Clinical characteristics and prognosis of Neuro-Behçet’s disease

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Abstract

Objective: Neuro-Behçet’s disease (NBD) is a rare manifestation of Behçet’s disease (BD) and may cause severe disability. The aim of this study was to evaluate the treatment response in patients with NBD and to investigate the parameters that may influence the prognosis of the disease in patients with severe to mild-moderate disability.

Methods: The files of 60 patients admitted to our outpatient clinic for NBD between January 2007 and June 2014 were retrospectively reviewed. We compared the BD duration, time to NBD, NBD type and course, clinical findings of BD, functional neurological system involvement, localization of lesions on brain MRI, and all the medications between the severe and mild-moderate disability groups.

Results: The mean time to the onset of NBD was significantly longer (17.8±4.6 years) and the mean age was significantly higher (50.25±9.1 years) in patients with severe disability than in those with mild-moderate disability (7.5±8.0 years and 37.5±10.9 years; p=0.01 and p=0.03, respectively). Moreover, hemispheric involvement was significantly associated with severe disability (p=0.006). No difference was found with regard to other investigated parameters between the groups.

Conclusion: We believe that severe neurological disability may be associated with older age at the onset of NBD or longer time to NBD and hemispheric lesions on brain MRI. However, our results should be cautiously evaluated with further research.

Keywords: Neuro-Behçet’s disease, neurological involvement, functional system involvement, cranial MRI lesions, prognosis

Introduction

Behçet’s disease (BD) is an inflammatory disorder of unknown etiology, characterized by recurrent aphthous stomatitis, genital ulceration, and uveitis triad. It was first described by Hulusi Behçet (1). The highest incidence of BD has been observed in the Middle East, Mediterranean basin, and Far East region (2). Its diagnosis has been based on the International Diagnostic Criteria for BD (3). Although the neurological involvement of BD is a rare manifestation, it is one of the most serious causes of long-term morbidity. NBD is more common in males, and neurological involvement usually develops after the onset of other systemic manifestations within 3-6 years. In only 6% of patients, neurological involvement may be the first symptom of BD (4, 5). Common involvement patterns include focal parenchymal lesions, vascular thrombosis, arterial vasculitis, aseptic meningoencephalitis followed by intracranial aneurysm, extracranial aneurysm/dissection, optic neuropathy, and tumor-like lesions (3, 6).

Treatment for an acute attack of NBD includes steroids, whereas preventive treatment includes prednisolone, azathioprine, cyclophosphamide, chlorambucil, methotrexate, etanercept, and infliximab administration (4, 7-14). The aim of this study was to evaluate the treatment response in patients with NBD and to compare the parameters that may influence the prognosis of the disease in patients with severe to mild-moderate disability.

Methods

The files of patients admitted to our outpatient clinic for NBD between January 2007 and June 2014 were retrospectively reviewed. Approval was obtained from the research ethic committee in advance of the study. Written informed consent was obtained from all the patients who participated in this study. Before the diagnosis of NBD, we excluded other etiologies that may mimic NBD. None of the patients had any risk factors and etiological causes (large artery atherosclerosis, cardioaortic embolism, and small artery occlusions) for cerebral vascular disease. The diagnosis of BD was made according to the criteria set by the International Study Group for Behçet’s Disease (3).
<table>
<thead>
<tr>
<th>Age, year, mean±SD</th>
<th>Total NBD n=60</th>
<th>Mild-moderate NBD n=56</th>
<th>Severe NBD n=4</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>45.4±11.7 (21-70)</td>
<td>44.8±11.7 (21-70)</td>
<td>53.8±9.1 (43-65)</td>
<td>0.1</td>
<td></td>
</tr>
</tbody>
</table>

Sex, n (%)

- Female 23 (38.3) 22 (39.3) 1 (25) 0.5
- Male 37 (61.7) 34 (60.7) 3 (75)

Onset age of BD

30.3±10.1 (14-56) 30.18±10.3 (14-56) 32.52±6.55 (27-42) 0.6

Age at onset of NBD

38.37±11.2 (16-62) 37.5±10.9 (16-61) 50.25±9.1 (42-62) 0.03

NBD type

- Parenchymal, n (%) 48 (80) 44 (78.6) 4 (100) 0.3
- CVT, n (%) 6 (10) 6 (10.7) 0 (0) 0.5
- Parenchymal+CVT, n (%) 2 (3.3) 2 (3.6) 0 (0) 0.7
- Pseudo tumor cerebri, n (%) 4 (6.7) 4 (7.1) 0 (0) 0.6

