Prognosis of Neuro-Behçet's Syndrome

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Behçet's Syndrome

Behçet's syndrome (BS) is a multisystemic and inflammatory vasculitis. The major features include skin lesions, recurrent painful oral aphthous ulcers, genital ulcerations, and either anterior or posterior uveitis. Furthermore, patients may also experience venous and arterial thrombosis, aneurysms, arthralgia, intestinal lesions, or epididymitis [38]. The frequency of these symptoms mainly depends on the ethnicity and gender of the patients [39].

Behçet's Syndrome Prognosis

Yazici and Kural-Seyahi et al. found that younger age at onset has less favorable outcome. In their 20-year outcome study with 387 patients, they observed that the major cause of mortality in Behçet's syndrome is major vessel involvement. They reported 50% of the patients with pulmonary artery aneurysm (n=24) deceased within one year [9]. While after a 10-year follow-up, 5-year survival was reported to be 62%. They stated that earlier onset of treatment can lead to better outcome [21, 37]. In their series, central nervous system involvement and heart diseases were the second leading causes of mortality. Renal involvement and neoplasms were detected to be other causes [21, 37]. Studies of the Pediatric Behçet Disease Study Group and the Italian investigators stated that the ocular and neurological involvements are the major reasons of mortality and morbidity [7, 19].

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Neuro-Behçet's Syndrome

Central nervous system (CNS) disease occurs in 5–25% of the patients with Behçet's syndrome. Kural-Seyahi et al. [21] reported the frequency of the neurologic disease as 11%. In another series, 5.3% of the 323 patients had neurological symptoms in 1-year period [29]. The prevalence of the neurological manifestations is 24.2% in the Japanese nationwide registration data of the 6627 Behçet patients [14]. In the Iraqi prospective study, the prevalence of neuro-Behçet's syndrome (NBS) is 14% [4]. A retrospective French series reported the NBS frequency as 14% [25].

Behçet's syndrome can affect both central and peripheral nervous systems. Central nervous system lesions can be parenchymal or nonparenchymal. Parenchymal syndrome can present as brain stem symptoms, cranial neuropathy, cerebellar or pyramidal dysfunction, spinal cord involvement, myelopathy, optic neuropathy, and cerebral symptoms such as encephalopathy, hemiparesis, hemisensory loss, seizures, dysphasia, and mental changes including cognitive and mood disturbances. Nonparenchymal syndrome involves vascular manifestations, especially cerebral venous thrombosis, intracranial hypertension syndrome, and acute meningeal syndrome [16].

Parenchymal disease could be either acute (acute meningoencephalitis) or progressive according to its treatment response. Acute NBS is usually self-limiting and responds well to corticosteroid therapy [30].

Headache is the most common neurological symptom among Behçet patients (up to 88.9%) [3]. Nearly 5% of the patients with headache is associated with neurological involvement [27]. Approximately half of the patients are referred to neurology clinic with motor symptoms [31]. Cerebellar or brain stem findings are not as common as pyramidal findings on the onset of NBS. Cognitive impairment is relatively rare but is a debilitating condition. Psychiatric symptoms are diverse. Common psychiatric symptoms are euphoria, loss of insight, disinhibition, indifference to their disease, psychomotor agitation or retardation, psychosis, and obsessive behaviors [3, 5, 30].

Adult neurological symptoms usually start after 3–5 years following the systemic onset [2, 3, 18, 31, 33]. Talarico et al. [32] showed in their 117-patient retrospective analysis that the onset of CNS involvement was in the first 10 years, with a higher incidence rate in the first 5 years.

Disability Scales for Neuro-Behçet's Syndrome

Several disability scales are used to define the prognosis of NBS. In their report, published in 1999, Akman-Demir et al. stated a disability status. They summarized being self-sufficient as "1," being physically dependent as "2," being mentally dependent as "3," being both mentally and physically dependent as "4," and death as "5" [2].

Expanded Disability Status Scale (EDSS) is another disability scale from 0 to 10. EDSS 6 represents the moderate disability in which a patient requires assistance in walking and daily life activities [23]. EDSS is generally used for multiple sclerosis disability evaluation. EDSS covers most of the functional systems in NBS apart from the visual disability. Hence, several authors chose EDSS for the prognostic evaluation [13, 31]. In NBS, uveitis caused most of the visual symptoms; therefore, Siva et al. eliminated visual problems from the original EDS scale [31].

