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Clinical trial

Clinical features and disease course of neurological involvement in Behcet's disease: HUVAC experience

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ABSTRACT

Background/Aim: Neurological involvement (Neuro-Behcet's Disease: NBD) is a rare manifestation of Behcet's Disease (BD) and it is related with significant mortality and morbidity. We aimed to evaluate disease course and outcome of NBD patients registered in Hacettepe University Vasculitis Center (HUVAC) prospective database starting from October 2014.

Methods: Totally, 419 patients (329 of the patients had fulfilled the International Study Group (ISG) criteria and 90 patients were considered as incomplete BD) were recorded as BD to March 2018. We retrospectively reviewed the charts of 123 patients with neurological complaints/ symptoms according International Consensus Recommendations (ICR) Criteria for Neuro-Behçet's disease. In final analysis, 77 NBD patients (Definite NBD = 61, possible NBD = 16) were included. Demographics, clinical features, treatment characteristics, disability status and survival status of the patients were evaluated.

Results: Forty-seven (61%) of the patients were male. Median time to neurological involvement from first diagnosis of BD is 6 (IQR = 8.8) years in patients who had diagnosis of BD before neurological involvement. Distribution of NBD: parenchymal (pNBD), non-parenchymal (npNBD), mixed (mNBD) and peripheral nervous system (pnsNBD) were 47 (61%), 22 (28.6%), 5 (6.5%), 3 (3.9%), respectively. Eye involvement was more frequent in pNBD compared to npNBD. Brainstem (72.9%) was the most frequently affected parenchymal area and followed by cerebellum (43.8%) and diencephalon (37.5%). Twelve patients had spinal cord involvement (n = 12, 24.5%). Among the patients with pNBD and mNBD (total n = 52), 48 patients were considered as acute onset parenchymal disease and 4 patients were evaluated as chronic progressive disease. Fifty-eight percent of the patients with acute onset parenchymal disease had only one attack. Totally 14 BD patients deceased during a median 9.4 (IQR = 13) years disease duration and 9 of these patients had NBD (pNBD = 6, mNBD = 2, pnsNBD = 1). Corticosteroids (IV pulse = 75.5% and oral medium-high dose = 90%), alpha-interferon (76.9%), cyclophosphamide (57.1%), and TNF inhibitors (23.5%) were the most frequently preferred treatment options for pNBD.

Conclusions: Neurological involvement is seen about 5 years after the diagnosis of BD, and ocular involvement more commonly seen in these patients than non-NBD patients. More than half of the patients with acute onset parenchymal NBD had only one attack. No death was observed in the patients with non-parenchymal NBD. Biologic agents (Interferon-alpha and anti-TNF agents) were used in most patients.

1. Introduction

Behçet's disease (BD) is a systemic variable vessel vasculitis involving the skin, mucosa, joints, eyes, arteries, veins, nervous system and the gastrointestinal system (Hatemi et al., 2018). Neuro-Behcet's disease (NBD) is a special name given to the form of nervous system involvement of BD. NBD frequency was reported as 3–10% in large BD cohorts (Akman-Demir et al., 1999; Davatchi et al., 2010). Although

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NBD is not common in the course of BD, it is associated with significant mortality and morbidity (Kural-Seyahi et al., 2003). Neurological involvement often affects central nervous system (CNS), however peripheral nervous system (PNS) involvement is rarely seen (Saip et al., 2014). CNS involvement in NBD can be categorized into mainly two groups as parenchymal and non-parenchymal. In a systematic review, frequency of parenchymal disease and non-parenchymal disease (cerebral sinus thrombosis and pseudotumor cerebri) were 74.9% and 17.7% in 1031 NBD cases, respectively (Al-Araji and Kidd, 2009). NBD cohorts had substantial differences in terms of disease course and outcomes due to not only regional variations but also different treatment approaches and origins (e.g. hospital or community based) (Al-Araji and Kidd, 2009). In this retrospective study, we aimed to present the clinical features, treatment choices, disease course and outcomes of NBD patients registered at Hacettepe University Vasculitis Center (HUVAC).