BD duration (year), mean±SD (Min-Max) 15.08±8.94 (2-42) 14.6±9.1 (2-42) 21.3±3.9 (16-25) 0.09

Time to NBD (year) Mean±SD (Min-Max) 8.2±8.2 (0-32) 7.5±8.0 (0-32) 17.8±4.6 (13-23) 0.01

Parenchymal NB course, n (%)

- Relapsing form 54 (90) 52 (92.9) 2 (50) 0.4
- Progressive form 6 (10) 4 (7.1) 2 (50)

Functional system involvement

Pyramidal (+) 32 (53.3) 28 (50) 4 (100) 0.12
Brain stem (+) 17 (28.3) 15 (26.8) 2 (50) 0.3
Sensory (+) 23 (38.3) 22 (39.3) 1 (25) 0.5
Bowel and bladder functions (+) 3 (5) 3 (5.4) 0 (0) 0.8
Visual (+) 3 (5) 3 (5.4) 0 (0) 0.8
Cerebellar (+) 21 (35) 19 (33.9) 2 (50) 0.4
Mental (+) 3 (5) 3 (5.4) 0 (0) 0.8

HLA B51, n=30 3 (5) 3 (5.4)

Findings of BD, n (%)

- Oral aphthous ulcers 60 (100) 56 (100) 4 (100) 0.9
- Genital ulcer 46 (76.6) 42 (75) 4 (100) 0.6
- Uveitis 34 (56.67) 31 (55.4) 3 (75) 0.6
- Pathergy test, n=54 31 (51.67) 28 (50) 3 (75) 0.6
- Arthritis 29 (48.3) 28 (50) 1 (25) 0.6
- Skin involvement 27 (45) 26 (46.4) 1 (25) 0.6
- DVT 10 (16.6) 10 (17.9) 0 (0) 0.9
- GIS involvement 6 (10) 6 (10.7) 0 (0) 0.9
- Epididymitis 2 (3.2) 2 (3.6) 0 (0) 0.9
- Lung involvement 1 (1.6) 1 (1.8) 0 (0) 0.9
- Thrombophlebitis 1 (1.6) 1 (1.8) 0 (0) 0.9

MRI, n (%)

- Brainstem 36 (60) 27 (48.2) 4 (100) 0.11
- Thalamus 9 (15) 8 (14.3) 1 (25) 0.6
- Cerebellum 6 (10) 5 (8.9) 1 (25) 0.4
- Hemisphere 18 (30) 14 (25) 4 (100) 0.006

Treatment, n (%)

- Colchicine 46 (76.6) 42 (75) 4 (100) 0.6
- Prednisolone 12 (20) 11 (19.6) 1 (25) 0.9
- Azothioprine 34 (56.67) 31 (55.4) 3 (75) 0.6
- Diazomide 2 (3.2) 2 (3.6) 0 (0) 0.9

mRS at last examination, median (Min-Max) mean±SD 1 (0-5) 1.47±1.27 1 (0-3) 1.27±1.1 4 (4-5) 4.3±0.5 <0.001

BD: Behçet’s disease; NBD: Neuro-Behçet’s disease; SD: Standard deviation; mRS: Modified Rankin Scale; CVT: Cerebral venous thrombosis; DVT: Deep venous thrombosis; GIS: Gastrointestinal system.
For each NBD patient, information such as the age, sex, clinical findings of BD, date of diagnosis of BD and NBD, type and course of NBD, all medications, and functional neurological system involvement (assessed using the Kurtzke Functional System Scale for each system) was collected. BD duration was defined as the time from diagnosis of BD to the last examination. Period from the diagnosis of BD to the onset of the symptoms of NBD was defined as the time to NBD.

The severity of NBD was evaluated using the modified Rankin Scale (mRS) scores at the last examination. The mRS score is commonly used for measuring the degree of disability or dependence in daily activities of individuals who have suffered a stroke or have other causes of neurological disability (0: no symptoms; 1: no significant disability; 2: slight disability; 3: moderate disability; 4: moderately severe disability; 5: severe disability; 6: dead). In addition, the localization of lesions on brain magnetic resonance imaging (MRI) was also recorded.

The patients with mRS scores of 0-3 at the last examination were included in the mild-moderate disability group and those with scores of 4-6 in the severe disability group. We compared the BD duration, time to NBD, type and course of NBD, clinical findings of BD, functional neurological system involvement, localization of lesions on brain MRI, all medications, and mRS scores at the last examination in the severe and mild-moderate disability groups.