Hirohata et al. evaluated the disability with the Steinbrocker functional classification, which is a scale for rheumatoid arthritis. Class 3 defines the patients who need assistance for their daily activities; class 4 defines the bedridden state. This scale does not include the neuropsychiatric and cognitive symptoms, which cause critical dependency [11]. Noel et al. [25], evaluated the disability with Rankin scale which defines stroke severity. It is a 0 to 6 scale, where 0 refers to normal examination, 6 refers to death, 4 represents the need for assistance at some level, and 5 is for bedridden patients. In another study, prognosis of neurological status was defined by bedridden state, dependency, or death [28].

In some of the studies, authors used specific scoring systems to evaluate Behçet's syndrome prognosis. Clinical severity score (CSS) is one of these scoring systems. This system assesses each symptom: 1 point for each mild symptom (oral aphthous lesions, genital ulcerations, skin lesions, headaches, etc.), 2 points for each moderate symptom (arthritis, deep vein thrombosis, anterior uveitis, gastrointestinal bleeding, etc.), and 3 points for each severe disease manifestation (NBS, posterior or panuveitis, major vein thrombosis, arterial involvement, bowel perforation) [20]. International consensus recommendations for NBS highlight the use of Neuro-Behçet's disability score (NBDS) [16]. This scoring system is proposed by Kürtüncü et al., and it evaluates motor and cognitive functions ranging from 0 to 8 [22].

Prognosis of Different Subgroups

Prognosis of Parenchymal Neuro-Behçet's Syndrome

Akman-Demir et al. retrospectively evaluated 200 patients with neurological involvement. They classified the disease into subgroups as primary progressive, secondary progressive, and as silent neurological involvement. One hundred sixty-two patients had parenchymal CNS involvement, whereas the rest of the patients had vascular involvement. Sixty-seven percent of patients had a course with a relapse. The rest of them had slowly progressive form. The median number of the attacks was 1.5 in 6 years. One-third of the patients had severe sequela. During the relapses, 19% were dependent on another person either physically or mentally. The median time for dependency or death is 115.7 months. The univariate analysis showed that brain stem involvement, having two or more attacks, dependency at admittance, relapse during corticosteroid tapering, progressive course, and abnormal CSF

findings like elevated protein levels and pleocytosis were related with poor prognosis [2]. In another study, this group also reported a 7-year prognosis of 42 patients. They stated that 67% of 27 patients initially presenting with headache and normal neurological examination had still normal neurological examination. In the follow-up, 26% of these patients had no attacks but either minor neurological findings or abnormal neuropsychological or electrophysiological test results. The lumbar punctures were performed in the first attack. The CSF findings of all ($n = 5$) progressive NBS patients (33% of all NBS patients) revealed high protein levels and pleocytosis. This could be related with poor prognosis. Uveitis was significantly higher in the NBS group than the headache-only group [1] (Table 1).

Siva et al. reported the characteristics of 107 neuroimaging studies of 164 patients and 72.1% had parenchymal involvement. After a 10-year follow-up, the survival rate was 95.7 ± 2.1%; 45.1% of all NBS patients had an EDSS score of 6 or more at the end of the follow-up period. They summarized that the duration of the neurological disease, progressive disease course, dysarthria, cerebellar symptoms other than dysarthria, and motor symptoms at onset were poor prognostic factors. Factors with favorable outcome were disease course limited to a single episode and headache at onset. Headache at onset was negatively correlated with progressive disease. Similar with the data of Akman- Demir, they found headache to be positively correlated with the course limited to a single episode [31].

