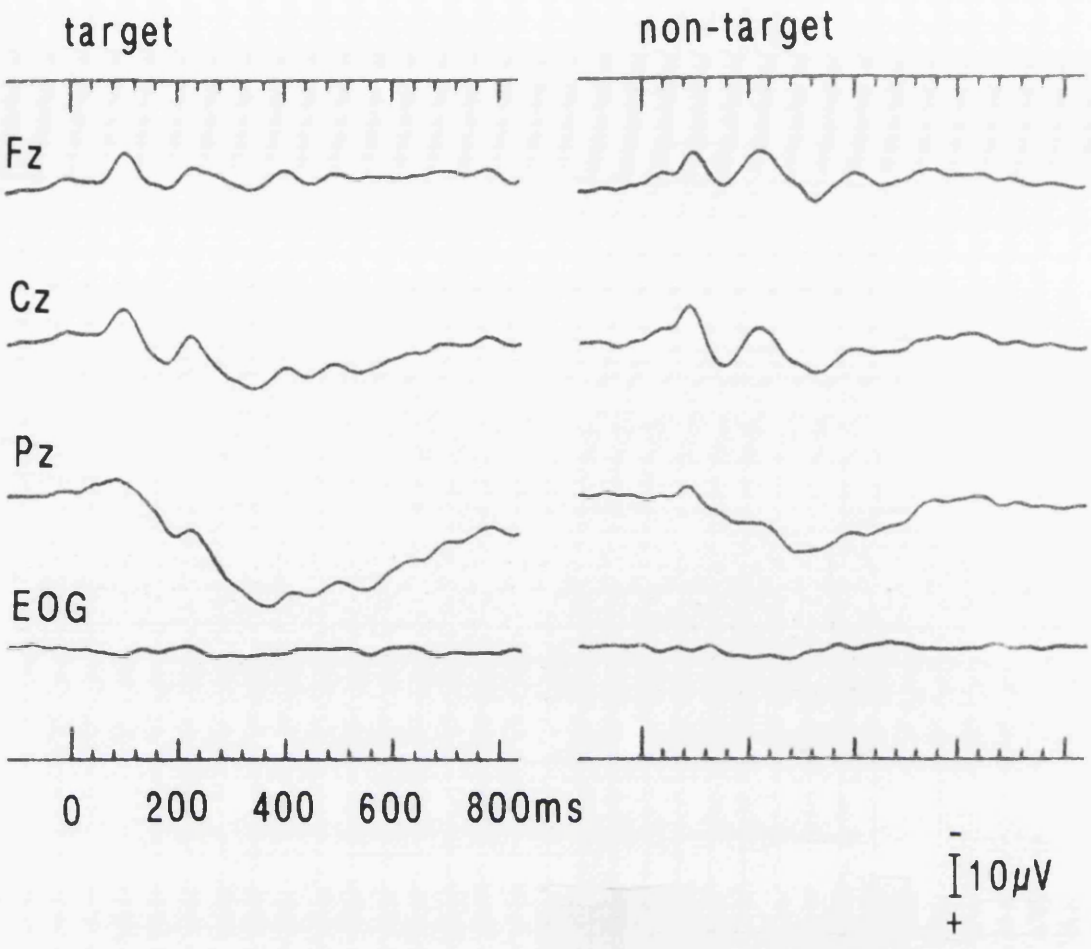
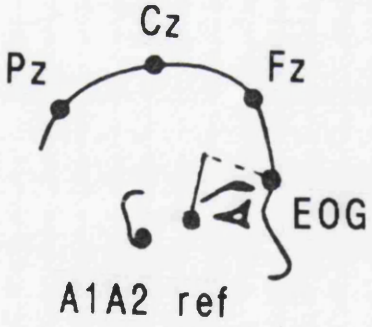

Cz
Pz
Fz
EOG
A1A2 ref

Fig.4.3

Fig. 4.4 **Case 1** (25 year-old female). Top: normal cognitive ERPs. Bottom: brain MRI, axial views. Areas of increased signal are visible in the left occipital lobe and near the occipital horns of the lateral ventricles.


target
non-target
Fz
Cz
Pz
EOG
0 200 400 600 800ms
10μV


Cz
Pz
Fz
EOG
A1A2 ref

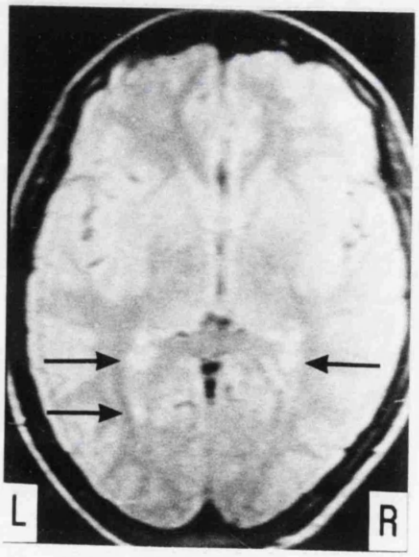
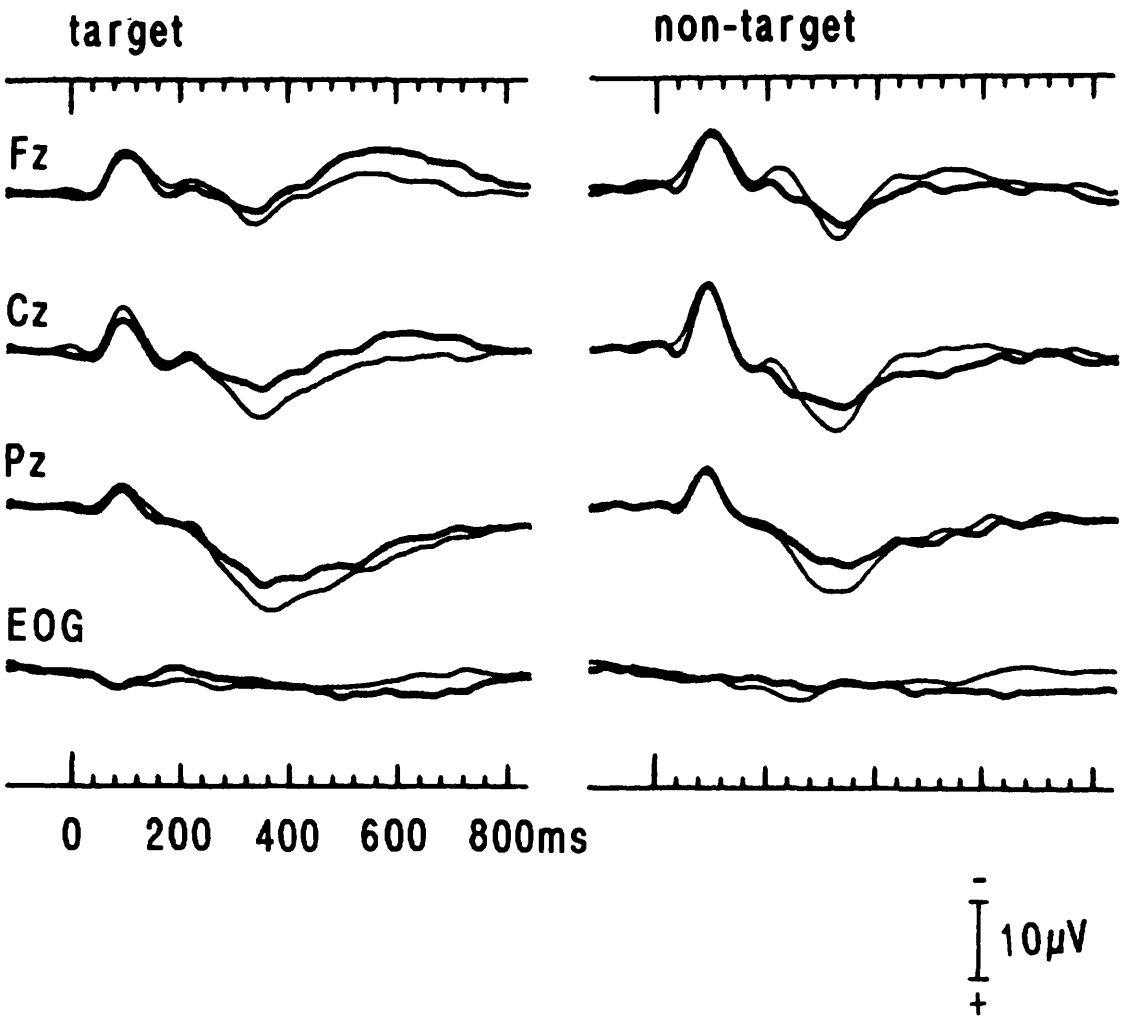

L
R

Fig.4.4

Fig. 4.5. Superimposition of group average waveforms recorded from patients with a larger lesion area (thick line N=9) and patients with smaller lesion area (thin line N=12). The N2-P3 is smaller in the former group as compared to the latter and this difference is more evident at Cz and Pz than Fz.


target
non-target
Fz
Cz
Pz
EOG
0 200 400 600 800ms
10μV
-
+

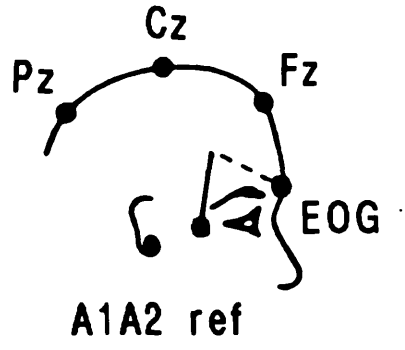

Cz
Pz
Fz
EOG
A1A2 ref

Fig.4.5

CHAPTER

5

THE PATHOPHYSIOLOGY OF ACUTE OPTIC NEURITIS: CORRELATION BETWEEN VEPs, MRI AND CLINICAL DEFICITS

5.1 GENERAL INTRODUCTION

In its early stages, MS usually develops in relapses and remissions. The onset of symptoms is sudden, while recovery occurs usually in a matter of weeks. The pathophysiological mechanism underlying this clinical evolution has been an object of interest for many years, since it may have a bearing on the development of successful forms of treatment. The study of the correlation between EP and MRI findings may be a useful approach to such a question, by elucidating the relationship between physiological and morphological abnormalities associated with demyelinating lesions.

Acute optic neuritis is a typical example of relapse in MS. It usually presents with cloudiness or obscuration of vision and ocular discomfort, which is exacerbated by eye movement. These symptoms tend to improve quickly and the visual acuity typically recovers within a month or two, although frequently not to its original level. An optic nerve lesion is particularly suitable for studying clinical and physio-pathological correlations for the following reasons: it manifests with a characteristic pattern of neuro-ophthalmological deficits, its morphology can be studied on MRI and alterations of the conduction through the optic nerve can be quantified by recording VEPs.

The present chapter is divided into two sections: part 1 examines the correlations between clinical, MRI and VEP abnormalities during the acute and recovery phase of optic neuritis; part 2 considers serial electrophysiological and morphological changes of optic nerve lesions occurring once the acute episode has resolved.

PART 1

CORRELATION OF GADOLINIUM-DTPA LEAKAGE WITH VEPs AND NEURO-OPHTHALMOLOGICAL DEFICITS

5.1.1 INTRODUCTION

The pattern VEP is abnormal in the majority of patients with acute optic neuritis, estimates of the frequency ranging from 67% (Asselman et al., 1975) to more than 90% (Halliday et al., 1972; Halliday et al., 1973b). In the acute stage, the amplitude of the response is reduced to a degree usually commensurate with the reduction in visual acuity and the latency is increased; during the recovery phase, the amplitude increases in parallel with the improvement of vision, although not reaching the normal level in every case, whereas the latency usually remains prolonged. Thus, throughout the course of acute visual loss and recovery there is a clear dissociation between the amplitude and latency of the VEP and the former appears

closely related to the level of the visual acuity (Halliday et al., 1973a). It has been postulated that the more stable increase of the VEP latency is due to persistence of demyelination in a proportion of optic nerve fibres, whereas the amplitude recovery is related to restoration of conduction which had been blocked by oedema and swelling of the nerve (Halliday and McDonald, 1977).

To a certain extent, MRI allows the study of the pathology of a demyelinating optic nerve lesion in vivo. Using a STIR (short time inversion recovery) sequence, the signal from the orbital fat is greatly reduced and the image of the optic nerve improved (Miller et al., 1986). An important pathological feature of acute demyelinating lesions is inflammation (Allen, 1991). This can be demonstrated on MRI using the contrast agent Gadolinium-DTPA (Gd-DTPA), leakage of which indicates breach of the blood-brain-barrier (BBB). Serial studies in clinically definite MS cases have shown that reversible Gd-DTPA enhancement is a consistent feature of new MRI abnormalities and usually lasts less than one month (Isaac et al., 1986; Miller et al., 1988d). The distribution of enhancement corresponds to the localisation of inflammation in acute and sub-acute MS lesions (Kermode et al., 1990b). In chronic relapsing experimental allergic encephalomyelitis Gd-DTPA enhancement detected at the time of a clinical relapse was associated with active inflammation on pathological examination (Hawkins et al., 1990). Given

the clinical and pathological similarities between this disease and MS (Lassman, 1983), it can be assumed that leakage of Gd-DTPA indicates inflammation in MS too.

The aim of the present study was to clarify the pathophysiological mechanism of recovery from an attack of acute optic neuritis. In particular, the relationship was examined between leakage of Gd-DTPA (and therefore, presumably, the presence of inflammation) within the optic nerve lesion and the VEP and the pattern of neuro-ophthalmological changes.

5.1.2 CASE MATERIAL

5.1.2.1 Patients

The patient group consisted of 11 subjects, 7 females and 4 males, aged 18 to 37 years (mean 28±6 years). They presented with a clinically isolated acute optic neuritis, which was unilateral in 9 cases and bilateral and simultaneous in 2. Diagnosis was based on standard clinical criteria (Compston et al., 1978) and was supported by the presence of an abnormal VEP. The general neurological examination was normal in each patient and there was no history of previous significant neurological symptoms. On ophthalmological investigation there was no evidence of

retinal or intra-ocular pathology. None of the patients was treated with corticosteroids during the period of the study.

5.1.2.2 Controls

Normal limits of VEP amplitude and latency were obtained separately from 29 healthy females, aged 20 to 36 years (mean 26±6 years) and 20 healthy males, aged 18 to 32 years (mean 23±6 years).

5.1.3 METHODS

Neuro-ophthalmological examination, VEP recording and MRI of the optic nerves were performed two to 13 days (mean 7±3 days) after the onset of blurring of vision and repeated 20 to 32 days (mean 29±4 days) later in nine cases. On each occasion, these investigations were carried out on the same day.

5.1.3.1 Neuro-ophthalmological examination

The neuro-ophthalmological investigation included assessment of distance visual acuity (wearing glasses if necessary), colour vision, visual fields, afferent pupillary reflex and fundus. Distance vision was recorded from Snellen charts, while colour vision was assessed by record-

ing the number of errors on viewing 13 Ishihara plates. Visual fields were plotted using both a Goldmann perimeter (static and dynamic isopters to I2 and I4 targets) and Bjerrum screen and attention was paid to establish the presence or absence of a central scotoma. For analysis purposes, visual acuity was considered abnormal if below 6/9 and colour vision was classified as defective if the patient made more than one error.

5.1.3.2 Visual evoked potentials

Full and hemifield VEPs were recorded monocularly using the technique which was described in detail in paragraph 3.3.3. The present study focused on the changes of the full field responses. However, hemifield components were recorded in order to distinguish a possibly delayed P100 from a P135, which has a different scalp distribution on hemifield stimulation and may predominate over the P100 when the latter is attenuated in the presence of a central scotoma (Blumhardt et al., 1978). Thus, hemifield responses were examined to confirm the presence of the P100 and not analysed further.

Normal latency limits of the P100 were defined by the mean + 2.5 SD of the absolute latency and mean ± 2.5 SD of the inter-ocular latency difference (left eye-right eye) in

the control group. Normal amplitude limits were defined by the mean - 2.5 SD of $\log_{10}$ amplitude and mean ± 2.5 SD of $\log_{10}$ amplitude ratio [left eye/right eye].

5.1.3.3 Magnetic Resonance Imaging

MRI was performed in a Picker 0.5 Tesla superconducting scanner using a binocular orbital surface coil. The optic nerves were imaged with a STIR sequence ($SE_{2000/40/150}$) to suppress the signal from the orbital fat. Contiguous coronal slices 5 mm thick were obtained through the orbits from the head of the optic nerve to the optic chiasm, before and after the injection of Gd-DTPA 0.2 mmol/Kg (Schering AG). Pilot scans in the three planes enabled accurate repositioning. Scans were interpreted independently by two neuroradiologists, who were blind to clinical and electrophysiological details.

In pre-contrast images, lesions were defined as foci of increased signal within the nerve. After contrast, leakage of Gd-DTPA across an abnormal blood-optic nerve barrier produced a reduction of signal in the previously identified lesions. The location of the lesions was distinguished in orbital, intracanalicular and intracranial slices. The MRI lesion length was recorded as the number of consecutive slices on which the lesion was visible. This measurement allowed only an approximate evaluation of the lesion length. In demyelinating lesions the degree of sig-

nal abnormality varies markedly due to substantial variations in water proton density and T_1 and T_2 relaxation times. A lesion seen on a single slice can therefore have a length which is considerably longer or shorter than the slice thickness. If the lesion has a very long relaxation time it may be visible when only 1 or 2 mm in length; if it produces only a minor elevation in relaxation time compared with normal white matter, it could extend several millimetres into the neighbouring slices without producing any change of signal. Nevertheless it was felt to be worthwhile to examine the correlation between an estimate of lesion length and VEP parameters, since it was shown by Miller et al. (1988b) that lesion length is one factor influencing the long term prognosis of optic neuritis.

5.1.3.4 Statistical analysis

Comparisons of the mean VEP amplitude or latency between symptomatic and asymptomatic eyes or between first and second recordings were made using the paired t-test (two tailed probability). The association between the presence of a lesion in the intracanalicular portion of the optic nerve and a visual acuity reduced to below 6/9 was assessed using the Fisher exact probability test. The correlation between lesion length and acuity level was analysed using the Spearman rank correlation test with cor-

rection for ties. The relationship between the length of the optic nerve lesion and the VEP amplitude or latency was determined by calculating linear regression.

5.1.4 RESULTS

5.1.4.1 Neuro-ophthalmological findings

a) First examination

Vision was subjectively blurred in all 13 symptomatic eyes and there was pain on eye movement in 12. Distance visual acuity was below 6/9 in eight eyes and colour vision was impaired in 11. In 10 eyes there was an absolute or relative central scotoma. Discs were mildly to moderately swollen in 11 eyes and the afferent pupillary reflex was absent in all 13 [Table 5.1.1].

b) Second examination

Ten clinically affected eyes (nine patients) were followed-up. Vision had subjectively improved in all of these and pain on eye movement had recovered in 6/9 eyes in which it was initially present. Distance visual acuity had improved to 6/9 or better in all six eyes in which it had been significantly reduced and colour vision had improved in 5/8 previously abnormal eyes. A central scotoma had dis-

appeared in 4/8 eyes, but was detected for the first time in another. Swelling had disappeared in 2/8 discs but had developed in a previously normal one; the afferent pupillary reflex was elicited in five eyes and remained absent in the others [Table 5.1.1].

5.1.4.2 VEP findings

a) First recording

VEPs were abnormal in all 13 symptomatic eyes. The P100 was absent in 3 eyes, showed increased latency with reduced amplitude in 6, a prolonged latency (without reduced amplitude) in 3 and reduced amplitude (without delay) in one. In 2 asymptomatic eyes (Cases 5 and 11) the VEP had an increased latency [Table 5.1.1 and Fig. 5.1.1].

In 8 patients with unilateral optic neuritis (Cases 1, 3, 5, 6, 7, 9, 10 and 11), the mean VEP amplitude from the symptomatic eye was reduced to about one third of that recorded in the asymptomatic eye ($p<0.001$), while the mean latency was increased by 28 ms ($p<0.01$). Case 8 was excluded from this analysis as the response from the affected eye was absent [Table 5.1.2].

b) Second recording

Responses were abnormal in 8/10 symptomatic eyes. The P100 showed an increased latency in 5 eyes and a reduced amplitude with increased latency in 3. Thus, the VEP latency had returned to within normal limits in 2 eyes (Case 2), but had become prolonged in another (Case 5). The amplitude had recovered to within normal limits in 5 eyes (Cases 2, 5, 7 and 9), but had become attenuated in an additional one (Case 1). In another eye, in which responses were previously unidentifiable (Case 8), the P100 was now recorded with increased latency. In 2 clinically unaffected eyes (Cases 5 and 11) the VEP latency remained prolonged [Table 5.1.1].

In the symptomatic eyes of 8 patients with unilateral optic neuritis (Cases 1, 3, 5, 7, 8, 9, 10 and 11), the mean VEP amplitude was now about half of that recorded in the asymptomatic ones ($p<0.05$), while the mean latency was prolonged by approximately 20 ms ($p<0.001$) [Table 5.1.2].

5.1.4.3 Magnetic Resonance Imaging

a) First scan

A region of abnormal MRI signal was seen in all 13 affected optic nerves. Eight lesions extended from anterior or mid-orbital level into the optic canal (Cases 1, 2, 3,

4, 7 and 10), four were totally intra-orbital (Cases 5, 8, 9 and 11) and one occupied the optic canal only (Case 6). Leakage of Gd-DTPA was seen in all lesions but did not extend the whole length of these. It was located at mid-orbital level in 7 nerves (Cases 3, 5, 7, 8, 9, 10 and 11), in the optic canal in one (Case 6) and extended from the mid-orbital level to the optic canal in 5 (Cases 1, 2 and 4). No lesion was seen in the unaffected optic nerves, including the two with abnormal VEPs [Table 5.1.1].

The lesion length in pre-contrast scans varied from 2 to 6 slices (mean 3.5±1.3 slices), while the length of the leakage varied from 1 to 5 slices (mean 2.5±1.5 slices).

b) Second scan

A region of abnormal MRI signal was still present in all 10 affected optic nerves. This was intra-orbital in 5 nerves (Cases 2, 5, 8, 9 and 11), extended from anterior or mid-orbital level to the optic canal in 4 (Cases 2, 3, 7 and 10), and from mid-orbital to intracranial level in one (Case 1). Gd-DTPA leakage was seen in only one nerve (Case 7): it was located at mid-orbital level and occupied one slice only. No lesion was seen in the unaffected optic nerves, including the two with delayed VEPs [Table 5.1.1].

The lesion length varied from 1 to 6 slices (mean 3.2±1.5 slices) and showed no significant change in comparison to the first scan.

5.1.4.4 Correlation between visual acuity and MRI

a) Lesion location

The presence of a lesion in the optic canal was not significantly associated with a visual acuity reduced below 6/9. On first examination, the visual acuity was impaired in six out of nine eyes in which MRI showed a lesion in the optic canal and in 2/4 studies which displayed intra-orbital involvement. In addition, the visual acuity was impaired in 4/6 studies showing leakage in the optic canal and in 4/7 studies displaying leakage only outside it. At follow up, 5 nerves showed a lesion in the optic canal, while 5 had only an intra-orbital lesion: the visual acuity was 6/9 or better in all these patients.

b) Lesion length

In order to test the correlation between lesion length and acuity levels, visual acuities were given arbitrary values according to the following criterion: perception of hand movements=1; counting fingers=2; 1/60=3; 3/60=4; 6/60=5; 6/36=6; 6/24=7; 6/18=8; 6/12=9; 6/9=10; 6/6=11; 6/5=12; 6/4=13.

A significant negative correlation was found between visual acuities and lesion length in pre-contrast scans on first examination $r=-0.5$ ($p<0.05$) but not at follow up. There was no significant correlation between length of Gd-DTPA leakage and acuity levels.

5.1.4.5 Correlation between MRI and VEPs

a) Gd-DTPA leakage and VEP

In eight affected optic nerves, in which VEPs were present in both recordings (Cases 1, 2, 3, 5, 9, 10 and 11), Gd-DTPA leakage was present on first MRI but not at follow up. Between first and second recording the mean VEP amplitude in the symptomatic eyes increased by about 100% ($p<0.05$), while the mean latency decreased by about 12 ms ($p>0.05$) [Table 5.1.3 and Figs. 5.1.2 and 5.1.3].

b) Lesion length and VEP

The lesion length in pre- and post-contrast scans was compared with the VEP amplitude and latency, both on first examination and at follow up. Only one significant correlation was observed: at follow up, there was a negative linear relationship between VEP amplitude and pre-contrast lesion length, with a correlation coefficient of -0.84 ($p<0.01$) and a slope of -1.92 μV/5 mm slice (SE 0.5). The

effect accounted for 71% of the variance. The regression line intercepted the ordinate at a value of 14.8 μV, which is close to the mean amplitude for the clinically unaffected eye (13.8 μV), recorded on the same occasion [Fig. 5.1.4].

5.1.5 DISCUSSION

It was found that during the acute phase of optic neuritis, leakage of Gd-DTPA was associated with a reduction of the VEP amplitude and an increase of the VEP latency. The disappearance of leakage after clinical recovery was paralleled by a significant increase of the VEP amplitude, while the VEP latency remained prolonged. In addition, the degree of attenuation of the VEP at follow up was inversely correlated with the length of optic nerve lesions in pre-contrast scans.

There is strong, though indirect, evidence that leakage of Gd-DTPA in acute demyelinating lesions indicates inflammation (Hawkins et al., 1990). Leakage is consistently seen in new MS lesions and usually persists less than one month (Miller et al., 1988d). The duration of leakage observed in the present study in all but one lesion is consistent with these previous findings.

The VEP is an indicator of the conduction through the optic nerve: its amplitude is likely to reflect the number of activated fibres (although there are many other factors

contributing to amplitude variability) and its latency their speed of transmission. It should be remembered, however, that the numerous synapses located between the retina and the visual cortex also contribute to the latency of this potential. In the present study, the evolution of the VEP amplitude and visual acuities suggests that conduction was blocked in a certain proportion of fibres at the time of active inflammation and was then restored to a significant extent, though not completely, with resolution of inflammation. The prolongation of the VEP latency both acutely and at follow up suggests the persistence of demyelination in the optic nerve fibres (Halliday and McDonald, 1977). Demyelination is also likely to contribute to the reduction in the amplitude of the VEP. Extensive loss of myelin produces conduction block (McDonald, 1963; McDonald and Sears, 1970), while partial demyelination causes temporal dispersion of the afferent volley by affecting individual fibres to differing degrees. Thus, in the patients of this study the persistence of demyelination could have been one of the factors responsible for incomplete recovery of the VEP amplitude at follow up.

How does inflammation cause conduction block? An essential pathological feature of inflammation is oedema, which is an important component of the MRI abnormality in recently occurring lesions in MS. Oedema alters the MRI signal by increasing the density of hydrogen ions in the extra-cellular tissue. In acute experimental lesions it has

been shown that the location and extent of areas of abnormal MRI signal correspond to zones of oedema seen on pathological examination (Barnes et al., 1987). In addition, in MS the size of new MRI abnormalities appears to decrease with time and it seems likely that resolution of oedema is responsible for this change (Kermode et al., 1990a). In the optic nerve, fibres are arranged in bundles which are separated by fibrous septa; in addition, a segment of the nerve passes through the bony optic canal, which it almost fills. These structures limit the possibility of expansion, and the pressure associated with oedema will then exert its effect mainly on the optic nerve fibres themselves. Moderate compression can induce a reversible conduction block in optic nerve fibres (Kayan and Earl, 1975). More severe pressure can induce demyelination or axonal loss (Clifford-Jones et al., 1985). In favour of this mechanism is the finding that in acute optic neuritis the presence of a lesion in the optic canal seems to be associated with a poorer visual acuity or slow visual recovery (Miller et al., 1988b). In the present study, intracanalicular lesions were not significantly associated with impairment of the visual acuity, although a significant effect might have been missed owing to the fact that the total number of lesions was small. An alternative possibility is that during inflammation conduction block may be mediated by cytokines, which interfere with nerve conduction both directly (Tracey et al., 1986) and by in-

ducing demyelination (Selmaj and Raine, 1988). However, not much is known at the present about the role of cytokines in demyelinating diseases.

What is the precise cause of visual impairment and pain in acute optic neuritis? We found that with the disappearance of Gd-DTPA leakage visual acuity returned to normal in all clinically affected eyes and pain on eye movement recovered in 67%. Conduction block, associated with inflammation, could have been responsible for the impairment of visual acuity, and restoration of conduction after resolution of inflammation could have determined its recovery. Ocular discomfort is probably due to stimulation of nerve endings in the meningeal sheath and fibrous septa of the optic nerve by pressure and pain mediators released during inflammation, as in peripheral nerve (Asbury and Fields, 1974). An increase in discomfort during eye movement has been found to be related to increase in tension on the inflamed nerve endings at the extremes of gaze (Liu et al., 1990).

