

Evoked potentials in the diagnosis of multiple sclerosis: a follow up study

WB MATTHEWS, JRB WATTAM-BELL, ERIKA POUNTNEY

From the University Department of Clinical Neurology, The Radcliffe Infirmary, Oxford

SUMMARY Visual, somatosensory and brain stem auditory evoked potentials were recorded in 84 patients in whom the diagnosis of multiple sclerosis was under consideration. The patients were followed up for a maximum of 38 months or until a definite diagnosis of multiple sclerosis or of some other condition was established. Seven patients were found not to have multiple sclerosis. Abnormal evoked potentials indicating clinically silent lesions were found at the initial investigation in fourteen of the twenty-eight patients in whom a diagnosis of clinically definite multiple sclerosis was accepted during the period of follow up. In the thirty-seven patients in whom no change in clinical category occurred during the period such abnormalities were found in five. The visual evoked potential was found to be of greatest predictive value.

It is now fully established that in a high proportion of patients with clinically definite multiple sclerosis averaged responses evoked (EP) by visual,¹ somatosensory² and auditory stimuli³ are abnormal. These findings are of great intrinsic interest but of no practical diagnostic value as, by definition, multiple sclerosis has already been accepted in these patients on other grounds. In categories of lesser diagnostic certainty the proportion of abnormal findings is lower, either because EP do not frequently become abnormal until later in the clinical course or because the diagnosis is at fault. Many reports have recognised that a laboratory diagnostic technique, once validated in definite cases, is only of use where there is doubt on clinical grounds. The intention to follow up patients in whom the diagnosis of multiple sclerosis has been considered and in whom EP have been recorded has often been expressed but seldom implemented. The significance of either normal or abnormal EP in patients in whom multiple sclerosis is no more than a possibility is unknown.

The use of EP in the diagnosis of multiple sclerosis lies mainly in the detection of abnormalities in regions of the central nervous system not otherwise known to be involved. Unless the nature of the disordered EP can be shown to be specific for multiple sclerosis, of which there is little evidence,

the detection of, for example, abnormal visual evoked potentials (VEP) in a patient with a clear history of optic neuritis, is merely confirmatory rather than diagnostic. In most recent reports this has been clearly recognised.

We describe a follow-up study of patients in whom VEP, cervical and cranial somatosensory EP (SEP) and brainstem auditory EP (BAEP) had been recorded when the diagnosis of multiple sclerosis was being considered.

Method

Eighty-four consecutive patients in whom the three techniques had been used were included in the study. They had been referred for investigation because the diagnosis of multiple sclerosis was suspected. They were classified according to McAlpine's⁴ criteria as definite, probable and possible cases. These criteria, while convenient and widely adopted, have certain disadvantages. Progressive paraparesis with no clinical evidence of multiple lesions is classified as "possible" although the severity and tempo of the disease is often strongly contrasted with that in other patients in this category. Also an initial episode, however typical, is not admitted to any diagnostic category. As it is precisely in this group of patients that a laboratory technique would be most useful, a further category of "acute, not diagnosed" was used as in a previous report from this laboratory.² The scheme of McDonald and Halliday,⁵ while admitting first attacks, cannot be used in the assessment of the diagnostic value of EP as they are already accepted as evidence of multiple lesions. The category "acute, not diagnosed" comprised patients who had experienced a single episode of neurological symptoms

Address for reprint requests: Professor WB Matthews, The Radcliffe Infirmary, Oxford OX2 6HE, UK.

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of a nature compatible with multiple sclerosis of less than three months' duration at the time of examination. No patient with isolated optic neuritis was included.

Six patients in whom the diagnosis had been thought by the referring physician to be in doubt fulfilled the criteria of definite multiple sclerosis at the time of investigation. Fifteen were classified as probable cases; 38 were possible cases of whom nine had progressive paraparesis. Twenty-five patients were classified as "acute not diagnosed".

It was further possible to subdivide the patients according to clinical features: paraparesis without evidence of multiple lesions; sensory symptoms in isolation; predominantly motor; other than paraparesis without evidence of multiple lesions, sometimes combined with sensory deficits; brainstem or cerebellar, including vertigo, diplopia, cranial nerve lesions and cerebellar ataxia; isolated paroxysmal symptoms; isolated sphincter disturbance and multisystem disorder. The distribution of these categories is shown in table 1.

