Research Article

Exteroceptive Suppression of Masseter In Behçet’s Disease

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Objectives: Brainstem is the most frequently affected neural substrate in neurological involvement due to Behçet’s disease (neuro-Behçet). The demonstration of brainstem involvement in Behçet’s disease (BD) is important in the management of this disorder. The evaluation of some brainstem reflexes (blink reflex and exteroceptive suppression of masseter) and brainstem auditory evoked potentials (BAEP) may provide additional information concerning CNS involvement in the patients with BD.

Materials and Methods: We studied 37 patients with BD. Six out of 37 patients had neurological involvement in their neurological examination or history (neuro-Behçet). Exteroceptive suppression of masseter, blink reflexes and BAEP were analyzed in patients and in 18 healthy controls.

Results: Four out of six patients with neuro-Behçet showed abnormalities involving exteroceptive suppression patterns of masseter (unrecordable in 3 and prolonged latency of S2 in 1), two showed BAEP abnormalities (absent of wave V in 1 and increased I-III interpeak latency in 1), and one showed blink reflex (increased latency of R1 and R2) abnormality. Electrophysiological parameters did not showed significant difference in the patients with BD without neurological involvement.

Conclusions: Our findings suggest that exteroceptive suppression of masseter may be useful test in disclosing brainstem involvement only in patients with neuro-Behçet.

Keywords: Behçet’s disease, Neuro-Behçet, Exteroceptive suppression of masseter, Blink reflex, Brainstem auditory evoked potentials, brainstem reflexes
Sonuçlar: Nöro-Beşchet hastalığı tanısi olan 6 olgunun 4’ünde masseter eksteroseptif supresyonunda anormallikler (3 olguna S2 dönemini elde edilememesi, 1 olguna S2 latans uzaması) gözlenirken, 2 olguna BAEP anormallikleri (1 olguna V. komponent kaybı, 1 olguna I-III interpik latansında uzama) ve 1 olguna ise göz kırpma refleks anormallikleri (R1 ve R2 latanslarında uzama) gösterdi. Nörolojik tutuluş olmayan BD olgularında ise elektrofizyolojik testlerde istatistiksel anormallik gözlenmedi.

İzlenimler: Elde edilen bulgular klinik nörolojik tutuluş olan Behçet olgularında çalışılan testlerin anlamlı sonuçları gösterdiğini göstermiştir.

Anahtar Kelimeler: Behçet Hastalığı, Nöro-Beşchet, Masseter eksteroseptif supresyonu, Göz kırpma refleksi, Beyinsapışitsel uyarılması potansiyelleri, Beyinsapı reflkesleri

Introduction
Behçet’s Disease (BD) is a multisystem disorder mainly characterized by oral and genital ulcers and uveitis. Neurological involvement [neuro-Behçet] has been reported in about 5-49% of patients with BD 1,2. It has been determined that brainstem is the most frequently affected neural structure and that brainstem involvement is associated with poor prognosis in BD 3. Lesions due to BD are commonly located in the brainstem or periventricular white-matter in the radiological investigation 4. The sensitivity of MRI is not very high in the detecting of CNS lesions due to BD 1,5. When neurological involvement is present, early diagnosis and treatment is essential in reducing progression of CNS disease 6.

Electrophysiological studies may provide functional information complementary to magnetic resonance imaging (MRI). Among them, brainstem auditory evoked potentials (BAEPs) have been investigated in patients with BD previously 5,7,8. BAEP abnormalities may demonstrate a conduction failure of lateral lemniscus in the brainstem in patients with BD. Some amplitude and latency alterations have been observed. BAEP abnormalities were between about 50-65% in patients with neuro-Behçet 5,7.

Brainstem reflexes may provide valuable functional information about the clinical or subclinical involvement of nervous system due to BD. Blink reflexes has been investigated in patients with BD 9,10. The R1 component of this reflex is originated from the pons. On the other hand, R2 component is originated from medulla and it contains a polysynaptic neural pathway located in the brainstem 11. The abnormalities of R2 component (absence or delayed latency) are the main abnormalities observed in the BD 9,10.

Exteroceptive suppression of masseter (ES) is a trigemino-trigeminal reflex response evoked by electrical stimulation of trigeminal afferents 12. There are two different suppression periods after electrical stimulation of trigeminal nerve (S1 and S2). The first period (S1) begins at about 10-12 ms and the second period (S2) begins at about 45-55 ms. S1 period is formed by the interneurons located at the pons dorso-medially to the trigeminal motor nucleus in an area called nucleus supratrigeminalis 13. It was demonstrated that this component originates from inhibitory interneurons located at bulbar reticular formation 13. This reflex is a potent tool in the demonstration of small brainstem lesions 12,14. To our knowledge, ES has not been studied in patients with BD previously.