2. Methods

2.1. Study protocol and patients

Five hundred and eighty-five adult patients were recorded as BD with "M35.2 Behçet's disease" code according to the International Classification of Diseases codes (ICD) - 10 system in HUVAC. One hundred and sixty-six patients were excluded due to lack of data and incorrect coding. Three hundred and twenty nine patients met the International Study Group (ISG) criteria. Additionally, 90 patients who did not fulfill the criteria set were considered to have incomplete BD after a review of an experienced rheumatologist (OK) (International Study Group for Behcet's Disease, 1990). The presence of both arterial and venous vascular involvement, BD-specific uveitis, neurological involvement consistent with NBD or HLA-B*51 positivity were taken into account for the diagnosis of incomplete BD. In final analysis, 419 patients were included. One hundred and twenty-three patients with neurological complaints or symptoms were evaluated according to International Consensus Recommendations (ICR) Criteria for Neuro-Behçet's disease, retrospectively (Kalra et al., 2014). Seventy-seven patients (definite NBD = 61, possible NBD = 16) were considered as NBD and these patients were classified according to ICR criteria as parenchymal (pNBD), non-parenchymal (npNBD), mixed (mNBD) and peripheral nervous system NBD (pnsNBD). flowcharts about the inclusion and classification of the patients were given in Fig. 1.

Demographics, clinical features, treatment characteristics, magnetic resonance imaging (MRI) findings and survival status of patients were assessed retrospectively. Analyzes were based on the available data.

2.2. Neurological terms

Neurological attack was defined as acute or subacute neurological findings that last longer than 24 h and have at least 2 months between two episodes (Akman-Demir et al., 1999).

Acute onset parenchymal disease was defined as acute onset meningoencephalitis that started with an acute attack and continues with remissions and relapses.

Chronic progressive parenchymal disease was defined as slow, progressive form that does not present with attacks (Akman-Demir et al., 1999; Hirohata et al., 2012).

Neurological event: neurological attack recurrence or death after first attack.

Event-free survival (EFS) time: The length of time without neurological event.

Disability status of NBD patients was evaluated with **modified Rankin Scale (mRS)** (Banks and Marotta, 2007; Uyttenboogaart et al., 2005).

0 = No symptoms at all.

1 = No significant disability: despite symptoms, able to carry out all usual duties and activities.

2 = Slight disability: unable to perform all previous activities but able to look after own affairs without assistance.

3 = Moderate disability: requiring some help but able to walk without assistance.

4 = Moderately severe disability: unable to walk without assistance and unable to attend to own bodily needs without assistance.

5 = Severe disability: bedridden, incontinent and requiring constant nursing care and attention.

6 = Death (Used commonly in clinical trials).

2.3. Statistical analysis

Statistical analysis was performed using SPSS version 23.0 (IBM, Armonk, NY, USA). Continuous data were described as median (interquartile range, IQR) and categorical variables as percentages. Chi-square test was used to compare categorical variables and Mann–Whitney U test/Student's T-test was used to compare continuous variables. Kaplan-Meier test was used for survival analysis. P-values of <0.05 were considered as significant. This study has been approved by Hacettepe University Ethics Commission (Approval number: GO 17/494-20).

3. Results

3.1. Demographic and clinical features

Forty-seven (61%) NBD patients were male. The mean ages for diagnosis of BD and NBD were 27.7 ± 9.4 and 33.5 ± 10.4 years, respectively. In 23 (29.9%) of patients, neurological problems were the presenting features of BD. Fifty-four (70.1%) patients had diagnosis of BD before neurological involvement and median time between BD and NBD was 6 (IQR = 8.8) years.