**Table 2. Epidemiological and clinical characteristics of patients with severe disability**

<table>
<thead>
<tr>
<th>Case No</th>
<th>Age (years)/sex</th>
<th>Duration of BD/time to NBD (years)/Age at onset age of NBD</th>
<th>CNS involvement</th>
<th>Disease course</th>
<th>Neurological findings</th>
<th>MRI lesions</th>
<th>Follow up mRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>55/M</td>
<td>25/23/30</td>
<td>Parenchymal</td>
<td>Relapsing type</td>
<td>Pyramidal Brainstem</td>
<td>Brainstem Cerebellum Hemisphere</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>65/M</td>
<td>23/20/42</td>
<td>Parenchymal</td>
<td>Relapsing type</td>
<td>Pyramidal Brainstem Cerebellar Visual</td>
<td>Brainstem Thalamus Hemisphere</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>52/F</td>
<td>21/13/31</td>
<td>Parenchymal</td>
<td>Progressive type</td>
<td>Pyramidal Cerebellar Sensory</td>
<td>Brainstem Hemisphere</td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td>43/M</td>
<td>16/15/27</td>
<td>Parenchymal</td>
<td>Progressive type</td>
<td>Pyramidal Visual</td>
<td>Brainstem Hemisphere</td>
<td>4</td>
</tr>
</tbody>
</table>

M: Male; F: Female; CNS: Central nervous system; BD: Behçet’s disease; NBD: Neuro-Behçet’s disease; mRS: Modified Rankin Scale

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The patients with mRS scores of 0-3 at the last examination were included in the mild-moderate disability group and those with scores of 4-6 in the severe disability group. We compared the BD duration, time to NBD, type and course of NBD, clinical findings of BD, functional neurological system involvement, localization of lesions on brain MRI, all medications, and mRS scores at the last examination in the severe and mild-moderate disability groups.

**Statistical analysis**

Qualitative variables were presented with their distribution of frequencies and are summarized as the mean and standard deviation (SD). Group rates were compared using the chi-square test and means using the Mann-Whitney U test. A p value of <0.05 was considered statistically significant. The statistical analysis was performed using the Statistical Package for Social Sciences, version 11.5 (SPSS Inc., Chicago, IL, USA).

**Results**

A total of 60 patients with BD (37 male (61.7%) and 23 female (38.3%); mean age, 45.42±11.73 (21-70) years) were diagnosed as having neurological involvement. The mean duration of BD was 15.08±8.94 (2-42) years and that of NBD was 7.05±8.94 (2-18) years. Among the patients with NBD, 48 (80%) had parenchymal involvement, 6 (10%) had cerebral venous thrombosis (CVT), 2 (3.3%) had parenchymal involvement with CVT, and 4 (6.7%) had pseudotumoral cerebral. Non-neurological involvements included oral ulcers (n=60), genital ulcer (n=46), uveitis (n=34), arthritis (n=29), skin involvement (n=27), deep venous thrombosis (DVT; n=10), gastrointestinal system (GIS) involvement (n=6), epididymitis (n=2), lung involvement (n=1), and thrombophlebitis (n=1). Fifty-four patients (90%) had a relapsing course, and 6 (10%) had a progressive course. The most common functional system involvement was pyramidal (n=32), which was determined using the Kurtzke Functional System Scale in recent neurological examinations. Sensory (n=23), cerebellar (n=21), brain stem (n=17), visual (n=3), and mental (n=3) functional system involvements were also observed (Table 1). The mean mRS score was 1.62(0-5) in males and 1.22(0-4) in females; the difference was not statistically significant (p=0.17; Table 1).

The lesions on brain MRI were located in the brainstem (n=36), thalamus (n=9), cerebellum (n=6), or hemisphere (n=18) (Table 1). All the patients were treated with prednisolone in case of an acute attack. As a prophylactic treatment, 34 patients were administered azathio-
most common neurological findings in paren- chymal NBD, which is in agreement with previ- ous studies (4, 8, 11-13, 29-31).

Akman-Demir et al. (4) reported the clinical features of 200 NBD cases. In their study, 157 patients received intravenous (IV) high-dose corticosteroids at the time of acute attacks and oral maintenance therapy thereafter. Cyclophosphamide (n=52), azathioprine(n=63), chlorambucil (n=5), and methotrexate (n=2) were administered for preventive treatment [4]. Gökçay et al. (29) identified 54 patients with NBD; they used IV methylprednisolone (1 g/day for 7 days) during the acute stage and cyclophosphamide therapy (750-1000 mg/ month) during the follow-up for patients with parenchymal involvements. Patients with vas- cular BD were treated with anticoagulants (29).

