second-tier superintensive care unit. We know results as good (or as bad) as ours are often obtained in well-established district hospital units, so their results may be as good as the best that is available at present. If we staff and equip our district hospitals properly, the necessity for second-tier units may disappear. There is a further argument for increasing the capability of the district unit since it has to cope with asphyxiated neonates; if they are equipped for them they should be equipped for the preterm infants also. This seems to us to be the all-important reason for upgrading those district neonatal units that require it.

But the last word, on this occasion, may be with the obstetricians. Our figures show that the number of very small infants being born is declining disproportionately to the fall in the birth rate. For instance, in 1970 before the birth rate in Sheffield started dropping dramatically there were 44 babies in our series under 1500 g and 214 weighing 2001-2500 g; in 1975 there were 16 and 124, respectively. This is a drop of 67·64% in the under 1500 g group compared with a drop of 42·06% in those weighing 2001-2500 g. It is not for a paediatrician to say how near the obstetricians are to controlling spontaneous premature labour, but interest in seeking the predisposing causes with a view to preventing spontaneous labour is already increasing.[8-10]

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Evoked potentials, saccadic velocities, and computerised tomography in diagnosis of multiple sclerosis

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Summary

One hundred and two patients with suspected or established multiple sclerosis (MS) were investigated by one or more of the following techniques: measurement of visual evoked potentials (VEP); measurement of cervical and cortical somatosensory evoked potentials (SEP); measurement of horizontal saccadic eye movement velocities (SV); and computerised axial tomography of the cranium and orbits (CT). Each of the techniques was valuable in detecting abnormalities, some of which were subclinical, in many patients. More abnormalities were found in patients studied by more than one technique, the most being detected in patients who were studied by all five techniques. We conclude that the techniques have a complementary role in investigating suspected MS.

Introduction

The diagnosis of multiple sclerosis (MS) may be difficult to establish in patients who present with an initial episode of neurological dysfunction, with manifestations referable to only one site in the central nervous system (CNS), and in patients with atypical presentations or few neurological signs.[1] Some electrophysiological techniques[2-11] have been found useful in confirming involvement of certain CNS pathways in such patients and, more importantly, in detecting subclinical lesions of these pathways, thereby indicating the existence of more than one lesion in the CNS. Moreover, demyelinating lesions in the brain,[12-18] and possibly in the optic nerves,[12-14] may be detected by computerised axial tomography of the cranium and orbits.

We have studied the relative and complementary value of measuring visual and somatosensory evoked potentials and saccadic eye movement velocities, and of computerised axial tomography of the cranium and orbits in a group of patients with established or suspected MS.

Patients and methods

We used the criteria of McDonald and Halliday[19] to classify 102 unselected patients, 30 men and 72 women, aged 19-62 years into "clinically definite" (40), "early probable or latent" (30), and "suspected" (32) MS categories. The mean duration of the disease from onset of symptoms was 8·6 years in the first group, 4·4 years in the second group, and 11·4 months in the third group. Some of the techniques became available during the course of the study, so not all patients were studied by each technique.

Visual evoked potentials (VEPs) generated by pattern reversal were recorded from an active midline occipital electrode at Oz (10-20 system) and a reference electrode at Pz, during bilateral monocular stimulation in 102 patients.[3 7 20] Responses were regarded as abnormal if the latency of the major surface-positive component exceeded 118 ms (normal mean +2·5 SD), or if there was a latency difference of greater than 6 ms between the two eyes, provided that other causes for delay such as uncorrected refractive errors and other ocular conditions had been excluded.

Somatosensory evoked potentials were recorded from active electrodes over the spinous process of the second cervical vertebra (cervical SEP), and over the hand area of the contralateral sensory cortex (cortical SEP) during separate stimulation of each median nerve at the wrist with two and a half to three times threshold electrical

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pulses.[7 20] Cervical SEPs were recorded in 82 patients and cortical SEPs in 40 of these. Cervical SEPs were regarded as abnormal if the latency of the major surface-negative peak exceeded 15·8 ms (normal mean +2·5 SD) or if the amplitude was less than 1·1μV. For the cortical SEP we paid particular attention to delays in the first negative component (N1 > 21·5 ms), the first positive component (P1 > 32 ms), or to latency differences of greater than 3 ms, or significant differences in amplitude in the responses from the two sides.[21] Patients with symptoms or signs of cervical spondylotic radiculopathy or median neuropathy were excluded. On-line data was collected and analysed during the evoked potential studies with a PDP 11/40 computer.[20]

A computerised electro-oculographic technique that simultaneously measures abducting and adducting velocities for each eye was used to measure eye movement velocities during 25° horizontal refixation saccades in 54 patients.[22] The range of velocities in normal subjects was 266-522°/s for the abducting eye and 287-563°/s for the adducting eye (normal mean ±2 SD). Patients on anticonvulsants or other drugs known to affect the ocular motor system[23] were excluded.