Distribution of NBD patients were as follows; 47 (61.0%) parenchymal (pNBD), 22 (28.6%) non-parenchymal (npNBD), 5 (6.5%) mixed (mNBD) and 3 (3.9%) peripheral nervous system (pnsNBD). Eye involvement was more frequently observed in patients with NBD than non-NBD (65.8% vs 47.2%, $p = 0.003$). There was no difference about other clinical features between NBD and non-NBD group. When pNBD and npNBD groups were compared, eye involvement was more frequent in pNBD group (76.6% vs 38.1%, $p = 0.002$). However, venous vascular involvement was more common in npNBD in comparison with pNBD (42.9% vs. 8.5%, $p = 0.002$). Detailed characteristics of patients were summarized in Table 1.

3.2. Clinical and imaging features of patients with NBD

Pyramidal (32/50, 64%), ataxia/extrapyramidal (29/50, 58%) and sensory findings (28/50, 56%) were the most common neurological findings in patients with parenchymal disease (pNBD and mNBD, $n = 52$). On the other hand, headache was the most frequent neurological symptom (21/21, 100%) in npNBD patients. In patients with parenchymal involvement, brainstem (72.9%) was the most affected part, followed by cerebellum and diencephalon (43.8% and 37.5%) (Table 2). Three patients (5.8%) had optic neuritis. Twelve of pNBD patients with parenchymal involvement (24.5%) had spinal cord involvement and 2 of these patients had isolated spinal cord disease. Three patients had pnsNBD that cannot be better explained with another disease.

3.3. Treatment characteristics

Corticosteroids (IV pulse: 75.5% and oral:90%), interferon alpha (79%), cyclophosphamide (57.1%) and TNFα (Tumor Necrosis Factor-α) inhibitors (23.5%) were the most preferred treatment choices for

