SMGroup

Differential Diagnosis of Patients with Multiple Sclerosis and Neurobehcet's Disease in Aspects of Evoked Potentials

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ABSTRACT

Although rarely seen, the differential diagnosis of Neurobehcet's Disease **(NB)** may sometimes be complicated and Multiple Sclerosis **(MS)** is the major disease that takes place in the differential diagnosis. In this study, we performed Evoked Potentials **(EPs)** and Electroneuromyography **(ENMG)** in patients with MS and NB and in normal volunteers. Our aim was to investigate parameters of electrophysiological tests that might be useful in the differential diagnosis of NB and MS. A total of 95 persons, 55 MS patients, 20 patients with NB and 20 normals were studied electro physiologically. Pattern Visual Evoked Potentials **(VEPs),** Brainstem Auditory Evoked Potentials **(BAEPs),** posterior tibial Somatosensory Evoked Potentials **(SEPs),** nerve conduction studies and needle Electromyography **(EMG)** studies were performed in all patients and normals. All parameters of EPs were compared between the groups. The Visual Evoked Potential **(VEP)** study indicated that the amplitude values of P100 potentials in the NB and MS groups were lower than those of the normal group ($p<0,01$), however the amplitudes in the NB group were still lower than those of the MS group ($p<0,05$). To our knowledge VEPs were not compared between NB and MS patients before and our results confirmed that there could be differences in VEP studies which might be useful in the differential diagnosis of these two patient groups.

Keywords: Neurobehcet's disease; multiple sclerosis; evoked potentials; visual evoked potentials; Electromyography

INTRODUCTION

Behçet's disease is a multisystemic vascular inflammatory disorder of unknown origin. It is relatively rare and central nervous system involvement is seen in 5% of affected individuals [1]. This 5% of patients with Neurobehcet's Disease **(NB)** may lead to diagnostic difficulties especially with Multiple Sclerosis **(MS)**, a demyelinating disease of the central nervous system. Visual evoked potentials, although performed in several studies before, have not been examined thoroughly as a differential diagnostic tool in NB and MS patients. In this study, we performed Evoked Potentials **(EPs)** and Electroneuromyography **(ENMG)** in patients with MS and NB and in normal volunteers. Our aim was to investigate parameters of electrophysiological tests that might be useful in the differential diagnosis of NB and MS.

MATERIALS AND METHODS

Patient Data

A total of 95 persons, 55 MS patients, 20 patients with NB and 20 normal volunteers were enrolled in the study. Patients having other diseases of the central and peripheral nervous system were excluded. All MS patients were evaluated as definite MS according to Mc Donald's criteria [2] and their MRI findings were compatible with MS regarding Bark off criteria [3]. The onset of disease was mono symptomatic in 3 patients and poly symptomatic in the remaining 52. All NB patients fulfilled the diagnostic criteria of ISGBD (International Study Group for Behçet's Disease – 1990) [4]. In the MS group nine patients had unilateral optic neuritis in the history of their diseases. Only one patient had diagnosis of uveitis in the NB group. The demographic data and imaging findings of patient groups are summarized in (Table 1).

Table 1: Demographic data and imaging findings of MS and NB patients

	Total Number of MS patients N=55	Total Number of NB patients N=20
F/M	33/22	5/15
Mean age (mean S.D.)	33.3 ± 9.2	33.6 ± 8.1
Mean duration of disease (years) (mean S.D.)	5.0 ± 4.2	4.3 ± 1.0
Mean EDSS	2.2	-
Mean number of attacks	2.5	2
Clinical form	33 RRMS; 14 SPMS; 8 PPMS	Diencephalic Lesions* 6
Cranial infratentorial Lesion*	13	7
Cranial supratentorial Lesion*	40	12
Spinal lesions*	2[2]	3[2]

F, female; M, mean; RRMS, replasting remitting MS; SPMS, secondary progressive MS; PPMS, primary progressive MS.

*Number of patients having such lesions

[a]Cervical spinal lesions

[o]Both Ms and NB may be replasting-remitting diseases and "attacks" stand for the relapses.

