

EVOKED RESPONSE STUDY AMONG MALAYSIAN MULTIPLE SCLEROSIS PATIENTS

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ABSTRACT

A study of visual evoked potential (VEP), brainstem evoked potential (BAEP) and median nerve somatosensory evoked potential (SSEP) in 26 Malaysian patients with clinically definite Multiple Sclerosis (MS). This study showed an overall high rate of abnormality, with 85% of patients for VEP, 31% for BAEP and 65% for median nerve SSEP. The rate of abnormality was particularly high for patients who were symptomatic, reaching 100% of patients for VEP, 50% of patients in BAEP, 83% of nerves for median nerve SSEP. The rate of abnormality among those who were asymptomatic was lower, varying from 32% of eyes in VEP, 27% of patients in BAEP and 31% of nerves in median nerve SSEP. Three out of 10 patients with optic spinal form of MS have abnormal BAEP. These show the usefulness of the evoked potential studies in confirming the clinical lesions as well as demonstrating subclinical involvement. The rate of abnormal evoked responses for the asymptomatic patients in this study is generally lower than that published elsewhere.

Keywords: Multiple Sclerosis, Evoked Potentials.

SINGAPORE MED J 1992; Vol 33: 575-580

INTRODUCTION

Multiple sclerosis (MS) is an important neurological disease of worldwide distribution. It has been well recognized that the prevalence of the disease is low among Asian patients. There are differences in the pattern of clinical manifestations among the Asian MS patients as compared with white patients. Patients from Asia have been characterised by the following: a rare occurrence of a similar family history; a higher incidence of visual failure at the onset of illness; a more severe visual impairment during follow-up; a more frequent occurrence of recurrent acute transverse myelitis; clinical forms of optic-spinal recurrence and optic-brain-stem-spinal recurrence, with Devic's disease being more common; and a more severe involvement of the spinal cord with greater functional disability and less frequent involvement of the cerebellum^(1,2). When comparing the pathology of the Japanese and the Western cases of MS, differences were also noted with the Japanese patients showing more severe involvement of the optic nerve and the spinal cord, often with necrosis and destructive tendencies; there is also poor reaction of inflammatory cells and glia cells among the Japanese⁽³⁾.

The Malaysian MS patients are quite similar to those found in the rest of Asia. The prevalence is low at 2 per 100,000. There is a high female-male ratio of 5:1. Optic-spinal recurrence is the most common clinical pattern of the disease, accounting for 63%. Severe spinal cord and visual disability, high mortality, transient involvement of the cerebrum, cerebellum and brain-stem are the other characteristic clinical manifestations⁽⁴⁾.

Since the application of the evoked response technique in MS patients by Namerow using the somatosensory evoked potential in 1968, there have been numerous studies confirming the useful role of evoked potential studies in the assessment and diagnosis of MS patients. However, there are few studies available assessing the role of evoked response studies among Asian MS patients. This is a report of the visual evoked potential (VEP), brainstem evoked potential (BAEP) and median nerve somatosensory evoked potential (SSEP) findings among 26 Malaysian MS patients seen more recently in the University of Malaya Medical Centre.

MATERIALS AND METHODS

VEP, BAEP and median nerve SSEP were done in 20 patients with clinically definite MS. The following diagnostic criteria were used: (1) remitting and relapsing history with two or more episodes; (2) evidence of lesions at two or more necessary sites in the central nervous system; (3) lesions predominantly in the white matter; (4) age at onset of symptoms, 10 to 60 years; (5) history of signs or symptoms for one year or longer; and (6) no better explanation for the observed abnormalities.

The normal values for the VEP were based on 40 healthy subjects, that of BAEP were based on 66 healthy subjects, that of median nerve SSEP were based on 24 healthy subjects and that of posterior tibial nerve SSEP were based on 16 healthy subjects. Unless specifically stated, a value of more than 2.5 SD of the mean was taken as abnormal.