No significant correlation was found between the lesion length and the degree of the VEP delay, either in the acute stage or at follow up. This is not surprising if we consider that the alteration of the MRI signal is mainly produced by vasogenic oedema due to damage of the BBB in acute lesions, and by gliosis with a residual amount of extracellular water in chronic ones (Barnes et al., 1987; Barnes et al., 1988). Demyelination "per se" contributes

little to the alteration of the signal, using a standard proton MRI, and there is no evidence that the degree of demyelination is related to that of inflammation or oedema. Furthermore, the present resolution, 5 mm thick slices, does not allow an accurate measurement of the lesion length (see paragraph 5.1.3.3). Serial studies performed with administration of Gd-DTPA have shown that the size of MRI lesions decreases after enhancement ceases (Kermode et al., 1990b), leaving a residual abnormality which is likely to correspond more closely to the area of nerve damage. It is of interest, therefore, that in the present study the length of non-leaking lesions at follow up was inversely correlated with the VEP amplitude; the longer the lesion the more internodes were likely to have been damaged and the higher the chance of conduction block (Rasminsky, 1973). This could explain the previous observation that longer lesions are associated with poorer visual acuity (Miller et al., 1988b). In the present study, a significant negative correlation was found between visual acuity and lesion length on first but not on second examination, although the smaller number of observations at follow up might have caused a real effect to be missed.

In conclusion, in acute optic neuritis the impairment of the visual acuity is probably related to conduction block, mainly mediated by inflammation. Improvement of vision appears to be produced by partial or complete restoration of conduction following the resolution of inflamma-

tion. Demyelination contributes to the clinical deficits to a lesser extent but is probably responsible for the incomplete electrophysiological recovery. Since the clinical evolution of acute optic neuritis is similar to that of other relapses in MS, it may be concluded that inflammation plays a crucial role in symptom production and resolution of inflammation is an important factor in remission.

TABLE 5.1.1: NEURO-OPHTHALMOLOGICAL, VEP AND MRI FINDINGS

First examination

Case	Sex	Age	Side	Days	Pain	VA	CV	CSc	DSw	APD
1	F	20	Left	13	+	6/60	0/13	-	+	+
2	M	31	Left	4	+	6/5	13/13	+	+	+
			Right	5	+	6/12	11/13	+	+	+
3	F	35	Right	2	+	6/9	12/13	+	+	+
4	M	18	Left	8	+	HM	0/13	+	+	+
			Right	8	+	HM	0/13	+	+	+
5	F	37	Left	5	+	1/60	2/13	+	-	+
6	F	24	Left	8	+	6/6	6/13	-	+	+
7	F	31	Right	9	+	6/60	0/13	+	+	+
8	F	27	Left	7	+	CF	0/13	+	+	+
9	F	29	Left	6	-	6/9	11/13	+	-	+
10	M	27	Left	2	+	HM	0/13	+	+	+
11	F	28	Right	9	+	6/6	10/13	-	+	+

	VEPs				Lesion length (slices)			
	Left eye		Right eye		Plain		Leakage	
Case	µV	ms	µV	ms	Left	Right	Left	Right
1	8.1	140	19.6	100	3*	-	3*	-
2	2.2	123	1.6	136	4*	4*	4*	4*
3	10.2	106	2.7	148	-	4*	-	2
4	abs	abs	abs	abs	5*	5*	5*	5*
5	3.2	106	19.0	118#	3	-	2	-
6	8.3	125	17.4	104	2*	-	1*	-
7	10.2	101	1.3	**110**	-	2*	-	1
8	abs	abs	11.5	104	3	-	1	-
9	2.9	153	13.5	106	2	-	2	-
10	1.6	159	16.0	109	6*	-	1	-
11	11.8	118#	9.6	145	3	-	2	-

continued /

TABLE 5.1 continued

Second examination

Case	Sex	Age	Side	Days	Pain	VA	CV	CSc	DSw	APD
1	F	20	Left	38	+	6/9	11/13	-	+	+
2	M	31	Left	32	-	6/5	13/13	-	+	+
			Right	33	-	6/5	13/13	-	+	+
3	F	35	Right	34	-	6/5	13/13	+	+	-
5	F	37	Left	25	-	6/9	13/13	-	+	-
7	F	31	Right	37	+	6/6	11/13	+	-	+
8	F	27	Left	37	+	6/5	13/13	+	+	-
9	F	29	Left	37	-	6/9	11/13	-	-	+
10	M	27	Left	33	-	6/9	11/13	+	+	-
11	F	28	Right	41	-	6/5	13/13	+	-	-

	VEPs				Lesion length (slices)			
	Left eye		Right eye		Plain		Leakage	
Case	μV	ms	μV	ms	Left	Right	Left	Right
1	4.6	130	19.5	104	5*	-	-	-
2	9.7	117	10.0	118	3*	4*	-	-
3	10.3	105	4.6	151	-	4*	-	-
5	13.3	130	17.0	125#	2	-	-	-
7	11.5	102	5.2	131	-	2*	-	1
8	9.2	138	7.8	113	2	-	-	-
9	7.0	126	14.8	106	3	-	-	-
10	3.3	145	14.2	110	6*	-	-	-
11	15.4	119#	11.5	131	-	1	-	-

Legend: Days = days since onset of visual blurring; VA = visual acuity; CV = colour vision; CSc = central scotoma; DSw = disk swelling; APD = afferent pupillary defect; + = present; - = absent; HM = perception of hand movements; CF = counting fingers; abnormal VEP values underlined; underlined and bold = significant inter-side difference; # = delayed VEP in asymptomatic eye; * = lesion in the optic canal.

TABLE 5.1.2: MEAN±SD OF AMPLITUDE (μV) AND LATENCY (ms) OF THE P100 IN EIGHT UNILATERAL OPTIC NEURITIS CASES (Inter-ocular comparisons)

	First recording		Second recording	
	μV	ms	μV	ms
Symptomatic eye	4.7±3.4	136±19.8	7.3±3.6	131±8.7
Asymptomatic eye	14.7±3.8	108±6.9	13.8±3.8	111±8.1
t	-6.68	3.68	-2.57	5.53
p	<0.001	<0.01	<0.05	<0.001

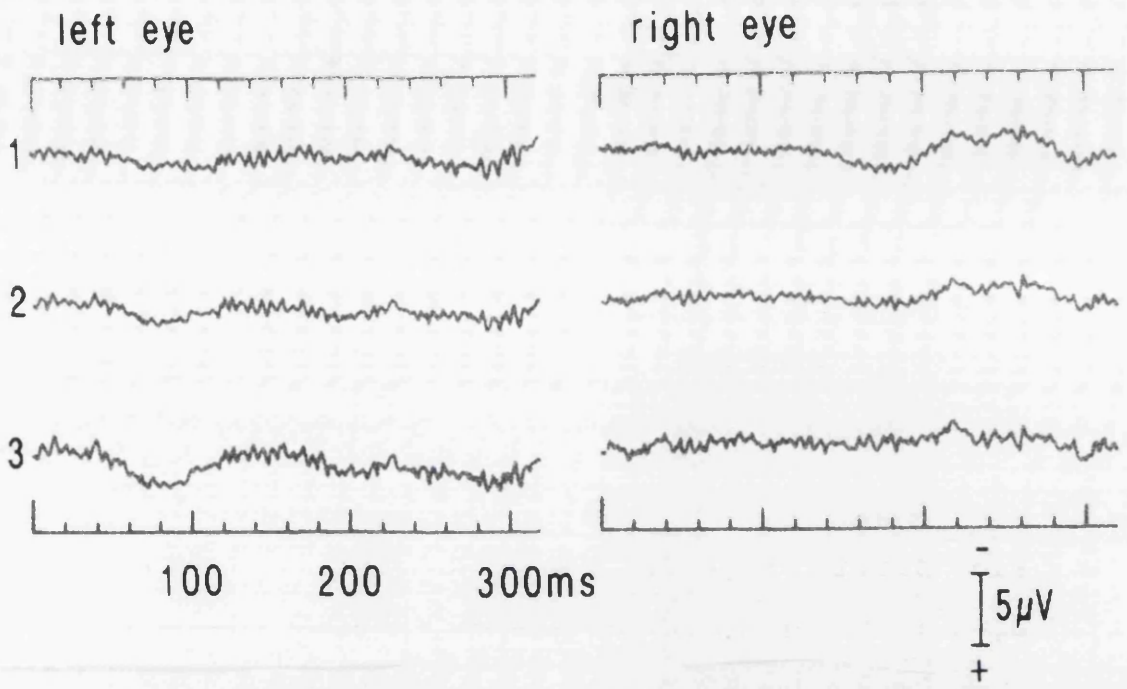
First recording includes: Cases 1, 3, 5, 6, 7, 9, 10 and 11.
Second recording includes: Cases 1, 3, 5, 7, 8, 9, 10 and 11.

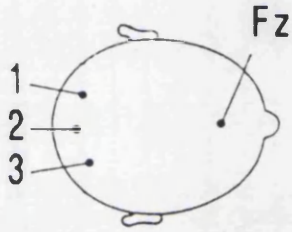
TABLE 5.1.3: CHANGES IN THE MEAN±SD AMPLITUDE (μV) AND LATENCY (ms) OF THE P100 IN RELATION TO THE DISAPPEARANCE OF Gd-DTPA LEAKAGE IN THE OPTIC NERVE LESION (8 eyes, 7 patients)

	Amplitude	Latency
First recording (leakage present)	4.0±3.1	139±17.2
Second recording (leakage absent)	8.0±3.7	127±9.9
t	-2.5	2.02
p	<0.05	NS

Included: Cases 1, 2, 3, 5, 9, 10 and 11.

Fig. 5.1.1 **Case 4** (18 year-old male), bilateral optic neuritis, eight days since the onset of visual blurring. Visual acuity in both eyes: perception of hand movements. Top: full field VEPs. The P100 component is unidentifiable from either eye. Bottom: optic nerve MRI. The pre-contrast scan (left) reveals increased signal in both optic nerves, while the post-contrast image (right) displays decrement of signal in the lesion, consistent with leakage of Gd-DTPA.


left eye
right eye
1
2
3
100
200
300ms
5μV
-
+


Fz ref
1
2
3

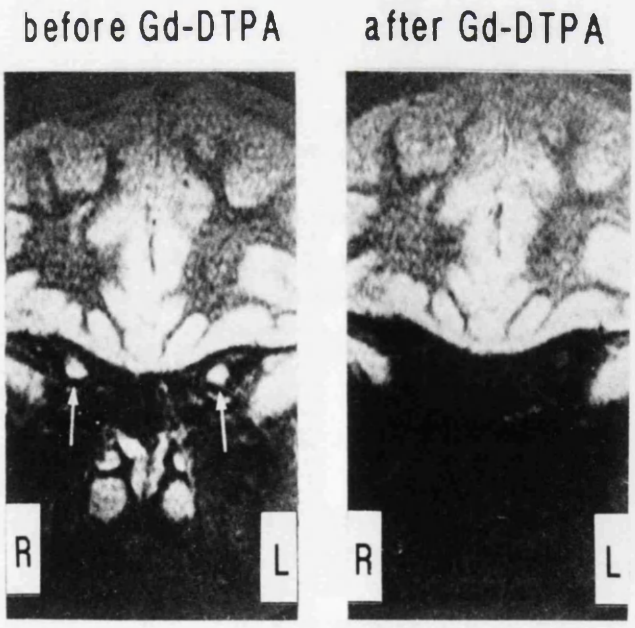
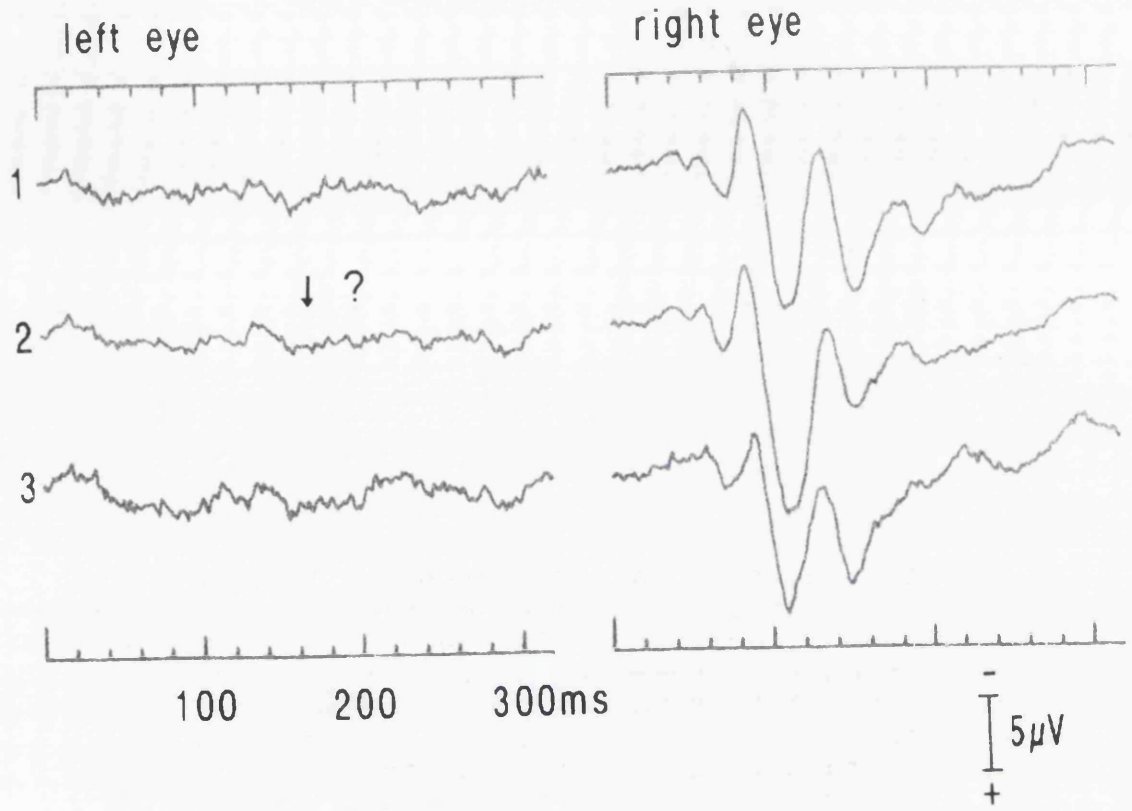
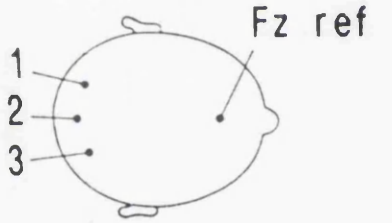

before Gd-DTPA
after Gd-DTPA
R
L
R
L

Fig.5.1.1

Fig. 5.1.2a **Case 10** (27 year-old male), left optic neuritis, two days since the onset of visual blurring. Visual acuity in the affected eye: perception of hand movements. Top: full field VEPs. The P100 is markedly degraded and delayed from the left eye. Bottom: optic nerve MRI. The pre-contrast scan reveals increased signal in the left optic nerve; after injection of Gd-DTPA, there is signal decrement in the lesion, consistent with leakage of Gd-DTPA.


left eye
right eye
1
2
3
↓ ?
100
200
300ms
5μV
-
+


Fz ref
1
2
3

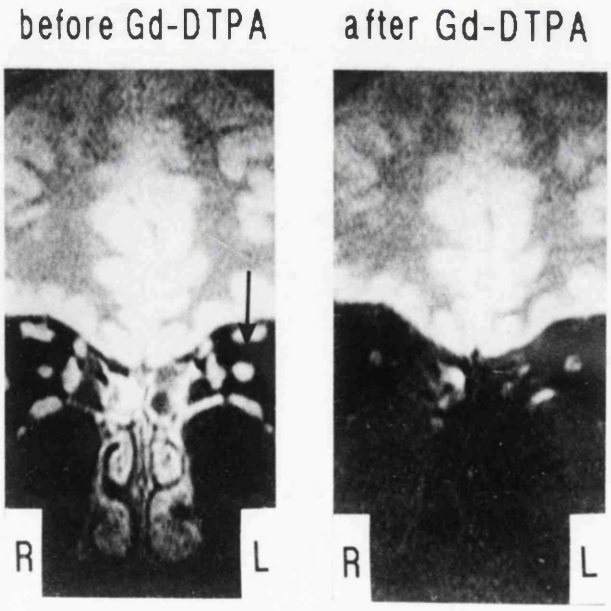
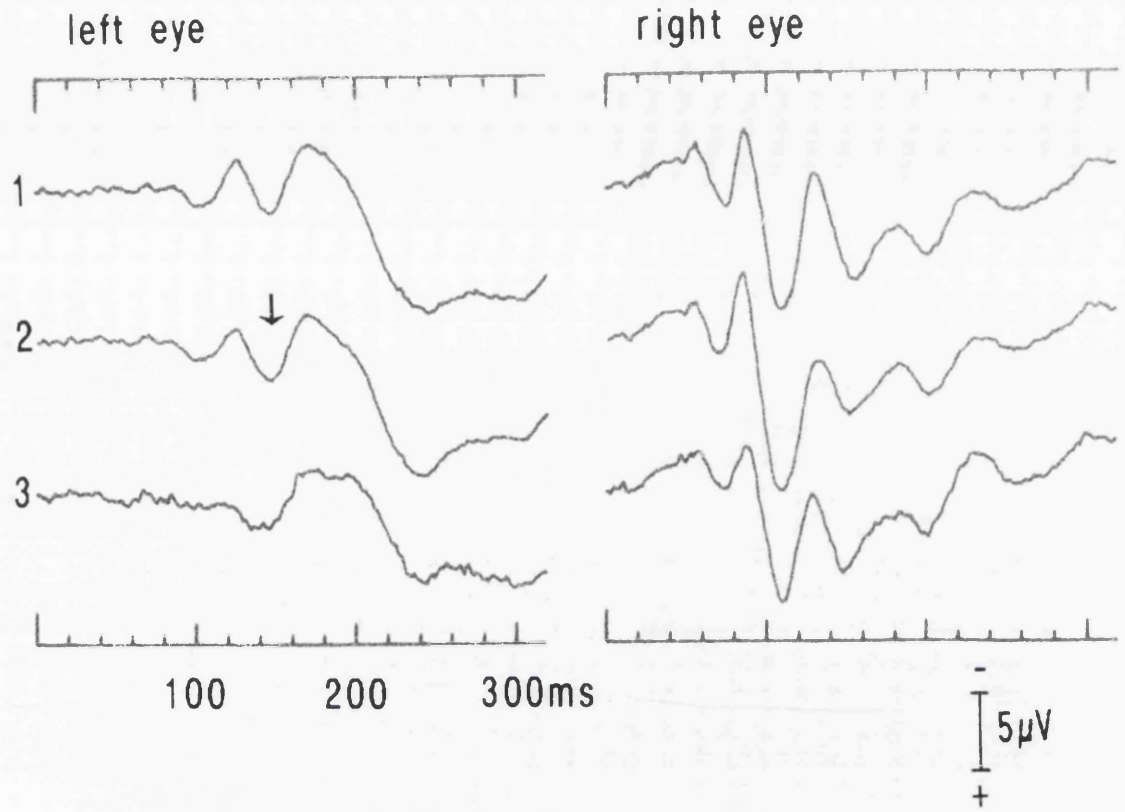
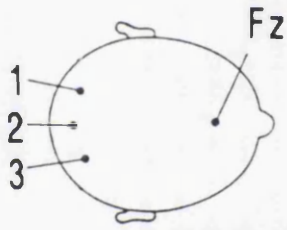

before Gd-DTPA
after Gd-DTPA
R
L
R
L

Fig.5.1.2a

Fig. 5.1.2b **Case 10**, follow up after 31 days. Visual acuity in the affected eye: 6/9. Top: full field VEPs. Since the first recording, the amplitude of the P100 has increased remarkably in the left eye and its latency has decreased by 14 ms. Bottom: optic nerve MRI. The pre-contrast scan reveals increased signal in the left optic nerve; there is not decrement of signal in the lesion after injection of Gd-DTPA, consistent with absence of leakage.


left eye
right eye
1
2
3
100
200
300ms
5μV
-
+


Fz ref
1
2
3

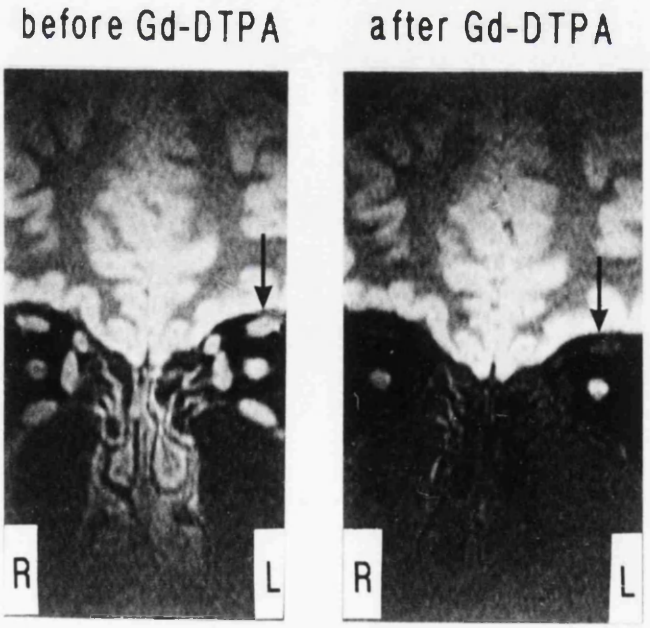
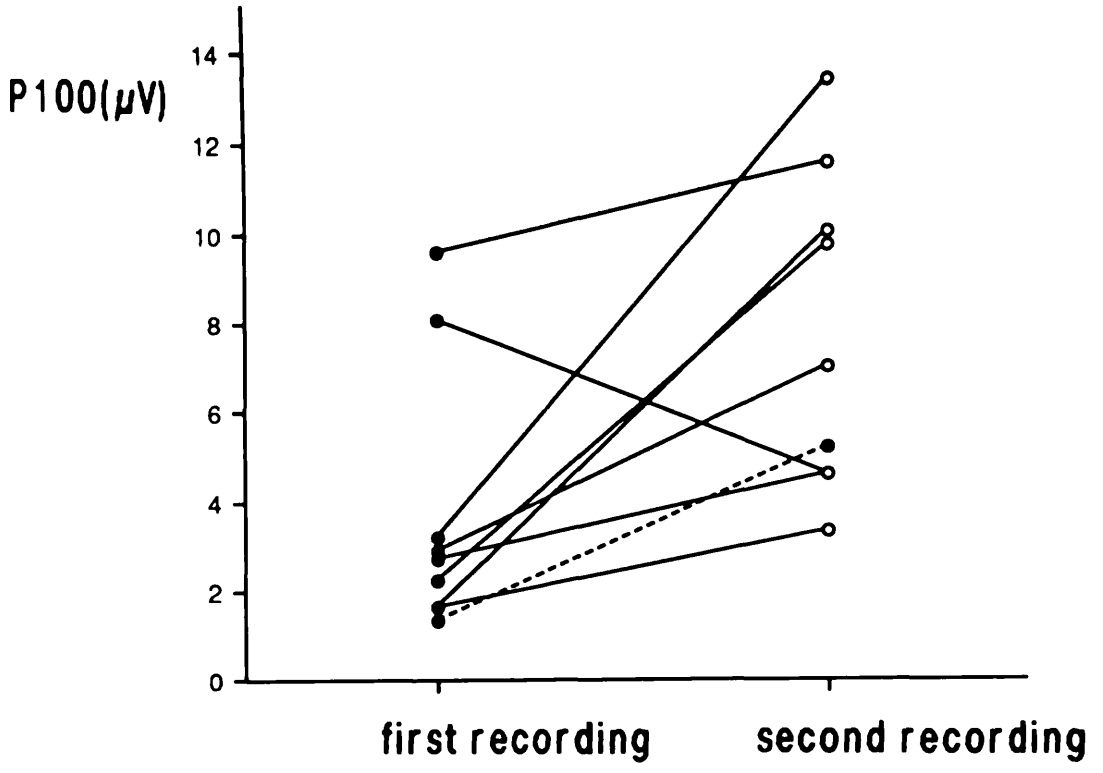

before Gd-DTPA
after Gd-DTPA
R
L
R
L

Fig.5.1.2b

Fig. 5.1.3. Serial changes of the P100 amplitude (top) and latency (bottom) in 9 symptomatic eyes (9 patients). Filled circles and squares = leakage of Gd-DTPA; empty circles and squares = absence of leakage.


P100(μV)
14
12
10
8
6
4
2
0
first recording
second recording

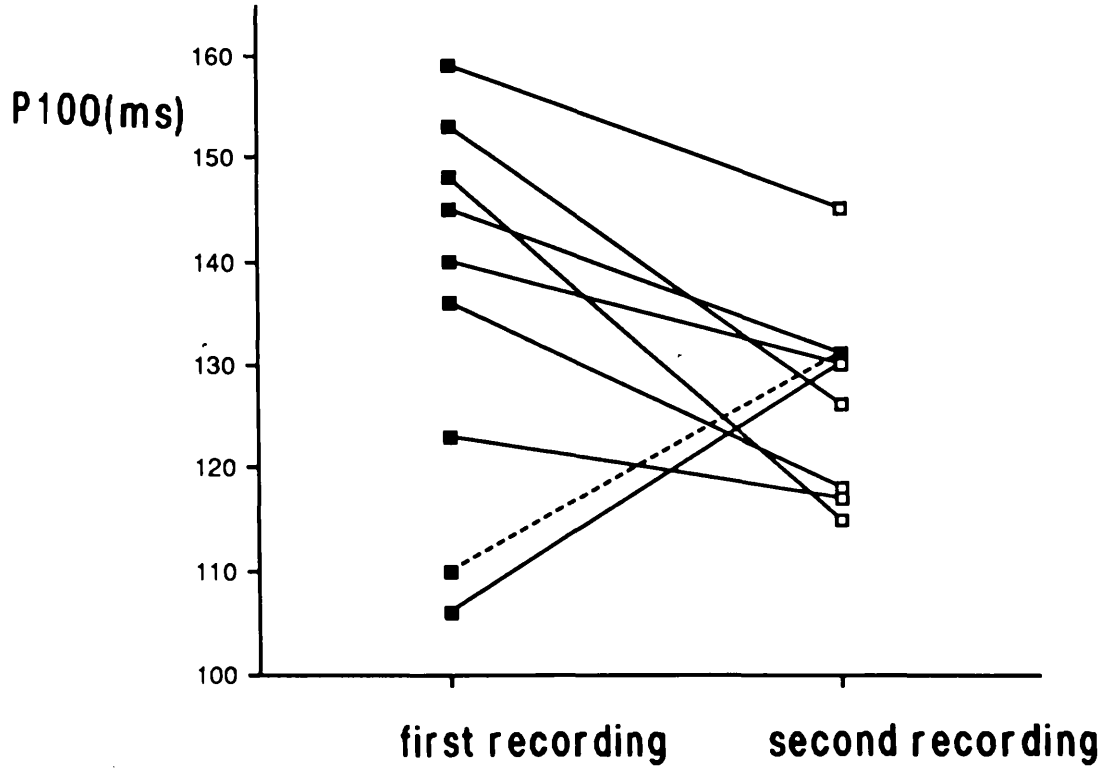

P100(ms)
160
150
140
130
120
110
100
first recording
second recording

Fig.5.1.3

Fig. 5.1.4 Relationship between VEP amplitude (μV) and lesion length (slices) in pre-contrast scans at follow up. G.O.F.=goodness of fit.

slope=-1.9 μV/5 mm slice

G.O.F=71% (p=0.01)

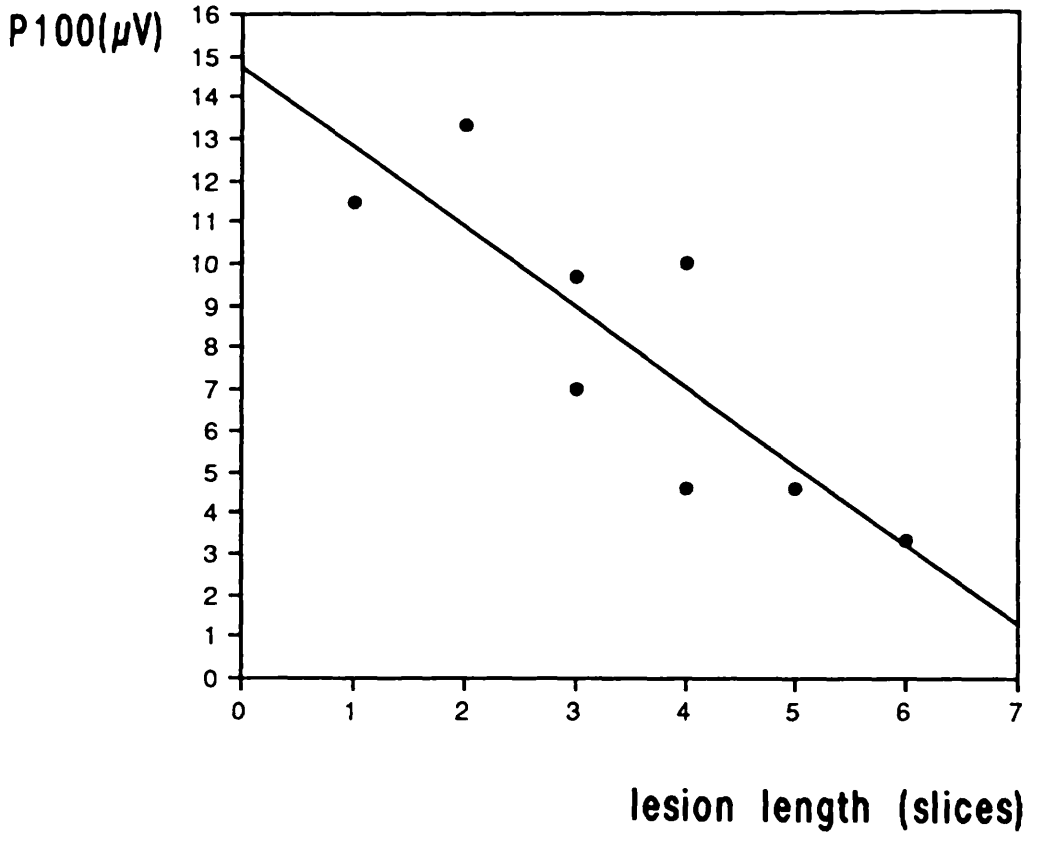


Fig.5.1.4

PART 2

ELECTROPHYSIOLOGICAL AND MRI EVOLUTION OF OPTIC NERVE LESIONS FOLLOWING ACUTE OPTIC NEURITIS

5.2.1 INTRODUCTION

In the weeks and months following an attack of optic neuritis, the VEP latency tends to decrease and returns to within the normal range in some cases. In published series, the incidence of improvement has been quoted as 32% in 34 days (Diener and Scheibler, 1980), 26% in 14 weeks (De Weerd and Jonkman, 1982), 14% in 12 months (Confavreux et al., 1982), 24% in 18 months (Matthews and Small, 1979) or and 39% in 46 months (Hely et al., 1984). Normalisation of latency has been reported in less than 10% of eyes followed up for up to 18 months (Matthews and Small, 1979; De Weerd and Jonkman, 1982), but the chance of normalisation tends to increase with the time elapsed since the onset of the attack (Hely et al., 1984; Matthews and Small, 1983). The improvement of the VEP latency appears to be a more consistent finding in childhood: in one study (Kriss et al., 1988) the latency had returned to normal a mean of 8.8 years after an episode of acute optic neuritis in 55% of subjects who were under 15 years of age at the time of the attack.