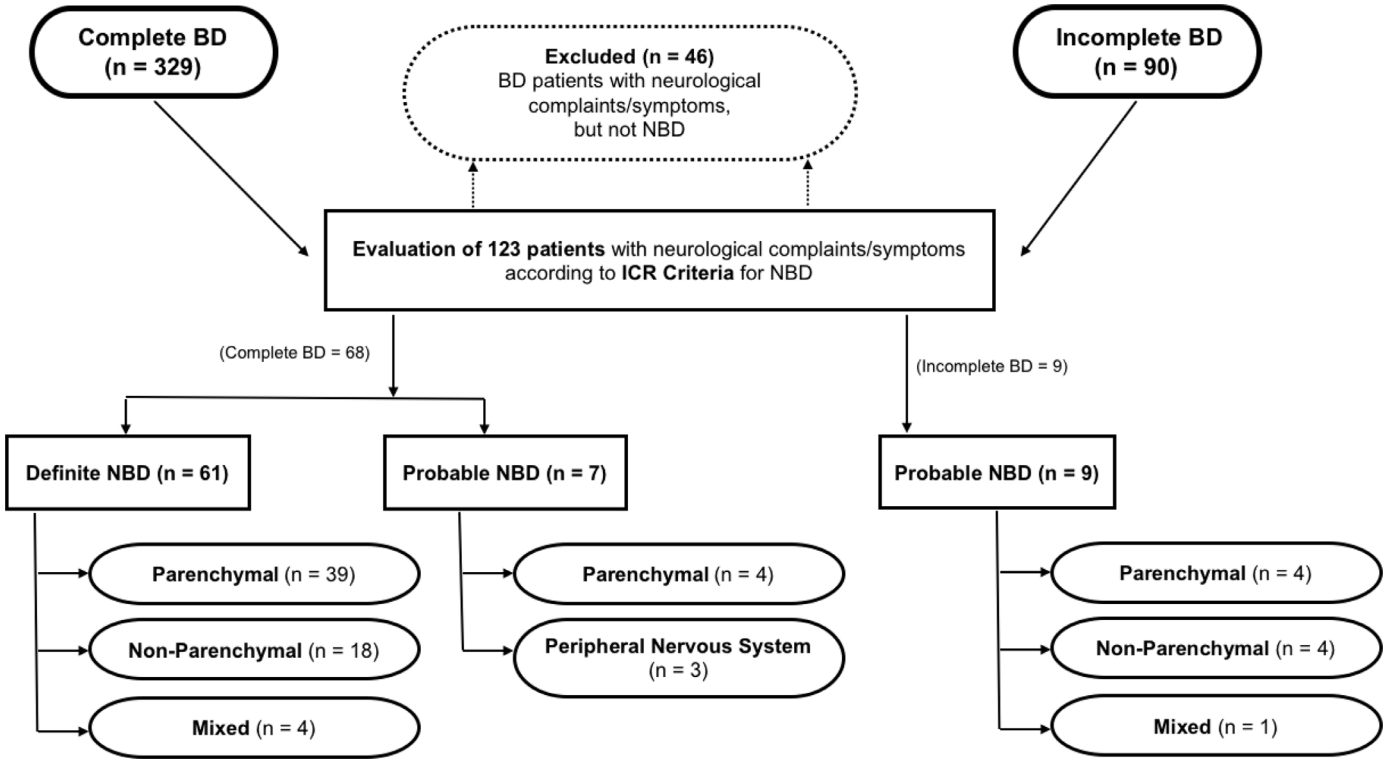

Fig. 1. Flowchart for inclusion and classification of the BD patients.

parenchymal involvement (Table 1). Anti-coagulants (warfarin or low molecular weight heparin) and anti-platelet agents (acetyl salicylic acid or clopidogrel) were used in 76.2% (16/21) and 59.1% (13/22) of patients with npNBD, respectively. In four npNBD patients, invasive procedures were performed; lumboperitoneal shunt surgery (2 patients), surgical encephalocele repair (1 patient) and surgical

Table 1
Characteristics of BD patients.

	All (n = 419)	Non-NBD (n = 342)	Parenchymal NBD (pNBD, n = 47)	Non-parenchymal NBD (npNBD, n = 22)	p*
Gender (Male), n (%)	225 (53.7)	178 (52)	29 (61.7)	45.5	0.20
Age at diagnosis of BD, mean ± SD	29.2 ± 9.0	29.5 ± 8.9	28.3 ± 8.8	25.4 ± 10.2	0.19
Median disease duration, years	9.36	8.81	12.4 (IQR = 13.4)	13.1 (IQR = 12.5)	0.73
Age at diagnosis of NBD, mean ± SD	–	–	34.5 ± 9.28	29.7 ± 11.3	0.07
Neurological involvement at BD diagnosis, n (%)	–	–	12 (25.5)	7 (31.8)	0.59
Median time to NBD after diagnosis years†	–	–	5.8 (IQR = 11)	6.3 (IQR = 5.77)	0.63
HLA B51 Positivity‡, n (%)	104/150 (69.3)	90/129 69.8	9/12 (75)	4/8 (50)	0.36
Oral aphtae, n (%)	414/416 (99.5)	338/340 (99.4)	47/47 (100)	22/22 (100)	–
Genital ulceration, n (%)	303/407 (74.4)	248/332 (74.7)	37/47 (78.7)	13/21 (61.9)	0.15
Skin pathergy test§, n (%)	72/164 (43.9)	54/131 (41.2)	10/20 (50)	6/10 (60)	0.71
Skin involvement, n (%)	306/409 (74.8)	250/334 (74.9)	33/47 (70.2)	18/21 (85.7)	0.17
Eye Involvement, n (%)	209/413 (50.6)	159/337 (47.2)	36/47 (76.6)	8/21 (38.1)	**0.002**
Arthritis, n (%)	117/408 (28.7)	98/334 (29.3)	11/47 (23.4)	5/20 (25)	1
Vascular involvement (except CNS), n (%)	110/413 (26.6)	89/338 (26.3)	7/47 (14.9)	11/21 (52.4)	**0.001**
Arterial, n (%)	43/412 (10.4)	31/337 (9.2)	5/47 (10.6)	5/21 (23.8)	0.26
Venous, n (%)	88/412 (21.4)	73/337 (21.7)	4/47 (8.5)	9/21 (42.9)	**0.002**
GIS Involvement, n (%)	22/416 (5.3)	17/340 (5)	3/47 (6.4)	2/22 (9.1)	0.65