In summary, in almost all the studies published to date, parenchymal NBD has been report- ed to be treated with prednisolone during acute attacks. It has been suggested that ste- roids should be given at least 6 months after an acute attack, and appropriate preventive treatment should be started as soon as possible after the diagnosis of NBD (32). Colchium, prednisolone, azathioprine, cyclophospha- mide, chlorambucil, methotrexate, etanercept, and infliximab have been given after an acute attack to prevent recurrence (4, 9-14, 23, 27). It is known that cyclosporin is effective for the treatment of ocular BD, but it may be associ- ated with a higher risk for NBD development; therefore, cyclosporine should not be used for the treatment of NBD (33-36). Diazomid and lumboperitoneal shunts have been reported to be beneficial for reducing intracranial hyper- tension (7, 10). Warfarin and acetylsalicylic acid have been given for CVT treatment (7-10).

Akman-Demir et al. (4) reported that one-third of their patients had severe sequela due to NBD. Parenchymal involvement, elevated protein level and/or pleocytosis in CSF, brainstem involvement with other brain regions, primary or secondary progressive course, and relapse during steroid tapering were associated with a poor prognosis (4). Siva et al. (19) reported that 45.1% of patients with NBD had EDSS of ≥6 (indicating the need of a walking aid) in 10 years from the onset of BD. Cerebellar symp- toms at the onset or progressive course were associated with unfavorable outcomes, where- as a headache at the onset or diagnosis of CVT was associated with favorable outcomes (19). In contrast to these reports, in our study population, only 7% of patients had severe dis- ability. In agreement with previous treatment recommendations (32), all our patients were treated with oral or IV high-dose prednisolone in case of acute attacks. Steroid treatment was continued for at least 6 months after acute attacks immediately followed by preventive treatment; therefore, we did not observe any recurrence due to early steroid tapering. Because only a small percentage (7%) of our patients had a poor outcome, we speculated that the recommended treatment modality re- sulted in a better prognosis, unlike in previous reports that showed a worse prognosis (4,19). Peno et al. (13) suggested that delayed treat- ment and younger age could lead to an ag- gressive disease. In contrast to Peno et al. (13), we found that older age at the onset of NBD had a worse prognosis. This issue should be evaluated with further research. We also found that the time to NBD was longer in the severe disability group than in the mild-moderate dis- ability group. Probably, when NBD begins at an older age, the time to NBD becomes longer; therefore, both age at the onset of NBD and time to NBD may have the same implications.

In other words, when brain involvement is seen relatively early based on the onset of BD or when NBD begins at a younger age, the re- sponse to the suggested treatment modality may be better; therefore, the prognosis may also be better. Conversely, when NBD is seen later based on the onset of BD or when NBD begins at an older age, the response to the suggested treatment modality may not be suf- ficiently good therefore, the outcome may be worse. Brainstem involvement has been most com- monly reported in patients with parenchymal NBD, followed by hemispheric, basal ganglia, thalamus, and spinal cord involvement, which is compatible with our study (4, 8, 10, 11, 17, 18, 20, 21, 23, 25, 29, 30-32). We found that hemi- spheric lesions were predominant in patients with severe NBD compared with mild-moder- ate NBD (p=0.006). Therefore, severe disability may be associated with hemispheric lesions on brain MRI.

In conclusion, severe neurological disability may be associated with older age at the onset of NBD or longer time to NBD and hemispheric lesions on brain MRI. Our results confirme the success of previous treatment recommen- dations which stated that high-dose steroids should be immediately administered in case of an acute NBD attack, steroid treatment should be continued for at least 6 months after the attack, and other immunosuppressive agents should also be administered after the attack to prevent recurrence and progression of NBD in patients with younger age or those with a shorter time to NBD. However, in patients with an older age at the onset of NBD or in those with a longer time to NBD, this treatment mo- dality may be unsuccessful. However, our re- sults should be cautiously evaluated because our severe disability group included only four cases; to decide whether the results represent all the older onset NBD or longer time to NBD cases, further research that includes more pa- tients with severe disability is needed.

Informed Consent: Written informed consent was ob- tained from all the patients who participated in this study.

Conflict of Interest: The authors have no conflict of interest to declare.

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References