All the evoked potential studies were done on the Nicolet compact 4 machine. For the VEP, the visual acuity of the subjects were checked and corrected. The test was done in a quiet and darkened room. The stimulus was a black and white checkerboard pattern projected on a television screen. The pattern field which subtended an angle of 14.6 degrees was placed 1 metre from the subject's eye. The standard check size used was 27.4 minutes. Three channels of EEG were amplified and computer averaged using a transverse occipital chain of silver/silver chloride recording electrodes placed so that the midline electrode was 5 cm above theinion with the others 5 cm lateral to this. All were referred to a midfrontal electrode and the vertex was the site for a ground electrode. The subject fixated on a red spot at the screen centre and the other eye patched. Pattern reversal occurred at 1.9 Hz and the EEG was sampled and averaged after the onset of each reversal with the sweep time set to 250 msec. The time constant was 0.15 seconds and the high frequency filter was at 100 Hz (-3db). A

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display of the ongoing EEG activities allow for assessment of the artefact and EMG. At least two runs of 100 reversals of consistent results were averaged for each eye separately.

For the BAEP, the stimulation consisted of 100 μ sec pulse rarefaction click with intensity of 65 db above hearing threshold. 11.4 clicks were given each second monaurally. Silver/silver chloride disc electrodes were applied to the vertex and the inner aspect of the ear lobes, with inter-electrode impedance at less than 5 Kohms. The low frequency filter was set at 150 Hz (-3db), high frequency cut off of -30db at 3 KHz and a sensitivity of 25 μ v/Div. The average of at least two separate runs of 2000 clicks was obtained in each test. The decision of how many runs for each test was decided by the state of patient's relaxation and the inter-trial variability of the waveforms. The sweep time of 10 msec with 512 points resolution was collected.

The evoked potential time locked to each stimulus were summated or averaged. The amplitude of wave IV/V complex was determined as the lowest valley to the peak after wave V. The amplitude of wave I was measured similarly. The latency and amplitude were both read with digital cursors to the nearest 0.04 msec and 0.02 μ volts.

For the median nerve SSEP, the test was done in a quiet room with the patient relaxed in a couch. The stimulus was a constant current pulse of 100 μ sec duration applied twice per second to the median nerve at the wrist. The sensory threshold was defined as the strength at which the subject first consistently perceived the stimulus; a twitch of the thumb was usually seen at 2 - 2.5 times this sensory threshold. The stimulus intensity for the recording was adjusted to 3 times the sensory threshold; or the level that is tolerable to the patient (usually at least twice the sensory threshold). Three channels of electrical potentials were recorded from the silver/silver chloride electrodes which were attached with colloidion or adhesive tape as follows: channel 1 - over the mid-clavicular point ipsilateral to the stimulated limb, Channel 2 - C6 vertebra, Channel 3 - over the hand area of the sensory cortex contralateral to the stimulation. The electrode was placed 7 cm lateral to the vertex and 2 cm posterior to this. Each electrode was referred to mid frontal electrode with a plate earthing electrode placed just above the elbow of the stimulated arm, and the resistance of each electrode was tested to below 5 Kohms. The arm length of the subject was measured between the lowest fold of the wrist and the seventh cervical spine. The amplifiers had a low frequency cut off at 5 Hz (-3db), a high frequency cut off at 1500 Hz (-3db). The sensitivity was 100 μ v. A display of ongoing EEG activities allow for assessment of the patient's relaxation and detection of any electrode artefacts. The sweep time was 40 msec and 200-300 responses were summed and averaged. At least 2 separate averages were recorded for each arm to obtain a consistent result.

RESULTS

The Normal Values

VEP: The normal values were based on 21 female and 19 male healthy subjects. The age ranged from 19 to 52 years with average of 34 years. The visual acuity were all 6/9 or better. The mean latencies of the female subjects were: N1=75.9 msec (SD=2.8), P1=99.0 msec (SD=4.4), N2=133.8 msec (SD=12.3). The mean latencies of the male subjects were: N1=76.4 msec (SD=5.8), P1=100.3 msec (SD=4.7), N2=137.6 msec (SD=8.6). The mean interocular difference for P1 was 1.9 msec (SD=1.4). Amplitude of P1 from trough to peak of less than 3 μ v was taken as abnormal.