In this study, our aim was to determine the values of BAEP, blink reflexes and exteroceptive suppression of masseter in evaluation of CNS involvement in patients with BD.
Methods

Subjects:
We studied 37 patients with BD (22 male, 15 female). Mean age was 39.1 ± 9.4 years old (ranged from 23 to 60). Disease duration was ranged from 3 months to 21 years. All patients fulfilled the diagnostic criteria proposed by the International study group for BD. Thirty-one out of 37 patients with BD had no history related to neurological involvement due to BD. Their neurological examinations were also normal during electrophysiological investigations. Six out of 37 patients with BD had neurological findings and/or history of neurological dysfunction. These patients were classified as neuro-Behçet due to intra-axial CNS involvement of BD. Other disorders causing similar clinical and radiological findings were excluded by history, neurological examinations and appropriate laboratory tests. In the neuro-Behçet group, clinical course of one (patient 2) was secondary progressive; two patients (patients 1 and 4) had only one attack due to neurological involvement; three patients (patients 3, 5 and 6) had two attacks due to neurological involvement in their history. Five out of six patients were self-sufficient and not dependent to another person. One patient (patient 2) was moderately physical dependent. There was no other system involvement due to BD other than cutaneous and joint dysfunction due to BD. The electrophysiological data obtained from patients with BD were compared with the data obtained from 18 healthy controls (11 male and 7 female). Mean age of them was 42.1 ± 9.2 (ranged from 24 to 54) years. There was no statistical difference in ages between patients and controls (p>0.05). There was no organ failure or systemic disorders other than BD in all subjects. All patients and controls were informed about the study and their consent was also recruited.

Electrophysiological Investigations

Brain-stem auditory evoked potentials (BAEPs): BAEPs were recorded in a quiet and dim room in our laboratory. All subjects were requested to sit on a comfortable armchair and were instructed to avoid eye and head movements during the test. Medelec Synergy EMG equipment was used for electrophysiological investigations. “Click” stimulations were used. Firstly, auditory threshold level was analyzed. Stimulation level was determined by threshold level plus 60 decibel (db) for each side. Stimulation frequency was 10 Hz. Recordings were performed using silver plated surface electrodes. At least, 1200 responses were averaged for each analysis. At least, two traces were recorded and superimposed for each side. For recording, active electrodes were located on the both mastoid bone (A1 and A2). These electrodes were referenced to Cz electrode located according to 10-20 system. Oscilloscope sweep time was 10 ms. Amplifier filters was set between 100 Hz-2kHz.

The latencies and amplitudes of first (I), third (III) and fifth (V) waves, interpeak latencies of I-III, I-V and III- V were analyzed.

Blink reflexes: The electrical stimulation of both supraorbital nerves was performed to obtain reflex responses. The stimulation intensities were adjusted according to the response. It was between 80 to 120 V for all subjects. Recordings were performed using silver plated surface electrodes from both orbicularis oculi muscles. Active electrode was placed infraorbitally. Reference electrode was placed on arcus of the zygomatic bone. Stimuli were delivered to the right and left supraorbital nerves. The reflex responses of both ipsilateral and contralateral orbicularis oculi muscles were recorded simultaneously.

The frequency filter of amplifier was set between 10 Hz-10kHz. Oscilloscope sweep time was 100 ms. Gain was 0.1-0.5 mV/division. At least 5 responses were
recorded. The latencies and amplitudes of R1 and ipsilateral R2 responses were analyzed.

**Exteroceptive Suppression of Masseter Muscle:** During the electrophysiological investigation, subjects were instructed to make a forceful tooth clenching. The stimuli were delivered to the mental nerve during voluntary contraction from the mental nerve at the inferior border of the corner of mouth. Active recording electrode was placed over the belly of the masseter muscle. Reference electrodes were placed on the arcus of the zygomatic bone. For recording, AgCl surface electrodes were used. Initially the suppression patterns of the both masseter muscles were recorded. The oscilloscope sweep time was 200 ms. Amplifier filter was set between 10 Hz-10kHz. Gain was 0.2-0.5 mV/division. Stimulus duration was 0.2 ms. Stimulation parameters used in present study were relatively comfortable and not too painful for subjects.

At least 10 successive responses were recorded and superimposed for each side. When onset and end points of S2 suppression periods were equivocal, 20 stimuli were recorded and averaged. Only ipsilateral response was considered during analysis. To avoid habituation, the interstimulus interval was 10 s. Durations and onset latencies of the S1 and S2 periods were analyzed. The determination of the onset and the end points of S2 period were performed by averaging of 10 responses. Sometimes a few muscle activities were seen during S2 period. The EMG activity, exceeding 20% of maximal amplitude of prestimulus EMG signal was not considered as silent period.