Methods

Pattern Visual Evoked Potentials **(VEPs),** Brainstem Auditory Evoked Potentials **(BAEPs),** posterior tibial Somatosensory Evoked Potentials **(SEPs),** Nerve Conduction Studies **(NCS)** and needle Electromyography **(EMG)** were performed in all patients and normals. Evoked potential studies were performed bilaterally. A total of 190 VEPs, 190 BAEPs and 190 posterior tibial SEPs were studied. NCS and needle EMG were performed in three extremities of each subject, thus a total of 285 extremities were studied. Every patient and control had detailed physical and neurological examinations and patients had proper imaging tests (Cranial MRI and/or cervical, thoracal and lumbar spinal MRI) where necessary.

All of the electrophysiological studies were performed on Dantec Key point. Patients and controls signed informed consents and each of the procedures was explained thoroughly to all of them. The subjects were informed that if they felt pain or any other displeasant sensations, the test would be stopped. All of the patients and controls could tolerate the electrophysiological tests.

Pattern Visual Evoked Potentials (VEPs)

VEP recordings were performed in a darkened room. Correcting glasses were applied for each subject if needed. Active recording electrodes (silver surface electrodes) were placed 2.5 cm above the inion and referred to Cz. Subjects were seated at a distance of 1 meter eye-level from a TV-monitor screen and were instructed to fixate on the center of the screen indicated by a red mark. Full field stimulation was performed monocular. The stimuli consisted of a black and white checker board pattern (checker size 12x16). Filter setting was 1Hz-0.1 kHz, whereas the sweep speed was adjusted as 30ms/div. The analysis time was 300msec and 750 responses were averaged twice and overlapped. Peak latencies of N75, P100 and N135 were measured besides a peak to peak amplitude of P100 calculated as the amplitude from N75 peak to P100 peak (Figure 1).

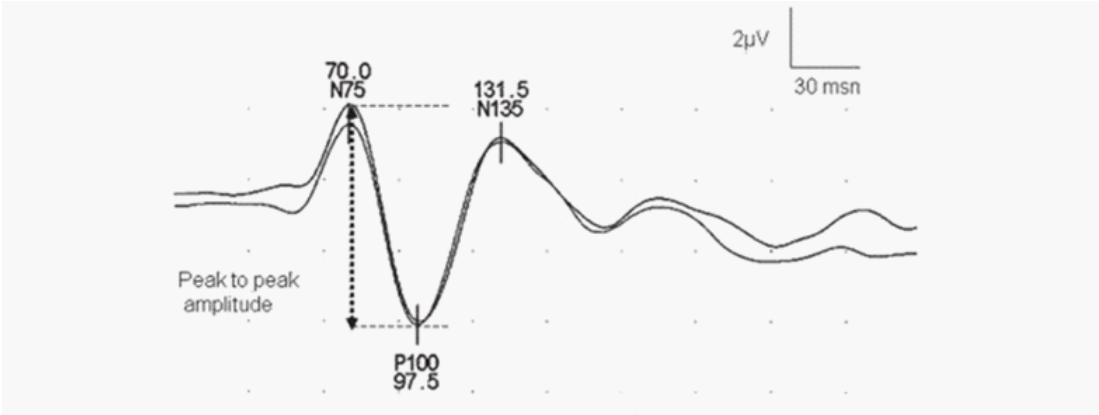

Figure 1: Measurement of peak to peak amplitude of P100 potential.

Brainstem Auditory Evoked Potentials (BAEPs)

BAEP recordings were performed in a quiet room, while the subjects were in supine position. Active recording electrode (needle scalp electrode) was placed on the ipsilateral mastoid process and was referred to the vertex (Cz). The polarity of the stimulus was alternating clicks with a stimulus intensity of 60 dB above the hearing threshold for each individual. Monoaural stimulation was performed using electromagnetic shielded ear-phones with the contralateral ear masked by white noise (40 dB below the stimulus intensity). The frequency of stimulation was 10/sec, filtering was adjusted as 3 Hz-100 Hz. Analysis time was 10 m sec and 1000 responses were averaged twice and overlapped for reliability. Peak latencies of waves I, II, III, IV and V, together with interpeak latencies of I-III, III-V and I-V were measured.

