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Visual Evoked Potentials in Differential Diagnosis of Multiple Sclerosis and Neurobehcet's Disease

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Behcet's disease, a multisystemic vascular inflammatory disorder of unknown origin, is relatively rare and central nervous system involvement is seen in 5% of affected individuals. This form of the disease, called as neurobehcet's disease (NB), can be misdiagnosed as multiple sclerosis (MS), a demyelinating disorder of central nervous system, so their differential diagnosis is important. In this study, to identify the parameters of electrophysiological testing that might be useful in their differential diagnosis, we performed evoked potentials (EPs) and electroneuromyography (ENMG) on patients with MS and NB, and on normal volunteers. A total of 95 persons, 55 MS patients, 20 NB patients and 20 normal volunteers between ages 31 and 55, were studied electrophysiologically. Visual evoked potential (VEP), brainstem auditory evoked potential (BAEP), posterior tibial somatosensory evoked potential (SEP) and nerve conduction and needle electromyography studies were performed on all patients and volunteers. All parameters of EPs were compared among the groups. The results of the BAEP and SEP studies did not show statistically significant difference between NB and MS. However, the VEP study indicated that the amplitude values of cortical VEP potentials (P100) in the NB and MS groups were lower than those of the normal group ($p < 0.01$), and that the amplitudes in the NB group were lower than for the MS group ($p < 0.05$). Therefore, P100 amplitude measured from peak to peak seems to be more reliable and thus should be used in the differential diagnosis of MS and NB. ———— Neurobehcet's disease; multiple sclerosis; evoked potentials; visual evoked potentials; electromyography.
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Behcet's disease is a multisystemic vascular inflammatory disorder of unknown origin. The reported frequency of neurological involvement among patients with Behcet's disease ranges from 2.2 to 49% (Siva et al. 2004). However, larger series have shown a rate of approximately 5% (Akman-Demir et al. 1999). Paraparesis and quadriparesis, pseudobulbar palsy, cranial nerve palsies, cerebellar ataxia and aseptic meningoencephalitis are the most common presentations (Al-Kawi 1992). The disease mostly involves the diencephalon, brain stem and spinal cord (Al-Kawi et al. 1992; Akman-Demir et al. 1999). This 5% of patients with Neurobehcet's disease

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(NB) may lead to diagnostic difficulties, especially in differentiating it from multiple sclerosis (MS), a demyelinating disease of the central nervous system (i.e., the brain and/or spinal cord) where myelin degeneration is due to autoimmune processes (Mumenthaler et al. 2004).

The VEP (Visual evoked potential) is an evoked electrophysiological potential that can be extracted, using signal averaging, from the electroencephalographic activity recorded at the scalp. It can provide important diagnostic information regarding the functional integrity of the visual system (Odom et al. 2004). VEPs, 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) on patients with MS and NB, and on normal volunteers. Our objective 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 NB patients 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 ascribed as definite MS according to McDonald's criteria (Mc Donald et al. 2001) and their MRI findings were compatible with MS according to Barkoff's criteria (Barkhof 2002). Thirty three (60%) of these patients were diagnosed as RRMS (Relapsing remitting MS), 14 (25%) were diagnosed as SPMS (Secondary progressive MS) and 8 (15%) were diagnosed as PPMS (primary progressive MS). The onset of disease was monosymptomatic in 3 (5.5%) patients and polysymptomatic in the remaining 52 (94.5%). All NB patients fulfilled the diagnostic criteria of the 1990 International Study Group for Behçet's Disease (ISGBD). The majority of patients in the NB and MS groups had supratentorial lesions (60% and 73% respectively). In the MS group, nine (16.3%) patients had a history of unilateral optic neuritis, and one (5%) patient in the NB group had uveitis. The patients in both of the groups did not show statistically significant differences when compared regarding mean age, mean duration of disease and mean number of attacks. The detailed demographic data and imaging findings of patient groups are summarized in Table 1.