Treatments	pNBD + mNBD (n = 52)	npNBD (n = 22)
Pulse corticosteroid, n (%)	37/49 (75.5)	10/21 (47.6)
Cyclophosphamide, n (%)	28/49 (57.1)	8/21 (38.1)
Azathioprine, n (%)	32/51 (62.7)	11/21 (52.4)
Oral corticosteroids, n (%)	45/50 (90)	15/21 (71.4)
Interferon-alpha, n (%)	40/52 (76.9)	15/21 (71.4)
TNF inhibitors, n (%)	12/51 (23.5)	5/21 (23.8)
Interferon alpha and/or TNFi, n (%)	43/52 (82.7)	15/21 (71.4)

* Parenchymal NBD versus non-parenchymal NBD.
† Among patients that have not neurological involvement at BD diagnosis.
‡ HLAB51 has been studied in 150 patients.
§ Skin Pathergy test data of 160 patients was analyzed. IQR: Interquartile range, GIS: Gastrointestinal system, N/A: not applicable (mixed parenchymal NBD and peripheral nervous system NBD weren't shown in this table).

Table 2
Involvement sites according to MRI findings of patients with parenchymal disease (pNBD + mNBD, $n = 52$) during disease course.

Localization	*n* (%)
Brain Stem	35/48 (72.9)*
Mesencephalon	23/48 (47.9)
Crus Cerebri	9/48 (18.8)
Pons	28/48 (58.3)
Medulla Oblongata	10/48 (20.8)
Diencephalon	18/48 (37.5)
Thalamus	18/48 (37.5)
Hypothalamus	2/48 (4.2)
Cerebellum	21/48 (43.8)
Cerebellar Peduncles	17/48 (35.4)
Cerebellar White Matter	4/48 (8.3)
Basal Ganglia	15/48 (31.3)
Spinal Cord	12/49 (24.5)
Cranial Nerves	2/48 (4.2)†
Meninges	1/48 (2.1)‡

* Three patients had isolated brainstem involvement.
† In one patient, there was neuritis of 3rd cranial nerve. The other patient had contrast enhancement around 5th, 7th and 8th cranial nerves.
‡ One patient had leptomeningeal involvement accompanying pons and diencephalon involvement.

supraclinoidal aneurysm clipping (1 patient). Eleven (21.2%) patients with parenchymal involvement had used cyclosporine before NBD due to ocular involvement.

3.4. Neurological outcomes and survival

Forty-three (91.5%) of pNBD and all mNBD patients had acute onset parenchymal disease. Only 4 (8.5%) patients had chronic progressive parenchymal disease. Fifty-eight percent of patients with acute onset parenchymal disease had only one attack.

For acute onset parenchymal disease, median event-free survival (EFS) time was 113 months during follow-up (min-max: 3.5 - 404 months) (Fig. 2).

Distribution of mRS scores in patients with NBD at last control visit were shown in Fig. 3. None of the patients with npNBD had mRS scores of ≥ 2. Notably, 14 numbers of pNBD patients had moderate/severe neurological sequel (mRS = 3–5). Totally 14 (3.3%) BD patients deceased during follow-up (median disease duration after BD diagnosis was 9.4 years (IQR:13.0)). Nine of these patients had NBD (pNBD = 6, mNBD = 2, pnsNBD = 1) and no death was observed in npNBD group.

4. Discussion

In this study, we aimed to assess the clinical characteristics and outcomes of neurological involvement in a Turkish BD cohort. Frequency of NBD was 18.4%. In the literature, there is substantial number of studies describing the prevalence and clinical features of NBD from different countries. Although NBD prevalence was reported between 3% and 10% in relatively large BD cohorts, there are some other studies indicating higher frequencies (Akman-Demir et al., 1999; Al-Araji and Kidd, 2009; Davatchi et al., 2010; Talarico et al., 2012). Our hospital is a tertiary-referral center for vasculitides (Karadag et al., 2017). This increased frequency for NBD may be partially explained with hospital-based nature of our population.