Somatosensory Evoked Potentials (SEPs)

Posterior tibial nerves were electrically stimulated and during SEP recordings, surface electrodes were used while the impedance was kept under 5 k ohm. The active electrode was placed on 2 cm posterior to the vertex (Cz) and it was referred to Fz. The electrical stimuli applied to the posterior tibial nerve consisted of rectangular pulses of 0, 2 msec in duration. Sweep speed was 5 ms/div, sensitivity was 5÷v/div and the amplifier had a frequency band of 20 Hz–2 kHz. P1 and N1 peak latencies and amplitude of P1 were measured.

Nerve Conduction Studies (NCS)

All subjects underwent NCS that were composed of median and ulnar motor nerve conduction studies in the upper extremity and posterior tibial nerve and peroneal motor nerve conduction studies in the lower extremity. Sensory nerve conduction studies included median, ulnar and sural nerve conduction studies. NCS were performed in three extremities of every subject. Silver surface recording electrodes were placed according to the belly-tendon method for motor nerves, whereas ring electrodes were used while recording the Sensory Nerve Action Potentials **(SNAPs).** Recording sites for median and ulnar motor nerves were abductor pollicis brevis and abductor digiti minimi muscles respectively, while median nerve was stimulated at the wrist and medial forearm. Ulnar nerve was stimulated at the wrist, the elbow and above the elbow. Recording sites for peroneal and posterior tibial nerves were extensor digitorum brevis and abductor hallucis longus muscles, respectively. Stimulations of peroneal nerve were made at the ankle, caputulum fibulum and lateral poplitea, whereas posterior tibial nerve was stimulated behind the medial malleol and mid-poplitea. Median and ulnar sensory nerves were stimulated antidromically at the wrist, the recording sites being the third and fifth fingers, respectively. Compound Muscle Action Potentials **(CMAPs)** of motor nerves and SNAPs were measured for latencies, amplitudes and nerve conduction velocities.

Needle Electromyography (EMG)

Concentric needles were used in needle EMG studies. Two muscles, one proximal and one distal, were sampled from each of one upper and two lower extremities. Deltoid and extensor digitorum communis muscles and tibialis anterior and rectus femoris muscles were sampled from the upper and lower extremities, respectively. The activity of muscles during rest and activity as well as recruitment patterns were reported.

RESULTS

Mean age of both of the patient groups did not differ from each other and from normals statistically (p>0, 05). Mean disease duration did not show statistical differences between the two patient groups, either (p>0, 05). No statistically significant difference existed in comparison of body height between the patient groups and the normal group (p>0, 05).

SPSS (Statistical Package for Social Sciences) for Windows 10.0 program was used for the statistical analysis. Mean values and standard deviations of every parameter were calculated in both of the groups. Apart from the statistical comparison tests (Oneway Anova and Mann Whitney U tests) that were used to compare the parameters between the groups, additional tests (Tukey HSD test and Kruskal Wallis test) were used to determine the group responsible from the differences. Fisher's Exact Ghi-square and Student t tests were used to perform statistical comparison of age, mean disease duration and body height between the groups. The statistical significance was evaluated as p<0, 05. Most VEP amplitude data have a non-normal distribution with significant skew and kurtosis. Therefore, calculating mean and standard deviation on the raw data is inaccurate. The data must first be transformed to approximate normal distribution. This transformation can be achieved by taking the natural logarithm, the square root, or the reciprocal of values that have non-normal distribution. The mean and standard deviation can then be calculated on the transformed data [5]. We took the natural logarithm of values that had non-normal distribution and then calculated the mean and standard deviations.

Results of VEP Study

Results of VEP study confirmed that N75 latencies of the MS group were statistically higher than normals, whereas no statistical difference was seen in comparison of the NB group with normals and with the MS group. P100 latencies of the two patient groups were higher than the normals, but no statistically meaningful difference was found when the patient groups were compared with each other (Table 2).

Table 2: Statistical distribution of N75 and P100 latencies over the groups

Groups		N75 Latency Mean ± S.D.		P100 Latency Mean ± S.D.	
N		70.2 ± 3.9		103.3 ± 16.5	
NB		74.8 ± 13.5		113.18 ± 19.9	
MS		78.5 ± 17.6		114.4 ±20.5	
Test Value; *p*		F=4.44	0.013*	KW=10.2	0.006*
N-NB	*p*	Tukey HSD = 4.59	0.553	Z=2.53	0.011*
N-MS	*p*	Tukey HSD = 8.23	0.009**	Z=2.98	0.003**
NB-MS	*P*	Tukey HSD = 3.64	0.636	Z=0.10	0.915*

N, Normal group; F, Oneway Anova test and Post hoc tests Turkey HSD; KW, Kruskal Wall is test; Z, Mann Whitney U test.