BAEP: The normal values of BAEP were based on 39 female and 27 male healthy subjects. The age range was 18 to 50 years with the average of 29.5 years. All the subjects have

hearing threshold of less than 15 db. The mean interwave latencies for the female subjects were I-III=2.06 msec (SD=0.13), III-V=1.85 msec (SD=0.13), I-V=3.91 msec (SD=0.17), I-V Inter-ear difference=0.07 msec (SD=0.07). The mean interwave latencies for the male subjects were I-III=2.09 msec (SD=0.13), III-V=1.92 msec (SD=0.15), I-V=4.01 msec (SD=0.22), I-V Inter-ear difference=0.10 msec (SD=0.07).

The Median Nerve SSEP: The mean latencies of wave N9, N13, N20 and interwave latency of wave N9-N13 with their SD were plotted against the arm length. The mean interwave latency of N13-N20 was 5.9 msec (SD=0.59). The mean inter-arm latency difference for wave N9 was 0.17 msec (SD=0.18), N13 was 0.19 msec (SD=0.16), N20 was 0.27 msec (SD=0.23). An amplitude of less than 2 μ v for N20 was taken as abnormal.

The Results on the MS Patients

VEP: The VEP were done on 52 eyes of 26 patients. Twenty-two patients (85%) involving 35 eyes (67%) were abnormal. Among these with abnormal test results, 9 patients with 11 eyes (31%) were asymptomatic. Of these 9 patients who had asymptomatic abnormal VEP, 5 patients with 5 separate eyes had past history of optic neuritis but had recovered clinically. Thus, out of the 22 patients with 35 eyes who had abnormal VEP, 4 patients with 6 eyes (17%) had no past nor present clinical evidence of optic nerve involvement.

Expressed in another way, 3 out of 10 patients (30%) and 6 out of 27 eyes (22%) with no past nor present history of optic neuritis had abnormal VEP. Ten out of 31 eyes (32%) which have no present visual symptom had abnormal VEP. All the 18 patients involving 27 eyes who had symptomatic optic neuritis during the evoked potential tests had abnormal VEP. Five out of 6 eyes (83%) from 6 patients with a past history of optic neuritis but had clinically healed, continued to have abnormal VEP.

The types of abnormalities seen were: absence of consistent cortical evoked potential in 26 tests (55%), delay of the cortical evoked potential with or without decrement of the evoked potential amplitude was seen in 21 tests (45%). Eight of the 26 patients (31%) had absence of pattern response in one or both eyes at least 4 months after an acute attack of optic neuritis.

BAEP: The BAEP were done on 52 ears of 26 patients. Of these, 8 patients (31%) involving 13 ears (25%) were abnormal. Among those with abnormal test result, 6 patients with 10 ears (77%) had no current clinical evidence of brainstem involvement. Among these 6 patients involving 10 ears who had abnormal BAEP but clinically asymptomatic, 2 patients involving 3 ears had past history of brainstem involvement but had recovered clinically. Thus out of the 8 patients with 13 ears with abnormal BAEP, 4 patients with 7 ears (54%) had no past nor current clinical evidence of brainstem involvement.

Expressed in another way, 2 out of the 4 patients (50%) with clinical features of current brainstem involvement had abnormal BAEP. On the other hand, 6 out of 22 patients (27%) with no current clinical brainstem involvement had abnormal BAEP, and 4 out of 16 patients (25%) with no past nor current brainstem involvement clinically had abnormal BAEP.

Other than one case in whom no consistent wave V nor wave IV/V complex was seen in the right ear, the abnormalities of the rest all consisted of delayed wave I - V. The delay was seen particularly in the I-III and III-V segments in 3 cases each. Of the 26 patients with BAEP done, 10 had optic-spinal form of MS. Out of these, 3 (30%) had abnormal BAEP. In all the 3 cases, the abnormalities were found in both ears.