In their retrospective analysis of 275 NBS patients, Noel et al. included 115 patients with only parenchymal involvement. They classified the group as acute ($n = 78$) and progressive ($n = 37$) NBS. For acute patients, they formed two subgroups as "single episode" and "relapsing-remitting form." For the progressive NBS group, they made a classification as "primary progressive form" and "progressive form with further relapses." They evaluated the disability with Rankin score. In acute NBS patients, 47% had only one episode, and 21% had further relapsing NBS. In progressive form, 20% had a primary progressive course, and 12% had further attacks [25]. In their series, patients presenting with a progressive neurologic course were found to be older at the time of diagnosis for both BS and NBS. Between acute and progressive onset, no difference was found either for mucosal or systemic symptoms and for geographic origin. Confusion occurred more frequently at the onset of progressive course, whereas the frequency of meningitis was similar for both groups [25]. In a follow-up of nearly 6 years of these 115 patients, 33% experienced at least one neurologic relapse. They state that the presence of HLA-B51 antigen and coma as a presenting symptom can be associated with risk of NBD relapse. However, in multivariant analysis, only HLA-B51 antigen was found to be related with NBD relapse. Noel et al. defined poor outcome as inability to perform activities of daily living and/or death. In univariate analysis, longer time to NBD diagnosis, the presence of hemiparesis or paraparesis, sensory symptoms, sphincter dysfunction, and poor baseline disability were related with poor outcome. In multivariate analysis, the presence of baseline hemiparesis or paraparesis and brain stem lesions were independently associated with poor outcome [25].

Hirohata et al. evaluated 37 chronic progressive NBS (CPNBS) cases with their clinical data, magnetic resonance imaging, and cerebrospinal fluid findings and with

Table 1 Review of the literature of neuro-behçet's syndrome prognosis

Author	Year	Number of NBS patients	Follow-up years (median)	Better prognosis	Poor prognosis
Akman-Demir et al.	1999	200	6		Abnormal CSF findings like elevated protein levels and pleocytosis, brain stem involvement, having 2 or more attacks, dependency at admittance, relapse during corticosteroid tapering, and progressive course
Akman-Demir et al.	1996	42	7	Initially presenting with headache and normal neurological examination	High protein levels and pleocytosis
Siva et al.	2001	164	10	Disease course limited to a single episode and headache at onset	Duration of neurological disease, progressive disease course, dysarthria, cerebellar symptoms other than dysarthria, and motor symptoms at onset
Noel et al.	2014	275	6		Longer time to NBD diagnosis, the presence of hemiparesis or paraparesis, sensory symptoms, sphincter dysfunction, and poor baseline disability In multivariate analysis: the presence of baseline hemiparesis or paraparesis Brain stem lesions HLA- B51 positivity related with relapse rate
Hirohata et al.	2015	37	16	Methotrexate use	Brain stem atrophy, higher CSF IL-6 levels
Sbai et al.	2003	109	8	Continuous treatment	Brain stem and internal capsule lesions and rhombencephalitis
Joseph et al.	2007	22	10		Repeated attacks, incomplete recovery, progressive disease course, extensive or spinal involvement, early neurological involvement, and CSF pleocytosis
Farahangiz et al.	2012	58	3.6		Initial brain stem atrophy
Houman et al.	2013	121	3		Male gender CNS parenchymal lesions
Gerber et al.	1996	12	3.5		New small lesions Increase in the atrophy

(continued)

Table 1 (continued)

Author	Year	Number of NBS patients	Follow-up years (median)	Better prognosis	Poor prognosis
Kalra et al.	2014	Diagnosis and management of neuro-Behçet's disease: International consensus recommendations			Brain stem and spinal cord presentation, frequent relapses, early disease progression, high CSF pleocytosis, disability and dependent status at initial presentation, a primary or secondary progressive course, relapse during steroid dose tapering, fever, meningeal signs, and bladder involvement

interleukin-6 levels. The patients were under corticosteroid and/or methotrexate treatment. After 100 and 200 months of the therapy initiation, the overall survival rate was 87.6% and 54.8%, respectively. They analyzed the cumulative ratios of either bedridden state or death. After 100 months of treatment, the ratio was 23.9% and increased to 65.4% after 200 months. The univariate and multivariate analyses revealed that only methotrexate use was associated with better prognosis. The CSF IL-6 levels were higher in nine Steinbrocker class 3–4 patients, whereas among the 19 Steinbrocker class 1 and 2 patients, IL-6 levels were lower. The authors emphasized the need for further prospective studies to clarify the relationship of the IL-6 with the NBS prognosis; 89.2% of the patients had brain stem atrophy in their magnetic resonance imaging (MRI) scans, which could be an indicator for the poor prognosis of the CPNBS patients [11]. In their retrospective series of 144 patients (acute NBS–CPNBS and non-NBS patients), they also highlighted that smoking was significantly higher among CPNBS group (91%) [10].