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)

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 lesions*	13	7
Cranial supratentorial lesions*	40	12
Spinal lesions*	2[a]	3[a]

F, female; M, male; RRMS, relapsing 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 relapsing-remitting diseases and ''attacks'' stand for the relapses.

were performed in all patients and normal subjects. Evoked potential studies were performed bilaterally. A total of 190 VEPs, 190 BAEPs and 190 posterior tibial SEPs were performed. Nerve conduction studies and needle EMG were performed in three extremities of each subject, thus a total of 285 extremities were studied. Every patient and volunteer had detailed physical and neurological examinations, and patients had proper imaging tests (cranial MRI and/or cervical, thoracic and lumbar spinal MRI) where necessary.

All of the electrophysiological studies were performed with Dantec Keypoint. Patients and volunteers gave informed consent and each of the procedures was explained thoroughly to all. All techniques in the study were performed in compliance with the laws and principles of medical ethics and the relevant institutional committee approved our study. The subjects were informed that if they felt pain or any other displeasant sensations, the test would be stopped. All of the patients and control volunteers tolerated the electrophysiological tests.

Pattern visual evoked potentials (VEPs)

VEP recordings were performed in a darkened room. Correcting glasses were used 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 eye level at a distance of 1 meter from a TV screen and were instructed to focus on the center of the screen indicated by a red mark. Full field stimulation was performed monoocularly. The stimuli consisted of a black and white checker board pattern (checker size 12 × 16 mm). Filter setting was 1 Hz-0.1 kHz and the sweep speed was adjusted to 30 ms/div. The analysis time was 300 msec and 750 responses were averaged twice and overlapped. Peak latencies of N75, P100 and N135 were measured, and also a peak to peak amplitude of P100 calculated as the amplitude from the N75 peak to the P100 peak (Fig. 1).

Brainstem auditory evoked potentials (BAEPs)

Brainstem auditory evoked potential recordings were performed in a quiet room, while the subjects were in supine position. An 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 to 3 Hz-100 Hz. Analysis time was 10 msec and 1,000 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 during SEP recordings, surface electrodes were used while the impedance was kept under 5 kohm. The active electrode (Cz) was placed 2 cm posterior to the vertex and was referenced against the Fz. The electrical stimuli applied to the posterior tibial nerve consisted of rectangular pulses of 0.2 msec duration. Sweep speed was 5 ms/div, sensitivity was 5 μv/div and the amplifier had a frequency band of 20 Hz-2 kHz. P1 and N1 peak latencies and amplitude of P1 were measured.

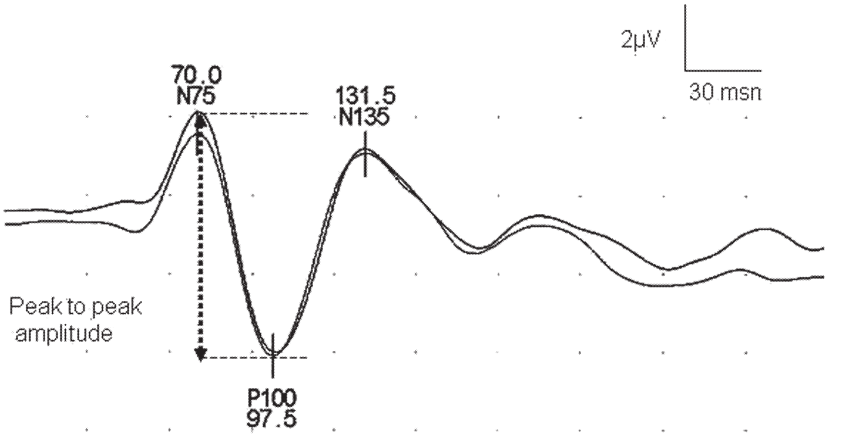

Fig. 1. Measurement of peak to peak amplitude of P100 potential.

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. Nerve conduction studies 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 the abductor pollicis brevis and abductor digiti minimi muscles respectively, while median nerve was stimulated at the wrist and medial forearm. The ulnar nerve was stimulated at the wrist, the elbow and above the elbow. Recording sites for peroneal and posterior tibial nerves were the extensor digitorum brevis and abductor hallucis longus muscles, respectively. Stimulations of the peroneal nerve were made at the ankle, caputulum fibulum and lateral poplitea, whereas the 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 to determine 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.