Table 1 EP results expressed as number of patients in whom abnormalities were found. Those of diagnostic value are in parentheses. Multiple abnormalities were found in some patients. For abbreviations see text

Clinical presentation	N	Abnormal EP			Total
		VEP	SEP	BAEP	
Definite	6	5	2	1	5
Probable					
Sensory symptoms, isolated	4	2 (2)	1	0	2 (2)
Predominantly motor	4	3 (3)	1 (1)	1 (1)	3 (3)
Multisystem disorder	7	5 (1)	1	0	5 (1)
Total	15	10 (6)	3 (1)	1 (1)	10 (6)
Possible					
Paraparesis	9	4 (4)	4	3 (3)	4 (4)
Sensory symptoms, isolated	13	0	2	1 (1)	3 (1)
Brain stem or cerebellar	4	0	0	0	0
Predominantly motor	5	3 (3)	1	0	3 (3)
Paroxysmal symptoms	1	1 (1)	1 (1)	0	1 (1)
Multisystem disorder	2	2 (1)	1 (1)	2 (1)	2 (1)
Total	34	10 (9)	9 (2)	6 (5)	13 (10)
Acute, not diagnosed					
Sensory symptoms, isolated	11	1 (1)	1	3 (3)	3 (3)
Brain stem or cerebellar	4	1 (1)	0	0	1 (1)
Predominantly motor	4	0	0	0	0
Paroxysmal symptoms	1	0	0	0	0
Sphincter disturbance	1	0	0	0	0
Multisystem disorder	1	0	0	0	0
Total	22	2 (2)	1	3 (3)	4 (4)

Follow-up The method of follow-up was necessarily varied. Most of the patients with mild or transient symptoms did not know that multiple sclerosis had been considered possible and it was not thought ethical to

attempt to recall them for detailed examination. Their general practitioners were consulted by mail approximately two years and three years after the investigation. Patients who continued to attend hospital were either examined personally or reports were received from the neurologist in charge. In only two patients was no follow-up information obtained. Follow-up continued to a present maximum of 38 months; or until the establishment of a diagnosis other than that of multiple sclerosis; or until multiple sclerosis became clinically definite; or the patient could no longer be traced.

Evoked potentials The techniques of eliciting and recording pattern reversal VEP and SEP and normal values have already been published.²⁻⁶ BAEP were elicited by clicks of 100 μ s duration originated by square waves of alternating polarity and delivered through an attenuator to earphones, the stimulus being delivered at 20 Hz at 60 dB above threshold. Monaural and binaural stimulation were used, 1024 responses being averaged at each recording. With monaural stimulation the opposite ear was not masked. Recording electrodes were on the left mastoid process and the vertex. At the time the recordings were made (1978) the differences in latency found with ipsilateral and contralateral recording had not been appreciated.⁷ Although interpeak latencies can usually be measured in normal recordings the early waves may be difficult to identify when abnormal. Assessment of abnormality was therefore based on the latency from stimulus of component V and the amplitude of this wave. In 25 normal subjects the mean latency was 5.8 ms \pm SD 0.3. The shorter latency observed in females had not at that time been established⁸ and as many of the controls were female an upper limit of normal was taken as mean + 3 SD. A value of 6.7 ms or greater or an amplitude of less than 0.5 μ V were regarded as abnormal.

Results

The six patients classified as definite at the time of the examination are of little interest in this context but the results are presented as representative of the usual findings in early but established disease. There were two men and four women with an average age of 37 yr. As shown in table 1 abnormal EP were found in five.

Of the 15 probable cases two were men and 13 women, average age 35.8 years. Many had multi-system involvement but were not accepted as definite cases because of atypical features or a brief history. In ten patients abnormal EP were found and in six these were of diagnostic value as implicating regions of the CNS not clinically involved (table 1). Two patients could not be followed. Two were still classified as probable after a follow-up of eight and 36 months respectively. Eleven were re-classified as definite cases during the course of follow up (table 2). Of these abnormal EP of diagnostic value were present in five.

Table 2 Clinical course related to EP results expressed as numbers of patients in whom abnormalities were found, those of diagnostic value being in parentheses

Course	N	Abnormal EP			Total
		VEP	SEP	BAEP	
Probable	15				
No change	2	1	0	0	1
Definite	11	7 (5)	3 (1)	1 (1)	7 (5)
Not followed	2	2 (1)	0	0	2 (1)
Possible	34				
No change	19	3 (2)	1	2 (1)	3 (2)
Probable	2	0	1	0	1
Definite	13	7 (7)	7 (2)	4 (4)	9 (8)
Acute, not diagnosed	22				
No change	14	1 (1)	1	2 (2)	3 (3)
Possible	3	0	0	0	0
Probable	1	0	0	0	0
Definite	4	1 (1)	0	1 (1)	1 (1)

Of the 38 possible cases, 16 were male and 22 female; average age 43.6 yr. Four were found not to have multiple sclerosis. Two had an acoustic neuroma, the BAEP being abnormal or absent on the appropriate side in each. One had an Arnold Chiari malformation with no abnormality of EP and one had myelitis, probably related to pelvic infection.