The Median Nerve SSEP: The median nerve SSEP were done in 26 patients with 52 median nerves. Of these, 17 patients (65%) involving 29 median nerves (56%) were abnormal. Among those 17 patients involving 29 median nerves, 6 pa-

tients involving 8 median nerves (28%) had no current sensory symptom in the relevant limb, and 3 patients with 4 median nerves (14%) had no past nor current sensory symptom in the relevant limb.

On the other hand, of the 23 median nerves with normal SSEP, 2 patients experienced sensory symptom in 3 relevant limbs. None of these 2 patients, however, had objective proprioceptive sensory loss.

Expressed in another way, 24 of the 29 (83%) median nerve SSEP done on patients with sensory symptom were abnormal. Fifteen of the 49 median nerve SSEP (31%) done on those without sensory symptom were abnormal.

Out of the 39 abnormal median nerve SSEP, delayed N20 which could also be small was seen on 22 occasions (56%). Small or absent N20 was seen on 13 occasions (33%). A delay in N9-N13 was seen in one case and N13-N20 was seen in two cases. Since it was found that a consistent cervical potential was very much dependent on the co-operation of the patients and their relaxation, and difficult to achieve, an inconsistent N13 alone was not taken as abnormal in this study.

Table I summarises the abnormal evoked response seen in relation to the clinical symptom.

DISCUSSION

Since Namerow studied MS patients by using the somatosensory evoked potential in 1968⁽⁹⁾, there has been an explosion in the development of evoked potential techniques in MS. In this study, the choice of the technique was based on two considerations; the first, to adopt those from well established laboratories so that comparative data are available. The second consideration was to adopt a technique which has good patient acceptance and can be applied reliably in the everyday clinical

Table I - Rate of abnormal evoked potentials in relation to clinical symptom

	VEP	BAEP	median n SSEP
Overall abnormality	85%	31%	65%
% of patients	(22/26)	(8/26)	(17/26)
% of eyes/ears/nerves	67%	25%	56%
	(35/52)	(13/52)	(29/52)
With symptoms:	100%	50%	83%
% eyes-VEP/patient-BAEP/nerves-SSEP	(27/27)	(2/4)	(24/29)
Without symptom:	32%	27%	31%
% eyes-VEP/patient-BAEP/nerves-SSEP	(10/31)	(6/22)	(15/49)

*22% of those with no history of optic neuritis and abnormal VEP.

situations. For example, it has been shown that the use of small stimulus field in VEP may improve the detection rate in optic neuritis^(6,7). However, subject co-operation then becomes a more important factor making routine application of the technique impractical⁽⁸⁾.

The overall 85% abnormal VEP among the 26 patients tested corresponds to the high rate of abnormal VEP reported in the literature. The following are among the larger series reported with their percentage of abnormal VEP are: 83%⁽⁹⁾, 82%⁽¹⁰⁾, 75%⁽¹¹⁾. None of the patients with symptomatic optic neuritis had normal VEP. This demonstrates the usefulness of VEP in confirming the clinical presence of optic neuritis.

As for the more interesting group of patients who did not have any past nor current symptom of optic neuritis, only 3

Fig 1 - VEP Fig. 1a (Left) showing delayed P1 latency at 135 msec. The visual acuity is normal at 6/6. Fig 1b (Right) is normal.