Reports concerning long term changes of the VEP amplitude are fewer: Matthews and Small (1979) detected a significant deterioration of amplitude in 51 MS patients followed-up for a mean period of 18 months; Carroll et al. (1984) reported no significant overall change in the VEP amplitude in 116 MS or optic neuritis cases over 14 to 28 months follow-up.

The aim of the present study was to examine the electrophysiological and morphological evolution of demyelinating optic nerve plaques in the long term, after recovery from acute optic neuritis, and compare changes of the VEP amplitude and latency to modifications in length or axial area of the optic nerve lesions seen on MRI.

5.2.2 CASE MATERIAL

The patient group included 14 subjects, 11 females and 3 males aged 17 to 50 years (mean 32±9 years). They all had had an episode of clinically isolated acute unilateral optic neuritis, the onset of visual blurring occurring 20 to 188 days (mean 65±49 days) prior to commencement of the study. Optic neuritis had been diagnosed according to standard clinical criteria (Compston et al., 1978) and had not been associated with any signs of primary ocular or retinal pathology on neuro-ophthalmological examination. At the time of the initial testing, the visual acuity had returned virtually to normal (6/9 or better on Snellen chart) in

every case, the general neurological examination was normal and the history did not suggest any past significant neurological deficits outside the visual pathway. None of the patients was on corticosteroid treatment during the study period, nor had any been treated in the acute phase.

5.2.3 METHODS

VEP recording and optic nerve MRI were performed on the same day on two occasions: 20 to 188 days (mean 65±92 days) and 348 to 625 days (mean 477±92 days) from the onset of visual blurring. The two examinations were separated by 322 to 567 days (mean 412±77 days).

5.2.3.1 Visual evoked potentials

The recording methods were similar to those described in paragraph 3.3.3, except that the chequerboard pattern was delivered by two television displays, stimulating the left and right eye separately but simultaneously (this was part of an investigation of binocular interaction after optic neuritis). Subjects sat one metre away from the screens which subtended an angle of 23.3° (horizontal) or 17.5° (vertical) at the eye. The subtense of each check was 50' and the brightness of the white squares was 14.5 cd/m^2, with a contrast of 93%. The relatively low luminance of this stimulus caused VEP latencies in the unaffected eyes

to be longer than those recorded with the conventional slide projector and screen (Galvin et al., 1980). The reversal was produced every 610 ms, the time taken for the screen to change fully being 10 ms.

Full- and half-field responses were recorded, but only the former were used for statistical evaluation; left and right hemifield components were examined to help to identify the P100 following full-field stimulation and not analysed further.

After the study was carried out, it was noticed that the stimulus delivered from the right television was slightly dimmer than that produced by the left television. For this reason, during statistical analysis inter-ocular comparisons were avoided and in each patient the response from the left or right eye was compared to that recorded from the same eye of a sex- and age-matched control.

5.2.3.2 Magnetic Resonance Imaging

MRI was performed in a Picker 0.5 Tesla superconducting scanner, using a binocular surface coil. Images of the optic nerve were performed in a STIR ($IR_{2000/40/150}$) sequence. Contiguous coronal slices of 5 mm thickness were obtained throughout the orbit from the head of the optic nerve to the optic chiasm. Pilot scans in three planes enabled accurate repositioning. Two neuroradiologists, who had no knowledge of the clinical and electrophysiological data,

viewed the images independently and then reached consensus as to the number and position of slices with abnormal signal. A lesion was defined by an area of increased signal within the optic nerve. The location of the lesions with respect to the surrounding anatomical structures was not analysed in detail. The lesion length was given by the number of 5 mm contiguous slices in which an increased signal was seen. The cross-sectional area of affected and unaffected optic nerves was measured in 11 patients. Dimensions were judged against the processed image in horizontal (x) and vertical (y) axes as determined by the internal markers on the pilot scan. The separation of the instrument's point was then measured using a graticule marked in tenths of a mm, under 4x magnification. The slice encompassing the mid-point of the lesion for affected nerves and the corresponding anatomical slice for unaffected nerves were measured independently, without co-reference. Follow up measurements were also made independently, on equivalent slices. The nerve cross-sectional area was estimated using a mean of x and y as diameter, after application of an image magnification factor.

5.2.3.3 Statistical analysis

Differences in VEP amplitude and latency between previously affected and control eyes were evaluated using the independent t-test (two tailed probability). Serial dif-

ferences in VEP amplitude and latency in previously affected eyes were computed using the paired t-test (two tailed probability). Comparisons of the mean lesion length or axial area between affected and unaffected optic nerves of the same patients or between first and second scan were made using a non parametric method (Wilcoxon matched pairs). The correlation between VEPs and lesion length was evaluated using the Spearman rank correlation test. The relationship between VEP amplitude or latency and optic nerve cross-sectional area was assessed using the linear regression.

5.2.4 RESULTS

Individual VEP and MRI findings are illustrated in Table 5.2.1.

5.2.4.1 Visual evoked potentials

On first recording, the mean VEP amplitude in previously symptomatic eyes was reduced to about 70% of that recorded in the control eyes (8.5±4.3 μV and 11.8±5.2 μV, respectively, $t=-1.8$ $p>0.05$), while the mean latency was increased by 22 ms (138±17.4 ms and 116±5.7 ms, respectively, $t=4.5$ $p<0.001$).

At follow up, the mean VEP amplitude in the previously affected eyes was about 90% of that recorded in the control eyes (10.9±5.7 μV and 11.8±5.2 μV, respectively, $t=-0.4$ $p>0.05$), whereas the mean latency was 11 ms longer (127±12.1 and 116±5.7, respectively, $t=3.2$ $p<0.01$).

In previously affected eyes, the mean VEP amplitude had increased by about 20% from first to second recording ($p<0.05$) and the latency had decreased by 11 ms ($p=0.05$) [Table 5.2.2 and Fig. 5.2.1a].

5.2.4.2 Magnetic Resonance Imaging

On first examination, a lesion was seen in 13/14 affected optic nerves, whereas there was no abnormality in the unaffected fellow nerves. The lesion length varied from one to five contiguous slices (mean 2.7±1.3 slices). The mean cross-sectional area of affected optic nerves (measured in 11 cases), was not significantly different from that of the unaffected fellow nerves [Table 5.2.3].

At follow up, a lesion was still seen in 13/14 nerves of the previously symptomatic eyes. The lesion length varied from one to six contiguous slices (mean 3.2±1.7 slices) and did not show any significant change from first to second examination. The mean cross-sectional area of affected optic nerves was reduced to about 80% of that of the unaffected fellow nerves ($p<0.01$). From first to second

scan, the mean cross-sectional area of 11 affected optic nerves showed a decrement of about 13% and this change just failed to reach the 5% significance level (p=0.06) [Table 5.2.3].

In Case 12, a lesion was seen in the previously unaffected right optic nerve, according to the fact that this patient developed right optic neuritis during the follow up period [Fig. 5.2.1b]. The remaining previously unaffected nerves had normal MRI.

5.2.4.3 MRI and VEP correlations

a) Lesion length

Neither on first nor on second examination was there a significant correlation between the length of optic nerve lesions and the VEPs recorded in previously symptomatic eyes.

b) Optic nerve axial area

In previously symptomatic eyes of the 11 patients whose optic nerve axial area was measured, the mean VEP amplitude showed an increment of about 22% between first and second recordings (from 7.8±4.1 μV to 10.9±4.5 μV), which just failed to reach statistical significance (t=

-2.03 p=0.07). The mean latency showed a decrement of 9 ms (from 138±16.8 ms to 129±13.0 ms) , which was also not significant (t=1.7 p>0.05).

On first examination, the VEP amplitude in previously symptomatic eyes was directly correlated with the cross-sectional area of affected optic nerves (r=0.87 p<0.001), with a slope of 0.8 μV/mm2 area. The effect accounted for 75% of the variance [Fig. 5.2.2]. This correlation was not confirmed on second examination, due to the fact that during the follow up period the axial area had decreased in 9/11 optic nerves while the VEP amplitude had increased in 9/11 eyes.

The VEP latency was not significantly correlated with the optic nerve axial area on either examination.

5.2.5 DISCUSSION

This study involved a small number of optic neuritis cases, studied serially about 2 and 16 months after the onset of visual blurring. The results can only be considered preliminary, because of the following methodological deficiencies. The TV monitors used to generate the chequerboard pattern yielded less reliable results than the conventional slide projector and screen. It has been reported that television displays produce responses which show a more variable latency (Bartl et al., 1978) or occur later (Galvin et al., 1980) than those obtained using the

mirror/projector stimulus. In addition, the cross-sectional area of the optic nerves was measured from the MRI by sight and the measurer was not blind to whether the scans had been obtained at first or second examination.

Despite these shortcomings, a significant improvement in the amplitude and latency of the VEP was detected in the whole series. A long term improvement of some VEP latencies after an episode of acute optic neuritis has been reported in several previous studies (Matthews and Small, 1979; Diener and Scheibler, 1980; de Weerd and Jonkman, 1982; Confraveux et al., 1982; Matthews and Small, 1983; Hely et al., 1984; Kriss et al., 1988). Amplitude changes have been less often investigated, possibly because of the large variability of this parameter and the consequent difficulty in quantifying abnormalities, and have been reported as not significant (Carroll et al., 1984) or tending towards deterioration (Matthews and Small, 1979). In the present study, the amplitude increment of the VEP suggests restoration of conduction in a certain proportion of optic nerve fibres (Halliday and Mcdonald, 1977), while the latency decrement is consistent with partial remyelination (Prineas and Connell, 1979; Prineas et al., 1987) of the optic nerve lesions.

The other main finding was that the cross-sectional area of 11 affected optic nerves was significantly less than that of the unaffected fellow nerves at follow up but not in the first MRI, although the serial reduction of this

measurement failed to reach the 5% significance level. In the same eyes, the VEP amplitude and latency showed a non-significant trend to improve. Since in the full group of patients an improvement of these parameters was detected, it is possible that in the 11 eyes a significant effect was missed due to the small number of observations.

What could be the pathological mechanism underlying the reduction in diameter of affected optic nerves? One possibility is the following. After optic neuritis, a reduction of the optic nerve cross-sectional area is probably related to loss of some axons and reduction of the diameter of the surviving fibres, due to demyelination. Oedema may initially counter these changes, by increasing the diameter of the optic nerve. In the present series, 16 months after the onset of the attack oedema had probably fully resolved, thus unmasking the reduction of the axial area of the affected optic nerves. The presence of demyelination in the optic nerve lesions is reflected by the relatively stable increase of the VEP latency, while the loss of some fibres could be responsible for the incomplete recovery of the VEP amplitude and visual acuity. Partial remyelination and resolution of oedema could account for the improvement of the VEP latency and amplitude, the latter possibly through relief of compression.

No significant change in the length of the optic nerve lesions was detected from first to second scan. It is possible that during the follow up period no change occurred.

Alternatively, small changes might have been missed. The lesion length was defined by the number of 5 mm contiguous slices in which an increased MRI signal was seen. This measurement is rather approximate and may sometimes fail to reflect the real longitudinal extent of a given lesion. In paragraph 5.1.3.3 it was pointed out that the possibility of detecting altered signal in one slice depends on the value of the T_1 and T_2 relaxation times in the pathological tissue. If these are markedly altered a lesion will easily be seen, but if they are moderately modified a lesion will not be distinguishable from the surrounding normal tissue and, consequently, changes in lesion length will be missed.

In a previous investigation (Kakisu et al., 1991) a significant correlation was found between the length of optic nerve lesions and VEP amplitude or latency in patients who had experienced an attack of optic neuritis at least four months prior to the study. The present investigation failed to detect any significant relationship between lesion length and VEP amplitude or latency.

On first examination, the axial area of affected optic nerves was directly correlated with the VEP amplitude. This suggests that the larger the diameter of the optic nerve, the higher the number of axons and the larger the amplitude of the VEP. Unfortunately, this correlation was not confirmed at follow up and the reasons for this result are obscure.

In conclusion, the present study has shown that during a mean follow up period of 14 months after clinical recovery from acute optic neuritis the VEP amplitude and latency improve. At follow up, the diameter of the affected optic nerves was reduced as compared to that of the unaffected fellow nerves, probably as a consequence of demyelination and axonal loss incurred during the acute lesion. Further studies are required in order to confirmed this finding which suffered from certain methodological deficiencies.

TABLE 5.2.1: CLINICAL, VEP AND MRI FINDINGS

First examination

Case	Sex	Age	Side	Onset (days)	VEPs			
					Left eye		Right eye	
					μV	ms	μV	ms
1	F	50	left	120	7.2	158	7.9	129
2	F	36	left	34	7.8	139	11.0	131
3	F	26	right	38	22.8	115	10.6	158
4	M	31	right	55	NR	NR	15.0	164
5	M	34	left	118	6.2	129	8.8	123
6	F	25	left	75	9.8	151	11.4	128
7	F	24	right	24	15.6	109	13.0	119
8	M	35	right	65	9.0	118	5.7	130
9	F	21	right	188	8.7	116	7.2	123
10	M	42	left	2	7.9	128	7.5	124
11	F	33	right	26	18.2	120	17.6	111
12	F	38	left	31	4.8	153	7.0	125
13	F	17	right	84	8.1	108	4.9	148
14	F	39	right	30	8.7	116	1.5	118

Case	Side	MRI lesion		
		axial area		
		length (slices)	left (mm^2)	right (mm^2)
1	left	2	13.3	14.8
2	left	1	12.9	18.9
3	right	3	15.2	16.8
4	right	2	NMS	NMS
5	left	2	11.9	13.3
6	left	3	18.5	19.3
7	right	-	-	-
8	right	2	NMS	NMS
9	right	1	13.7	13.3
10	left	5	18.5	20.2
11	right	3	19.5	22.2
12	left	5	13.3	12.2
13	right	2	14.4	14.4
14	right	4	12.2	10.9

continued /

Table 5.2.1 continued

Second examination

Case	Sex	Age	Side	Onset (days)	VEPs: Left eye μV	VEPs: Left eye ms	VEPs: Right eye μV	VEPs: Right eye ms
1	F	50	left	530	4.7	153	8.5	125
2	F	36	left	601	11.9	131	12.6	124
3	F	26	right	375	15.2	115	6.4	110
4	M	31	right	532	19.0	123	18.0	134
5	M	34	left	501	10.0	119	6.9	126
6	F	25	left	560	12.3	140	13.0	124
7	F	24	right	455	9.8	113	20.1	114
8	M	35	right	430	13.2	124	3.4	131
9	F	21	right	553	13.3	119	15.7	120
10	M	42	left	388	10.8	120	8.1	128
11	F	33	right	348	19.4	115	17.8	140
12	F	38	left	383	11.1	130	11.7	124
13	F	17	right	625	4.5	110	6.0	136
14	F	39	right	398	16.5	118	3.2	115

Case	Side	MRI lesion: axial area length (slices)	left (mm^2)	right (mm^2)
1	left	5	16.6	19.1
2	left	1	4.4	12.6
3	right	6	16.2	13.6
4	right	2	NMS	NMS
5	left	2	9.1	10.3
6	left	4	17.0	19.5
7	right	-	-	-
8	right	2	NMS	NMS
9	right	1	16.2	16.2
10	left	6	14.3	16.6
11	right	3	19.5	17.8
12	left	3	11.6	18.6
13	right	3	13.6	10.6
14	right	3	14.7	8.8

Legend: NR = not recorded; NMS = not measured;
- = no lesion found.

TABLE 5.2.2: CHANGES OF THE MEAN±SD AMPLITUDE (μV) AND LATENCY (ms) OF THE P100 FROM FIRST TO SECOND RECORDING (N=14)

	Affected eyes		Unaffected eyes	
	μV	ms	μV	ms
First recording	8.5±4.3	138±17.4	11.2±4.8	119±6.6
Second recording	10.9±5.7	127±12.1	11.7±4.1	120±5.7
t	-2.4	2.1	-0.5	-1.0
p	<0.05	0.05	NS	NS

TABLE 5.2.3: MEAN±SD OPTIC NERVE CROSS-SECTIONAL AREA (mm^2): COMPARISONS BETWEEN FIRST AND SECOND SCAN AND BETWEEN AFFECTED AND UNAFFECTED NERVES

	Affected (mm^2)	Unaffected (mm^2)	Z	p
First scan	15.1±3.4	15.3±3.1	-0.9	NS
Second scan	12.7±4.2	16.1±3.1	-2.8	<0.01
Z	-1.9	-0.4		
p	NS	NS		

Fig. 5.2.1a **Case 12** (38 year-old female), left optic neuritis, full field VEPs. Top, first recording performed 31 days since the onset of visual blurring. Visual acuity in the left eye 6/9. Bottom, second recording performed 12 months later. Visual acuity in the left eye 6/9. During the follow up period, the amplitude of the P100 from the left eye increases by about 100% and its latency decreases by 23 ms.

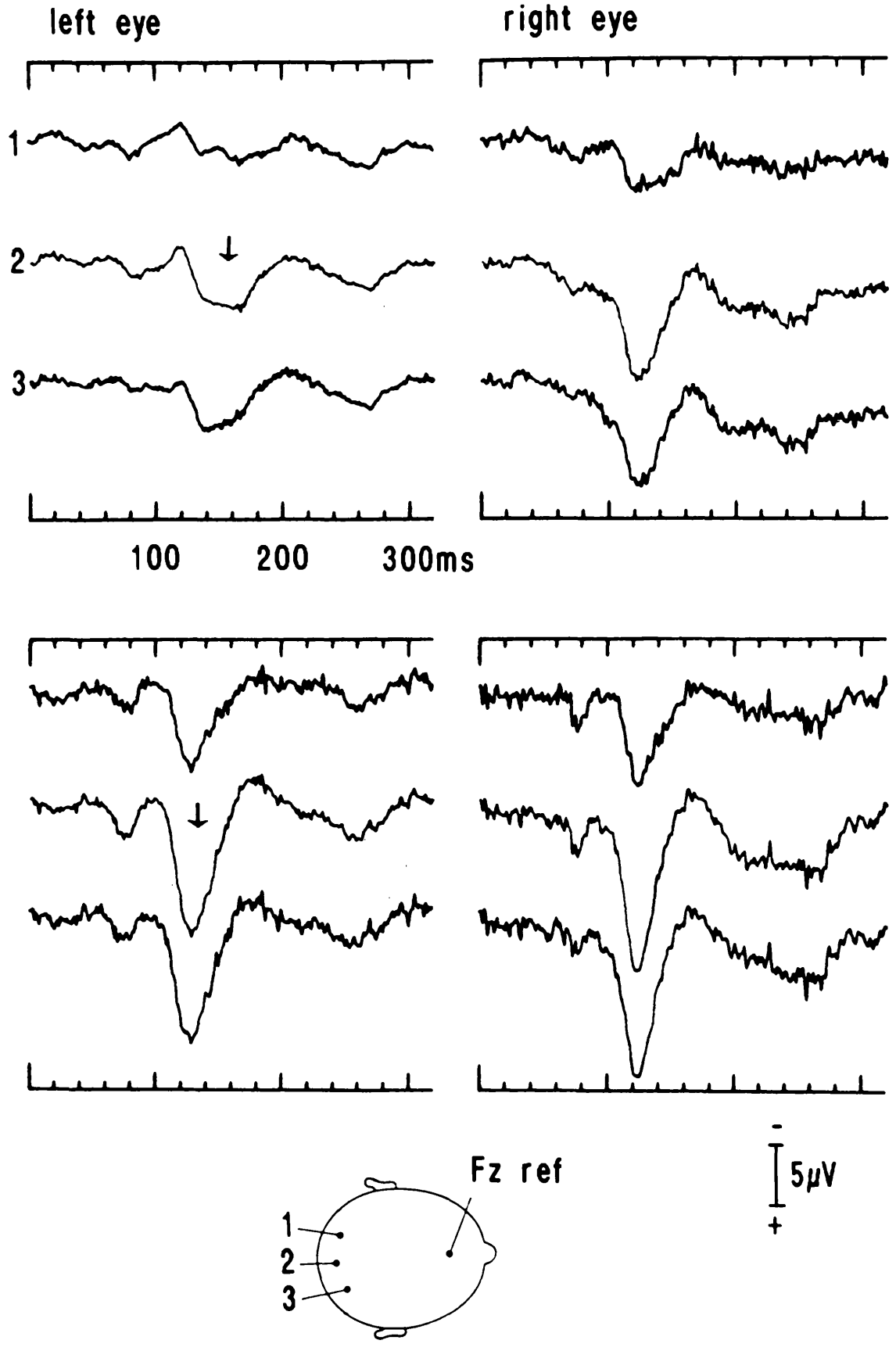


Fig.5.2.1a

Fig. 5.2.1b, optic nerve MRI. The first scan (left) shows an area of increased signal in the left optic nerve. The second scan (right) displays an area of increased signal in the left and right optic nerves, the latter due to the occurrence of right optic neuritis during the follow-up period.

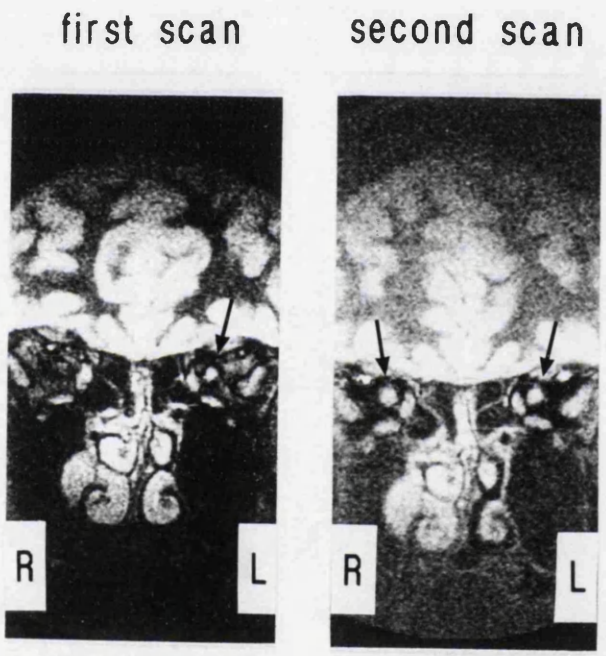


Fig.5.2.1b

Fig. 5.2.2. Relationship between the P100 amplitude and the optic nerve lesion area, on first examination. G.O.F.=goodness of fit.

slope=0.8 μV/mm²

G.O.F.=75% (p<0.001)

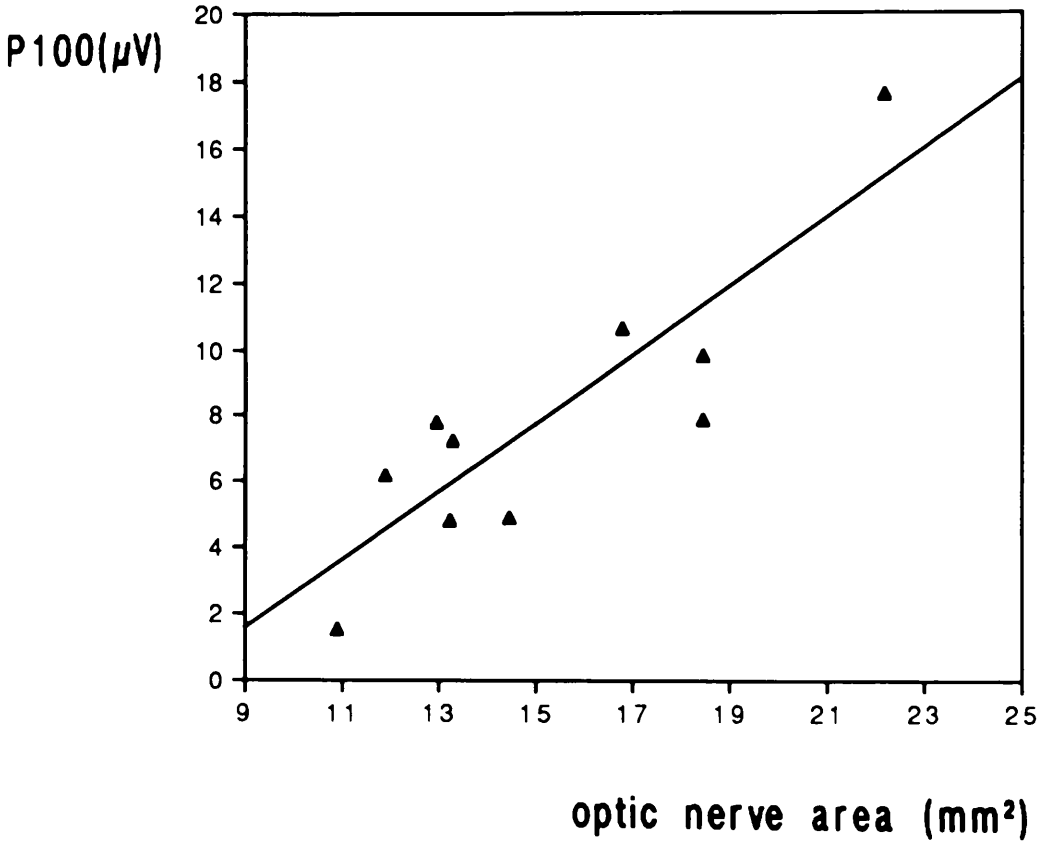


Fig.5.2.2

CHAPTER

6

GENERAL DISCUSSION

This thesis has illustrated some factors which affect the correlation between MRI, EP and clinical findings in MS.