In a literature review, 73.7% of patients were male in pooled analysis of 1031 patients from 19 studies (Al-Araji and Kidd, 2009). Majority of our patients (61%) were male and this is in accordance with literature. It is well known that male patients tend to have early onset and severe systemic disease (Kidd, 2017). However, in our cohort, there was no statistically significant difference between BD and NBD groups regarding male predominance. Ocular involvement was more frequent in patients with NBD and this finding was also in line with the literature (Bitik et al., 2016; Ideguchi et al., 2010).

HLA-B*51 positivity was reported about 50–70% of BD patients in studies from Turkey and Eastern Asia, although it is lower in European BD patients (Giza et al., 2018; Maldini et al., 2012; Muftuoglu et al., 1981; Ryu et al., 2018; Verity et al., 1999; Yazici et al., 2007). In this regard, prevalence HLA-B*51 positivity of our patients was similar with the previous data for Turkish BD patients. The relationship between HLA-B*51 positivity and clinical characteristics vary greatly across studies. In a systematic literature review, Maldini et al. reported no relationship between HLA B*5 / HLA B*51 positivity with neurological involvement (Maldini et al., 2012). Likewise, in our study, HLA B*5 / HLA B*51 positivity was similar in non-NBD and NBD groups and also among subtypes of NBD.

NBD mainly consists of two groups: parenchymal and non-parenchymal. Parenchymal involvement is more commonly seen and its frequency is about 80% in NBD patients (Serdaroglu et al., 1989; Siva and Saip, 2009). In our cohort, pNBD was also the most common type (%61) of NBD and brainstem (72.9%) was the most frequently involved area in consistent with other studies (Akman-Demir et al., 1999; Hirohata et al., 2012; Lee et al., 2001).

In this study, twelve (24.5%) of patients with parenchymal disease (pNBD and mNBD) had spinal cord involvement. Spinal involvement frequency was higher than other cohorts from Turkey, although demographics and clinical features of patients with spinal involvement were similar (Yesilot et al., 2007). However, the incidence of spinal involvement in a study from Italy was reported as 24% which is parallel to our result (Talarico et al., 2012).

High dose corticosteroids is still the keystone of the pNBD treatment. Addition of the steroid-sparing other immunosuppressive agents was frequently recommended. Azatioprine and anti-TNF biological agents are suggested therapies in addition to corticosteroids for parenchymal neurological disease in current BD treatment recommendations (Hatemi et al., 2018). Clinicians should avoid to use cyclosporine-A that may be associated with occurrence of neurological disease (Akman-Demir et al., 2008). However, cyclophosphamide and interferon-alpha are alternative treatment choices in addition to corticosteroids for NBD therapy in clinical practice (Calguneri et al., 2003; Desbois et al., 2016; Kotter et al., 2004a, 2004b; Nichols et al., 2001; Noel et al., 2014). Due to the fact that NBD is a rare disease, there are no studies that directly compare the efficacy and side effects of these drugs with each other. Therefore, the knowledge about NBD management is based on retrospective studies that derive from the experience of the reference centers and authors. Besides, other active involvements of BD (such as uveitis or vasculitis) accompanying with NBD or patient's status (e.g. infections) are needed to be considered for choosing the treatments. Interferon-alpha differs from the other agents because of its side effect profile (e.g. more less infectious diseases) and mechanism (immunomodulatory rather than immunosuppressive) (Bolek et al., 2019.). Anti-TNF agents may be useful for salvage therapy for refractory cases or first line in severe disease due to side effects and high costs (London et al., 2019). In compliance with data from real life, in our patients, corticosteroids, cyclophosphamide, interferon-alpha and TNF inhibitors were most commonly preferred treatment options.

In acute onset parenchymal disease, multiple neurological episodes may be seen during the disease course. In this study, most of the pNBD and all mNBD patients had acute onset parenchymal disease and more than half of these patients had only one neurological attack. Event free survival (EFS) in our cohort was 113 months and comparable with an other French study which reported EFS as 120 months (Noel et al., 2014). Another study from Turkey reported a lower EFS (72 months) (Akman-Demir et al., 1999). These outcomes may differ due to natural disease course, treatment regimens and temporal dissimilarity between studies.