**Statistical Analysis:**
Patients with BD (n:31) and controls (n:18) were considered for Statistical analysis.

Student-t test was used to compare electrophysiological data of controls and the patients with BD. Two-tailed tests were used. Normal limits were determined between as mean ± 2.5SD. A level of p

**Results**
Electrophysiological data were not significantly different between two sides of controls (p>0.05). All of the electrophysiological tests were recorded from control subjects.

Table1 demonstrates clinical and electrophysiological characteristics of patients with neuro-Behçet. All patients had neurological findings or history reflecting the brainstem involvement. No patient with extra-parenchymal CNS involvement was included to the study. Two out of six patients with neuro-Behçet showed MRI findings involving the brainstem involvement. Three patients had periventricular white matter lesions on their MRI investigation and one had normal MRI scan. Five out of six patients with neuro-Behçet had relapsing-remitting course (three of them had 2 attacks) and one patient had three attacks and secondary progressive course (patient 2). Their electrophysiological investigations were performed during remission period. S2 period of exteroceptive suppression could not be evoked in three patients with neuro-Behçet (patients 4, 5 and 6) (Figure 1). S2 period of one patient were prolonged at the both sides (patient 2). Two patients with neuro-Behçet showed BAEP abnormalities. One of them (patient 2) had prolonged I-III and I-V interpeak latencies of BAEP at the right side. I-III interpeak latency was 2.6 ms (normal values< 4.6 ms) (Figure 2). Wave V of BAEP has not been evoked in 5th patient. Blink reflex abnormalities was observed in only one patient with neuro-Behçet.
Table 1: Clinical and electrophysiological characteristics of patients with neuro-Behçet’s disease.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Attack number</th>
<th>Predominant syndrome (Examination and history)</th>
<th>MRI lesions</th>
<th>ES abnormality</th>
<th>Blink reflex abnormality</th>
<th>BAEP Abnormality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>48</td>
<td>M</td>
<td>2</td>
<td>Left pyramidal and oculomotor</td>
<td>Brainstem</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>34</td>
<td>M</td>
<td>3 (SP*)</td>
<td>Left pyramidal and cerebellar</td>
<td>Brainstem</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>40</td>
<td>F</td>
<td>1</td>
<td>Cerebellar and oculomotor</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>60</td>
<td>F</td>
<td>2</td>
<td>Cerebellar and right pyramidal</td>
<td>Periventricula</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>37</td>
<td>M</td>
<td>2</td>
<td>Left pyramidal and sensorial</td>
<td>Periventricula</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>25</td>
<td>M</td>
<td>1</td>
<td>Right oculomotor and cerebellar</td>
<td>Periventricula</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>
The abnormality observed in this patient was the prolonged latencies of R1 and R2 responses of blink reflex. All of the electrophysiological tests were accepted as abnormal in 2nd patient. On the other hand, electrophysiological investigations of two patients with neuro-Behçet were completely normal (patient 1 and 3) (Figure 3).

Table 2: The duration and onset latencies of S1 and S2 periods obtained from patients with Behçet’s disease (BD) and controls

<table>
<thead>
<tr>
<th></th>
<th>Behçet’s disease (n:31)</th>
<th>Controls (n:18)</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td><strong>S1 onset</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>13.3 ± 1.5</td>
<td>13.2 ± 1.4</td>
<td>0.6</td>
</tr>
<tr>
<td>Left</td>
<td>13.1 ± 0.4</td>
<td>13.4 ± 1.4</td>
<td>0.5</td>
</tr>
<tr>
<td><strong>S1 duration</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>15.6 ± 3.8</td>
<td>15.8 ± 2.4</td>
<td>0.6</td>
</tr>
<tr>
<td>Left</td>
<td>16.2 ± 3.3</td>
<td>16.4 ± 2.3</td>
<td>0.6</td>
</tr>
<tr>
<td><strong>S2 onset</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>52.6 ± 5.6</td>
<td>47.2 ± 3.0</td>
<td>0.06</td>
</tr>
<tr>
<td>Left</td>
<td>52.9 ± 6.0</td>
<td>47.9 ± 3.8</td>
<td>0.08</td>
</tr>
<tr>
<td><strong>S2 duration</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>43.5 ± 25.4</td>
<td>40.2 ± 8.1</td>
<td>0.2</td>
</tr>
<tr>
<td>Left</td>
<td>39.8 ± 23.0</td>
<td>40.7 ± 18.4</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Onset latency of S2 period showed a slight prolongation in patients with BD. Although, this difference did not show statistical significance (p: 0.06 for right side, p: 0.08 for left side). S2 period could not be evoked in two patients with BD. The onset latency of S1 period and durations of S1 and S2 periods did not show significant difference between patients and controls. BAEPs and blink reflexes did not show significant difference between patients with BD and controls. Table 3 demonstrates the electrophysiological data involving BAEPs and blink reflexes in patients with BD and controls.
While neuro-behçet may affect any part of the central nervous system, brainstem is one of the most frequently affected neural structures in this disorder. Electrophysiological tests evaluating brainstem dysfunction would give valuable information for neurological involvement in patients with BD. Since brainstem involvement is associated with poor prognosis, early demonstration of brainstem involvement may be important in the treatment of neuro-Behçet. Our results demonstrated that the abnormalities of these electrophysiological tests can be useful in only patients with neuro-Behçet. However, electrophysiological investigations have not showed any finding in patients with BD without neurological dysfunction.