In chapter 2, SEPs were compared with MRI abnormalities thought to involve the somatosensory pathways at spinal and supraspinal levels. Lesions occupying the posterior quadrants of the cervical cord were significantly associated with abnormal SEPs from the ipsilateral median nerve; conversely, MRI lesions in the periventricular areas, believed to involve the somatosensory radiations, apparently did not cause SEP abnormalities and were also clinically silent. These findings may be explained in terms of the difference between the density of sensory fibres in the cervical cord and thalamo-cortical radiations. In the cervical cord, the somatosensory fibres are placed in a relatively small volume, so that the proportion affected by a lesion is very likely to give rise to abnormal SEPs. Conversely, in the periventricular areas sensory fibres occupy a larger volume and, therefore, may not be involved by MRI lesions (which are usually small and spatially disseminated) or the proportion affected may be insufficient to produce demonstrably abnormal somatosensory responses. An additional important factor explains why even quite extensive MRI lesions in the cord are sometimes not associated with SEP or clinical abnormalities. MRI detects changes in the density and behaviour of mobile protons: an increase in

extracellular or intracellular water (as produced by oedema or gliosis) alters the MRI signal, whereas demyelination itself contributes little to it since in the myelin the mobility of protons is low.

Sensory-motor deficits in the upper and lower limbs were not closely related to the distribution of SEP or MRI abnormalities. This may be partly due to the fact that both techniques and the neurological investigation are of limited power and usually do not allow a precise delineation of the total extent of a lesion in terms of the anatomical structures involved. In fact, in some patients in whom the clinical deficit was extremely well defined, appropriate SEP and MRI abnormalities were observed.

Similar to the situation with regard to MRI lesions in the somatosensory radiations, areas of altered signal in the optic radiations rarely give rise to homonymous hemianopic defects in patients with MS. The study presented in chapter 3 was designed to elucidate the morphological and electrophysiological features of symptomatic retrochiasmal lesions. On MRI, these were large and shrank in coincidence with the recovery of the homonymous field defect. In MS, shrinkage of brain MRI abnormalities appears to be indicative of resolution of oedema. Therefore, oedema present in acute retrochiasmal lesions might have played a

crucial role in producing homonymous field defects, probably through conduction block due to a compressive mechanism.

VEPs including hemifield recordings showed a low sensitivity in detecting retrochiasmal lesions (less than one third of the patients). The amplitude of the responses from affected hemifields was significantly reduced only in severe cases and the latency was seldom increased. The former finding was mainly due to the fact that the amplitude of responses from heteronymous hemifields of the same eye shows a large intra- and inter-individual variability in the healthy population, presumably due to differences in the exposure of the primary visual area on the convexity of the occipital pole. The finding that the latency of the hemifield responses is occasionally increased suggests that the extent of demyelination affecting the activated retrochiasmal fibres is only rarely sufficient to be reflected in the VEP latency.

In patients with a clinically isolated optic neuritis, brain MRI abnormalities are quite frequently found and are, by definition, asymptomatic. The study presented in chapter 4, however, suggests that white matter lesions may interfere with cognitive functions such that their extent correlates with the degree of cognitive impairment and with the electrical brain activity associated with the performance of certain cognitive tasks. This was

assessed by recording auditory cognitive ERPs and performing psychometric investigations in patients who experienced an episode of optic neuritis within about a month prior to the study. Extensive brain MRI lesions were associated with a degraded ERP waveform and a poor performance on tests of attention and speed of information processing. These findings show that asymptomatic brain MRI abnormalities may not always be totally "silent", but may correlate with subtle deficits which are not detected on routine neurological investigation. The occasional observation of abnormal ERPs in the absence of MRI lesions suggests, either that the latter may be present but below the resolution of MRI, or that there may be other factors associated with the presence of an active demyelinating lesion which affect cognitive functions in the absence of structural lesions.

In chapter 5 two studies of VEP and MRI correlations in optic neuritis were presented. One addressed the question concerning the mechanism of acute impairment and remission from the attack, while the other examined the electrophysiological and MRI evolution after recovery. In the first study, MRI of the optic nerve was performed using the contrast agent Gd-DTPA, in order to highlight the presence of blood-brain-barrier breakdown (believed to be a concomitant of inflammation) within the optic nerve lesion. At the time of the attack, leakage of Gd-DTPA was associated with an impaired visual acuity and a VEP of

reduced amplitude and increased latency. After approximately one month, the disappearance of Gd-DTPA leakage coincided with the return to normal acuity levels and a significant improvement of the VEP amplitude, although its latency was unchanged. This suggests that inflammation plays an important role in the pathogenesis of sudden visual impairment by causing a conduction block, which recovers in association with the resolution of inflammation. In the longer term, any residual visual deficit is more likely to be due to demyelination and axonal loss than acute inflammation. In more general terms, restoration of conduction concomitant with resolution of inflammation is likely to be a crucial factor in determining symptom remission in the early stages of MS.

In the same investigation, the length of the optic nerve lesion was inversely correlated with the VEP amplitude at follow up but not on first examination. It is possible that at follow up, the length of the MRI lesions reflected more faithfully the length of the real lesion, due to resolution of oedema which contributes a great deal to the alteration of the MRI signal in acute lesions. The longer the lesion length, the greater the leakage of axonal current at the level of the lesion and the higher the likelihood of conduction block. In the long term, therefore, both axonal loss and conduction block due to demyelination may contribute to any residual loss of VEP amplitude or visual acuity.

The findings of the second study of chapter 5 should only be considered preliminary, because of certain methodological deficiencies which limited the reliability of the results. The pattern stimulus was generated by a television display, which produces responses of longer and more variable latency than the conventional mirror and slide projector system. In addition, on MRI, the optic nerve cross-sectional area was measured on visual inspection by a neuro-radiologist who was aware as to whether measurements were effected on the first or second scan. In spite of these shortcomings, the amplitude and latency of the VEP showed an improvement during a period of approximately 14 months subsequent to acute optic neuritis, while the cross-sectional area of affected optic nerves, measured at the mid-point of the length of the lesion, showed a concomitant tendency to decrease. The VEP changes suggest restoration of conduction in some optic nerve fibres and acceleration of conduction in others. Somewhat paradoxically, the concurrent decrement of the optic nerve axial area could be due to loss of some fibres and reduction of the diameter of surviving ones consequent to demyelination. This change may be initially counteracted by oedema, such that in the first scans the area appeared normal, but becomes evident with time after resolution of the latter. Although other studies are required to confirm

these findings, it is likely that after an acute demyelinating episode, reparative mechanisms are activated aiming at restoring the function of damaged nerve fibres.

In conclusion, in MS there is a good degree of correlation between EP and MRI findings. Areas of altered signal area associated with abnormalities of sensory conduction in regions of the central nervous system in which there is a high density of sensory fibres (i.e. cervical cord, optic nerve). The correlation breaks down when fibres are placed in a large volume, as compared to that occupied by the MRI lesions (sensory radiations). Since the area of altered signal is not always conterminous with that of myelin loss, the infrequent finding of extensive MRI lesions, presumably involving a high proportion of fibres, in the absence of electrophysiological abnormalities is not surprising.

The study of the correlation between EP and MRI abnormalities is a useful approach to address pathophysiological questions in MS. The findings of the present thesis have shown that inflammation is a crucial factor of symptom remission after acute optic neuritis, while demyelination and axonal loss are probably responsible for the incomplete recovery of the visual function. It would be of interest to see whether the same sequence of events encountered in acute optic neuritis can be observed in relapses involving

other areas of the central nervous system, such as the cervical cord. This would give more strength to the findings of the present work and could lead to the identification of other factors which may have a role in the mechanism of remission. A further development of this type of investigation would be the study of the pathophysiological features of long-standing MS lesions, which would help to identify the factors responsible for clinical progression. Finally, the study of the serial changes of MRI and EP abnormalities could help to better understand the pathophysiological evolution of MS lesions. This approach could also be exploited to elucidate the effect of drugs on MS lesions, which would lead to the implementation of appropriate therapeutic trials.

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CORRELATION OF SEP ABNORMALITIES WITH BRAIN AND CERVICAL CORD MRI IN MULTIPLE SCLEROSIS

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SUMMARY

In 31 patients with definite or suspected multiple sclerosis (MS) presenting with a cervical cord syndrome, somatosensory evoked potentials (SEPs) were recorded to median and posterior tibial nerve stimulation, using cephalic and noncephalic reference electrodes. Magnetic resonance imaging (MRI) of the brain and cervical spinal cord was performed, the latter in sagittal and axial views. SEPs were abnormal in 67.7% of patients, whereas MRI showed cervical cord lesions in 74.2% and intracranial lesions possibly involving the somatosensory pathways in 64.5% of cases. A significant correlation was found between abnormalities of cervical (N13) and cortical (N20) potentials following median nerve stimulation with Fz reference and MRI abnormalities involving the ipsilateral or posterior half of the cervical cord, but not the contralateral or anterior half. The N13 potential, recorded from the low cervical region to a supraglottal reference, was most frequently abnormal in patients with MRI lesions at C6 or C7, whereas P14, recorded from the scalp to a clavicle reference, was most often affected by lesions at C1 or the cervicomedullary junction. Abnormalities of the cortical P40 to tibial nerve stimulation were less significantly correlated with cervical MRI lesions. The latency of N20 measured from N9 at the clavicle and the absolute latency of P40 were significantly correlated with the length of MRI abnormalities in the ipsilateral cervical cord. No significant correlation was observed between SEP abnormalities and brain MRI lesions, which it was considered might possibly involve the intracranial somatosensory pathways. It was concluded that (1) the morphological lesions seen in MRI of the cervical cord usually give rise to appropriate electrophysiological deficits, but the occasional finding of a widespread MRI lesion with normal SEP suggests that myelin damage is not the only or the major factor responsible for abnormal MRI signal; and (2) 'clinically silent' lesions apparently involving the radiations and other sensory structures of the brain appear not to give rise to detectable SEP abnormalities, using the methods of the present study.

INTRODUCTION

The physiological properties of nerve fibres are to a large degree dependent on the integrity of their myelin sheaths. Experimental demyelination causes either slowing or blockage of conduction (McDonald, 1963). When an electrical stimulus is applied to a nerve trunk and recording electrodes are placed at appropriate locations over the neck and scalp, somatosensory evoked potentials (SEPs) can be recorded, which reflect the passage of the afferent volley at different levels of the somatosensory system. In the presence of a demyelinating process affecting sensory nerve fibres, defects in axonal conduction can frequently be detected as delay, reduction or absence of the SEPs (*see* Jones, 1982*a* for review).

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Previous studies have demonstrated a high incidence of abnormal SEPs in patients with suspected or clinically definite multiple sclerosis (MS), with or without deficits of proprioceptive or discriminative tactile sensation (Baker *et al.*, 1968; Small *et al.*, 1978; Gambi *et al.*, 1982). The demyelinating lesions of MS can be detected by magnetic resonance imaging (MRI) in the brain (Young *et al.*, 1981) and spinal cord (Maravilla *et al.*, 1984). These changes usually appear as focal areas of altered signal and are most often located in the deep cerebral white matter. Previous investigations have demonstrated MRI abnormalities in a high percentage of patients with MS, in both the early and advanced stages of the disease (Young *et al.*, 1981; Lukes *et al.*, 1983; Runge *et al.*, 1984; Ormerod *et al.*, 1987; Honig *et al.*, 1988).

Whereas the diagnostic usefulness of SEPs and MRI in MS has been widely investigated and is now well established, little is known about the correlation between the abnormalities shown by these techniques. In this study we examined 31 patients with a cervical cord syndrome, believed to be due to a demyelinating lesion. In some cases this was clinically isolated and in others it appeared associated with clinically disseminated deficits; in the latter the criteria for MS, established by Poser *et al.* (1983), were fulfilled. SEPs were recorded from the upper and lower limbs and compared in detail with MRI of the cervical spinal cord and brain. SEPs and MRI findings were also compared with the pattern of clinical abnormalities.

MATERIAL AND METHODS

Patients

The patient group consisted of 31 subjects, 21 females and 10 males, aged 22–51 (mean 35.4) yrs. Each patient presented with a cervical cord syndrome, involving the sensory and/or motor pathways, and 12 also showed clinical evidence of lesions located elsewhere in the central nervous system (CNS). When clinical features, evoked responses, cerebrospinal fluid analysis for oligoclonal IgG bands and MRI findings were all considered, 27 patients were classified by the Poser criteria (Poser *et al.*, 1983) as having MS: clinically definite MS, 3 patients; laboratory supported definite MS, 11 patients; clinically probable MS, 13 patients. The other 4 cases, who did not show evidence of abnormalities except in the cervical spinal cord, were classified as having an isolated cord lesion: the clinical and radiological findings in these patients provided no evidence of traumatic, compressive, degenerative or vascular pathology and the lesion was therefore considered compatible with demyelination. The cord syndromes had at the time of study a duration of 1–139 (mean 31.7) months and appeared relapsing and remitting in 21 cases, progressive (duration longer than 6 months without remission or exacerbation) in 7 cases and acute (1 episode lasting less than 1 month) in 3 cases.

Controls

The SEP control group consisted of 31 healthy volunteers, 16 males and 15 females, aged 18–43 (mean 29.9) yrs.

SEPs

Two or more SEP recordings were obtained from each stimulated limb in each subject. The stimulus (200 μs constant voltage square wave) was delivered at 3.2 impulses/s to the median nerve at either wrist and the tibial nerve at either ankle, with an intensity sufficient to produce a moderate twitch of the thenar and plantar muscles respectively.

Responses were recorded by silver/silver chloride disc electrodes, located over the midpoint of each clavicle, the spinal vertebrae C7 and C2, the anterior aspect of the neck on the midline above the thyroid cartilage ('supraglottal' location), the mastoid processes, both hand areas of the sensory cortex (2 cm posterior to the vertex and 7 cm towards each tragus) and the foot area of the sensory cortex (2 cm posterior to

the vertex); all the active electrodes were referred to Fz (International 10-20 System). Later in off-line analysis, the supraglottal waveform was subtracted from the C7 response and the clavicle response (contralateral to the stimulated arm) was subtracted from all channels, in order to obtain noncephalic-referred neck and scalp waveforms.

The amplifiers' high frequency response was less than 3 dB down at 5 kHz and the time constant was 1 s. Four hundred sweeps were averaged in each run. In recordings from the median nerve the averager epoch was 32 ms (8 sample points/ms) starting 3 ms after the stimulus pulse, and in recordings from the tibial nerve the epoch was 64 ms (4 sample points/ms) with a 13 ms poststimulus delay. When it was impossible to identify a significant cortical response within this period, the averager epoch was doubled (64 or 128 ms, respectively).

Using the Fz reference, the major components evoked from the median nerve were N9 (clavicle), N13 (C7) and N20 (scalp), whereas from the tibial nerve the main component recorded was P40 (scalp). The responses obtained in the noncephalic reference waveforms were N13 (C7-supraglottal) and P14 (scalp-clavicle) (fig. 1). N9-N20 and N13-N20 interpeak latencies were measured in the Fz reference recordings, but only the former was used for statistical evaluation, as N13 in some waveforms was abnormally degraded and its latency difficult to measure.

The normal latency limit for each SEP component was defined by the mean+2.5 SD of the absolute latency, interpeak latency and left-right latency difference in the control group. The amplitude limit was defined by the mean−2.5 SD of log amplitude, log (left/right) and log (P14/P9) amplitude ratio (the latter as suggested by Garcia Larrea and Mauguière, 1988).

MRI

All patients were imaged on a Picker 0.5 Tesla superconducting scanner within 10 days of the SEP recordings. Brain MRI was interpreted by one author (G.H. du B.) and cord MRI by another (D.H.M.), both of whom were blind to the electrophysiological data. Lesions were defined as areas of unequivocally increased signal on T_2-weighted sequences or of decreased signal on T_1-weighted sequences.

The brain was imaged using a 30 cm spherical receiver coil. A moderately T_2-weighted sequence ($SE_{2000/60}$) was performed in every case and, when changes were equivocal, a more heavily T_2-weighted sequence ($SE_{2000/120}$) and/or a T_1-weighted sequence ($IR_{2000/40/500}$) was added. Contiguous 5 or 10 mm thick axial slices were obtained through the whole brain.

A saddle-shaped surface receiver coil was provided by the manufacturer to image the cervical spinal cord. Contiguous 5 mm thick sagittal slices through the cord were obtained in every case using T_1 ($SE_{500/40}$) and T_2-weighted ($SE_{1500/80}$) sequences. Additional contiguous axial 5 mm slices were obtained through regions where intrinsic abnormalities (i.e., high signal foci on the $SE_{1500/80}$ sequence) were suspected on the sagittal image. Abnormalities were accepted only when identified on both sagittal and axial images. The longitudinal extent of the lesion between the cervicomedullary junction and C7 was determined from sagittal images. The transverse extent of the lesion was classified from axial images, by dividing the cord into 4 quadrants: left anterior and posterior, and right anterior and posterior. A lesion was said to be present in a given quadrant when an area of altered signal occupied the greater part of the quadrant. The resolution of the imager did not allow identification of individual fibre tracts within the cord. In correlating the morphological, clinical and electrophysiological data, an assumption has been made that lesions in a posterior quadrant of the cord probably involve the posterior columns, while lesions in an anterior quadrant are likely to involve the spinothalamic tracts.

RESULTS

Clinical findings

The patients with cervical cord syndromes included 24 with involvement of both sensory and motor systems, 4 with isolated sensory and 3 with isolated motor impairment. The sensory symptoms consisted of numbness and paraesthesiae; the sensory signs suggested lesions in the posterior columns (abnormality of joint position sense, two-point discrimination or vibration sense) and/or the spinothalamic tracts (abnormality of temperature or pain sensation). The motor symptoms included weakness and sometimes

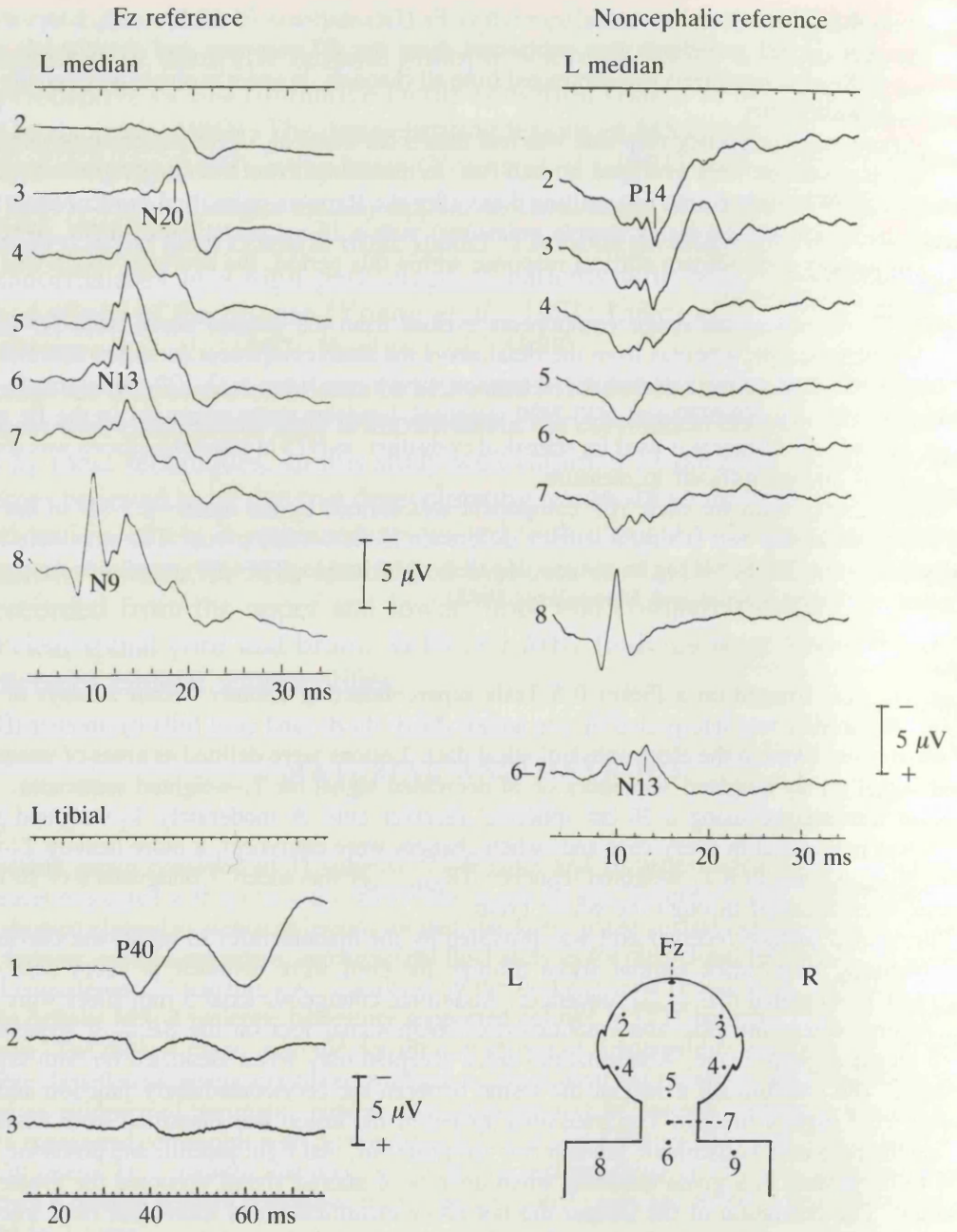

FIG. 1. Normal left median and tibial SEPs recorded over the foot cortical area (1), left and right hand cortical areas (2, 3), ipsilateral mastoid process (4), C2 (5), C7 (6), the anterior aspect of the neck on the midline above the thyroid cartilage ('supraglottal' location) (7) and the left and right clavicle (8, 9) with Fz reference. The upper limb responses were also transformed off-line to noncephalic reference: channels 2–8 referred to clavicle (9) and channel 6 referred to channel 7.

stiffness with difficulty in walking; the motor signs were typical of lesions in the pyramidal pathway (spasticity, exaggerated tendon reflexes, extensor plantar reflexes, either decrease or absence of the abdominal reflexes). In the majority of cases sensory and motor deficits were asymmetrically distributed on the two sides. Clinical evidence of a lesion located in one side of the cord was found in 7 patients: 3 of these presented with the Brown-Séquard syndrome and 4 showed proprioceptive sensory loss in one hand, defined

as the 'useless hand of Oppenheim'. Three patients of the latter group had also uni or bilateral motor deficits. Ten patients exhibited Lhermitte's sign and 10 had sphincter disturbance (Table 1).

SEP and MRI abnormalities

Cord and/or brain MRI was abnormal in 28 patients (90.3%), whereas SEPs were abnormal in 21 patients (67.7%). In the group comprising 27 cases of MS, 18 patients showed abnormal SEPs (66.7%), 18 from the median and 8 from the tibial nerve (in 2 patients the latter was not performed) and 25 showed abnormal MRI (92.6%), including 21 with cervical cord and 21 with brain lesions. In the group comprising 4 patients with isolated cord lesions, 3 showed abnormal SEPs (75%), 3 from the median and 2 from the tibial nerve (in 1 patient the latter was not performed), and 3 showed abnormal cord MRI (75%). In the Fz reference recordings, N13 and/or N20 components were abnormal in 18/31 cases (58.1%), whereas P40 was affected in 10/28 cases (35.7%). With the clavicle reference, P14 appeared abnormal in 14/31 patients (45.2%) and was ill-defined and so not interpretable in 4 cases. In the supraglottal reference waveforms, N13 was abnormal in 10/30 cases (33.3%), 2 of whom had normal Fz reference responses (Table 1). The most frequently observed abnormalities were decreased amplitude of N13 (Fz and supraglottal reference) and increased latency of N20, P40 and P14. N20 was absent in 1 case and P40 in 2 cases (fig. 2A).

MRI abnormalities of the cervical cord, affecting one or both sides, were of various sizes and extended from one to all cervical segments. In some cases the lesions were localized either anteriorly or posteriorly, whereas in others they involved both anterior and posterior regions. Similarly, in some cases the lesions were predominantly left or right-sided, whereas in others they were bilateral. In 5 cases the lesions were associated with swelling and in 3 cases with atrophy of the spinal cord (fig. 2B). Brain MRI lesions which it was considered might possibly involve the somatosensory pathways at supraspinal levels were observed in 20 patients. They were located bilaterally, unilaterally or centrally in the medulla (5 cases), pons (5 cases), internal capsule (3 cases), sensory radiations (17 cases) and sensory cortex (1 case). In 17 cases they were associated with MRI abnormalities of the cervical cord (Table 1).

Correlation between SEPs and MRI

SEPs and cord MRI were compared and the significance of correlations examined using the Fisher exact probabilities test.

In the Fz reference recordings from the median nerve there was a statistically significant correlation between N13 and/or N20 abnormalities and the presence of cervical cord MRI lesions ($P = 0.012$); this was demonstrated for left and right median nerve responses in relation to cervical cord lesions involving the left and right side, respectively ($P = 0.002$ and $P = 0.018$), and for median nerve responses from either arm in relation to lesions involving the posterior cervical cord ($P = 0.013$). Conversely, no significant correlation was observed comparing left and right median SEPs with right and left cervical cord lesions, respectively, or between median SEPs from either side and lesions involving the anterior cervical cord ($P > 0.05$). No significant overall correlation was observed comparing tibial or noncephalic reference median nerve SEP abnormalities with cervical cord lesions on MRI ($P > 0.05$) (Table 2).