Of the remainder 13 had abnormal EP, ten of potential diagnostic value (table 1). Of the 13 cases progressing to the definite category during the period of follow up, eight had been found to have abnormal EP indicating subclinical lesions as opposed to only two of the 19 remaining in the possible category. Of particular interest are the patients with progressive paraparesis. Of the five who developed clinical evidence of disease beyond the spinal cord abnormalities in VEP or BAEP had been found in three, but not in the other two. In the other four patients with paraparesis remaining in the possible group, one had evidence from EP of multiple lesions. The mean period of follow up in the patients in the possible category was 29 months (range 6-36).

Of the 25 patients classified as "acute not diagnosed", ten were male and 15 female; average age 33 years. Three were found not to have multiple sclerosis. One had neurosarcoidosis with normal EP. In two women the diagnosis was revised on clinical grounds to cerebral infarction during the course of follow up and in one of these a slight increase in VEP latency in one eye had been found, apparently a "false positive".

In the remaining 22, abnormal EP were found in only four (table 1). Of these patients one developed definite multiple sclerosis but in the other three patients who had abnormal EP of diagnostic value no further clinical evidence of multiple sclerosis developed during follow-up periods of 29, 36 and 36 months respectively. In contrast, three further

patients who progressed to the definite category and the four who became possible or probable cases had shown no abnormality of EP. Of the four patients who were re-classified as definite, two had presented with sensory symptoms, one with weakness and one with retention of urine.

Of the 71 patients in the probable and possible categories of multiple sclerosis and in the "acute not diagnosed" group, abnormalities of VEP were found in 22, of which 17 were of diagnostic value; 13 had abnormal SEP, three being diagnostic, and ten had abnormal BAEP of which nine were diagnostic. Fourteen of the 28 patients who progressed to the stage of clinically definite multiple sclerosis during the period of follow-up had abnormal EP indicating clinically silent lesions at the time of the initial investigation.

Discussion

The use of multiple as opposed to single EP techniques in patients suspected of having multiple sclerosis has, not unexpectedly, resulted in an increase in the proportion in whom abnormalities are detected. Thus Mastaglia *et al.*,⁹ Small *et al.*,² and Trojaborg and Petersen¹⁰ found that the combination of VEP and SEP was more effective in this respect than either technique separately. A combination of VEP, SEP and BAEP has been used by Deltenre *et al.*,¹¹ Chiappa,¹² Kjaer,¹³ Green *et al.*,¹⁴ Purves *et al.*,¹⁵ and Khoshbin and Hallett.¹⁶ In some instances the blink reflex has also been examined^{11 13 16} and Clifford Jones *et al.*¹⁷ combined VEP and SEP with the crossed acoustic response. The relative ability of the methods to demonstrate unsuspected abnormalities has varied but there is general agreement that the blink reflex is the least useful. The number of clinically silent lesions detected by SEP techniques depends on the clinical criteria adopted. Abnormal SEP in the absence of clinically detectable sensory loss are commonly found² and have even been identified at necropsy as being due to a plaque,¹⁸ but it is more realistic to adopt the requirement used in the present study and by Purves *et al.*,¹⁵ that abnormal SEP could only be regarded as of diagnostic value if they indicated disease in a region of the nervous system not known to be involved. Thus abnormal SEP in a patient with obvious spinal cord disease can only be regarded as confirmatory. Differences in definition and sampling no doubt account for the differing proportions of abnormalities detected using the individual techniques.

The relative preponderance of diagnostic abnormalities of VEP in the present study is partly accounted for by selection of patients in whom the diagnosis was in doubt. Overt clinical evidence of

involvement of the visual system would have placed many of these patients in the definite category and they would not have entered the investigation. The strict interpretation of the diagnostic value of abnormal SEP also reduced the number of patients in which this technique gave diagnostic results.

Inevitably as diagnostic certainty decreases the proportion of patients with abnormal EP also declines. It is the significance of abnormal EP apparently indicating silent lesions in patients in whom the clinical diagnosis is uncertain that has never been established. Is it justifiable to use such results to "transfer" patients from one diagnostic category to another?^{5,13} It has not been established that abnormal EP in such patients do in fact indicate multiple lesions and therefore multiple sclerosis. Necropsy confirmation cannot be expected and reliance must be placed on the subsequent clinical course. Most follow-up studies have been more concerned with the nature of the EP than with clinical diagnosis. Robinson and Rudge¹⁹ attempted to follow patients suspected of having multiple sclerosis in whom auditory evoked potentials had been recorded, but numbers were small and follow up incomplete. In the studies of the use of multiple EP techniques cited above no follow up was reported.