$^{*}p<0.05$, $^{**}p<0.01$.

Amplitudes of P100 potential were lower in both of the patient groups, when compared with the normals (p<0, 01), but the amplitudes in the NB group were much lower than the MS group (p<0, 05) (Table 3).

Table 3: Statistical distribution of P100 amplitude over the groups

Groups		P100 Amplitude Mean ± S.D.	Test Value; *p*
Normal		10.5 ± 3.8	F=7.8
NB		6.2 ± 1.8	
MS		8.0 ± 4.7	0.001**
Normal -NB	*p*	Tukey HSD = 4.4	0.001**
Normal -MS	*p*	Tukey HSD = 2.6	0.004**
NB-MS	*P*	Tukey HSD = 2.4	0.018*

F, Oneway Anova test and Post Hoc tests Tukey HSD.

$^{*}p<0.05$, $^{**}p<0.01$.

Results of Posterior Tibial Nerve SEP Study

In posterior tibial nerve SEP study P1 cortical latencies of all groups were compared statistically. P1 latencies of posterior tibial SEPs were delayed in both of the patient groups when compared with normal's (p<0, 05), whereas the values in the MS group were more prolonged when compared with the NB group (p<0, 05). The amplitude of P1 and latency of N1 did not show statistical differences between the patient groups (p>0, 05).

Results of BAEP Study

The results of the BAEP study showed that the absolute latencies of waves III and IV in the NB group were prolonged when compared with the normals statistically (Tukey HSD: 0, 413, p: 0, 045, p<0, 05 and Tukey HSD: 0,880, p: 0, 035, p<0, 05, respectively). The interpeak latency values of waves I- III, I-V and III-V did not differ statistically from each other in all three groups (p>0, 05).

Results Of Nerve Conduction Studies (NCS) and Electromyography (EMG)

Only two of all 75 patients showed pathological results of NCS and EMG. One of them was a MS patient, showing demyelinating features in NCS. The motor nerve conduction studies in the lower extremities indicated moderate prolongation of CMAP latencies, mild to moderate slowing in Nerve Conduction Velocity **(NCV)** and slight reduction of amplitudes, whereas the SNAPs had mild prolongation of distal latencies. Needle EMG yielded mild chronic denervation in lower extremity muscles. The other patient was with NB and showed signs of axonal polyneuropathic involvement, consisting of mild to moderate reductions of amplitudes of both CMAPs and SNAPs, prominent distally and in the lower extremities. These two patients showing pathologies in NCS and EMG studies did not have any risk factors of peripheral nervous system involvement.

DISCUSSION

Comparative studies of evoked potentials of neurobehcet patients with other patient groups that take place in the differential diagnosis are unfortunately very few in number in the medical literature, probably for the reason that patients with NB are seen rarely. In fact there is only one

study in the literature that compares the EPs between NB and MS patients [6]. This study includes the comparison of SEP and BAEP studies between the two patient groups, VEP studies and EMG are not included.

The differential diagnosis of NB may sometimes be complicated and MS is the major disease that takes place in the differential diagnosis. Evoked potentials are used in the diagnosis of both of the diseases. In this study our aim was to investigate parameters of electrophysiological tests that might be useful in the differential diagnosis of NB and MS.

Our results confirmed that there could be differences in EP studies between these patient groups that might be valuable in the differential diagnosis.

Latency has been shown to reflect the efficiency and speed of audio-visual, sensory or cognitive information processing in function related evoked potential studies. Thus this statement may be interpreted that prolonged latencies reflect slower speed of information processing. Amplitude abnormalities may refer to axonal loss in related areas.