Statistical Methods

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 for both of the groups. Apart from the statistical comparison tests (One-way 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 Chi-square and Student t tests were used to perform statistical comparisons of age, mean disease duration and height between the groups. Statistical significance was established at the 5% level. Most VEP amplitude data have a non-normal distribution with significant skew and kurtosis. Therefore, calculating mean and standard deviation on the basis of 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 (Celesia et al. 1999). We used the natural logarithm of values that had non-normal distribution to calculate the mean and standard deviations.

Results

Mean age, disease duration and height were not different among the two patient groups and normal group ($p > 0.05$).

VEP study

The VEP study confirmed that N75 latencies of the MS group were higher than for the normal group ($p < 0.05$), whereas there was no difference between the NB group and the normal and MS groups. P100 latencies of the two patient groups were higher than for the normals ($p < 0.05$) , but no difference was found when the patient groups were compared with each other (Table 2).

Amplitudes of P100 potentials were lower in both of the patient groups than normal group ($p < 0.01$), but the amplitudes in the NB group were much lower than the MS group ($p < 0.05$) (Table 3).

Posterior Tibial Nerve SEP study

In the 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 normals ($p < 0.05$), whereas the values in the MS group were more prolonged when compared with the NB group ($p < 0.05$). There was no difference for amplitude of P1 and latency of N1 between the patient groups ($p >$

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 HD = 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 Tukey HSD; KW, Kruskal Wallis test; Z, Mann Whitney U test.
*$p < 0.05$, **$p < 0.01$.

TABLE 3. Statistical distribution of P100 amplitude over the groups.

Groups		P 100 Amplitude Mean ± S.D.	Test Value; *p*
Normal		10.5 ± 3.8	F = 7.8 0.001**
NB		6.2 ± 1.8	
MS		8.0 ± 4.7	
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.
*$p < 0.05$, **$p < 0.01$.

0.05).

BAEP study

The BAEP study showed that the absolute latencies of waves III and IV of the NB group were prolonged in comparison with the normal group (Tukey HSD: 0.413, *p*: 0.045, $p < 0.05$ and Tukey HSD: 0.880, *p*: 0.035, $p < 0.05$). The interpeak latency values of waves I- III, I-V and III-V were not different from each other in all three groups ($p > 0.05$).

Nerve conduction studies (NCS) and electromyography (EMG)

Only two (2.7%) of all 75 patients showed pathological results for NCS and EMG; one was a MS patient whose NCS results demonstrated demyelination. 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 exhibited mild prolongation of distal latencies. Needle EMG demonstrated mild chronic denervation in lower extremity muscles. The other patient from the NB group 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. There were not any clinical signs of peripheral nervous system involvement in these two patients who showed pathologies in NCS and EMG studies.

Discussion

Differential diagnostic studies of the evoked potentials of NB patients and other patient groups are rare in the medical literature, probably because patients with NB are rarely seen. In fact, there is only one study in the literature that compares the EPs of NB and MS patients (Nakamura et al. 1989). Their study involved the comparison of SEP and BAEP test results for the two patient groups; VEP studies and EMG were not included.

EPs are used in the diagnosis of both NB and MS, but their electrophysiological differential diagnosis still bears unanswered questions. In this study, our objective was to investigate parameters of electrophysiological tests that may be useful in clarifying their 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 it may be inferred that prolonged latencies reflect slower speed of information processing; amplitude abnormalities may reflect 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 ($p < 0.01$), and that the amplitudes in the NB group were much lower than those of the MS group ($p < 0.05$). This finding may be consistent with the view that axonal involvement of visual pathways may be more common in NB patients.

This study was not undertaken with the assumption that a difference would be found regarding the latency of VEP and our results confirmed that this parameter did not differ between the two groups. We cannot compare our VEP findings with another study because the only study that compared the EPs of NB and MS patients did not include a VEP study (Nakamura et al. 1989).