TABLE 1. CLINICAL, SEP AND MRI ABNORMALITIES OF THE 31 PATIENTS INCLUDED IN THE STUDY

				Cord syndrome					*Median SEP*							
				Sensory		*Motor*		*Others*	*Left*				*Right*			
									Fz ref.		*NC ref.*		*Fz ref.*		*NC ref.*	
Case no.	*Age (yrs)*	*Sex*	*Diagnosis*	*L*	*R*	*L*	*R*		*N13*	*N20*	*P14*	*N13n*	*N13*	*N20*	*P14*	*N13n*
1	27	F	CDMS	σ	σ	σϕ	ϕ		*	*	*				*	
2	20	M	CDMS	σπ	σπ	σϕ	ϕ	Lh Bl	*	*	*	*	*	*	*	
3	35	F	CDMS	σ	σ	σϕ	σϕ		*	*	*	*	*	*	*	
4	33	F	LSDMS	σπα	σπα	ϕ	ϕ	Lh					*			
5	38	M	LSDMS	σπ	σπ											
6	22	M	LSDMS	α	σα			Lh Bl								
7	31	F	LSDMS	σ		σϕ	ϕ	Bl						*		
8	27	F	LSDMS	σα	σπα	ϕ	ϕ						*	*	*	
9	28	F	LSDMS	σ	σ			Lh				*	*	*	*	*
10	39	M	LSDMS	σα	σα	σϕ		Bl								
11	36	F	LSDMS	σπα	σ	ϕ		Lh	*	*	*					
12	28	F	LSDMS	σ	σα	σ		Lh Bl					*	*	*	
13	26	F	LSDMS	σ	σ	σϕ	ϕ									
14	36	F	LSDMS	σ		ϕ	ϕ	Bl								
15	50	F	CPMS			σϕ	σϕ						*	*	*	*
16	49	F	CPMS	σ	σ	σϕ	ϕ	Lh								
17	40	F	CPMS			σϕ	ϕ		*	*	NI	*	*	*	NI	
18	36	M	CPMS	π	π	σϕ	σϕ	Bl								
19	45	M	CPMS		α	σϕ	σϕ				*	*			*	*
20	26	F	CPMS	σ	σπ								*	*	*	
21	21	F	CPMS			σϕ	ϕ					NR			NI	NR
22	25	F	CPMS		σπ		σ						*	*	*	
23	44	M	CPMS	σ	σ	σϕ	σ	Bl	*		*					
24	48	F	CPMS	σ	σπα	σϕ	σϕ		*	*	NI		*	*	*	*
25	20	M	CPMS	σπ	σπ	ϕ	ϕ	Lh		*		*				
26	32	F	CPMS	α	σπ		σϕ									
27	34	F	CPMS	σα	σα	ϕ	ϕ					*				
28	38	F	ICL	σ	σ	ϕ	ϕ			*			*	*		
29	38	M	ICL	σπα	σπα	σϕ	σϕ	Lh Bl								
30	39	F	ICL	σ	σπα	ϕ	ϕ						*	*	*	
31	26	M	ICL	σα	σα	ϕ	ϕ	Lh Bl			NI	*			NI	*

Case no.	Age (yrs)	Sex	Diagnosis	Tibial SEP: Left Fz ref. P40	Tibial SEP: Right Fz ref. P40	Cervical cord MRI lesions: A/P	L/R	Levels	SW/AT	Brain MRI lesions: Somatosensory pathways: L	C	R	Other locations
1	27	F	CDMS		*	AP	R	2 3		Rad		Rad	*
2	20	M	CDMS	*	*	AP	LR	2 3 4 5 6	AT	Rad	Med		*
3	35	F	CDMS	*	*	AP	LR	4 5 6	SW	Int caps			*
										Rad		Rad	
4	33	F	LSDMS			P	LR	2		Rad	Med	Rad	*
5	38	M	LSDMS			AP	LR	3		Pons			*
										Rad		Rad	
6	22	M	LSDMS			AP	LR	3		Rad		Rad	*
												Int caps	
7	31	F	LSDMS							Rad		Int caps	*
8	27	F	LSDMS	*	*	P	LR	2 3 4 5					
9	28	F	LSDMS			AP	R	5 6		Rad	Med		*
10	39	M	LSDMS			P	LR	3 5		Rad			
11	36	F	LSDMS			P	L	2 3			Med	Pons	*
12	28	F	LSDMS			P	R	1 2		Rad			*
13	26	F	LSDMS			P	LR	3		Rad		Rad	*
14	36	F	LSDMS			AP	LR	4 5	SW				
15	50	F	CPMS	*	*	AP	LR	1 2		Rad	Med	Rad	*
16	49	F	CPMS							Rad		Rad	*
17	40	F	CPMS	*	*	AP	LR	1 2 3 4				Pons	*
								5 6 7		Rad		Rad	
18	36	M	CPMS										
19	45	M	CPMS	*	*					Rad		Rad	*
20	26	F	CPMS			P	R	5				Cor	*
21	21	F	CPMS										
22	25	F	CPMS	*	*	P	R	CMJ			Pons	Rad	*
23	44	M	CPMS			A	LR	CMJ					
24	48	F	CPMS	NR	NR	P	LR	2 3	AT	Rad		Rad	*
25	20	M	CPMS	NR	NR	P	LR	2	SW				
26	32	F	CPMS			A	R	2 3	SW	Pons			*
27	34	F	CPMS										*
28	38	F	ICL	*	*	AP	LR	2 3	AT				
29	38	M	ICL										
30	39	F	ICL		*	A	R	CMJ					
31	26	M	ICL	NR	NR	A	L	2 3	SW				

Abbreviations. CDMS = clinically definite MS; LSDMS = laboratory supported definite MS; CPMS = clinically probable MS; ICL = isolated cord lesion; σ = sensory and motor symptoms; π = sensory signs implicating the posterior columns; α = sensory signs implicating the spinothalamic tract; ϕ = motor signs; Lh = Lhermitte's sign; Bl = abnormal control of the bladder; NC = noncephalic; N13n = N13 (supraglottal reference); * = abnormal; NI = not interpretable; NR = not recorded; A = anterior; P = posterior; L = left; R = right; CMJ = cervicomedullary junction; AT = atrophy; SW = swelling; C = central; Rad = radiation; Med = medulla; Int caps = internal capsule; Cor = cortex.

Abnormalities of the latency and amplitude of N13 were assessed in relation to the levels of the cord lesions. The percentage of abnormalities of N13 recorded with supraglottal reference decreased in relation to the incidence of lesions at progressively higher levels, whereas the occurrence of abnormalities of N13 recorded with Fz reference was unrelated to the level of cord lesion (Table 3). Cord lesions located at C6 and C7 were significantly correlated with abnormalities of the supraglottal reference N13 ($P = 0.029$), but just failed to reach statistical significance with abnormalities of the Fz reference N13 ($P = 0.06$). When higher levels were examined, abnormalities of Fz reference N13 and clavicle reference P14 were significantly correlated with lesions located at C1 and/or the cervicomedullary junction ($P = 0.01$ and $P = 0.017$, respectively), whereas supraglottal reference N13 showed no such correlation.

The N9-N20 interpeak latency and the absolute latency of P40 were compared with the number of segments involved (i.e., the longitudinal extent of the lesion) on the ipsilateral side of the cervical cord. Both SEP measures were significantly correlated with the number of levels affected (left side r = 0.57 and 0.58, respectively, $P < 0.001$; right side r = 0.38 and 0.41, respectively, $P < 0.02$). For the tibial SEP the relationship between P40 latency and number of levels affected was approximately linear, equivalent to a delay of about 2 ms per level (fig. 3). However, since the variation in P40 latency was very wide for patients with lesions affecting 0, 1 or 2 levels and there were only 4 patients with longer lesions, too much weight should not be attached to this observation.

Using the Fisher test, no significant correlation could be demonstrated between abnormal SEPs from either side of the body and MRI lesions apparently involving

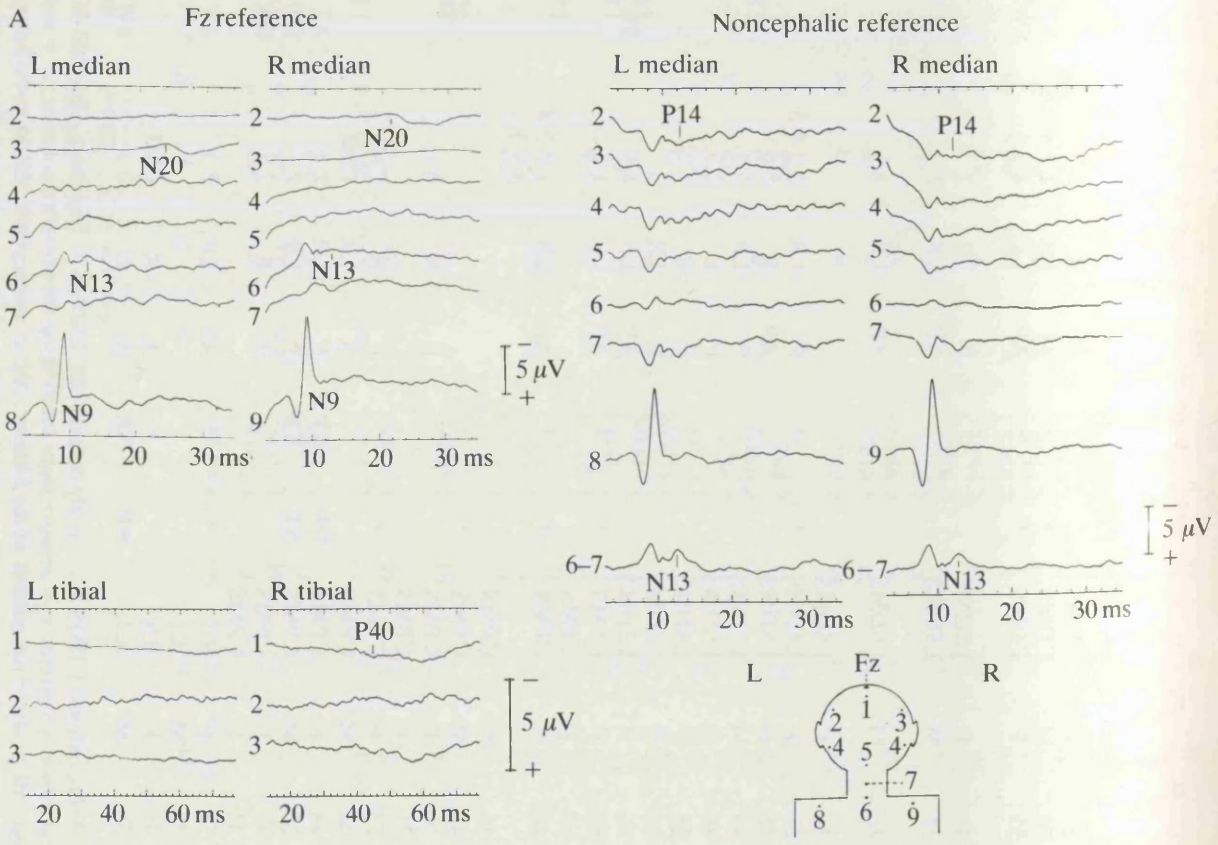

FIG. 2A.

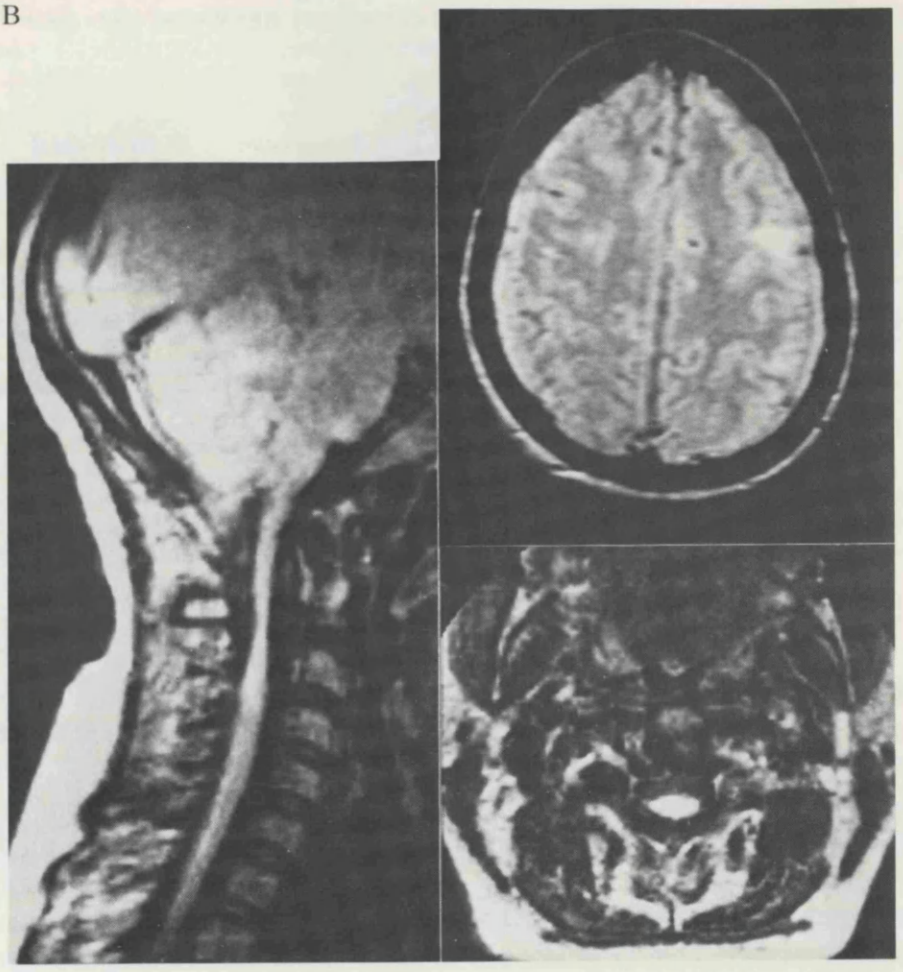

FIG. 2. *Case 28.* A, median SEPs recorded with Fz reference show bilaterally delayed N20 and degraded N13 on the right. From the tibial nerve, P40 is absent on the left and delayed and degraded on the right. In the noncephalic reference recordings, N13 is normal and P14, although not clearly defined, is within normal limits. B, *left*, sagittal view of the cervical cord, showing an area of increased signal at C2-C3 and marked atrophy at the same level. *Right lower*, axial view of the cervical cord, performed at the level of the lesion, showing anteroposterior flattening and increased signal throughout the cord. *Top*, axial view of the brain showing a left-sided lesion of the precentral cortex.

intracranial somatosensory pathways. Furthermore, the SEP abnormality involved the N13 component in 20/31 cases (27 arms), 17 of whom had ipsilateral MRI lesions in the cervical cord; 5 of the 17 also had lesions in the medulla, which might have contributed to the abnormality of N13, but the remaining 12 either had brain lesions which were located too far rostrally to affect N13 (6 cases) or had no brain lesions on MRI (6 cases). In 1 patient where the SEP abnormality involved only the cortically generated N20, it was possible that the defect could have been due to a lesion in the sensory radiations, visible on MRI.

Correlation between SEPs and cord syndromes

SEPs were abnormal in 17 out of 24 patients with sensory and motor impairment, in 2 out of 4 patients with only sensory abnormalities and in 2 out of 3 patients with isolated motor involvement. When SEPs were compared with sensory symptoms and signs separately, the latter showed a greater degree of correlation than the former,

TABLE 2. SIGNIFICANCE OF CORRELATION BETWEEN SEP AND MRI ABNORMALITIES*

	Median				
	Fz reference			*Noncephalic reference*	*Posterior tibial Fz reference*
	Both sides	*Left*	*Right*		
Cord	0.012			No correlation found	No correlation found
Left		0.002	n.s.		
Right		n.s.	0.018		
Post.	0.013				
Ant.	n.s.				
Brain	n.s.				
Left		n.s.	n.s.		
Right		n.s.	n.s.		

* Fisher's exact probabilities test.

TABLE 3. PERCENTAGE OF N13 ABNORMALITIES IN RELATION TO THE LEVELS OF CORD LESIONS

	N13 abnormalities	
Cord levels	*Supraglottal reference*	*Fz reference*
C6-C7 (4)	100% (4)	100% (4)
C5-C4 (8)	50% (4)	75% (6)
C3-C2 (17)	35.3% (6)	58.8% (10)
C1-CMJ (6)	33.3% (2)	100% (6)

No. of cases in parentheses. CMJ = cervicomedullary junction.

although in neither case was this statistically significant. Thirteen patients had sensory signs consistent with lesions in the posterior columns and 13 patients in the spinothalamic tracts. The same incidence of SEP abnormalities was observed in both groups (69.2%).

Using the Fisher test, no significant correlation could be demonstrated between abnormal SEPs from either side of the body and ipsilateral or contralateral sensory symptoms, posterior column signs or spinothalamic tract signs, neither was there any correlation when these factors were combined into the broader category of 'sensory involvement'.

Correlation between MRI and cord syndromes

Cord MRI was abnormal in 24 patients, 18 with sensory and motor impairment, 4 only sensory and 2 only motor deficits. In some cases the cord lesion appeared smaller and in others larger than the lesion suspected on clinical grounds. Ten patients had an MRI lesion apparently involving only the posterior cord: 9 of them showed clinical sensory and motor abnormalities, whereas 1 complained only of sensory impairment. The 4 patients with only anterior cord MRI lesions showed both sensory (2 posterior column and 3 spinothalamic tract) and motor clinical impairment. Ten patients had a lesion involving the anterior and posterior cord: 5 of them showed sensory and motor, 3 only sensory and 2 only motor abnormalities.

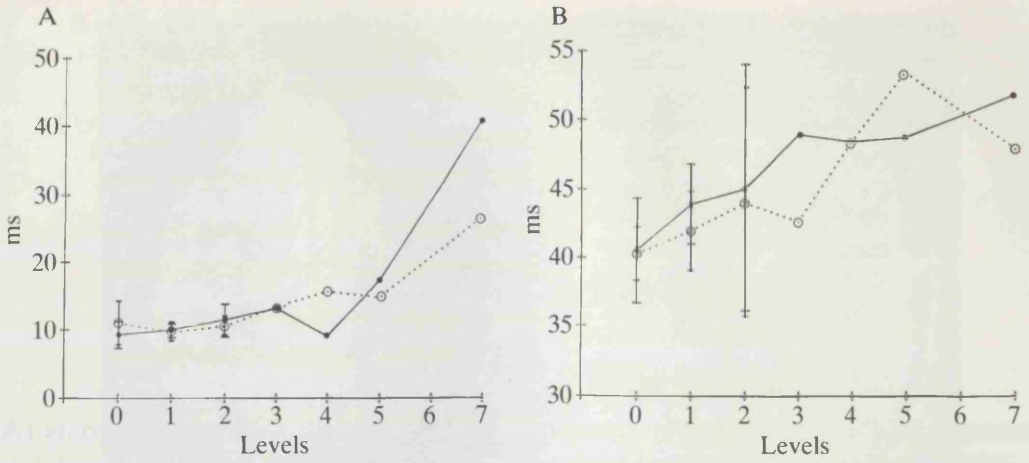

FIG. 3. Variation of N9-N20 interpeak latency (*left*) and P40 absolute latency (*right*) with the longitudinal extent of the cord lesion on the ipsilateral side. Continuous line = left side; dotted line = right side. Filled and empty circles = mean latency values for left and right side, respectively, vertical lines = their SDs. Only 4 patients showed cord lesions extending beyond 2 levels.

The extent of cord MRI abnormalities was examined in relation to the distribution of sensory involvement. Twelve patients had bilateral cord MRI lesions and bilateral sensory impairment; 8 patients had unilateral cord lesions and bilateral sensory abnormalities; 1 patient had a bilateral cord lesion and unilateral sensory involvement; 1 patient had unilateral cord and ipsilateral sensory abnormalities. When cord MRI was compared with sensory symptoms and signs separately, the latter showed a higher degree of correlation than the former, although in neither case was this statistically significant, neither was any significant correlation demonstrated when sensory symptoms and signs were combined together. The upper level of the lesion in the cervical cord, as suggested by the distribution of sensory impairment, was in all but 1 patient at or below the upper level of the cord lesions seen in MRI, although it was not possible to establish a definite level from clinical data in every case.

No significant correlation was found between the extent of cord MRI abnormalities and the distribution of clinical motor involvement. Using the Fisher test, no significant correlation could be demonstated between sensory symptoms and/or signs on either side of the body and brain MRI lesions apparently involving the intracranial somatosensory pathways.

A relatively close association between clinical, electrophysiological and morphological data was observed in 4 patients presenting with the 'useless hand of Oppenheim' (Cases 11, 20, 22, 30; *see* Table 1). In all these cases, abnormal SEPs were evoked from the impaired arm. The abnormalities involved N13 and N20 in Fz reference and P14 in the clavicle reference recordings; the N13 component recorded with supraglottal reference was normal in each case. An abnormal P40 was recorded from both sides in 1 patient (Case 22) and from the clinically affected side in another (Case 30). MRI of the cervical cord showed in each patient an ipsilateral lesion involving the posterior side (Cases 11, 20, 22) or the anterior side (Case 30). The abnormalities were located at C5 level (Case 20), C2 and C3 levels (Case 11) and the cervicomedullary junction (Cases 22, 30). Three of these patients also showed brain lesions in the medulla, pons, sensory radiations and sensory cortex (fig. 4A, B).

TABLE 4. SIGNIFICANCE OF CORRELATION OF N13 AND P14 ABNORMALITIES WITH LEVELS OF THE CORD LESIONS*

Cord levels	*N13 (Fz ref.)*	*N13 (Supraglottal ref.)*	*P14 (Noncephalic ref.)*
C1-CMJ	0.01	>0.4	0.017
C2-C3	>0.2	>0.3	>0.3
C4-C5	>0.1	>0.2	>0.2
C6-C7	0.06	0.029	>0.2

* Fisher's exact probabilities test.

DISCUSSION

Abnormal SEPs are frequently recorded in patients with multiple sclerosis (Anziska *et al.*, 1978; Small *et al.*, 1978; Matthews and Small, 1979; de Weerd and Jonkman, 1982; Walsh *et al.*, 1982). Their incidence is higher in clinically definite than suspected cases, probably due to an increase in the total number of lesions with progression of the disease (Eisen *et al.*, 1979; Eisen and Odusote, 1980; Ganes, 1980; Green *et al.*, 1980; Kjaer, 1980; Khoshbin and Hallett, 1981; Matthews *et al.*, 1982). Abnormalities are usually obtained from limbs showing sensory impairment and also, although less frequently, from limbs in which no sensory deficits are present in the territory of the nerve tested (Namerow, 1968; Small *et al.*, 1978; Jones, 1982*b*; van Buggenhout *et al.*, 1982). MRI appears to be a more sensitive technique in detecting asymptomatic abnormalities in the brain in patients with MS, especially in the early stages of the disease

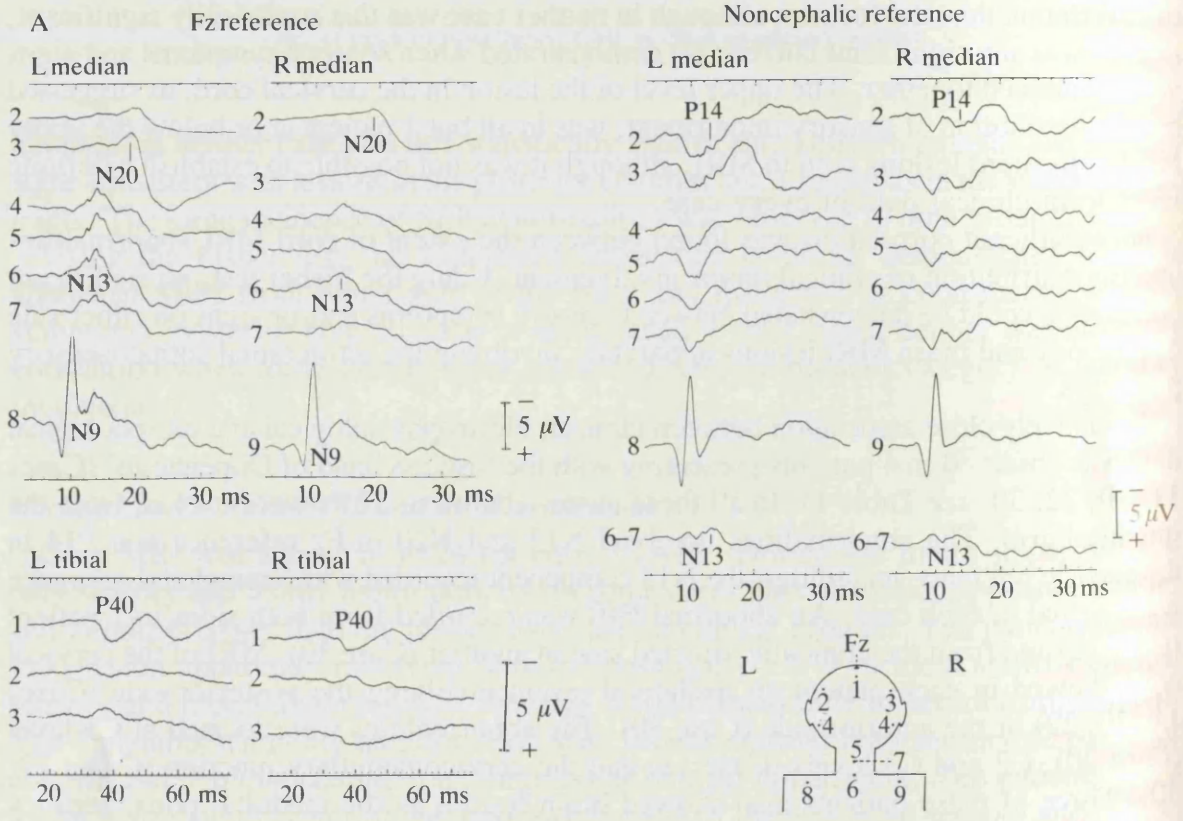

FIG. 4A.

B

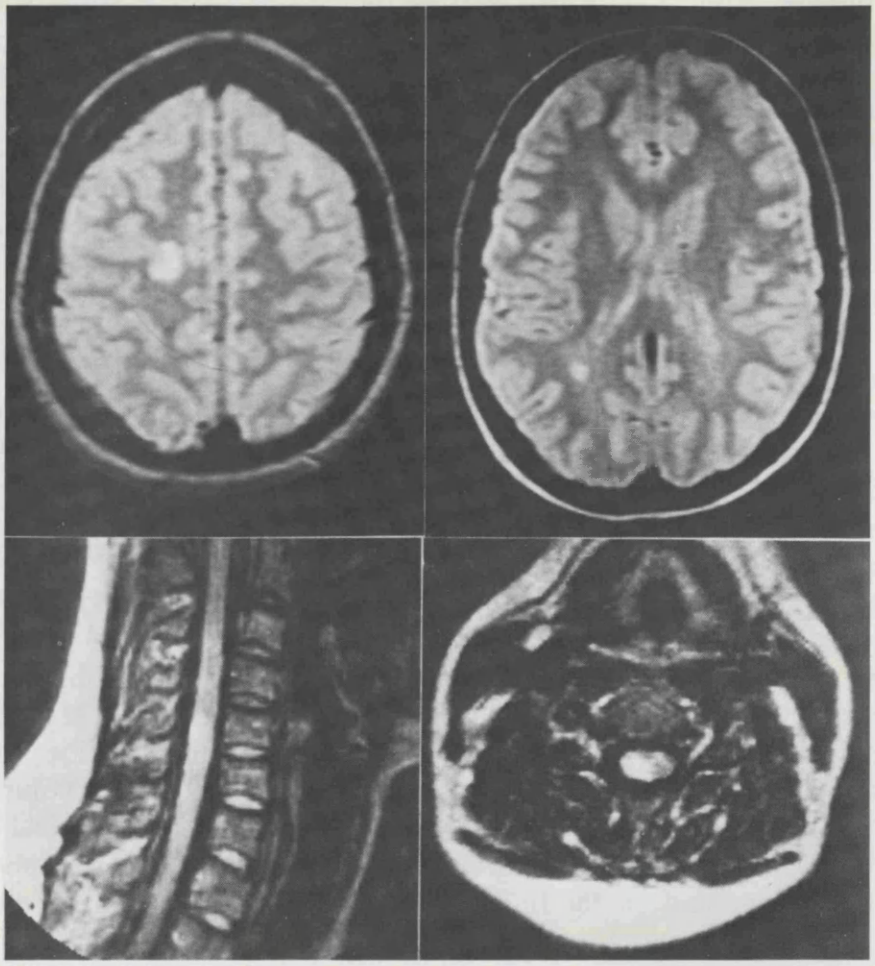

FIG. 4. *Case 20.* A, SEPs from the right median nerve show degraded N13 and slightly delayed N20 with Fz reference, and delayed P14 with clavicle reference. P40 from left and right tibial nerve is normal. B, *top*, axial views of the brain, showing areas of increased signal in the white matter of the right hemisphere. *Lower left*, sagittal view of the cervical cord, showing an area of increased signal at C5. *Lower right*, axial view of the cervical cord, performed at the level of the lesion, showing an area of increased signal in the right posterior quadrant.

(Miller *et al.*, 1987; Ormerod *et al.*, 1987; Paty *et al.*, 1988). Multifocal, asymmetric cerebral white matter lesions are seen in over 95% of patients with clinically definite MS (Young *et al.*, 1981; Lukes *et al.*, 1983; Runge *et al.*, 1984; Ormerod *et al.*, 1987).

The present study was performed in an attempt to come to a better understanding as to how morphological changes in the CNS shown by MRI correspond to electrophysiological changes in the somatosensory pathway detected by SEPs. We are aware of only one previous study (Matthews and Esiri, 1979) in which SEP abnormalities have been related to a plaque in the cervical cord, discovered at autopsy. We also wished to determine the degree of correlation between the abnormalities demonstrated by these techniques and specific clinical deficits.

It was found that abnormalities of N13 and/or N20, recorded after median nerve stimulation with a reference at Fz, were significantly correlated with MRI abnormalities located in the posterior half of the cervical cord (and hence probably involving the posterior columns) or on the ipsilateral side, but not in the anterior half or on the

contralateral side. Abnormalities of P40 following tibial nerve stimulation were less well correlated with MRI lesions involving the posterior or ipsilateral hemicord. The correlation between the length of the MRI abnormality in the ipsilateral hemicord and the N9-N20 interpeak latency or the absolute latency of P40 was significant, although the value of this observation was limited by the fact that only 4 patients showed lesions extending beyond two levels. These results provide evidence that MRI abnormalities involving the posterior half of the cervical cord are with high probability associated with electrophysiological abnormalities of sensory conduction. That there is a correlation of the longitudinal extent of MRI cord lesions with the amount of SEP delay suggests that demyelination is a factor in these lesions.

In the present study abnormal responses occurred less frequently from the tibial (35.7% of cases) as compared with the median nerve (67.7%). Conversely, previous studies (Chiappa, 1980; Trojaborg *et al.*, 1981; Bartel *et al.*, 1983; Rossini *et al.*, 1985) reported that in patients with MS the incidence of abnormalities is usually higher in the SEPs from the lower limbs, in accordance with the fact that the investigation of a longer segment of the somatosensory pathway increases the possibility of detecting abnormalities. One explanation for this discrepancy could be that the patients examined in this study were not representative of the MS population, having been selected for cervical cord involvement and without evidence of more caudal spinal cord lesions. All the patients with abnormal tibial nerve SEPs also had abnormal median nerve responses, hence a lesion at cervical level could have been responsible for both abnormalities. In the cervical cord, sensory structures related to the upper limbs occupy a greater volume than those associated with the lower limbs. For this reason, in patients with cervical cord lesions, abnormal SEPs from the upper limbs are likely to be more frequent than abnormal lower limb responses. Nevertheless, the finding of abnormal lower limb SEPs associated with normal median nerve responses might possibly occur due to a small lesion affecting the gracile tract only.