Computerised tomography (CT) of the cranium was performed in 62 patients using the EMI brain scanner.[12 13] In 36 of these patients the orbits were also examined. In all instances a computer printout of selected "cuts" was prepared to confirm abnormalities detected on the cathode-ray oscilloscope screen or the Polaroid photographs. The 80 × 80 matrix was selected in the early part of the study while the 160 × 160 mode was used for the remainder of the study.

Results and comment

The VEP was abnormal on one or both sides in 32 out of 40 (80%) of the clinically definite, 13 out of 30 (43%) of the early probable or latent, and seven out of 32 (22%) of the suspected cases. The abnormality was subclinical in 5 (16%), 8 (62%), and 7 (100%) cases with abnormal responses in these groups (table I).

TABLE I—*Visual evoked potentials (VEPs); numbers of patients with abnormal results*

Classification of multiple sclerosis	No of patients tested	No of patients with abnormal responses			Subclinical(%)*
		Unilateral	Bilateral	Total(%)	
"Clinically definite"	40	6	26	32 (80%)	5 (16%)
"Early probable or latent"	30	5	8	13 (43%)	8 (62%)
"Suspected"	32	1	6	7 (22%)	7 (100%)
Total	102	12	40	52 (51%)	20 (38%)

*Number of patients with abnormal VEPs who had normal visual acuity, colour vision (Ishihara plates), visual fields, optic discs, and pupillary reactions.

The cervical SEP was abnormal unilaterally or bilaterally in 22 out of 31 (71%) of the clinically definite, 13 out of 24 (54%) of the early probable or latent, and eight out of 27 (30%) of the suspected cases; and the cortical SEP in seven out of 14 (50%), six out of 15 (40%), and two out of 11 (18%) cases respectively in these groups. The incidence of abnormal results with either or both of these techniques was 23 (74%), 14 (58%), and 9 (33%) respectively (table II); of these patients, 5 (22%), 7 (50%), and 7 (78%) respectively had no sensory symptoms or signs in the upper limbs. Of the 40 patients in whom both cervical and cortical SEPs were recorded, the spinal response alone was abnormal in eight cases, the cortical response alone in four cases, and both spinal and cortical responses were abnormal in 11 cases.

TABLE II—*Somatosensory evoked potentials (SEPs); numbers of patients with unilateral or bilateral abnormal responses. Results expressed as proportion of patients studied*

Classification of multiple sclerosis	Cervical SEP (%)	Cortical SEP (%)	Cervical SEP, cortical SEP, or both (%)	No (%) without sensory symptoms or signs
"Clinically definite"	22/31 (71%)	7/14 (50%)	23/31 (74%)	5/23 (22%)
"Early probable or latent"	13/24 (54%)	6/15 (40%)	14/24 (58%)	7/14 (50%)
"Suspected"	8/27 (30%)	2/11 (18%)	9/27 (33%)	7/9 (78%)
Total (%)	43/82 (52%)	15/40 (38%)	46/82 (56%)	19/46 (41%)

Saccadic velocities were abnormal in 14 out of 22 (64%) of the clinically definite, eight out of 20 (40%) of the early probable or latent, and four out of 12 (33%) of the suspected cases. Abnormalities comprised unilateral, or, more frequently, bilateral slowing of adducting saccades suggesting involvement of the medial longitudinal fasciculus; unilateral slowing of abducting saccades suggesting abducens nerve involvement; or slowing of both adducting and abducting saccades on the same side or contralaterally suggesting involvement of supranuclear pathways.[24] No abnormality of ocular movements could be detected clinically in 10 of the 26 patients (38%) with abnormal saccadic velocities.

In 14 out of 23 (61%) of the clinically definite, 13 out of 25 (52%) of the early probable or latent, and two out of 14 (14%) of the suspected cases the CT scan detected areas from a few millimetres to several centimetres with reduced attenuation coefficients (4-11 EMI units) in the white matter of the cerebral hemispheres, or, less frequently, in the cerebellum and brain stem. These were compatible with plaques of demyelination. Such areas were found in the cerebral hemispheres in nine patients with purely spinal or brain-stem and cerebellar manifestations clinically. Focal areas with attenuation coefficients that were lower than expected were also found in the intraorbital segment of one or both optic nerves in 11 patients. While these areas may represent demyelinating lesions,[12] their nature and importance remain uncertain.[13]

TABLE III—*Overall incidence of abnormal findings with measurement of visual evoked potentials (VEP) alone and with other techniques. Results expressed as proportion of patients studied*

Classification of multiple sclerosis	VEP	VEP and SEP	VEP and either SEP or SV or both	VEP, and either SEP or SV or both, and CT
"Clinically definite"	32/40 (80%)	25/31 (81%)	20/22 (91%)	14/14 (100%)
"Early probable or latent"	13/30 (43%)	15/24 (63%)	15/19 (79%)	15/16 (94%)
Suspected	7/32 (22%)	10/27 (37%)	5/12 (42%)	4/7 (57%)
Total	52/102 (51%)	50/82 (61%)	40/53 (75%)	33/37 (89%)

CT = computerised tomography; SV = saccadic velocities; SEP = cervical and cortical somatosensory evoked potentials.