Results of VEP studies in Behcet patients vary. In a study by Stigsby et al., 44 Behcet patients with and without neurological involvement underwent VEP studies, and abnormal VEPs were seen in 14 patients. Absent potential, and 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 (Stigsby et al. 1994). 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 for P100 in patients was significantly delayed when compared to control subjects (Anlar et al. 2006). This study did not report any P100 amplitudes, but reported that P100 latency might be prolonged even in Behcet patients without neurological involvement.

Despite the fact that only one NB patient had a diagnosis of uveitis in our study, the VEP pathologies appear quite extensive, confirming the results of Anlar et al. (2006). Our results mainly coincided with the former study, and furthermore suggested that the amplitude of P100 might be more useful than the peak latency of P100 for differential diagnosis.

Considering that only 9 of the 55 (16.3%) MS patients had a history of optic neuritis, and only 1 of 20 (5%) Behçet patients had uveitis, the described differences in the majority of patients for VEP may point to subclinical pathologies. Any conclusions of this study would therefore seem to apply to a group of patients who are asymptomatic regarding visual signs. Although these findings may appear difficult to explain pathophysiologically, neurophysiological abnormalities may point to subclinical conditions which may not even be diagnosed by imaging studies.

There is a belief that amplitude loss of P100 in MS does not generally occur in the early course of the disease. Nevertheless, there are contradictory results from some studies. In a clinical study of 25 MS patients with normal visual acuity and unimpaired visual function, VEP amplitudes were significantly reduced when compared to control subjects (Diem et al. 2003). Another study offered support that even in the relapsing/remitting stage of MS, there was electrophysiological evidence for involvement of clinically asymptomatic axons (Jones et al. 2003).

Both of the patient groups in our study had

similar disease durations, so our results indicate that axonal loss of cortical visual pathways may occur earlier in the course of disease in NB patients. In addition, our study patients with NB showed more BAEP pathologies than the MS group, which was consistent with the results of Nakamura et al. (1989). Although the absolute latencies of waves III and V did not differ statistically from the normal group in the MS group, they were delayed in the NB group when compared with the normal group. This finding may be an indicator that brainstem involvement is more frequent in NB patients (Nakamura et al. 1989). The present study also found that the interpeak latencies of BAEP waves were not different among the three groups ($p < 0.05$).

SEP recordings in our study showed that the P1 cortical latencies of posterior tibial SEPs were delayed in both patient groups compared with normals, whereas the values in the MS group were more prolonged than the NB group. This result was also consistent with the findings that abnormal cortical P37 latencies of posterior tibial nerve SEPs were more frequent in MS patients than NB patients, indicating that lesions were mainly present in the spinal cord in MS (Nakamura et al. 1989).

Nerve conduction studies and the EMG in our study indicated that there might be peripheral nerve involvement in both patient groups. Patients with Behcet's disease may have axonal polyneuropathy, more prominent in the lower extremities (Birol et al. 2004; Yazıcı et al. 2001), while MS patients may also show signs of peripheral nervous system involvement, often as demyelination (Couratier et al. 2004; Quan et al. 2005). Our results were similar to the literature, but the frequency of abnormal electrophysiological findings in our study was very low.

The limitations of the present study may arise in part from the small number of patients, especially in the NB group. The follow-up of clinical statuses and electrophysiological data for a long period would also help clarify conclusions but most patients could not attend clinic after the initial testing period.

The most important results in the present study are those of the VEP study, because this is the first report showing the importance of VEP in the differential diagnosis of MS and NB. VEP was also used in assessing disease progression of chronic progressive MS patients (Sater et al. 1999). VEP studies, being the sole diagnostic tool for EP studies according to the new diagnostic criteria for MS, bear more importance in the field of differential diagnosis of MS (Mc Donald et al. 2001), although there is debate on the diagnostic value of other EP studies in MS (Djuric et al. 2005).

In conclusion, P100 amplitude measurements in VEP studies are more relevant and applicable than P100 latency measurements, and thus should be used in the differential diagnosis of MS and NB.

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