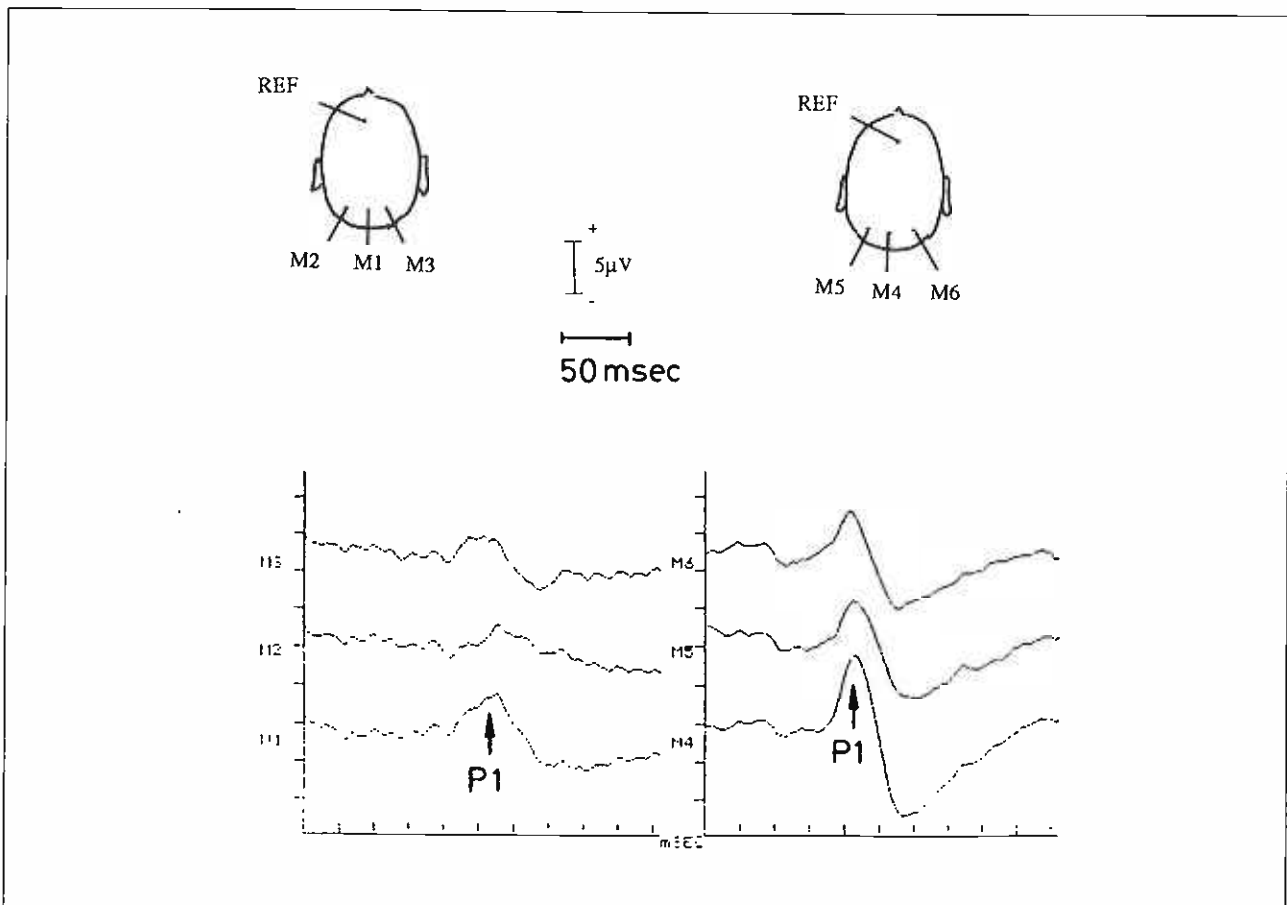


Fig 2 - BAEP Fig 2a (Left) and Fig 2b (Right) both showing delayed I-V inter-wave latencies at 4.7 msec and 4.6 msec. The patient has no brain stem involvement clinically.