Sbai et al. included 109 parenchymal NBS cases in their retrospective study. They excluded the dural sinus thrombosis cases. Their parameters were relapses, attacks of other systems, CSF, imaging findings, and therapeutic choices. After the first neurological attack, the median follow-up period was 97 months; 45.8% of patients recovered well after their first attack, whereas 11% remained stable and 5.5% had a progressive course. Dependency ratio was 52% at the beginning of the study; after the follow-up period, 19% of the patients were physically and/or mentally dependent. Neurological disability was related to brain stem and internal capsule lesions and rhombencephalitis. Continuous treatment was associated with better outcomes compared with interrupted treatment. Continuous corticosteroid use was associated with less disability [28].

Joseph et al. from a district hospital in Bristol reviewed 22 Caucasian English of Welsh NBD patients. The mean follow-up period was 10 years (0.25–29.8 years). They regarded repeated attacks, incomplete recovery, progressive disease course, extensive or spinal involvement, and early neurological involvement as poor prognostic factors. CSF pleocytosis was also related either with a more severe disease or an attack [15].

Farahangiz et al. [6] from Iran reviewed the MRI characteristics of 49 NBS patients. They divided the patients as monophasic (31%), polyphasic (27%), and progressive (20%) patients and headache attributed to BS patients (22%). The mean follow-up time was 3.6 (0.8–6.9) years. Forty percent of the patients with progressive course had brain stem atrophy on their first MRI evaluation. Thus, they related the initial brain stem atrophy with the progressive course.

A Tunisian center evaluated the data of 121 NBS patients among 430 patients with BS. Seventy-four patients had parenchymal NBS [12]. They associated male gender and CNS parenchymal lesions with a poorer prognosis.

International consensus recommendations in 2014 state brain stem and spinal cord presentation, frequent relapses, early disease progression, high CSF pleocytosis, disability and dependent status at initial presentation, a primary or secondary progressive course, relapse during steroid dose tapering, fever, meningeal signs, and bladder involvement are associated with poor prognosis [16]. Gender, presence of other systemic manifestations of BS, and age at onset do not have any influence over prognosis [16, 31].

Magnetic resonance imaging follow-up of 12 patients for 1.5–6 years (mean, 3.5 years) showed that half of the patients had new lesions and nine patients had cerebral atrophy [8]. They concluded that new small lesions and the increase in the atrophy could be prognostic signs for bad outcome.

Non-parenchymal Neuro-Behçet's Syndrome Prognosis

Prognosis of Cerebral Venous Thrombosis in Neuro-Behçet's Syndrome

Among all cerebral venous thrombosis cases (n = 182), Wasay et al. defined the poor prognostic factors as coma at presentation, being older than 60 years, intracerebral hemorrhage, and hypotension on admission and thrombosis of three major sinuses. They defined the good prognostic factors as age less than 45 years, thrombolytic treatment, and isolated transverse sinus thrombosis. Multivariate analysis narrowed the predictors. Poor prognostic factors are coma at presentation and intracerebral hemorrhage [34].

Yesilot et al. compared cerebral venous thrombosis cases under Behçet's syndrome with other etiologies. BS patients were mostly male, and the median age was younger. The onset of BS CVT group happened to be subacute or chronic, and they had better prognosis [40]. BS CVT group had fewer cortical infarcts, and this could be associated with the better prognosis of the BS CVT group. Wechsler et al.'s study investigated the MRI lesions among Behçet patients with neurological involvement [35] (n = 31, CVT patients: n = 10), and the same group also studied the long-term follow-up of 25 CVT patients [36]. Most of the cases had chronic onset. The initial symptom was intracranial hypertension. Neurological symptoms improved in

4 weeks. Uluduz et al. reviewed the pediatric CVT cases; 88.5% of their patients had cerebral venous sinus thrombosis (CVST). None of their CVST cases had cortical infarcts and had generally good outcome [33].

Prognosis of Pediatric Neuro-Behçet's Syndrome

Child-onset neuro-Behçet's syndrome is rarer than adult-onset NBS. According to Uluduz et al., 4% of the total NBS cases are child onset [33]. The onset of the first neurological symptom is approximately 2 years after the other systemic symptoms in the Pediatric Behçet Disease study group cohort [19], and it is 1.25 years in the Turkish series of Uluduz et al. [33]. Uluduz et al. evaluated the prognosis according to the initial response to treatment, and they stated the residual neurological deficit as bad outcome [33]. Their mean follow-up period was 6 ± 5 years. Two of 26 patients had residual neurologic symptoms after treatment, and one of them was independent. They explain this better prognosis with CVST being common in child-onset NBS [33].