The heavy burden of the disease occurs in the first years of course (especially in 5 years) and cause the greatest damage in those years and

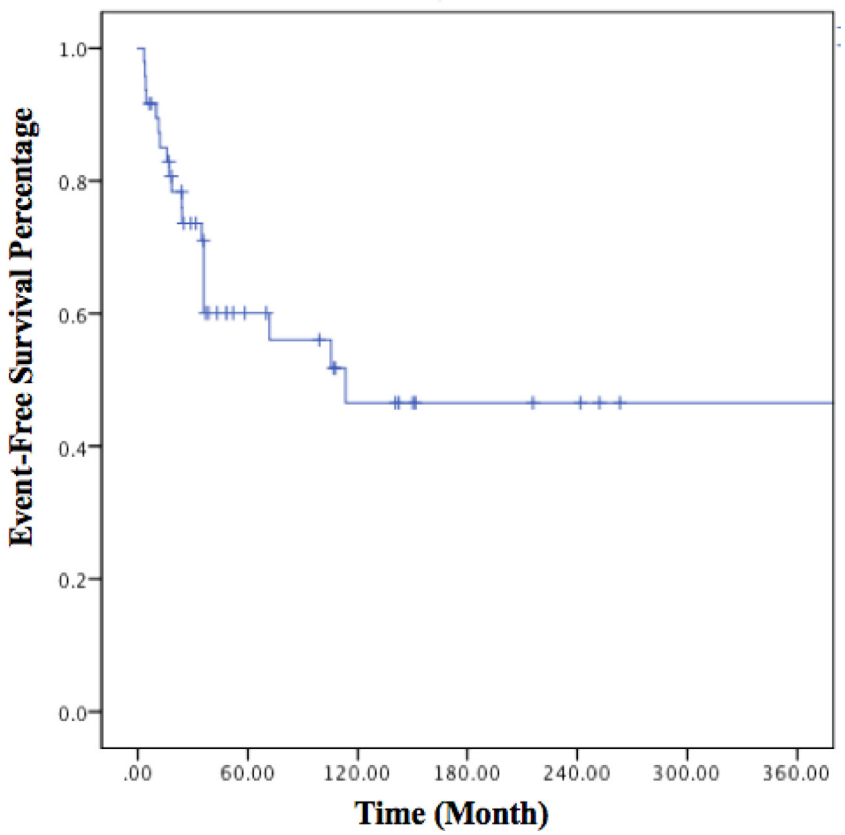

Fig. 2. Event-free survival analysis for acute parenchymal NBD patients.

then it simmers down. In the literature, it calls as "disease burns out" (Kural-Seyahi et al., 2003; Yazici, 2003). Neurological involvement usually begins more later (5 years after diagnosis) compared to other involvements such as uveitis. The disease activity of NBD also decreases over the years. So, in our study, all of the events, defined as death or neurological attack recurrence, were observed in first 10 years (Fig. 2). This pattern is not contrary to the “burn out” phenomenon which is a part of natural course of BD.

Causes of death in patients with BD were evaluated in a large study from Turkey. Totally, 387 BD patients were examined and 12% of deaths were considered to occur due to neurological involvement. According to this study, neurological involvement was the second most common cause of death after major vessel involvement (17/42, 41%) (Kural-Seyahi et al., 2003). Although definitive causes of deaths were