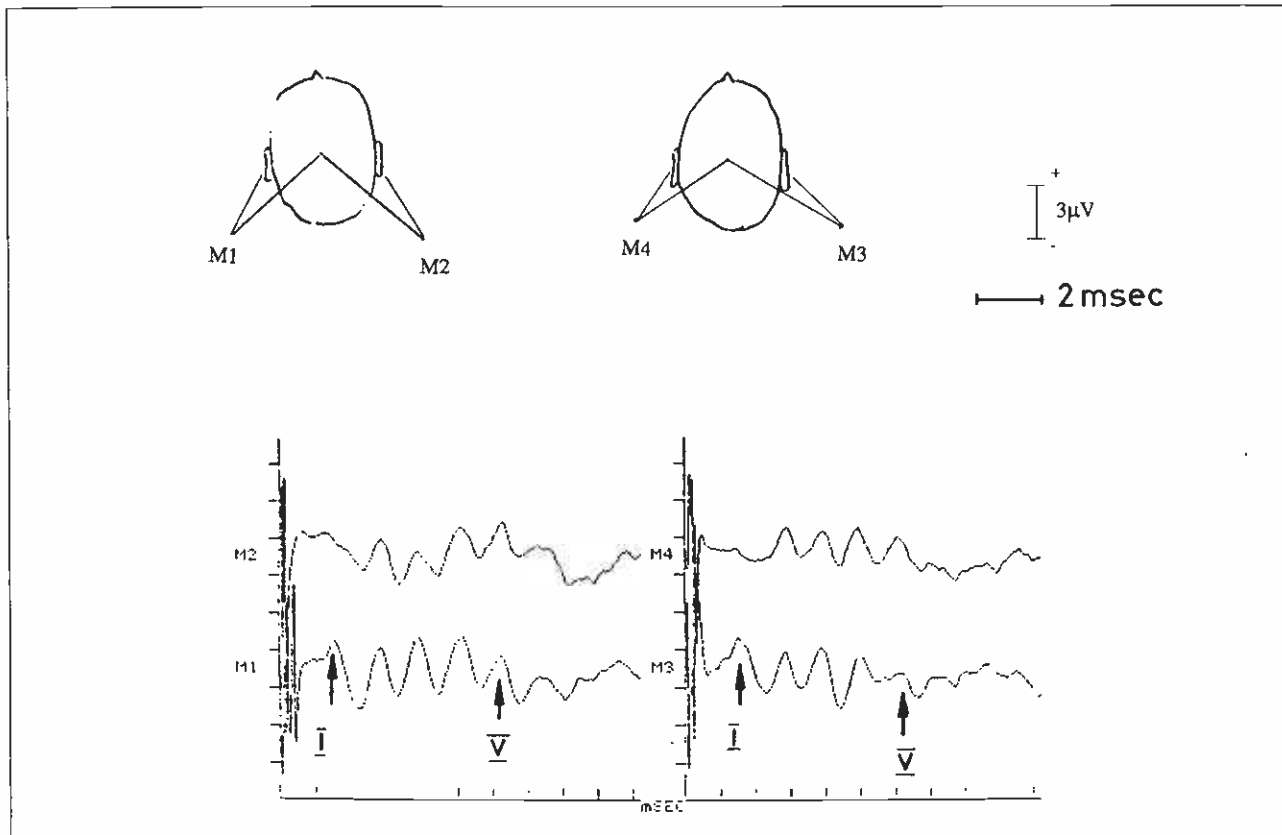
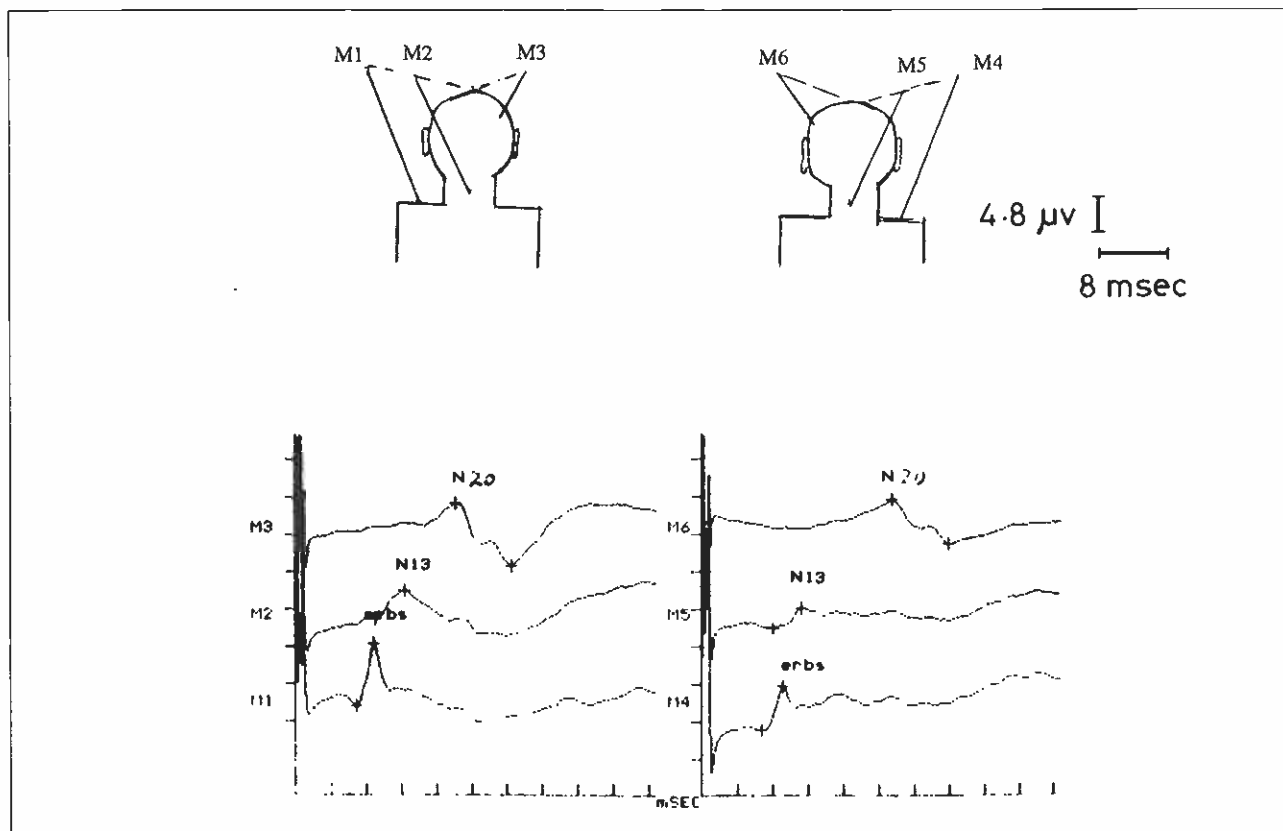