The overall incidence of abnormal findings was higher in patients studied by more than one technique (table III). Of 82 patients in whom SEPs and VEPs were recorded, abnormal results with either or both techniques were found in 25 (81%) of the clinically definite, 15 (63%) of the early probable or latent, and 10 (37%) of the suspected cases. Of 53 patients in whom SEPs or saccadic velocity or both were measured in addition to VEPs, abnormal results with one or more of these techniques were found in 20 (91%), 15 (79%), and 5 (42%) cases respectively in the three groups. In 37 of these patients who also had CT of the cranium, these figures rose to 14 (100%), 15 (94%), and 4 (57%) respectively (table III).

Discussion

We found that each of the techniques detected abnormalities in a substantial proportion of patients with established or suspected MS, and that the proportion of abnormal findings increased when more than one technique was employed. The ability to detect subclinical involvement of the visual, somatosensory, and ocular motor pathways with the electrophysiological techniques, and asymptomatic cerebral white-matter lesions with CT, is particularly important in establishing the presence of additional lesions in patients with a single symptomatic lesion in the CNS. We have found CT and measurement of VEPs and saccadic velocities particularly valuable when investigating patients with apparently isolated spinal cord, brain-

stem, or cerebellar lesions without clinical evidence of optic nerve or cerebral disease.

Measurement of VEPs gave the highest yield of abnormal results, a finding which correlates with the known high prevalence of involvement of the anterior visual pathways in MS.[25] The incidence of abnormal VEPs in the present study is comparable with that reported by Asselman *et al*,[6] but somewhat lower than that first reported by Halliday *et al*.[4] This may be due to differences in the method of patient categorisation or in that of obtaining and analysing the VEP. Possibly the sensitivity of the technique may be increased even further by using selective foveal stimulation[26] in patients whose responses to the conventional stimulation technique are normal. Another approach, which deserves further attention, and which is based on the known thermolability of conduction in demyelinated nerve fibres,[27] is recording VEPs after raising the central body temperature. Preliminary observations in patients with MS have shown reversible changes in response latency and amplitude after this.[28]

The overall yield of abnormal responses in the three groups of patients was essentially the same for the cervical SEP (52%) and the VEP (51%), and was lower than that reported by Small *et al*[29] in the United Kingdom. The lack of correlation between the cervical and the cortical SEP in some patients shows that the two techniques are complementary in evaluating the functional state of the central somatosensory pathway, and that by combining the two techniques it may be possible to differentiate a spinal cord lesion from a lesion at a higher level in the CNS.[1]

The measurement of saccadic eye movement velocities provides a means of confirming clinically apparent or suspected abnormalities of ocular movement. It is more valuable, however, in detecting nuclear, internuclear, and supranuclear disturbances of eye movement too mild to be found by clinical examination. The abnormalities found in the present study confirm the findings of Solingen *et al*[30] and of Bird and Leech[24] in small selected groups of patients with MS. Fewer abnormalities were detected in the clinically definite group than were found with the evoked potential techniques, but the overall incidence in the three groups of patients was essentially the same for all three techniques. Preliminary observations in a small group of patients with MS have shown an increase in the saccadic reaction time in addition to slowing of peak saccadic velocities, and we expect that a more complete quantitative evaluation of saccadic and pursuit eye movements will further increase the diagnostic potential of electro-oculography in suspected MS.

Our observations and those of others[14–18] suggest that CT has a place in the investigation of patients with suspected demyelinating disease. Firstly, it excludes other cerebral disorders such as tumour in patients whose initial presentation may be misleading.[31] Secondly, it may disclose the presence of single or multiple lesions, which, by virtue of their size and distribution, may suggest the diagnosis of MS. Thus finding multiple white-matter lesions, particularly in a paraventricular distribution, strongly suggests MS, and may provide firm support for the diagnosis in a patient with a compatible clinical syndrome. Moreover, if it can be confirmed that the low-density areas identified in the optic nerve[12–14] do represent demyelinating lesions, the diagnostic potential of the technique will be even greater.

We conclude that in addition to their individual roles in investigating suspected MS, the techniques used in the present study are complementary, and make it possible to establish the diagnosis of MS with more certainty. This has important implications regarding the avoidance of more invasive forms of investigation and the overall management of such patients.

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