Previous reports demonstrate that MRI investigations can be normal in patients with neuro-Behçet’s disease. Akman-Demir et al determined that MRI abnormalities can be observed in 70% of patients with neuro-Behçet’s disease. Nakamura et al (1994) reported that CNS involvement could be demonstrated by radiological methods in only two out of eight patients with neurological involvement due to BD. Therefore, it seems that there is a necessity to additional diagnostic tests to disclose neurological involvement in BD complementary to MRI. However, no superiority of electrophysiological tests to cranial MRI was observed in the diagnosis of neurological involvement in our study.

**Figure 1:** SSE period of exteroceptive suppression could not be evoked on left masseter in patient no 5. Suppression of right side is not clear.
Figure 2: Extroceptive suppression patterns and BAEP's of patient no 2. S2 period of extroceptive suppression was prolonged. I-III and I-V interpeak latencies of BAEP evoked by right ear stimulation showed slight prolongation.

Figure 3: Extroceptive suppression pattern of patient no 1. These data were accepted as normal.
There are a few studies evaluating blink reflexes in patients with BD. Sahiner and Aktan studied the blink reflexes in patients with BD without neurological involvement. They demonstrated that prolonged R1 and R2 latencies were observed in 27% of patients with BD. Ortega et al demonstrated the existence of blink reflex abnormality in a patient with BD with neurological involvement. They concluded that the analysis of blink reflex together with BAEP may be valuable in evaluation of brainstem functions in patients with neuro-Behçet. In contrast to these studies, we did not observe any difference in blink reflexes between controls and the patients with BD. Only one patient out of six with neuro-Behçet showed blink reflex abnormality and two (33.3%) showed abnormal BAEP. Similar results have been reported by different authors, previously. These results suggest that BAEP has limited value in demonstrating CNS involvement in patients with BD.

**Table 3:** Electrophysiological findings of BAEPs and blink reflexes in patients with Behcet's disease (BD) and controls. Mean values of both sides were demonstrated.

<table>
<thead>
<tr>
<th></th>
<th>Behçet’s disease (n:31)</th>
<th>Controls (n:18)</th>
<th>p</th>
</tr>
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<tbody>
<tr>
<td><strong>BAEP</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I* (ms)</td>
<td>1.7 ± 0.2</td>
<td>1.7 ± 0.1</td>
<td>0.3</td>
</tr>
<tr>
<td>III ** (ms)</td>
<td>3.9 ± 0.2</td>
<td>3.9 ± 0.2</td>
<td>0.8</td>
</tr>
<tr>
<td>V*** (ms)</td>
<td>5.9 ± 0.2</td>
<td>5.9 ± 0.2</td>
<td>0.7</td>
</tr>
<tr>
<td><strong>Blink reflex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R1 latency (ms)</td>
<td>10.6 ± 1.0</td>
<td>10.2 ± 0.8</td>
<td>0.3</td>
</tr>
<tr>
<td>R2 latency (ms)</td>
<td>32.1 ± 3.9</td>
<td>30.5 ± 4.0</td>
<td>0.2</td>
</tr>
</tbody>
</table>

The frank onset of neurological involvement is commonly occurs 4-6 years after the onset of BD. However, there are some patients with neurological involvement due to BD, prior to its characteristic oral and skin lesions. Therefore, it should not be surprised to diagnose of the subclinical neural involvement in patients with BD. Electrophysiological methods may be useful in demonstration of subclinical CNS lesions in BD. However, these electrophysiological tests were failed for this aim in present study.
In conclusion, our results suggest that the exteroceptive suppression of masseter was more valuable test than both BAEPs and blink reflexes in demonstration of CNS involvement in patients with neuro-Behçet. Main abnormalities of exteroceptive suppression were the absence of S2 suppression period and alterations in the duration of S2 period in the present study. These abnormalities were observed especially in the patients with neuro-Behçet. Three patients who showed this abnormality had no brainstem lesion on their MRI investigation. It seems that electrophysiological tests can be complementary tool to the MRI in patients with neuro-Behçet.

References


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