The mean annual relapse rate of multiple sclerosis is around 0.5 in early cases so that follow up must be prolonged. The patients of greatest interest in this context are, however, young, mobile and unaware that multiple sclerosis has ever been suspected. As a group they are naturally difficult to follow. Reporting our results after three years is a compromise between the desirable and the practicable.

The results go some way to confirm the validity of the assumption that EP techniques can reveal subclinical lesions. Of the cases that progressed to the clinically definite category, 50% had abnormal EP findings of diagnostic value when first examined. In the possible category and in those with a single episode of neurological symptoms there were patients in whom clinically silent lesions had been indicated but where no change in clinical category occurred during the period of follow-up. It is the intention to continue to monitor the clinical course in these patients.

In this follow-up study it has therefore been shown that abnormal EP apparently indicating clinically silent lesions are of some predictive value in the diagnosis of multiple sclerosis at a stage where there is clinical doubt. In such an assessment the lack of specificity of these changes must, however, be taken into account. The absence of such abnormalities is also of no diagnostic or predictive significance as EP may remain normal at all stages of clinical diagnostic certainty.

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References

- Halliday AM, McDonald WI, Mushin J. Visual evoked response in diagnosis of multiple sclerosis. *Br Med J* 1973;**4**:661-4.
- Small DG, Matthews WB, Small M. The cervical somatosensory evoked potential in the diagnosis of multiple sclerosis. *J Neurol Sci* 1978;**35**:211-24.
- Robinson K, Rudge P. Abnormalities of the auditory evoked potentials in patients with multiple sclerosis. *Brain* 1977;**100**:19-40.
- McAlpine D. In: McAlpine D, Lumsden CE, Acheson ED, eds. *Multiple Sclerosis: A Reappraisal*, 2nd ed. Edinburgh: Churchill Livingstone, 1972:202.
- McDonald WI, Halliday AM. Diagnosis and classification of multiple sclerosis. *Br Med Bull* 1977;**33**:4-8.
- Matthews WB, Small DG, Small N, Pountney E. The pattern reversal evoked visual potential in the diagnosis of multiple sclerosis. *J Neurol Neurosurg Psychiatry* 1977;**40**:1009-14.
- Stockard JJ, Stockard JE, Sharbrough FW. Non-pathologic factors influencing brainstem auditory potentials. *Am J Electroencephalogr Techn* 1978;**18**:177-209.
- Beagley HA, Sheldrake JB. Differences in brainstem response latency with age and sex. *Br J Audiol* 1978;**12**:69-77.
- Mastaglia FL, Black JL, Collins DWK. Visual and spinal evoked potentials in diagnosis of multiple sclerosis. *Br Med J* 1976;**2**:732.
- Trojaborg W, Petersen E. Visual and somatosensory evoked cortical potentials in multiple sclerosis. *J Neurol Neurosurg Psychiatry* 1979;**42**:323-30.
- Deltenre P, Vercruyse A, van Nechel C, et al. Early diagnosis of multiple sclerosis by combined multimodal evoked potentials: results and practical considerations. *J Biomed Engineering* 1979;**1**:17-21.
- Chiappa KH. Pattern shift visual, brainstem auditory and short latency somatosensory evoked potentials in multiple sclerosis. *Neurology (Minneapolis)* 1980;**30**:7 pt. 2: 110-23.
- Kjaer M. The value of brainstem auditory, visual and somatosensory evoked potentials and blink reflexes in the diagnosis of multiple sclerosis. *Acta Neurol Scand* 1980;**62**:220-36.
- Green JB, Price R, Woodberry SG. Short latency somatosensory evoked potentials in multiple sclerosis. Comparison with auditory and visual evoked potentials. *Arch Neurol* 1980;**37**:630-3.
- Purves SJ, Low MD, Galloway J, Reeves B. A comparison of visual, brainstem auditory and somatosensory evoked potentials in multiple sclerosis. *Can J Neurol Sci* 1981;**8**:15-9.
- Khosbin S, Hallett M. Multiple evoked potentials and blink reflex in multiple sclerosis. *Neurology (NY)* 1981;**31**:138-44.

- ¹⁷ Clifford Jones RE, Clarke GP, Mayles P. Crossed acoustic response combined with visual and somatosensory evoked responses in the diagnosis of multiple sclerosis. *J Neurol Neurosurg Psychiatry* 1979;**42**: 749-52.
- ¹⁸ Matthews WB, Esiri M. Multiple sclerosis plaque

related to abnormal somatosensory evoked potential. *J Neurol Neurosurg Psychiatry* 1979;**42**:940-2.

- ¹⁹ Robinson K, Rudge P. The use of the auditory evoked potential in the diagnosis of multiple sclerosis. *J Neurol Sci* 1980;**45**:235-44.