Mora et al. reviewed 130 cases with neuro-ophthalmological features between the years 1971 and 2011 [24]. Eighty percent of the patients recovered after treatment. Seventeen percent of the patients had visual or neurological sequelae, and one patient died after the rupture of a cerebral aneurysm [17, 24].

Gender Effect on Prognosis

Male predominance is a known fact in Behçet's syndrome. Most of the NBS series also emphasized the male dominance. Several studies evaluated the prognostic effect of gender. Studies stated male gender does not affect prognosis [11, 25, 31]. Akman-Demir et al.'s 7-year follow-up series showed that male-female ratio in the headache group was 0.87, whereas it increased to 2.85 in the group with neurologic involvement [1].

Epidemiologic Effect on Prognosis

Epidemiologic data about Behçet's syndrome reveals that gastrointestinal symptoms are more common in the Far East (Japan) and skin findings like pathergy positivity are more common in Turkey and Mediterranean countries [41]. There is no isolated epidemiologic data about the severity of NBS syndrome in the literature.

In an Israeli study ($n = 100$; 66 Jews, 34 Arabs), no difference was found between the two groups with respect to the rate of major oral ulcers, genital ulcers, ocular disease, skin lesions, positive pathergy reaction, or vascular or neurological involvement.

Genetic Effects on Prognosis

Genetic susceptibility to BS has been a study topic for many years. As HLA-B51 positivity is more common among patients with BS (approximately 60%), some authors proposed the disease as an MHC-I-opathy [38].

Hirohota et al. [11] stated that positivity of HLA-B51 was 86% in chronic progressive NBS. Noel et al. [25] showed HLA-B51 positivity increased the odds of relapse by 3.6-fold. Relapse rate was 50% among HLA-B51-positive patients, whereas it was 21% among HLA-B51-negative patients [25].

Mortality–Morbidity in Neuro-Behçet's Syndrome

Mortality rate of patients with Behçet's syndrome is higher among younger men (14–24 years of age and 25–34 years of age), whereas older men (35–50 years of age) and women had a normal life span [26, 38]. Mortality is also increased in earlier phases of the disease (the first 7 years), especially among the ones with major organ involvement. Major causes of mortality were large vessel disease and parenchymal central nervous system (CNS) disease [38].

A Turkish group collected 20-year follow-up data of 387 patients. The mortality rate was 9.8%. Five male patients died due to severe neurological involvement with recurrent attacks. At the end of 20 years, 25.8% ($n = 57$) of male patients and 8.2% ($n = 10$) of female patients (overall 17.3% of patients) were dependent. Visual loss (76.1%) and CNS disease (7.5%) caused the dependency in most of the patients [21]. In a cohort of 817 patients of a French group, mortality rate was 5% ($n = 41$). Median follow-up period was 8 years; 26.9% of those patients had CNS disease. Among the 41 patients, five died (12.2% of the patients who died) because of NBS, and the cause of death of one patient was cerebral aneurysm. In their series, multivariate analysis found male sex, arterial involvement, genital ulceration, and high frequency of BS flares were significantly and independently associated with mortality [26].

There are a few studies addressing the mortality rates of NBS. In Akman-Demir's 15-patient series, the mortality rate was 20% in 7 years [1]. Another study of the same group reviewed 200 patients (155 male; 45 female). Akman-Demir et al. reviewed 200 patients, and 110 had a follow-up period of 3 and more years [2]. Among those 110 patients, 28 patients became either physically or mentally dependent, and 22 were deceased (mortality rate was 20%).

In Siva et al.'s 15 years of retrospective evaluation, mortality ratio was 5.5%. They performed the survival analysis from the onset of BS. Ten and 15-year survivals were 95.7 ± 2.1% and 88.5 ± 4.5%, respectively. All of the three patients who died because of neurological problems had cerebellopyramidal syndrome; 45.1% of the patients had moderate to severe disability 10 years after the disease onset. But the authors stated that due to the short follow-up period, standard error is high [31].

Mortality ratio of a French group was 10.4% among 115 NBS patients. Five of those patients died due to central nervous system-related causes [25].

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