It was found that abnormalities of N13, recorded at C7 with a supraglottal reference, correlated well with MRI lesions located at the lower cervical levels, whereas abnormalities of P14, recorded from the scalp with a clavicle reference, correlated best with MRI lesions involving C1 and the cervicomedullary junction. These findings are in agreement with the general view that the N13 component is mainly generated by activation of interneurons in the grey matter of the dorsal horn, at levels where the dorsal roots from the upper limbs enter the spinal cord (Desmedt and Cheron, 1981), whereas the P14 component corresponds to the advancing front of propagating activity in the somatosensory pathways at or above the foramen magnum (Mauguière *et al.*, 1983; Mauguière and Ibañez, 1985).

With the methods used in the present study, it seems unlikely that brain MRI abnormalities are frequently responsible for the electrophysiological deficits detected by SEPs. This result is perhaps not surprising if we consider that the localization of MRI abnormalities in specific pathways of the brain can only be made with some approximation. Also most of the brain MRI lesions (85% in this study), which usually appear small and disseminated, are located in periventricular areas, where the fibres arising from the somatosensory nuclei of the thalamus diverge in their projection to various areas of the cortex. For this reason, it is possible that the fibres activated by median or tibial nerve stimulation may not have been involved in the MRI lesions, or

that the damaged proportion was insufficient to cause electrophysiological changes detectable by SEPs. Furthermore, demyelination is not necessarily present in all MRI lesions in MS. Oedema (which increases mobile water proton density and hence alters MRI signal) alone produces MRI abnormalities (Barnes *et al.*, 1987), and experimental and MRI/pathological studies have shown that abnormal MRI signals in demyelinating diseases are generated by lesions in which there are proportions of inflammation, oedema, gliosis and demyelinaton, changing with time (Barnes *et al.*, 1988; McDonald and Barnes, 1989; D. Barnes, D. G. MacManus and W. I. McDonald, unpublished observations). Demyelination per se produces little change in MRI signal (Bottomley *et al.*, 1984). These findings provide a possible explanation for the fact that SEPs appear sometimes to survive the existence of extensive lesions in the sensory radiations or the spinal cord (fig. 5A, B).

A previous study (Eisen *et al.*, 1987), carried out in possible and probable MS cases, showed a significant correlation of cortical median and tibial SEP abnormalities with MRI lesions involving the somatosensory pathways and mainly located in the periventricular areas. The most frequent SEP abnormality reported was distorted morphology of the cortical response, detected by a fast Fourier transform technique (Roberts *et al.*, 1983) or a method of dynamic time warping (Eisen *et al.*, 1986). The recording of cortical SEPs with restrictive (high band-pass) digital filtering was also used by Rossini *et al.* (1985) to detect high-frequency subcomponents normally contained within the latency range of N20 and P40. Abnormalities of these wavelets were reported in 2 suspected MS cases, in whom the cortical response recorded with open band-pass filtering appeared normal. The present study cannot confirm or refute these findings, although personal observation suggests that these high-frequency subcomponents may not be present even in some normal subjects.

In the full group of 31 patients no significant correlation was found between SEPs and sensory abnormalities on either side of the body. Abnormal SEPs were recorded from limbs with or without sensory deficits and no specific correlation could be observed with symptoms or impairment of particular sensory modalities. The same incidence of abnormalities was obtained from limbs showing impaired 'spinothalamic' (temperature and pain) or 'posterior column' (joint position, two-point discrimination, vibration) type sensation, although previous studies of MS and other conditions (e.g., Halliday and Wakefield, 1963; Yu and Jones, 1985) suggested a stronger correlation with the 'posterior column' modality. This finding may be partly explained by the fact that in this study components recorded with both cephalic and noncephalic reference were examined, whereas in previous investigations only the former were usually considered.

In the full group of 31 patients there was also no significant correlation between cervical cord MRI abnormalities, in axial and sagittal views, and the pattern of sensory or motor impairment. There are some possible explanations for such a discrepancy. First, the resolution of spinal MRI is still significantly limited. Interpretation of spinal images is impaired by surface coil inhomogeneity and CSF motion artefacts (Miller *et al.*, 1987). Also the limit of resolution to a voxel size of 15 mm^3 (pixel size 1.2 mm$\times$2.4 mm, slice thickness 5 mm) makes it likely that small lesions were not seen; MS plaques smaller than 15 mm^3 are seen at postmortem (Fog, 1950; Oppenheimer, 1978). Furthermore, localization of a lesion to a quadrant of the cord does not inevitably mean that a particular tract is involved, as has been implicitly assumed in this study. Despite all these factors,

it was observed that in patients with sensory deficits, the upper limit of the cervical cord abnormalities seen in sagittal views was consistently at or above the level suggested by the clinical examination. Therefore, it appears that spinal MRI often identifies the symptomatic pathological process, although not with a precise anatomical-functional correlation.

A greater degree of correspondence between electrophysiological, morphological and clinical abnormalities was found in 4 patients presenting with the 'useless hand of Oppenheim'. This is characterized clinically by a profound loss of joint position sense in one upper limb, largely sparing the lower limb, which has generally been attributed to a lesion in the cuneate tract. Abnormal SEPs were recorded from the affected arm in all 4 cases and an abnormal lower limb response in 2 cases; MRI showed in each case a lesion located in the appropriate side of the cervical cord between C5 and the cervicomedullary junction. The clear correlations in these 4 patients probably reflect the precise localization possible on clinical grounds: more often, demyelinating cord syndromes suggest a patchy, ill-defined lesion. These findings are in keeping with those in other syndromes, in which similar precise localization is possible: acute unilateral optic neuritis and deafness in MS (Barratt *et al.*, 1988; Miller *et al.*, 1988).

In conclusion, the present study has shown that in patients with demyelinating cervical cord lesions, the morphological changes seen in MRI of the cord are usually associated with appropriate electrophysiological abnormalities. On the other hand, the 'clinically silent' MRI lesions in the brain seldom, if ever, give rise to SEP abnormalities, using standard methods. Both SEP and MRI abnormalities correlate to some extent but not

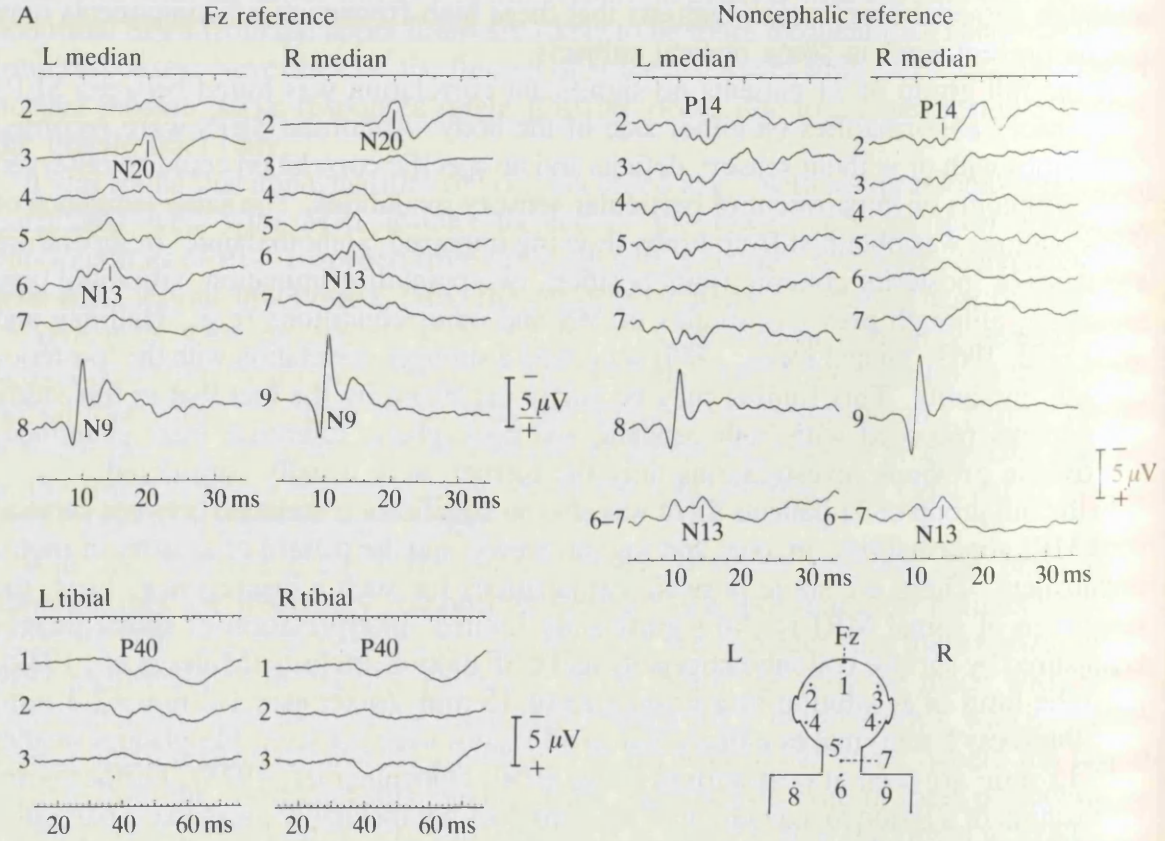

FIG. 5A.

B

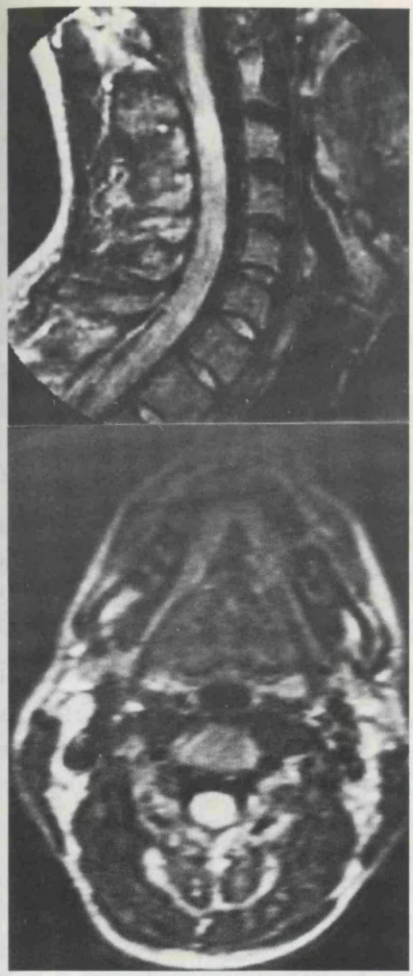

FIG. 5. *Case 6.* A, normal median and posterior tibial SEPs. B, *top*, sagittal view of the cervical cord, showing an area of increased signal at C3 level. *Bottom*, axial view, performed at the level of the lesion, showing an area of increased signal involving the whole cross-section of the cord.

perfectly with the pattern of clinical deficits. This could be partially due to the approximation introduced by the subjective evaluation of the clinical findings, the fact that SEPs provide only an incomplete measure of conduction in sensory pathways, and the likelihood that regions of abnormal signal seen in MRI are not always representative of or coterminous with an area of myelin damage.

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(Received December 28, 1989. Revised April 6, 1990. Accepted April 26, 1990)

Brain (1991), **114**, 2437–2450

THE PATHOPHYSIOLOGY OF ACUTE OPTIC NEURITIS

AN ASSOCIATION OF GADOLINIUM LEAKAGE WITH CLINICAL AND ELECTROPHYSIOLOGICAL DEFICITS

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SUMMARY

Eighteen patients with acute optic neuritis underwent optic nerve magnetic resonance imaging (MRI) before and after injection of gadolinium-diethylene triamine pentacetic acid (Gd-DTPA). Ten were re-examined 4 wks later. Leakage of Gd-DTPA across the blood-optic nerve barrier was a consistent finding in the acute lesion, and its presence was associated with abnormal visual acuity and colour vision, retro-ocular pain on eye movement, an afferent pupillary defect, and a reduced amplitude of the P100 component of the visual evoked potential. Gd-DTPA leakage had ceased in 9/11 nerves when restudied 4 wks later, and this evolution was associated with improved visual acuity and an increased P100 amplitude. Leakage is likely to reflect inflammation, and we conclude that the latter plays an important part in the production of conduction block and clinical deficit, and that its resolution is an important step in clinical remission from acute episodes of demyelination.

INTRODUCTION

In the early stages of multiple sclerosis (MS), the clinical pattern is characteristically one of relapse and remission. The pathophysiological mechanisms underlying this sequence of events are poorly understood because, until recently, there has not been a satisfactory means of characterizing *in vivo* the evolving pathological process. An improved understanding of such mechanisms is desirable as it may lead to new therapeutic strategies.

To some extent, magnetic resonance imaging (MRI) allows the observation of pathology *in vivo*. MRI in most MS patients shows a pattern of multifocal white matter cerebral lesions (Young *et al.*, 1981; Lukes *et al.*, 1983; Runge *et al.*, 1984), with a similar distribution to demyelinated plaques seen pathologically. That the lesions are indeed plaques is supported by post-mortem MRI/pathological correlations (Stewart *et al.*, 1984; Ormerod *et al.*, 1987). *In vivo* studies have shown that leakage of Gd-DTPA across an abnormal blood-brain barrier is a feature in some brain lesions (Grossman *et al.*, 1986), especially new ones (Miller *et al.*, 1988*a*; Bastianello *et al.*, 1990; Harris *et al.*,

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1991; Thompson *et al.*, 1991). In chronic relapsing experimental allergic encephalomyelitis, Gd-DTPA-enhancement correlates with inflammation (Hawkins *et al.*, 1990). Given the clinical and pathological similarities of this experimental disease and MS (Lassman, 1983), the correspondence between the pattern of enhancement and the known pattern of inflammation at post-mortem (Prineas and Connell, 1979), and the recent histological confirmation of inflammation a few days after a lesion had been shown to enhance (Katz *et al.*, 1990), it is probable that Gd-DTPA-enhancement represents inflammation in the human disease too.

Thus, it should be possible to ascertain, through a correlative MRI/clinical study, the relationship of a pathological feature (inflammation) to the clinical deficit in an acute demyelinating lesion. Most lesions in the brain are unsuitable for such a study as they are asymptomatic (Ormerod *et al.*, 1987; Paty *et al.*, 1988; Thompson *et al.*, 1990). In contrast, lesions in the optic nerve are particularly suitable because of their characteristic clinical presentation, acute optic neuritis. With the use of an MRI sequence which suppresses the signal from orbital fat, it is possible to identify the symptomatic lesion in patients with optic neuritis (Miller *et al.*, 1988*b*). There is also an opportunity to assess conduction through the lesion by using visual evoked potentials (VEPs). We therefore performed a correlative clinical/MRI/VEP study of a group of patients with acute optic neuritis.

METHODS

Patients

Eighteen adult patients, aged 18–48 yrs with clinically isolated acute optic neuritis were recruited from Moorfields Eye Hospital (we limited recruitment to those with isolated optic neuritis, since they are also enrolled in a separate, ongoing prospective study of the prognostic significance of brain MRI at presentation for subsequent progression to multiple sclerosis). Informed consent for the examinations was obtained from all patients. There were 11 females and 7 males. Diagnosis was based on standard clinical criteria (Compston *et al.*, 1978) and in each case was supported by the presence of an abnormal VEP. None of the patients was treated with corticosteroids during the study period.

Summary of investigations

Ten patients (9 unilateral optic neuritis, 1 bilateral simultaneous optic neuritis) had MRI on 2 occasions. The first MRI was performed 2–13 d (mean 6.4) after the onset of blurring of vision at which time both neuro-ophthalmological and VEP examinations were obtained in all 10 patients. Follow-up MRI was performed 20–32 d (mean 27.8) later at which time neuro-ophthalmological examination was repeated in all 10 patients, while VEPs were obtained in 9.

Eight patients (7 unilateral optic neuritis, 1 bilateral simultaneous optic neuritis) had a single MRI examination, 8–38 d after the onset of blurring of vision; neuro-ophthalmological and VEP examinations were performed on the same day only in the patient with bilateral simultaneous optic neuritis.

Overall, 20 clinically affected nerves were studied with MRI on a total of 31 occasions. The duration of visual symptoms (to the nearest day) was known for each occasion. Neuro-ophthalmological and VEP examinations were performed on the same day as MRI in 24 and 23 instances, respectively.

Neuro-ophthalmological examination

Patients were first seen by an ophthalmologist to exclude retinal or other intra-ocular pathology. They were then seen by a neurologist (B.D.Y.) who excluded previous significant neurological symptoms and abnormality on general neurological examination. Distance vision was recorded from Snellen charts and near vision was recorded using The Faculty of Ophthalmologists reading test type. Colour vision was assessed with Ishihara plates, the number of errors being recorded on viewing 13 plates. Visual fields were tested

to confrontation, and plotted using both a Goldmann perimeter (static and dynamic isopters to I2 and I4 targets) and a Bjerrum screen, and classed as normal or abnormal.

Magnetic resonance imaging

MRI was performed on a Picker 0.5T superconducting imager. The optic nerves were imaged using a STIR sequence ($SE_{2000/40/150}$) to suppress the signal from orbital fat. A binocular orbital surface coil was provided by the manufacturer. 5 mm contiguous coronal slices through the orbits from the head of the optic nerve to the optic chiasm were obtained, before and after the injection of Gd-DTPA 0.2 mmol/kg (Schering AG) (Youl *et al.*, 1991). All scans were independently reported by two neuroradiologists (B.E.K. and I.F.M.) who were unaware of the clinical details. Prior to contrast administration, lesions were defined as foci of increased signal within the nerve. The same 'window' and 'level' were used for the images obtained immediately before and after each injection of Gd-DTPA.

Unlike conventional T_1-weighted spin echo sequences, in which the accumulation of Gd-DTPA in regions with an abnormal blood-brain barrier results in a focal *increase* in signal (i.e. enhancement), there is a *decrease* in signal in such regions on the STIR sequence (Youl *et al.*, 1991). Thus, following contrast administration, Gd-DTPA leakage across an abnormal blood-optic nerve barrier was said to be present when the neuroradiologist determined that there was a definite *reduction* of signal in the previously identified lesion. Because of this 'negative' contrast effect, we refer to such regions as areas of Gd-DTPA 'leakage' rather than 'enhancement' (Fig. 1).

MRI lesions in MS (and by inference in optic neuritis) may vary markedly in their degree of signal abnormality, due to substantial variations in their water proton density and T_1 and T_2 relaxation times

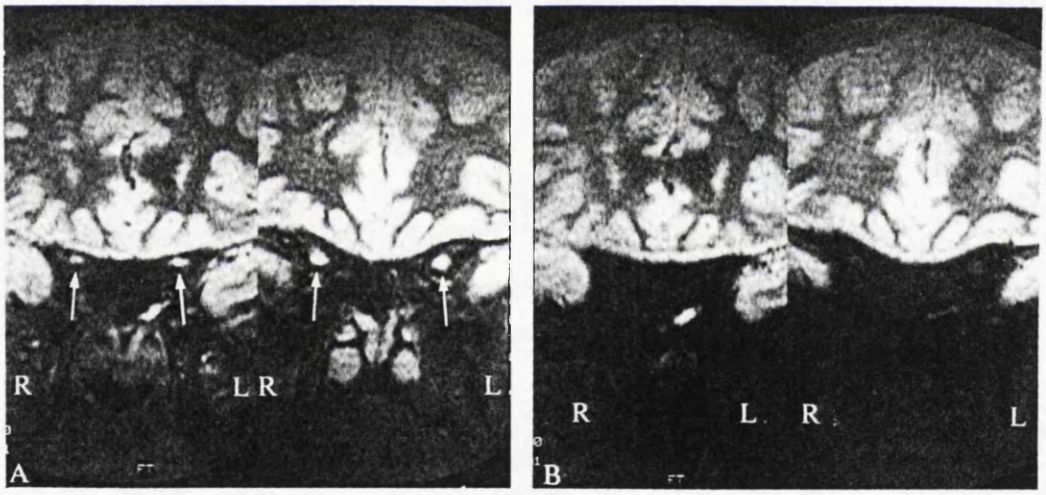

FIG. 1. MR examination ($IR_{2000/40/150}$) from an 18-yr-old male presenting with an 8 day history of bilateral central visual loss. A, pre-contrast scan reveals increased signal in both optic nerves (arrows); B, following Gd-DTPA, there has been a marked fall in signal from the affected segments, indicating 'enhancement' for this scanning sequence (Youl *et al.*, 1991). Signal is also lost from the relatively hyperaemic nasal mucosa, a normal finding.

(Ormerod *et al.*, 1987). A lesion seen on a single 5 mm slice could therefore have an actual length which is considerably shorter or longer. If the lesion has very long relaxation times, as occurs with vasogenic oedema (Barnes *et al.*, 1986), it might be visible when only 1−2 mm in length; if it exhibits only minor elevations in relaxation times compared with normal white matter, as may be seen in inflammation without oedema (Noseworthy *et al.*, 1988), it could extend several millimeters on to the neighbouring slices without producing signal change. We did not, therefore, consider the current resolution (5 mm thick slices) sufficient

to allow a precise measurement of the lesion length in millimeters. Thus, in correlating the VEP latency and amplitude with lesion length, the latter was recorded as the number of consecutive 5 mm slices on which it was visible.

Visual evoked potentials

VEPs were recorded monocularly to full field pattern reversal stimulation (GT/ADT). The stimulus was provided by a circular screen whose radius subtended an angle of 16° on to which a checkerboard slide of 50′ black and white squares was back-projected. Pattern reversal was produced every 505 ms by rapid (10 ms) horizontal displacement of the pattern through one square width. The luminance of the white squares was 230 cd/m^2 and the contrast was 98%. The patient was seated with the eye 1 m away from the fixation point, which was a red spot laser in the centre of the screen. Eight trans-occipital recording electrodes were arranged in a standard montage. This included a horizontal array of 5 electrodes placed on a line 5 cm above the inion, one of which was in the midline, with 2 electrodes on either side at an inter-electrode distance of 5 cm. Additional electrodes were placed 2.5 cm above the inion, at the inion and 5 cm below it. The reference electrode was located 12 cm above the nasion.

Two hundred responses were averaged in each run. The amplifier's high frequency response was less than 3 dB down at 5 kHz and the time constant was 1 s. The average sampling interval was 1.25 ms and the averaging window 320 ms. Normal limits were obtained separately from 2 groups of healthy individuals within roughly the same mean age as the patients: 39 females aged 18–38 yrs (mean 23.9 yrs) and 24 males aged 18–39 yrs (mean 25.4 yrs). The normal latency limits of the P100 component were defined by the mean ±2.5 SD of the absolute latency and inter-ocular latency difference. The normal amplitude limits were defined by the mean ±2.5 SD of log amplitude and log (left eye/right eye) amplitude ratio.

RESULTS

MRI-clinical correlations

First MRI. Clinical neuro-ophthalmological assessment was performed on the same day as the first MRI in 11 patients, 2 with bilateral simultaneous and 9 with unilateral optic neuritis. Gd-DTPA leakage was observed in all 13 symptomatic nerves. Compared with the 9 asymptomatic nerves, the 13 symptomatic nerves were significantly associated with reduced distance and near visual acuity, impaired colour vision, visual field abnormality, an afferent pupillary defect, pain on eye movement and swelling of the optic disc ($P = 0.001$ for each clinical feature; Fisher exact probability test).

Visual acuity was worse than 6/9 in 4/6 studies displaying intracanalicular leakage and in 4/7 studies where leakage was confined to the orbital portion of the nerve ($P = 0.25$; χ^2 with Yates' adjustment). Visual acuity was worse than 6/9 in 4/5 studies in which there was Gd-DTPA leakage on 3 or more consecutive 5 mm slices, and in 4/8 studies which displayed leakage on 1 or 2 slices only ($P = 0.1$).

Follow-up MRI. Neuro-ophthalmological assessment was performed on the same day as the follow-up MRI in 10 patients, 1 with bilateral simultaneous and 9 with unilateral optic neuritis. Gd-DTPA leakage was observed in only 2/11 symptomatic nerves. All 11 symptomatic eyes had recovered to a visual acuity of 6/9 or better. Compared with the 9 asymptomatic nerves, the 9 symptomatic nerves which did *not* display Gd-DTPA leakage at follow-up were not significantly associated with reduced distance, near or colour vision, or with pain on eye movement, although they were associated with an abnormal visual field ($P = 0.04$), an afferent pupillary defect ($P = 0.04$) and optic disc swelling ($P = 0.001$) (Fisher's exact probability test).

Lesions showing Gd-DTPA leakage at first MRI and not at follow-up (Table 1). At the time of the first scan there was a significantly higher frequency of abnormal distance,

TABLE 1. CLINICAL FINDINGS IN THOSE LESIONS WHICH 'LEAKED' AT FIRST STUDY BUT NOT AT FOLLOW-UP

	First scan (leaking) (n = 9)	*Follow-up (no longer leaking) (n = 9)*	
Distance acuity <6/5	8	3	$P = 0.04$
Near acuity <N5	8	2	$P = 0.03$
Abnormal colour vision	7	2	$P = 0.04$
Afferent pupillary deficit	9	4	$P = 0.04$
Pain	8	2	$P = 0.03$
Abnormal visual field	7	4	NS
Disc swelling	7	7	NS

(Fisher exact probability test.)

near and colour acuity, pain on eye movement and afferent pupillary defect (Fisher exact probability test.

Correlation of Gd-DTPA leakage with time from onset of symptoms. Of the 31 MRI examinations, Gd-DTPA leakage within the lesion was seen on 18 occasions, for which the time from onset of blurred vision varied between 2 and 37 d (mean 11.8 d). The time from onset in the 13 studies where no Gd-DTPA leakage was apparent varied between 12 and 41 d (mean 31.2 d). These times were significantly different ($P < 0.001$; 2-tailed Student's t test). Gd-DTPA leakage was seen in 6/6 lesions where the time from onset of blurred vision was less than 7 d, in 7/8 lesions where the time from onset was 7–13 d but in only 5/17 lesions where the interval was at least a fortnight (Figs 1–3).

MRI-VEP correlations

First MRI. VEPs were recorded at the time of first MRI in 11 patients, 2 with bilateral simultaneous and 9 with unilateral optic neuritis (Table 2). The VEPs were abnormal for all 13 symptomatic eyes, being absent in 3 eyes, and of increased latency in 9 eyes, in 6 of which there was also a reduced amplitude. In one eye, the VEP was of normal latency but reduced amplitude. In the 10 symptomatic nerves from which a VEP response was obtained (all of which displayed Gd-DTPA leakage) the mean amplitude of the P100 was reduced to about one-third of that in the 9 asymptomatic nerves ($P < 0.001$; t test), and the mean latency was increased by 23 ms ($P < 0.001$; t test).

Follow-up MRI. VEPs were recorded at follow-up in 9 patients (Table 2), 1 with bilateral and 8 with unilateral optic neuritis. Abnormal responses were found in 8 out of 10 symptomatic eyes, with an increased latency in all 8, but a reduced amplitude in only 2. In the 9 symptomatic nerves which no longer displayed Gd-DTPA leakage, the mean amplitude of the P100 was reduced to about half that recorded in the 9 asymptomatic nerves ($P = 0.008$; t test), and the mean latency was increased by 20 ms ($P < 0.001$; t test).

Lesions showing Gd-DTPA leakage at first MRI but not at follow-up. Table 3 and Fig. 4 compare the VEP findings at first scan and follow-up for the 8 eyes whose optic nerve lesion showed this MRI evolution. There was no significant latency difference between the recordings, but the amplitude was significantly larger at follow-up than at the first recording ($P = 0.02$; paired t test).