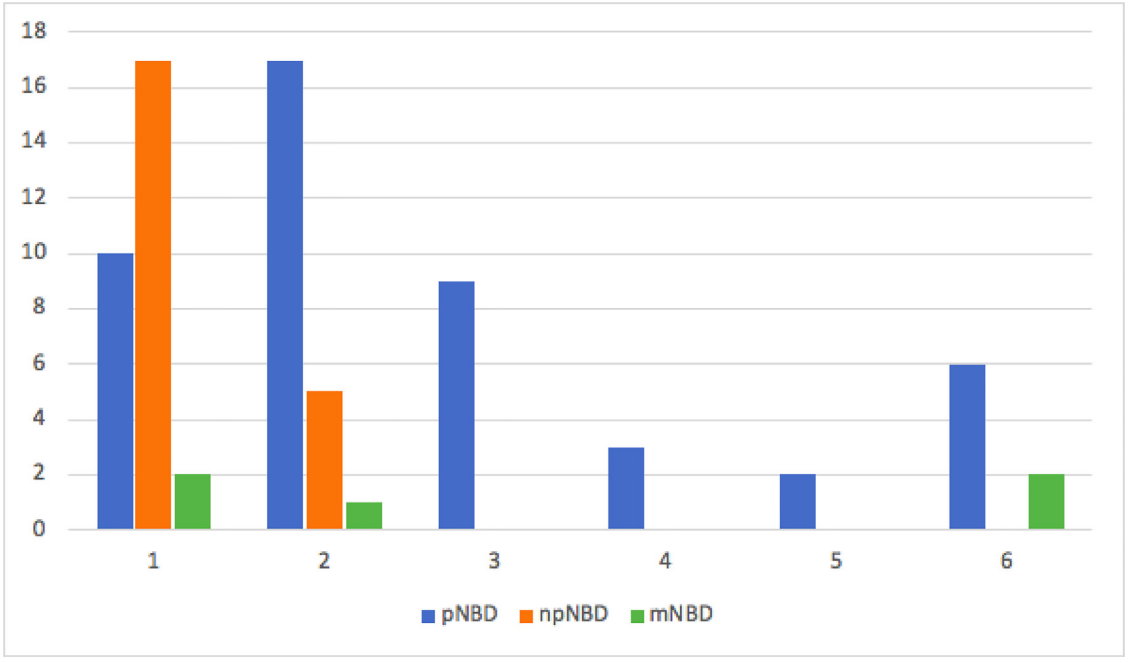

Fig. 3. Distribution of NBD patients according to modified Rankin Scale.

not known in our cohort, 14 deaths were recorded in all BD cohort and 9 of these patients had NBD.

Despite representing a large number of patients' data, retrospective design is the main limitation of the study with a possibility of data loss. In addition, some patients were not followed at our center from the beginning of the NBD diagnosis. Some patients applied at different stages and there were cases that were referred to us after the initiation of treatment. The imaging findings may not reflect the whole course of the disease chronologically due to assessment of patients in different phases of disease. Treatment choices for each patient were made individually as there is no strong evidence based data for the treatment of NBD. Moreover, other concurrent manifestations (especially vascular and eye involvement) might have effected treatment decisions.

High mortality and morbidity rates make NBD important in BD course, despite its rarity. Therefore, awareness, early recognition of the disease and effective systemic therapies may prevent/ minimize irreversible neurological and physical sequelae. However, commonly used criteria for the diagnosis of BD does not include the neurological manifestations (InternationalStudyGroupforBehcet'sDisease, 1990). In this study, there were some patients diagnosed as BD with onset of neurological involvement. In addition, 9 patients were considered to have probable NBD according to NBD ICR criteria although they did not fulfill the ISG 1990 criteria for BD. It suggests that including some manifestations (such as neurological and vascular involvement) may be considered to improve the sensitivity of diagnostic criteria for BD for evaluating some cases (International Team for the Revision of the International Criteria for Behcet's disease, 2014).

5. Conclusions

Neurological involvement (Neuro-Behcet's Disease: NBD) is a rare complication of Behcet's Disease (BD) but it is related with significant mortality and morbidity. Parenchymal neurological involvement is mainly seen within five years after the diagnosis of BD. More than half of the patients with acute onset parenchymal disease does not have recurrence during disease course. Cyclophosphamide, interferon-alpha and anti-TNF agents are the most preferred treatment options in addition to corticosteroids.

Declaration of Competing Interest

The authors have received no financial support or other benefits from commercial sources for the work reported here, and the authors have no other financial interests that could create a potential conflict of interest or the appearance of a conflict of interest regarding the present study.

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