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Original Article

Clinical characteristics and prognosis of Neuro-Behçet's disease

Mine Hayriye Sorgun[1], Mustafa Aykut Kural[2], Canan Yücesan[1]

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 toother 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

ORCID IDs of the authors:
M.H.S. 0000-0003-2370-7319;
M.A.K. 0000-0003-2540-6712;
C.Y. 0000-0001-8999-5355.

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[1] Department of Neurology, Ankara University School of Medicine, İbni Sina Hospital, Ankara, Turkey
[2] Department of Clinical Neurophysiology, Aarhus University Hospital, Aarhus, Denmark

Address for Correspondence:
Mine Hayriye Sorgun, Department of Neurology, Ankara University School of Medicine, İbni Sina Hospital, Ankara, Turkey

E-mail: drmsorgun79@hotmail.com

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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 HulusiBehçet (1). Thehighest 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 manifestationswithin 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-likeNBD (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 evaluatethe 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 1. Epidemiological and clinical characteristics of patients with NBD

	Total NBD n=60	Mild-moderate NBD n=56	Severe NBD n=4	p
Age, year, mean±SD	45.42±11.73 (21-70)	44.8±11.7 (21-70)	53.8±9.1 (43-65)	0.1
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	30.33+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 apthous 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
- Pathergytest, 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: Standarddeviation;mRS: Modified Rankin Scale; CVT: Cerebral venous thrombosis; DVT: Deep venous thrombosis; GIS: Gastrointestinal system

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

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

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

For each NBD patient, information such as the age, sex, clinical findings of BD, date of diagnoses 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. ThemRS score is commonly used for measuring the degree of disability or dependence in thedaily activitiesof individuals who have suffered a strokeor 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 mRSscoresof 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 pseudotumorcerebri. 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 inthe 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 azathioprineand 12 were administered oral prednisolone (Table 1).

While 56 cases had mild-moderate disability, 4 had severe disability. The mRS score was 4 in 3patients and 5 in 1 patient with severe disability; 2 had a progressive and others had a relapsing course; 3 of 4 patients were male, and 1 was female. The mean age at the onset of NBD was 37.5±10.9 years in the mild-moderate disability group and 50.25±9.1 years in the severe disability group; the difference was statistically significant (p=0.03). The mean time to NBD was significantly longer (17.8±4.6 years) in patients with severe disability than in those with mild-moderate disability (7.5±8.0 years; p=0.01). All the patients with severe disability had parenchymal involvement, as seenon brain MRI, and pyramidal signs on examination (Table 2). Moreover, hemispheric involvement was significantly associated with severe disability (p=0.006). No differenceswere found in the age of BD onset, sex, mean duration of BD, type and course of NBD, clinical findings of BD, neurological functional system involvement, and treatment modalities between the groups (p>0.05 for each; Table 1).

Discussion

To date, 260 patients with NBD have been reported in the English literature (4, 7-13, 15-32). Males have been the dominant category in most of these studies (4, 7-9, 11,12, 15-32); however, in some series, either females have been the dominant category (13, 20,26) or there were no differences based on sex (10). In the present study, we found that males (n=37, 61.7%) were more affected than females (n=23, 38.3%), which is in agreement with all previous Turkish studies as well as most other studies. We also found that pyramidal signs were the

most common neurological findings in parenchymal NBD, which is in agreement with previous 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 vascular BD were treated with anticoagulants (29).

In summary, inalmost all the studies published to date, parenchymal NBD has been reported to be treated with prednisolone during acute attacks. It has been suggested that steroids 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, cyclophosphamide, 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 associated 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 hypertension (7, 10). Warfarin and acetylsalicylic acidhave been given for CVT treatment (7-10).

Akman-Demir et al. (4) reported that one-third of their patients had severe sequelaedue 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 symptoms at the onset or progressive course were associated with unfavorable outcomes, whereas 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 disability. 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 resulted in a better prognosis, unlike in previous reports that showed a worse prognosis (4,19). Peno et al. (13) suggested that delayed treatment and younger age could lead to an aggressive 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 disability 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 response 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 sufficiently good;therefore, the outcome may be worse.

Brainstem involvement has been most commonly 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 hemispheric lesions were predominant in patients with severe NBD compared with mild-moderate 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 confirmedthe success of previous treatment recommendationswhich 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 modality may be unsuccessful. However, our results 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 patients with severe disability is needed.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ankara University Ethical Committee (Decision Date: 15/04/2015; Decision No.: 211-7023)

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

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