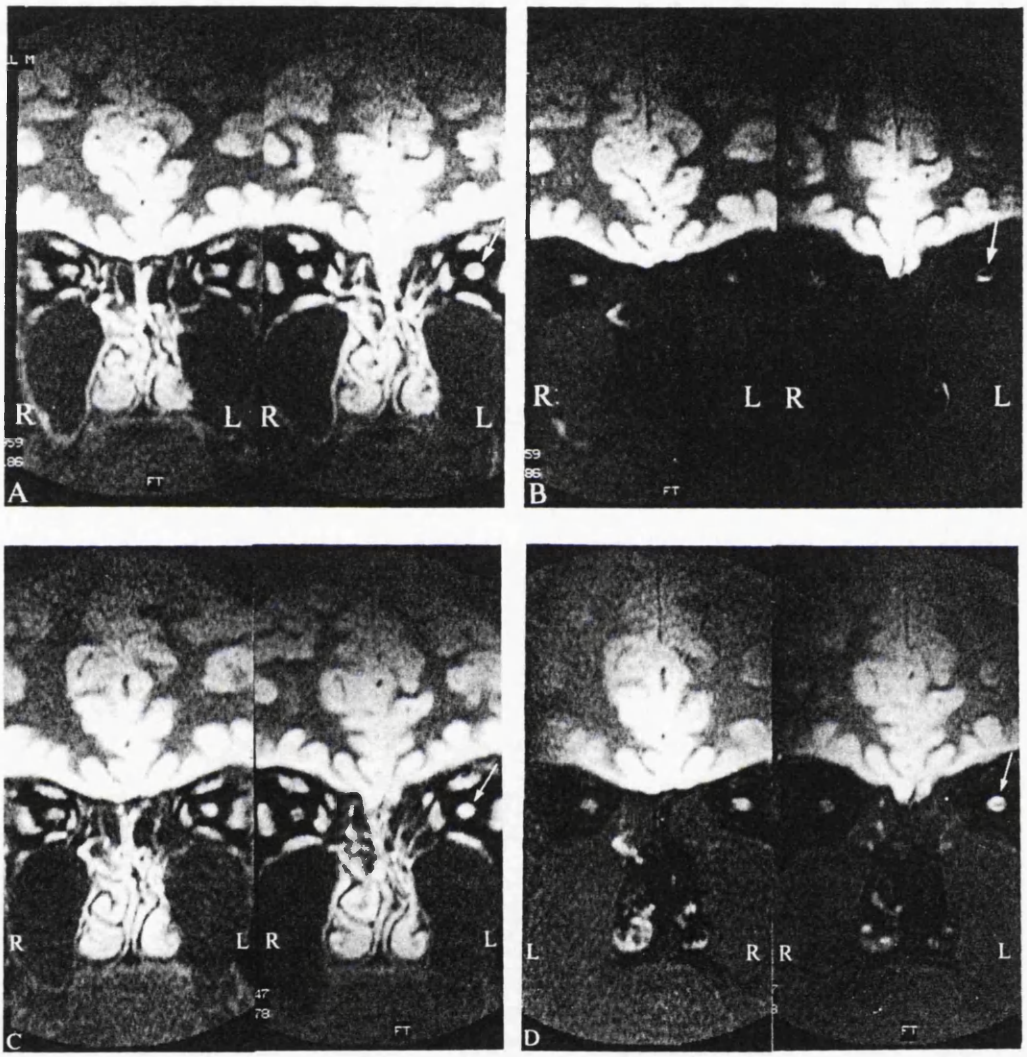

FIG. 2. Series $IR_{2000/40/150}$ scans from a 29-yr-old female (*Case 9*) with left ON. A, first pre-contrast scan (symptoms present for 6 d) reveals increased signal in the left optic nerve (arrowed). B, first scan following injection of Gd-DTPA shows signal decrement in the lesion (arrowed). C, follow-up pre-contrast scan (1 mth later) reveals a persisting high signal lesion (arrowed). D, follow-up scan following injection of Gd-DTPA no longer shows signal decrement in the lesion (arrowed).

Correlation of MRI lesion length with VEP amplitude and latency. We compared P100 latency and amplitude with the length of the pre- and post-contrast MRI lesion both at first MRI and at follow-up. Only one significant correlation was observed: at follow-up, VEP amplitude was inversely correlated with the length of the lesion on the pre-contrast sequence, with a correlation coefficient of -0.84 ($P < 0.01$) and a slope of -1.92 μV/5 mm slice (SEM 0.50) (Fig. 5). The effect accounted for 71% of the variance.

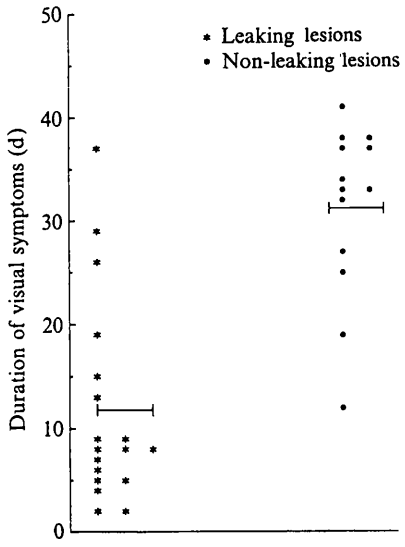

FIG. 3. Optic neuritis: relationship between duration of visual symptoms and presence of Gd-DTPA leakage in the optic nerve.

The regression line intercepted the ordinate at a value of 14.8 μV which is close to the mean amplitude for the asymptomatic eyes (14.1 μV) recorded on the same occasion.

DISCUSSION

There are two main findings in this study. First, the presence of Gd-DTPA leakage was a consistent feature of the early optic nerve lesion in the acute phase of optic neuritis. It was associated with symptoms and signs of an optic neuropathy (impaired acuity and colour vision, an afferent pupillary defect and pain on eye movement) and with a reduction in amplitude and an increase in latency of the pattern VEP. The disappearance of Gd-DTPA leakage at follow-up was associated with a recovery of the amplitude of the VEP to a mean value about half that of the response from the asymptomatic eye, and with resolution of the clinical features. Secondly, the VEP amplitude and latency changes during the acute stage showed no correlation with the length of the lesion or the length of Gd-DTPA leakage, but at follow-up, the persistent reduction in amplitude did correlate inversely with lesion length on non-contrast MRI.

The duration of enhancement in these acute optic nerve lesions (usually less than 1 mth) is similar to that reported in new brain lesions in patients with clinically definite MS (Miller *et al.*, 1988*a*; Bastianello *et al.*, 1990; Kappos *et al.*, 1990; Harris *et al.*, 1991; Thompson *et al.*, 1991), and the results help to illuminate a long-standing problem in the pathophysiology of MS: the explanation of the time course of relapse and the mechanism of remission so characteristic of the early stages of the disease.

The particular advantages of studying optic neuritis in tackling pathophysiological questions have already been mentioned; the symptoms and signs are readily recognized and quantified and conduction can be easily monitored by VEPs. Caution must be exercised in using the known properties of demyelinated nerve fibres to interpret evoked potentials which depend on the integrity of both the conduction pathway and numerous

TABLE 2. AMPLITUDE IN MICROVOLTS AND LATENCY IN MILLISECONDS OF P100 COMPONENT IN PATTERN REVERSED VEP AT FIRST AND SECOND MRI

Patient			First recording				Follow-up			
			Amplitude		Latency		Amplitude		Latency	
No.	*Sex*	*ON*	*L eye*	*R eye*	*L eye*	*R eye*	*L eye*	*R eye*	*L eye*	*R eye*
1	F	L	8.1§	19.6	140§	100	4.6	19.5	130	104
2	M	B	2.2§	1.6§	123§	136§	9.7	10.0	117	118
3	F	R	10.2	2.7§	106	148§	10.3	4.6	105	115
4	M	B	Absent§	Absent§	–§	–§	No follow up			
5	F	L	3.2§	19.0	106§	118*	13.3	17.0	130	125*
6	F	L	8.3§	17.4	125§	104	No follow up VEP			
7	F	R	10.2	1.3§	101	110+§	11.5	5.2§	102	131§
8	F	L	Absent§	11.5	–§	104	9.2	7.8	138	113
9	F	L	2.9§	13.5	153§	106	7.0	14.8	126	106
10	M	L	1.6§	16.0	159§	109	3.3	14.2	145	110
11	F	R	11.8	9.6	118*	145§	15.4	11.5	119*	131

Abnormal responses underlined; * = abnormal response in asymptomatic eye; § = leaking optic nerve lesion at time of VEP; + = increased inter-ocular latency difference.

TABLE 3. MEAN AMPLITUDE (μV) AND LATENCY (ms) OF P100 COMPONENT OF THE PATTERN REVERSAL VEP IN 8 SYMPTOMATIC EYES OF 7 PATIENTS WHOSE OPTIC NERVE LESION DISPLAYED Gd-DTPA LEAKAGE AT THE FIRST RECORDING BUT NOT AT FOLLOW-UP

	Amplitude	*Latency*
First recording	4.2 ± 3.2	140.9 ± 17.0
Follow-up	7.8 ± 3.9	133.1 ± 11.3

Amplitude difference: $P = 0.02$; latency difference: $P = 0.1$, paired t test; cases included in this group: 1, 2, 3, 5, 9, 10 and 11; *Case 8* had an absent response at the first recording, and *Case 7* still displayed Gd-DTPA leakage at follow-up and therefore both were excluded from this group.

synapses from retina to visual cortex. Nevertheless, there is good evidence that a rapidly reversible decrease in amplitude is principally due to conduction block and that slowing of conduction in partially demyelinated nerve fibres contributes to delay in evoked potentials (McDonald and Sears, 1970; Halliday and McDonald, 1977; Persson and Sachs, 1981). Other consequences of demyelination probably also contribute to the latter. They include the development of very slow conduction in persistently demyelinated axons (Bostock and Sears, 1978; Bostock and McDonald, 1982) and delay in generation of the cortical response as a result of a reduced and dispersed input deriving from conduction block and unequal slowing in different fibres. Dispersion would also contribute to the reduction in amplitude.

It is well known that in the acute stage of optic neuritis there is both a decrease in amplitude and an increase in latency of the VEP and that in the recovery phase the amplitude recovers (though not completely) but the delay persists (Halliday *et al.*, 1973).

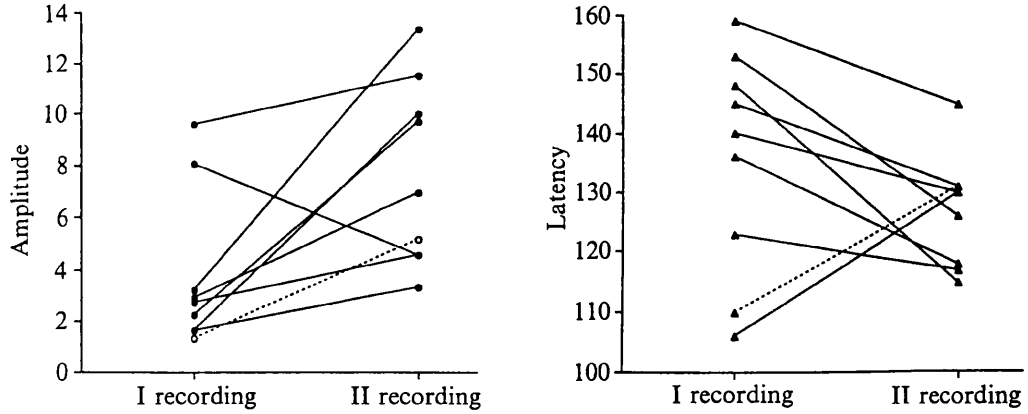

FIG. 4. Serial VEP P100 amplitude (μV) and latency (ms) changes in 9 symptomatic eyes (8 patients). ●—●, ▲—▲ = lesions leaking at first scan but not at follow-up; ○···○, △···△ = lesion leaking on both scans.

The use of Gd-DTPA as an MRI enhancing agent now allows us to interpret these findings more precisely in pathological terms. There is good evidence that recent MS lesions at post-mortem are characterized by inflammation and demyelination (Adams, 1989; Allen, 1991) and that Gd-DTPA leakage reflects the former (Guy *et al.*, 1990; Hawkins *et al.*, 1990; Katz *et al.*, 1990). It is the earliest detectable change in a new lesion and ceases after about a month (Miller *et al.*, 1988*a*; Bastianello *et al.*, 1990; Kappos *et al.*, 1990; Kermode *et al.*, 1990; Harris *et al.*, 1991; Thompson *et al.*, 1991).

Taking the evidence together we conclude, as others have, that demyelination is an early feature of the new lesion in optic neuritis and that it is still present after a month since the VEP is still delayed. Of particular interest is our finding that the recovery of amplitude (and vision) is associated with a cessation of leakage, i.e. resolution of inflammation. Our inability, using current techniques, to quantify the permeability of the blood-optic nerve barrier prevented us from detecting a graded relationship between amplitude and inflammation which would have established a causal connection between the two. Nevertheless, our results makes it likely that inflammation is the crucial factor in determining the reversible element of the conduction block.

How it does so is an open question. Several factors may contribute. Oedema is a prominent feature of acute MS lesions (Adams, 1989; Thompson *et al.*, 1991) and swelling of the optic nerve in optic neuritis is sometimes seen on CT or MRI (Mikol *et al.*, 1980; McCrary *et al.*, 1987; Miller *et al.*, 1988*b*; B. Youl and I. Moseley, unpublished observations). The anatomy of the nerve with its fibrous septa and its passage through the bony optic canal which it almost fills probably limits expansion and leads to the addition of a compressive element to the effects of demyelination in acute lesions. Pressure block which is rapidly reversible occurs in both peripheral and central nerve fibres (Lewis *et al.*, 1931; Merrington and Nathan, 1949; Kayan and Earl, 1975; Gutin *et al.*, 1980). More severe pressure can lead to demyelination or axonal loss (Ochoa *et al.*, 1972; Clifford-Jones *et al.*, 1985). In favour of such a mechanism sometimes operating in optic neuritis is the significant relationship between involvement of the

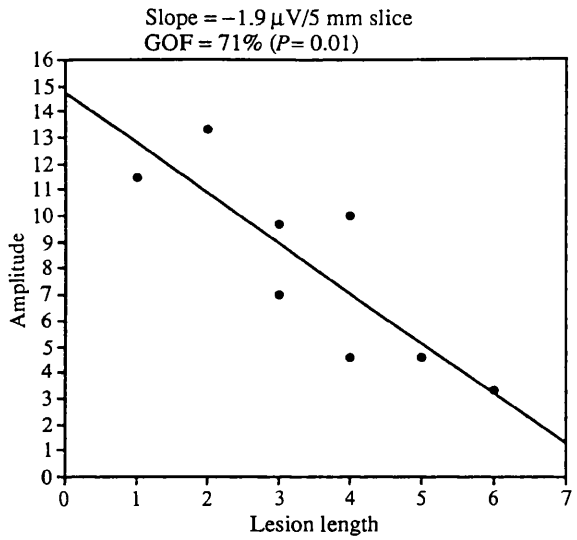

FIG. 5. Correlation of P100 amplitude (μV) with unenhanced lesion length (number of slices) on follow-up examination. GOF = goodness of fit.

optic nerve in the canal and delayed or incomplete recovery, implying irreversible axonal damage, perhaps on a vascular basis (Miller *et al.*, 1988*b*). It is also possible that cytokines released in inflammation interfere with conduction directly, or by inducing demyelination. Tumour necrosis factor produces a decline in membrane potential of muscle (Tracey *et al.*, 1986) and induces demyelination *in vitro* (Selmaj and Raine, 1988).

Turning to the origin of the clinical features of optic neuritis we have found a clear relationship between Gd-DTPA leakage, impairment of acuity and colour vision, an afferent pupillary defect and pain. The visual loss can be accounted for by the accompanying conduction block and its remission by recovery of conduction. The pain probably arises from the stimulation of nerve endings in the meningeal sheath and fibrous septa of the nerve (Hogan *et al.*, 1971) by pressure and pain mediators released during inflammation, as in peripheral nerve (Thomas, 1974; Asbury and Fields, 1984). The characteristic increase in pain on eye movement is probably due to the resulting increase in tension on the inflamed optic nerve at the extremes of gaze (Liu *et al.*, 1990).

The lack of correlation between length of lesion (with or without Gd-DTPA leakage) and latency of the VEP deserves comment. Though at first sight surprising it is less so when one considers the origin of the abnormal signal on MRI. In the acute lesion it is derived principally from vasogenic oedema due to impairment of the blood-brain barrier and in the chronic lesion from a combination of gliosis and a persistent increase in extracellular water (Barnes *et al.*, 1986, 1987, 1991; Miller *et al.*, 1988*a*). Demyelination *per se* is not visible on conventional proton MRI. Moreover, the present method of measurement is crude (maximum resolution 5 mm). Characteristically the acute MRI lesion in MS shrinks markedly (Willoughby *et al.*, 1989) after Gd-DTPA leakage ceases, leaving a smaller residual lesion which changes little unless reactivation of inflammation occurs (Thompson *et al.*, 1991). It is therefore of interest that we did

find a significant inverse relationship between the length of the residual (non-leaking) lesion and amplitude. The longer a lesion the more internodes will be damaged and the greater the chance of conduction block (Rasminsky, 1973). Our previous observation that longer optic nerve lesions in optic neuritis are associated with a poorer visual outcome (Miller *et al.*, 1988*b*) is also consistent with this pathophysiological explanation.

In conclusion, we envisage the following sequence of events in the acute attack of optic neuritis. A focal area of inflammation develops around venules in the optic nerve and is accompanied by an increase in permeability of the blood-nerve barrier. The release of inflammatory mediators and the development of oedema leads to pain which is increased by changes in tension on the nerve during eye movement. Demyelination occurs at about the same time, though the precise order of events is unknown. Both inflammation and demyelination produce conduction block which results in impairment of vision. The inflammation resolves within a few weeks, with the relief of pain and (though not completely) the conduction block. As a result vision improves. The persistent defect in amplitude of the VEP is probably due to a combination of persisting demyelination and the abnormal conduction which accompanies it (block, slowing and dispersion). These conduction defects account for the visual defects (in fields, colour vision, contrast sensitivity and motion perception) which can be detected in many apparently recovered individuals. Latency ultimately returns to normal in only about 10% of adults (Halliday, 1982) but in more than 50% of childhood cases of optic neuritis (Kriss *et al.*, 1988). Remyelination (Prineas and Connell, 1979; Prineas *et al.*, 1987) has probably occurred in these cases. The time course of the clinical and MRI features of a typical episode of optic neuritis is similar to that of many relapses of MS due to lesions in other parts of the central nervous system and it seems likely that an important factor in remission from them too is the resolution of inflammation. Other factors which influence the later stages of recovery are reviewed elsewhere (Thompson and McDonald, 1991).

ACKNOWLEDGEMENTS

This work was generously supported by the Multiple Sclerosis Society of Great Britain and Northern Ireland and the Medical Research Council.

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(Received March 12, 1991. Revised July 1, 1991. Accepted July 19, 1991)

Symptomatic retrochiasmal lesions in multiple sclerosis:

Clinical features, visual evoked potentials, and magnetic resonance imaging

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Article abstract—We have studied 18 patients with relapsing-remitting multiple sclerosis (MS) who had symptomatic visual field defects due to retrochiasmal lesions. In 17, the lesion responsible was identified by magnetic resonance imaging (MRI), computed x-ray tomography (CT), or both. The lesion responsible involved the posterior optic radiations in eight cases, the optic tract and lateral geniculate nucleus in six, and the posterior limb of the internal capsule in three. The prognosis for recovery of the field defect was good; complete recovery occurred in 14 patients, and only two showed no recovery at all. The striking characteristic of the lesions was that most were unusually large; indeed, many were detectable on CT as well as MRI. Half-field asymmetries of either amplitude or latency of the visual evoked potentials (VEPs), consistent with a postchiasmal lesion, were present in only five out of 13 patients acutely. In only three of these did the abnormality persist at follow-up. We conclude that only large postchiasmal lesions are likely to cause symptomatic homonymous field defects in MS, usually characterized by rapid recovery. Hemifield VEPs have a low sensitivity for the detection of postchiasmal as compared with prechiasmal abnormalities.

NEUROLOGY 1992;42:68-76

Autopsy studies of multiple sclerosis (MS) frequently disclose involvement of the postchiasmal visual pathways, especially the optic radiations. Lehoczky[1] specifically addressed the problem of visual pathway involvement in MS in a postmortem study of 20 cases and found lesions in the optic radiations in 85%. This observation may be related to the overall vulnerability of the periventricular white matter; in a subsequent autopsy study of 22 cases of MS,[2] plaques were present most commonly in relation to the lateral ventricles, the regions affected being the lateral angles of the anterior horns and bodies and around the inferior and posterior horns.

These findings have been confirmed in magnetic resonance imaging (MRI) studies of the brain in MS during life where evidence of pathology affecting the optic radiations is also common. In a study of 114 cases of MS,[3] the peritrigonal white matter was involved in 90% of cases and the white matter around the occipital horns in 83% of cases. Furthermore, a study described in our companion paper[4] found evidence on MRI of asymptomatic lesions affecting the optic radiations in 20 of 28 cases of clinically isolated optic neuritis.

Paradoxically, clinical evidence of homonymous visual field defects which can be attributed to retrochiasmal disease is not common in MS. Extensive series involving hundreds of cases have either failed to find evidence of homonymous visual field defects[5-7] or found very few examples.[8,9] Traquair,[10] however, recognized that cases of retrobulbar neuritis were occasionally seen with visual field defects, indicating that the pathologic process was located behind the chiasm. Subsequently, well-documented reports of homonymous visual field defects in MS have appeared,[11,12] and recently the lesions responsible have been identified by x-ray computed tomography (CT)[13] or MRI.[14] The purpose of this article is to report the clinical features, the prognosis for visual recovery, and the visual evoked potential (VEP) findings in 18 patients with MS who demonstrated symptomatic homonymous visual field defects in the course of their disease. In 17 cases, the lesion responsible was identified by MRI, CT, or both. Some of these results have been published in abstract form.[15]

Methods. *Patient selection.* Most of the cases reported were seen by the first author at the National Hospital for

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Received January 15, 1991. Accepted for publication in final form June 10, 1991.

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Table. Perimetric findings in the 18 cases are shown soon after the onset of the field defects. Follow-up fields are only shown if there was incomplete recovery. Filled areas are absolute scotomata, dotted areas indicate stato-kinetic dissociation. The imaging techniques employed and results in each case are also shown.

	CASE NO.	MRI AND CT IMAGING RESULTS	VISUAL FIELD VISUAL ACUITY ISHIHARA (NO. OF ERRORS) OS.	OD.	FOLLOW UP ASSESSMENT INTERVAL AND RESULT
GROUP 1 LESION UNCERTAIN	1	~~MRI~~ CT: NORMAL	6/9 (0)	6/9 (0)	FULL RECOVERY AT 4 WEEKS
GROUP 2 OPTIC TRACT (OT) AND LATERAL GENICULATE NUCLEUS (LGN)	2	MRI: LESION ANTERO-LATERAL TO LGN ~~CT~~	6/12 (0)	6/18 (0)	FULL RECOVERY AT 8 WEEKS
	3	MRI: LESION IN LEFT MEDIAL TEMPORAL LOBE AND THALAMUS INVOLVING OT AND LGN CT: NORMAL	ACUTE 6/5 (0) FOLLOW UP 6/5 (0)	ACUTE 6/5 (0) FOLLOW UP 6/5 (0)	INCOMPLETE RECOVERY AT 9 MONTHS
	4	MRI: LARGE LESION IN REGION OF RIGHT CEREBRAL PEDUNCLE AND THALAMUS INVOLVING OT AND LGN ~~CT~~	6/12 (2)	6/12 (2)	FULL RECOVERY AT 6 MONTHS
	5	MRI: LESION IN REGION OF LEFT OT AND LGN ~~CT~~	6/6 (0)	6/6 (0)	FULL RECOVERY AT 12 WEEKS
	6	MRI: LESION IN REGION OF RIGHT CEREBRAL PEDUNCLE INVOLVING OT CT: NO ENHANCEMENT	6/6 (0)	6/6 (0)	FULL RECOVERY AT 16 WEEKS
	7	MRI: LARGE LESION IN REGION OF RIGHT OT AND THALAMUS. GD ENHANCEMENT CT: MASS EFFECT	6/12 (5)	6/12 (0)	NO IMPROVEMENT AT 6 MONTHS
GROUP 3 POSTERIOR LIMB OF INTERNAL CAPSULE (IC)	8	MRI: LARGE LESION IN WM OF LEFT TEMPORAL LOBE ACROSS POSTERIOR LIMB OF IC CT: RING ENHANCEMENT	6/5 (0)	6/5 (0)	FULL RECOVERY AT 12 WEEKS
	9	MRI: LESION IN POSTERIOR LIMB OF LEFT IC ~~CT~~	6/5 (0)	6/5 (0)	FULL RECOVERY AT 12 WEEKS
	10	MRI: SMALL LESION IN POSTERIOR LIMB OF LEFT IC CT: NORMAL	6/5 (0)	6/5 (0)	FULL RECOVERY AT 8 WEEKS
GROUP 4 POSTERIOR OPTIC RADIATION (OR)	11	~~MRI~~ CT: LARGE OR LESION SHOWING RING ENHANCEMENT	ACUTE 6/6 (0) FOLLOW UP 6/7.5 (12)	ACUTE 6/6 (0) FOLLOW UP 6/7.5 (11)	NO IMPROVEMENT AT 7 YEARS
	12	MRI: LARGE LESION EXTENDING FROM RIGHT TRIGONE INVOLVING OR ~~CT~~	6/18 (4)	6/60 (9)	FULL RECOVERY AT 4 WEEKS
	13	MRI: VERY LARGE LESION INVOLVING WHOLE OF RIGHT OR EXTENDING FROM CEREBRAL GREY MATTER TO OCCIPITAL HORN OF LATERAL VENTRICLE CT: LOW DENSITY NON-ENHANCING	ACUTE 6/6 (3) FOLLOW UP 6/6 (2)	ACUTE 6/6 (2) FOLLOW UP 6/6 (2)	INCOMPLETE RECOVERY AT 18 MONTHS
	14	MRI: LARGE LESION IN RIGHT OCCIPITAL WM CT: LOW DENSITY NON-ENHANCING	6/5 (0)	6/5 (0)	FULL RECOVERY AT 12 MONTHS
	15	MRI: LARGE LESION EXTENDING FROM WM OF LEFT TEMPORAL LOBE CT: RING ENHANCEMENT	SEVERE OPTIC NEUROPATHY CF	6/6 (9)	FULL RECOVERY AT 4 MONTHS
	16	MRI: LARGE CONFLUENT LESION IN LEFT PARIETO-OCCIPITAL WM CT: NORMAL	6/6 (0)	6/6 (0)	FULL RECOVERY AT 12 WEEKS
	17	MRI: LARGE LESION IN WM OF LEFT TEMPORAL LOBE CT: RING ENHANCEMENT	CONFRONTATION FIELD		FULL RECOVERY AT 9 WEEKS
	18	MRI: LARGE LESION RIGHT OR CT: RING ENHANCEMENT	CONFRONTATION FIELD 6/6	6/6	NO FOLLOW UP AVAILABLE

Neurology and Neurosurgery or Moorfields Eye Hospital during a 3-year period. All patients presented with visual symptoms and on examination were found to have homonymous visual field defects, and all those included in the study either had clinically definite MS[16] at presentation or subsequently were shown to have on clinical criteria. Goldmann perimetry and MRI were carried out as soon as possible following the onset of visual symptoms, usually within 3 weeks. In one case visual recovery was so swift that the fields were normal by the time the patient was seen for perimetry (case 17, table), and in one case confrontation fields only were carried out at presentation and the patient was not available for follow-up (case 18, table). CT studies were available for comparison

in some cases where these had been carried out as part of the routine clinical evaluation prior to recruitment for the study. Two patients (cases 1 and 11, table) had been seen some years previously when MRI was not available but have been included in the series because adequate perimetry and VEPs were carried out at the onset of the symptoms, and the patients were available for a prolonged follow-up assessment.

Perimetry. Goldmann perimetry was carried out conventionally by the measurement of isopters dynamically to target I4e in all cases and, when time permitted, to additional targets. The extent of the field defect to static stimulation was also recorded. Perimetry was carried out as soon as possible after the patient noticed symptoms and repeated within 6 months. One patient was not available for the follow-up examination (case 18). The hemianopic field defect was judged to have resolved on follow-up if there were no longer significant differences between the isopters obtained in both nasal hemifields and both temporal hemifields. In one patient (case 15, table), this judgment was not possible because of a preexisting severe unilateral optic atrophy. If the field defect had not recovered at the second visit, the patients were reassessed at longer intervals. Where confrontation fields were recorded, these were carried out using a 4-mm target at 30 cm.