Our VEP study indicated that the amplitude values of P100 potentials in the NB and MS groups were lower than those of the normal group (p<0, 01), however the amplitudes in the NB group were much lower than those of the MS group (p<0, 05). This finding may be consistent with an understanding that axonal involvement of visual pathways may be more common in NB patients. The expectancy in VEP study of the two groups was that the delay of P100 latency would be more prominent in the MS group; however our results failed to confirm this expectancy and rather indicated that this parameter did not differ between the two groups. We cannot compare the VEP findings of our study with another study in literature because the only study that compared EPs between NB and MS patients did not include the VEP study [6].

Results of VEP studies in Behcet patients differ from each other. In a study of Stigs by et al, 44 Behcet patients with and without neurological involvement underwent VEP studies and abnormal VEPs were seen in 14 patients. Absent potentials, decreased amplitude with or without prolonged P100 latency accounted for the abnormalities in 75% of these, while the remaining 25% had prolonged P100 latency, but normal amplitude [7]. A recent study, however, reported interesting results in the VEP findings of 44 Behcet patients without neurological involvement. The mean latency value of positive peak P100 in patients was significantly delayed when compared to that of control subjects [8]. This study did not report any results concerning amplitudes of P100, but showed impressive results by reporting that P100 latency might be prolonged even in Behcet patients without neurological involvement. For the fact that only one of NB patients had a diagnosis of uveitis, the VEP pathologies in our study also seem quite extensive, confirming the results of this study. On the other hand, our results mainly overlapped with the former study and furthermore suggested that calculating the amplitude of P100 might be more useful for differential diagnosis. There is belief that amplitude loss of P100 in MS does not generally occur in the early course of the disease. Nevertheless there are contradictory results in some studies.

In a clinical study of 25 MS patients with normal visual acuity and unimpaired visual functions, VEP amplitudes were significantly reduced when compared to normals [9]. Another study confirmed a similar result that even in the relapsing/remitting stage of MS, there was electrophysiological evidence for involvement of clinically asymptomatic axons [10].

Both of the patient groups in our study had similar disease durations, so our results might be interpreted that axonal loss of cortical visual pathways may occur earlier in the course of disease in NB patients.

Our results in the BAEP study showed that patients with NB showed more BAEP pathologies than the MS group and showed a consistency with the results of Nakamura et al. Although the absolute latencies of waves III and V did not differ statistically from normals in the MS group, they were delayed in the NB group when compared with the normal group. This finding may be an indicator of the knowledge that brainstem involvement is more frequent in NB patients [6]. The interpeak latencies of BAEP waves did not differ from each other in the three groups.

SEP recordings in our study showed that the P1 cortical latencies of posterior tibial SEPs were delayed in both of the patient groups when compared with normals, whereas the values in the MS group were more prolonged when compared with the NB group. This result was also consistent with the findings of Nakamura et al, who also reported that abnormal cortical P37 latencies of posterior tibial nerve SEPs were more frequently found in the MS patients than in the NB patients indicating that lesions were mainly present in the spinal cord in MS [6].

Nerve conduction studies and EMG in our study indicated that there might be peripheral nerve involvements in both of the patient groups. Patients with Behcet's disease may have axonal poly neuropathy, more prominent distally and in the lower extremities [11,12], while MS patients may also show signs of peripheral nervous system involvement, often as demyelination [13,14]. Our results showed similar findings, overlapping the studies in the literature, but the rate of the findings in our study were very low.We believe that the most important results in this study are the results of the VEP study, for it produced observations that might be important in the differential diagnosis of MS and NB, considering that VEP parameters were not compared between these patient groups before. The importance of VEP studies in MS is underlined by various studies. In a study of a chronic progressive MS patient group, it was concluded that serial VEPs might even complement standard disability-based endpoints to assess disease progression [15].

As being the sole diagnostic tool of EP studies in the MS group according to the new diagnostic criteria of MS, VEP studies bear more importance also in the field of differential diagnosis of MS [2] although, there is debate going on the diagnostic value of other EP studies in MS [16]. On the other hand, there is still a gap of knowledge in the medical literature about the place of VEP studies in the differential diagnosis of NB.

We believe our study has produced results that have not been reported before in this aspect of VEP studies, while supporting most of the already known facts for other electrophysiological tests included in the study.

We propose that P100 amplitude measurements in VEP studies may be more valuable than P100 latency measurements, and thus should be used more frequently in the differential diagnosis of MS and NB.

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