Fig 3 - Median N SSEP Fig 3a (Left) is normal. Fig 3b (Right) shows delayed N20 at 21.4 msec and delayed N13-N20 at 10.2 msec.



out of 10 (30%) patients and 6 out of 27 eyes (22%) had an abnormal VEP. This figure is much less than those of others. The percentage of patients with abnormal VEP in some of the larger series in "definite" MS published are: 94%⁽¹²⁾, 75%⁽¹³⁾, 63%⁽¹⁰⁾, 61%⁽¹¹⁾. There are few published VEP studies in MS patients among the Asian patients. Shibasaki and Kuroiwa (1982)⁽⁴⁴⁾ reported 40% of their 20 cases of definite and probable MS patients without a past history of optic neuritis had abnormal VEP.

Chiang and Hung (1982)⁽¹⁵⁾ reported from Taiwan that 6 out of 9 eyes (67%) with no previous history of optic neuritis had abnormal VEP. As the methodology used in this study is similar to most of those reported, the reason for the lower percentage of abnormal VEP among those with no past history of optic neuritis is unlikely to be due to the technique of the test used. The percentage of abnormal VEP among those with no past history of optic neuritis probably increases with the duration of illness. Yet this factor is usually not mentioned in the reported series. As the number of patients involved in this study is small, further studies need to be done to decide whether there is a real lower frequency of subclinical optic neuritis among our patients.

In their study of VEP among Japanese MS patients, Shibasaki and Kuroiwa (1982)⁽⁴⁴⁾ also commented on the frequent occurrence of complete absence of a pattern visual response either in one eye or both eyes in 23% of their cases. This is higher than most of the series of the Western countries. Shibasaki and Kuroiwa (1982)⁽⁴⁴⁾ commented that this supported the clinical and pathological features of oriental MS with more frequent occurrence of severe non-remitting optic nerve involvement. Eight of our 26 patients (31%) had complete absence of a pattern response in one eye or both eyes at least 4 months after an episode of optic neuritis similar to the findings of Shibasaki and Kuroiwa (1982)⁽⁴⁴⁾.