Magnetic resonance imaging. The standard protocol in this study was to perform T_2-weighted MRI of brain on a Picker 0.5T machine using $SE_{2000/60}$ 5-mm contiguous slices and a 256 × 256 image matrix. Occasionally, 10-mm slices were obtained, and one examination (case 8) was carried out on a 0.26T imager. Where gadolinium-DTPA enhancement was employed, additional T_2-weighted images were obtained ($SE_{500/40}$). Imaging was carried out as soon as possible after the onset of the visual symptoms, always within 3 weeks, and the scans were assessed by a neuroradiologist (I.F.M.) without knowledge of the perimetric findings. The two patients included retrospectively who had not undergone MRI were investigated by CT. All abnormalities localized to the retrochiasmal visual pathways were noted. Follow-up images with careful repositioning[3] were obtained in six of 16 cases to document resolution of the lesions deemed responsible for the field defects.

Visual evoked potentials. Pattern reversal VEPs were recorded in 13 patients within 6 weeks of the onset of the visual symptoms. Subsequently, a follow-up study was carried out in eight of these. In two additional patients, a follow-up test only was carried out (cases 6 and 16). Two patients (cases 12 and 18) were unavailable for VEP recording, and in case 17 severe preexisting optic neuropathy rendered the results uninterpretable and they have been excluded from the analysis. Recordings were carried out using the technique described elsewhere.[17] Both full- and half-field responses were obtained, but since the study was concerned with VEP changes associated with postchiasmal lesions, only the half-field components were considered in the analysis.

Normal limits were obtained from 50 healthy subjects, aged 18 to 55 years, and defined by the mean ± 2.5 standard deviations (SD). Normal latency limits were as follows: absolute latency = 117 msec (mean, 104.7 ± 4.9 SD); monocular heteronymous hemifields latency difference (longer–shorter) = 8 msec (mean, 2.8 ± 2.3 SD). The normal limit of the amplitude asymmetry, measured as the ratio of the larger to the smaller amplitude, recorded 5 cm above the inion and 5 cm ipsilateral to the stimulated hemifield,[18] was 2 (mean, 1.3 ± 0.3 SD).

Results. *Clinical features.* All 18 patients in this series presented with visual symptoms at the onset of the clinical episode. In addition to the hemianopic field defects, six had hemiparesis, another clinical feature that is uncommon in MS[19] (cases 6, 7, 11, 15, 17, and 18). In cases 15 and 17, with left hemisphere lesions, there was also dysphasia.

The results of Goldmann perimetry obtained soon after development of visual symptoms are shown in the table. Seven patients had complete homonymous hemianopia or dense partial hemianopia when first seen (cases 5, 7, 8, 11, 13, 17, and 18), and four of these also had hemiparesis. Two patients manifested a general depression of the hemifield (cases 2 and 15) with complete hemianopia to I4e but marked statokinetic dissociation to larger targets (corresponding to shaded areas in the table). Eight cases had homonymous scotomata, often showing some incongruity, and statokinetic dissociation to larger targets. The remaining patient (case 14) showed a mild depression of isopters to I2e and I4e on perimetry and presented because of positive visual phenomena within the hemifield.

In all patients except cases 3, 7, 11, and 13, the visual field had recovered at the second visit. This occurred within 3 months of the onset of visual symptoms in all except case 15 (4 months) and case 4 (6 months). Case 18 was not available for follow-up. Where recovery was incomplete at the subsequent assessment, the follow-up fields are also shown in the table. Only two patients failed to show any improvement: case 7 had a persisting complete hemianopia at 6 months, and case 11 has a defect which has remained static for 7 years. Cases 3 and 13 have shown substantial incomplete recovery at 9 and 18 months, respectively.

Location of lesions and imaging features. All patients had multiple lesions on MR imaging, and in many cases there was more than one lesion involving the visual pathways. There was no difficulty in identifying the lesion responsible for the field defect because of its location, its change in size on subsequent examinations, or both. Two patients did not undergo MRI acutely (cases 1 and 11). In case 11 (but not in case 1), the lesion responsible could be identified on the contemporary CT study. Case 1 has been included because of the adequacy of the VEP and perimetry data. The lesion was visible on CT also in nine out of 13 cases in which CT was carried out (CT was not part of the study protocol) and demonstrated contrast enhancement in six of those. In two patients (cases 7 and 17), the initial MR was carried out with gadolinium-DTPA enhancement (0.2 mmol/kg) and the lesion causing the field defect enhanced.

In six patients, the lesion was in the region of the optic tract or lateral geniculate body (group 2, table); in three, it involved the posterior limb of the internal capsule (group 3); and in the remaining eight cases, it was situated more posteriorly in the

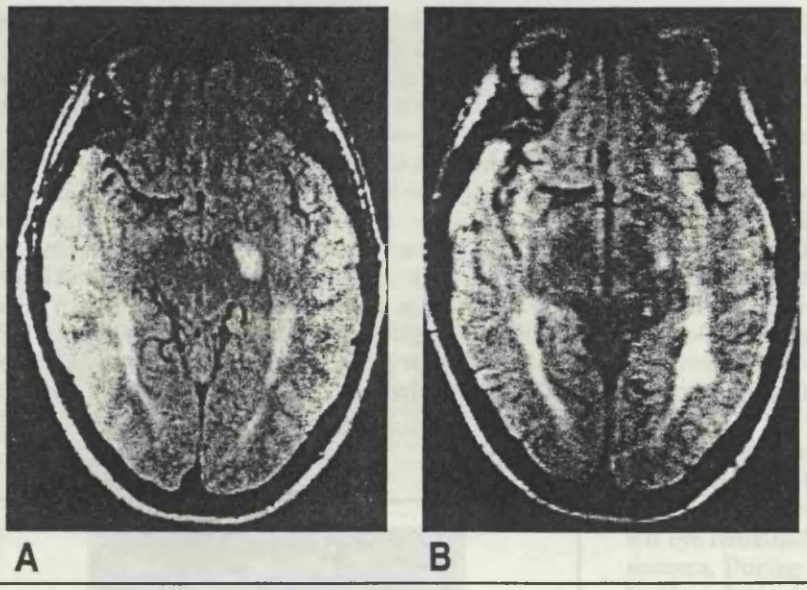

Figure 1. (Case 5) T_2-weighted MR images. (A) Two weeks after the onset of a right homonymous hemianopia. A lesion 1 cm in diameter is seen in the region of the left optic tract (in this and subsequent images, the left side of the brain is on the right). Increased signal is also seen around the occipital horns. (B) One year later, the anterior lesion is smaller, but there is much more extensive high signal in the white matter of the occipital lobes.

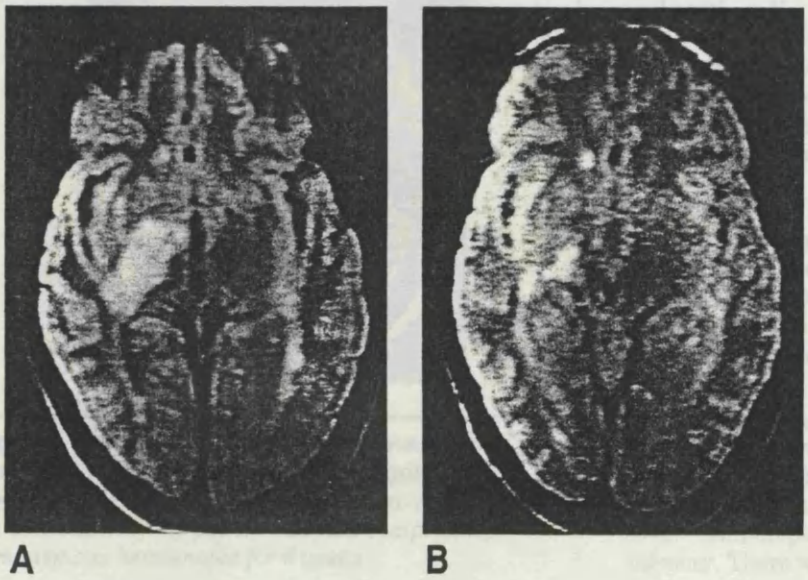

Figure 2. (Case 7) T_2-weighted MR images. (A) Three weeks after the onset of a left homonymous hemianopia. A very large plaque occupies the region of the right optic tract, extending laterally. (B) Four months later, there has been striking resolution.

optic radiations, involving the white matter of either the temporal or occipital lobes (group 4). Some specific examples are shown in figures 1 through 6. Representative clinical accounts are now given.

Case reports. Case 5. A 42-year-old man known to have symptoms of MS since age 25 presented with blurred vision. Two weeks following the onset of his symptoms, Goldmann perimetry revealed a complete, macular splitting, right homonymous hemianopia. MRI showed a discrete lesion in the region of the left optic tract/lateral geniculate nucleus (LGN) and multiple periventricular and discrete white matter lesions (figure 1A). Three months later, the Goldmann fields were within normal limits. One year later, the lesion responsible was still visible on MRI but much smaller. There had been an increase in high signal in the optic radiations (figure 1B) but no further change in the Goldmann fields (table).

Case 7. A 38-year-old woman known to have MS noticed "gaps" in her left field of vision. A few days later she developed a left hemiparesis, and the visual loss progressed over a further week. She experienced formed visual hallucinations in the left hemifield. Three weeks following the onset of visual symptoms, Goldmann perimetry revealed a complete left homonymous hemianopia. There was also a left hemiparesis, emotional lability, and impaired memory.

CT showed a large low-density lesion, exerting moderate mass effect and involving the whole of the right internal capsule. On MR (figure 2A), a very large lesion was confirmed in the region of the lentiform nucleus; several small foci of gadolinium enhancement were observed within it in an enhanced scan carried out at the same scanning session. Nonenhancing lesions in the white matter of the left parietal and both temporal lobes were also present. Four months later there was no change in the field defect, but on MRI the presumed causative lesion was much smaller (figure 2B). After 6 months there was still no change in the field defect.

Case 13. A 29-year-old man suddenly noticed impaired vision to his left. A week later, Goldmann perimetry revealed a complete left homonymous hemianopia to I4e and III4e. CT showed a low-density lesion in the right posterior parietal and occipital regions with moderate mass effect. MRI (figure 3) confirmed a large right occipitoparietal lesion extending from the cerebral gray matter to the occipital horn of the lateral ventricle. Other lesions were present in cerebral white matter and in the brainstem. The subjective visual disturbance resolved in 6 weeks. At 8 weeks, however, a lower quadrantic field defect remained, and even at 18 months a partial left lower homonymous quadrantic defect was detected to I4e, with marked statokinetic dissociation to III4e (table).

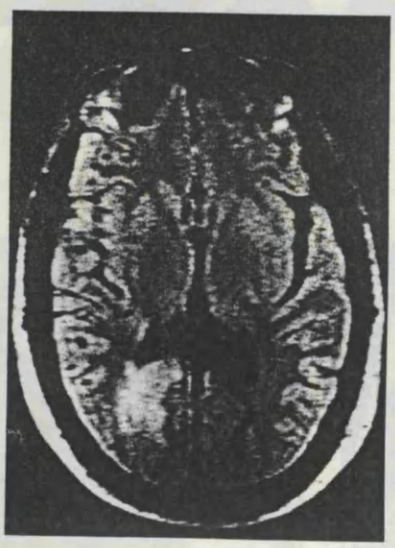

Figure 3. (Case 13) A large area of abnormal signal is seen in the white matter of the right occipital lobe involving the whole of the optic radiation. At the time of the examination, the patient had had complete left homonymous hemianopia for 6 weeks.

Case 14. A 27-year-old woman noticed shimmering in her left field of vision of abrupt onset becoming more intense over 15 minutes and subsiding after 1 hour. Six days later the symptom recurred, and on this occasion she was aware of partial loss of vision to her left. Two weeks following the initial episode, Goldmann perimetry revealed an incomplete left lower quadrantic field defect using targets I2e and I4e. CT showed a circumscribed subcortical lesion in the right occipital region. MRI (figure 4A) showed multiple lesions in the deep white matter of both cerebral hemispheres, the largest being in the right occipital region. Twelve weeks later the field defect had resolved totally, and on MRI the right occipital lesion was smaller (figure 4B).

Case 15. At age 27, this patient presented with an acute brainstem disturbance and bilateral optic neuropathy. He made a good recovery except that visual function of the left eye remained at counting fingers with a dense central scotoma. During the ensuing 10 years he had a number of further clinical episodes of MS, but at age 37, over 2 weeks, he developed a progressive dominant hemisphere syndrome characterized by difficulty with word finding and writing. He developed seizures and memory impairment and complained that his vision was worse. CT demonstrated a low-density lesion in the left temporoparietal region, showing ring enhancement. Goldmann perimetry, in his testable right eye, showed a complete hemianopia to I4e and statokinetic dissociation to II4e and III4e throughout the right hemifield. MRI (figure 5, A and B) confirmed an extensive abnormality in the white matter of the left temporal, parietal, and occipital lobes. Four months later, the field defect had recovered. Subsequent MRI demonstrated little change in the lesion, but it did not enhance with gadolinium-DTPA although previously it had shown contrast enhancement on CT.

Case 17. A 20-year-old woman presented with symptoms and signs of a brainstem lesion which recovered in several weeks. Later the same year, she developed visual disturbance and was found to have a complete left homonymous hemianopia to confrontation and a disturbance of memory. There was gradual improvement over 3 months.

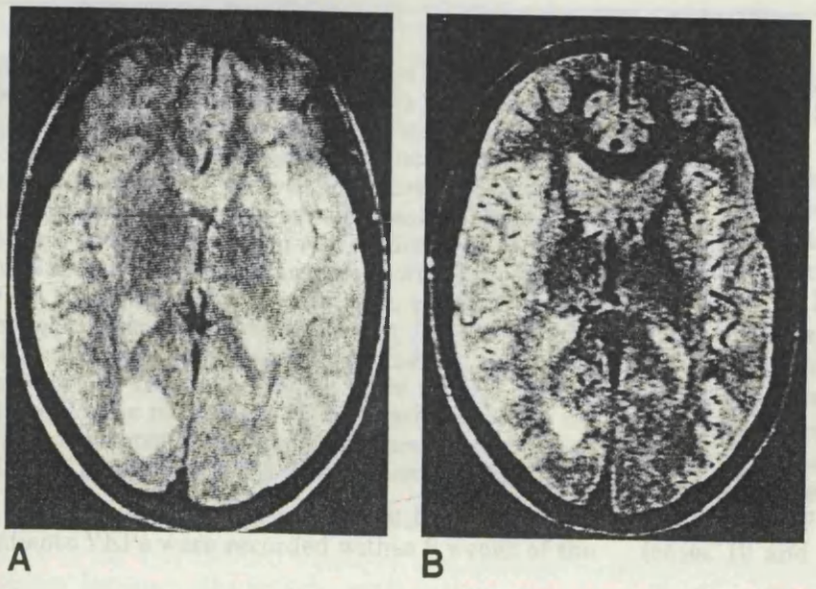

Figure 4. (Case 14) T_2-weighted MR images. (A) Two weeks after onset of an incomplete left lower quadrantic field defect. A large area of increased signal is seen in the right occipital white matter. (B) Twelve weeks later, the lesion is considerably smaller.

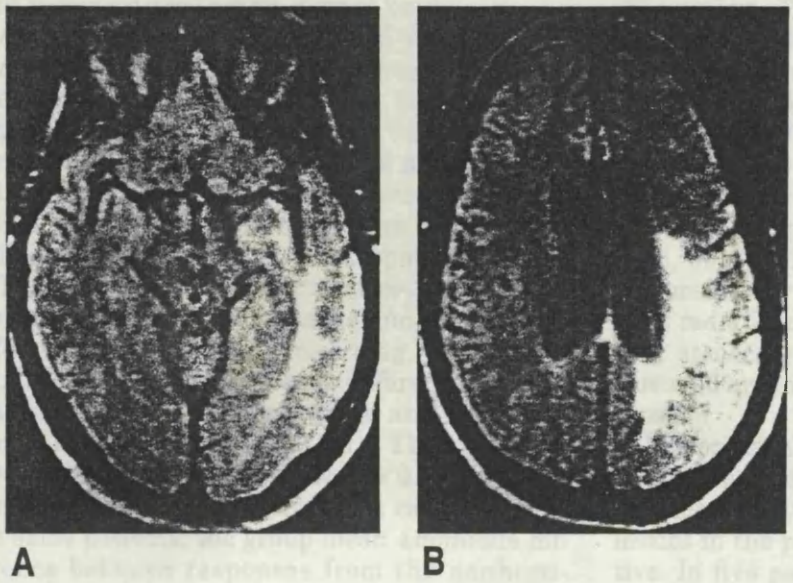

Figure 5. (Case 15) T_2-weighted MR images. (A and B) A very extensive high-signal area extends from the temporal and occipital lobes (A) to the parietal lobe (B).

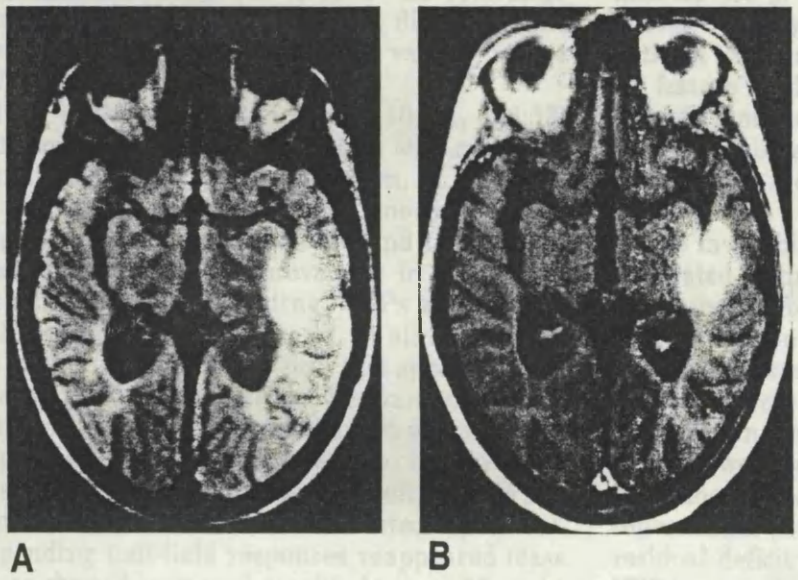

Figure 6. (Case 17) (A) T_2-weighted MRI ($SE_{2000/40}$) following acute onset of a right homonymous hemianopia. A large high-signal area is seen in the left temporal lobe, extending deeply. (B) On a T_1-weighted sequence ($SE_{500/40}$) the lesion displays gadolinium enhancement.

Over the next 5 years, other episodes occurred. When seen by us, she had woken with a right hemiparesis and dysphasia. Only confrontation visual fields were obtained acutely, which demonstrated a complete right homonymous hemianopia. CT showed an extensive lesion in the left hemisphere with ring enhancement and associated cerebral atrophy. The lesion was confirmed on MRI (figure 6A) and showed enhancement with gadolinium-DTPA (figure 6B). Three weeks later, unenhanced MRI showed an even more extensive lesion. Nine weeks later Goldmann fields were carried out, and the field defect could not be detected although there was evidence of bilateral optic neuropathy. Five months following the onset of symptoms, the lesion was barely detectable on MRI and gadolinium-DTPA enhancement was absent.

Visual evoked potentials. Acute findings. In 13 patients VEPs were recorded within 6 weeks of the onset of the visual symptoms, and in 12 of these a homonymous hemianopic defect could be detected by Goldmann perimetry. The defect consistently involved the central 0-15°.

Five of these patients (38.5%) showed a significant asymmetry between left and right half-field responses from each eye, consistent with a postchiasmal lesion. In every case, the asymmetry corresponded to the side of the homonymous visual field defect. In three patients there were absent responses from the homonymous hemifield (cases 1, 7, and 13), and in two others there was an increased latency difference between heteronymous hemifield responses in each eye or an abnormal amplitude ratio of the P100 in the two half-fields or both (cases 10 and 11). In all these patients, the full-

field responses were within normal limits.

An additional six patients out of the 13 (46.2%) had abnormal full- or half-field responses from one or both eyes (delayed, reduced, or absent), but without an asymmetry between heteronymous hemifield components in each eye and therefore not indicative of a postchiasmal lesion (cases 2, 4, 5, 8, 9, and 15). These findings were suggestive of unilateral or bilateral optic neuropathy. Two out of 13 cases had normal VEPs (cases 3 and 14). In the 12 patients showing a homonymous field defect at the time of VEP recording, there was a significant group mean latency difference between responses from the hemianopic and nonhemianopic hemifields: left eye, 10.8 ± 11.8 msec (p = 0.04); right eye, 9.7 ± 6.5 msec (p = 0.002). Absent responses were excluded from this calculation. In the same patients, the group mean amplitude difference between responses from the nonhemianopic and hemianopic hemifields was significant in the left eye (1.7 ± 2.8 μV, p = 0.04), but not in the right eye (1.1 ± 3.0 μV, one-tailed paired t test).

Follow-up findings. One or more VEP recordings were performed in 10 patients at different time intervals during a follow-up period varying from 4 to 77 months.

Four of these patients (cases 7, 10, 11, and 13) had shown abnormalities consistent with a postchiasmal lesion at the first examination. At follow-up, an asymmetry between heteronymous hemifield responses persisted in cases 7, 10, and 11, although case 10 showed some improvement in comparison with the previous recording. VEPs returned to within normal limits in case 13. In all these cases, the amplitude of the half-field VEPs appeared to be related to the extent of the hemianopic defect. Hemifield responses were unchanged when the corresponding visual defect showed no improvement (case 7, both eyes, and case 11, left eye). When recovery of the visual defect was detected, the corresponding half-field responses reappeared (case 13) or showed increased amplitude (case 10, right eye).

Of the remaining four patients who had been examined acutely, cases 2 and 3 were unchanged; the former showed an increased interfield difference in the left eye, whereas the latter was normal. Case 9 developed an amplitude asymmetry in the right eye responses. In case 8, the interfield latency difference of the left eye responses returned to within normal limits. In cases 6 and 16, VEPs were recorded at 18 and 16 weeks, respectively, from the onset of visual symptoms, when the homonymous visual field defect had fully recovered. They showed delayed responses from both eyes consistent with bilateral optic neuropathy. In all these patients, the homonymous defect had totally or partially recovered.

No specific relation was found between the changes of the VEPs at the follow-up and the location of the lesions in the postchiasmal pathways.

Discussion. This report of 18 examples of symptomatic retrochiasmal lesions in MS does not imply that these are more common than the previous literature would suggest. Since we initiated this study, over 2,000 individual cases of MS have been investigated by the MRI Research Group at Queen Square, and we selected the reported cases from this large group. On examination with MRI, CT, or both, only eight of the 18 patients had lesions responsible for their field defects in the posterior optic radiations, where plaques are commonly present at necropsy.[1,2] The other nine lesions were clustered around the optic tract, LGN, and internal capsule.

The principal distinguishing feature of the acute lesions was their size. Most were unusually large, as evidenced by the CT studies in six patients with lesions in the posterior optic radiations being positive. In five patients with more anterior lesions, three were visible on CT. In the largest previous series of postgeniculate lesions in MS,[13] four out of six lesions were visible on CT. It is therefore not surprising that hemianopia was an unusually common feature in the early reports of CT imaging of lesions.[19,20] It is also noteworthy that six of all 18 patients had hemiparesis, another uncommon clinical feature in MS,[21] in addition to the hemianopia. Therefore, one possible explanation for the rarity of homonymous field defects in MS may be that only unusually large lesions cause symptomatic field loss.

The favorable prognosis for recovery of vision illustrated in the series reported here may also in part account for the rarity of homonymous field defects in previous studies[5-7]: only two of 18 patients showed no improvement, and 14 had no detectable field defect on Goldmann perimetry at follow-up. In the previously cited series,[13] five of six cases showed complete recovery.

Psychophysical test of visual function other than conventional perimetry may provide evidence of a residual deficit in such cases. However, although VEP latency changes are a very sensitive technique for providing evidence of an optic nerve lesion in MS, we have found that the VEP-to-hemifield stimulation has a relatively low sensitivity for detection of postchiasmal lesions. This may be accounted for by the frequent occurrence of optic nerve lesions, which may mask minor abnormalities due to retrochiasmal pathology (eight cases in this study). A certain degree of amplitude asymmetry between monocular hemifield responses occurs in the normal population[18,22] due to the marked variability in the location of the primary visual area on the medial surface of the occipital lobe.[23-25] Therefore, the degree of asymmetry between monocular hemifield responses associated with a partial homonymous field defect may not exceed the normal limits. This argument does not apply to the failure to find latency changes in most of our cases. Also, in the primary visual cortex, the central 0-15° of the visual field are more largely represented than the

peripheral area.[26,27] For this reason, peripheral homonymous field defects are unlikely to cause a significant VEP asymmetry of any kind.

In our series, 11 cases presented with an acute homonymous field defect involving the central 0-15° at the time of the VEP recording. The majority of these still did not show a homonymous amplitude asymmetry that was beyond normal limits. However, in the group of patients as a whole, the responses from the affected hemifields tended to be smaller. We found a low frequency (two out of 15 cases) of increased monocular interfield latency differences, indicating a postchiasmal lesion, consistent with previous studies.[17,28] Despite this, there was a significant mean latency increase for the responses from the hemianopic as compared with the nonhemianopic hemifields in the group as a whole. It is clear that in the case of asymptomatic posterior visual pathway lesions, the VEP will show lower sensitivity; in the companion study,[4] 20 cases of isolated optic neuritis had no hemifield latency asymmetry in the unaffected eyes despite MRI abnormalities localized to the optic radiation. Furthermore, in the present series most cases had multiple lesions affecting the visual pathways and the asymptomatic lesions affecting the posterior pathways have not caused detectable alterations in the VEP, in marked contrast to long-standing optic nerve lesions.

The rarity of clinical evidence of retrochiasmal, as opposed to prechiasmal, lesions in MS must be due either to differences in the normal anatomy of different parts of the visual pathways and their relationship to the lesions or to the nature of the pathologic process. The latter is inherently improbable; at both sites the morphology of the lesions is similar,[29] and serial MRI with gadolinium-DTPA has shown that enhancement (signifying inflammation), lasting a few weeks only, is a consistent feature of the very early stages of their development.[30-32] The unlikely possibility that there is less demyelination in the cerebral lesions cannot, however, be excluded.

As for the question of anatomic factors, three factors require consideration. The first is the proportion of the nerve fibers subserving vision which are damaged by a lesion of a particular size in different locations in the visual pathways. In the optic nerve, all fibers are concentrated in a relatively small volume, whereas in the optic radiations, the fibers occupy a greater area, increasingly so posteriorly. Thus, a lesion occupying a cylinder 5 mm in diameter and 1 cm long (common in MS[29,33]) will affect most of the fibers from one eye in the optic nerve but a very much smaller proportion in the radiations. Secondly, the orientation of the lesion to the fibers will be important in determining the likelihood of conduction block—the final determinant of clinical deficits; as more internodes are damaged, the greater the risk. Since lesions are oriented to venules and not fiber tracts, a given lesion identified on MRI may have little effect posteriorly where the fibers follow a curvilinear course.

Finally, the effects of edema that accompany the acute lesion may differ at different sites. In the brain, the edema commonly extends far beyond the area of residual parenchymal damage[34-36] (see figures 2 and 6). In the optic nerve, the fibrous septa are likely to restrict expansion (though swelling of the nerve sometimes occurs), thus adding a compressive element to the effects of demyelination. This suggestion receives some support from the strong association between persistent visual loss in optic neuritis and involvement of the nerve within the bony optic canal,[33] where room for expansion is limited and the potential for secondary compressive damage correspondingly greater. By contrast, in the cerebral hemisphere the potential for spread of edema is much greater. A similar argument can be developed in relation to the ease of diffusion of the cytokines produced by inflammatory cells, but nothing is known at the present of their effects on conduction. The visual system offers a unique opportunity to clarify these issues further by serial study. Visual deficits are more amenable to quantification psychophysically and electrophysiologically than those in other motor and sensory systems. Correlating such data with that derived from new techniques of MRI that can be used to determine the time course of inflammation,[37] myelin breakdown,[38] and axonal loss[39] may help to establish the necessary pathologic conditions leading to the different patterns of clinical abnormality.

Acknowledgments

The MRI studies were carried out on a facility supported by the Multiple Sclerosis Society of Great Britain and Northern Ireland and also by the Medical Research Council of Great Britain. We also acknowledge the support of the Brain Research Trust. We are grateful to many colleagues at The National Hospital for Neurology and Neurosurgery and the Moorfields Eye Hospital who permitted us to study patients under their care. This article was written while G.T.P. was a Medical Research Council (UK) Travelling Fellow at the Smith-Kettlewell Eye Research Institute, San Francisco, to which we are grateful for secretarial help and assistance with the illustrations.

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