As for BAEP, for patients with clinically definite MS having clinical brainstem involvement, the proportion with abnormal BAEP as reported in the literature varied from 93%⁽¹⁶⁾, 79%⁽¹⁷⁾ to 57%⁽¹⁸⁾. Only 4 patients in the present study had clinical brainstem involvement, 2 with abnormal BAEP. Since this number is small it is not possible to make any firm comparison with the other published series. Nevertheless this small number of patients (2/4) does appear to suggest the usefulness of BAEP in confirming the presence of brainstem lesion among our patients.

As for the patients with clinically definite MS but without clinical evidence of brainstem involvement, among the larger series Robinson and Rudge (1977)⁽¹⁷⁾, 1980⁽¹⁹⁾ reported 51% and 57% BAEP abnormalities. Chiappa et al (1980)⁽¹⁸⁾ reported 19% of their cases were abnormal. These differences in the rate of abnormality is probably artificial and probably due to differences in the selection of patients.

Clinically, Malaysian patients with MS have less evidence of brainstem involvement when compared with Western patients⁽⁴⁾. It is thus interesting to find that 27% of our patients with no current clinical brainstem involvement had abnormal BAEP. Twenty-five percent of those with no past nor current brainstem involvement also had abnormal BAEP. Of the 10 patients with optic-spinal form of MS, 3 (30%) had abnormal BAEP. In all the 3 patients, the abnormality was seen in both ears. This demonstrates that subclinical involvement of the brainstem among our patients is not uncommon. It also confirms the usefulness of BAEP as a clinical tool for detecting subclinical brainstem lesion in the local patients. Monoaural BAEP rather than binaural BAEP was used in this study as it has been shown that monoaural BAEP increases the sensitivity of the test⁽²⁰⁾.

For the median nerve SSEP, a large number of studies have been done in patients with MS. The rate of positivity

depends on the clinical classification, whether it is definite, probable or possible. There has also been many studies demonstrating the relationship between the clinical sensory findings (particularly the position and vibration sense) and the SSEP in patients with MS (5, 21, 22). The varying degree of sophistication of the test would also affect the percentage of abnormality. For example, Small et al (1978)⁽²³⁾ emphasized the importance of cervical responses whereas, Trajborg and Petersen (1979)⁽²⁴⁾ relied on the scalp potential only. As an example, Chiappa (1980)⁽²⁵⁾ reported an overall 68% abnormality in his patients with definite MS. The rate of abnormality for those with sensory symptoms and/or signs was 86% but it was 50% for those without sensory symptoms and/or signs.

In the present study, the overall abnormality was 65% in all the patients and 56% of all the median nerves studied. Eighty-three percent of the nerves in the median nerve SSEP with sensory symptom was abnormal, whereas for those without sensory symptom, it was 31%. All those with proprioceptive sensory loss had abnormal SSEP in the relevant limbs. This demonstrates the usefulness of median nerve SSEP as a clinical tool to confirm the presence of somatosensory pathway abnormality. It also shows the usefulness of median nerve SSEP in demonstrating subclinical somatosensory pathology among local patients.

There were a number of studies comparing upper and lower limb SSEP in MS showing a greater yield with lower limb stimulation^(24,26-28). The likely explanation is the longer somatosensory pathway. The frequent and severe involvement of the spinal cord in the local MS patients⁽⁴⁾ also suggests lower limb SSEP to be particularly useful. We have previously studied the posterior tibial nerve SSEP in 11 clinically definite MS patients⁽²⁹⁾. Although the overall rate of abnormality was 68% of the nerves, for the legs without sensory symptom, the abnormal rate was low at 13%. The evoked potentials obtained from posterior tibial nerve stimulation is smaller than that from median nerve stimulation. The technical difficulties involved is probably the main reason for this low rate of abnormality.

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