Neurological Mysteries of Behcet's Disease Through Rheumatologist's Eyes

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ABSTRACT

The aim of this study was to describe the frequency, locations, and neurological symptoms in Behcet's patients to contribute to the understanding of the complexity of Neuro-Behcet's disease (NBD). A total of 187 patients diagnosed with Behcet's disease (BD) over five years were retrospectively examined. The gender of those with neurological involvement, areas of involvement seen on imaging, neurological symptoms, demographics, and treatments used were documented. Among the patients, 163 had no neurological involvement, and 24 were diagnosed with NBD. The frequency of neurological involvement was 12.8%. Among the neurological symptoms, headache was the most common (41%). No statistically significant relationship was found between neurological involvement and age, the year of BD diagnosis, gender, or *HLA-B51* positivity. A statistically significant relationship was observed between vascular and neurological involvement ($p < 0.05$). In areas where BD is common, young male patients presenting with headache and accompanying neurological symptoms should also be evaluated for NBD.

Key Words: *Behcet's disease, Neuro-Behcet's disease, Neurological involvement.*

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Behcet's disease (BD), also known as Behcet's syndrome, causes multisystemic lesions and can present with a wide variety of disease manifestations. It is defined as a chronic vasculitis that can involve skin, joints, gastrointestinal system, eyes, and nervous system. The country where BD is most common in the world is Turkiye, where it is estimated that 420 out of every 100,000 people are diagnosed with BD.[1]

Neuro-Behcet's disease (NBD) is a rare clinical manifestation seen in the course of BD, with a frequency defined as 5-50%. It is included in the clinical criteria for BD diagnosis and is characterised by the combination of neurological signs and symptoms associated with BD. However, diagnosing NBD is very difficult, and all other mimicking diseases that may lead to neurological involvement must be excluded.[2]

To enhance the understanding of the manifestations of NBD, this study aimed to evaluate the frequency of NBD in patients and identify the locations and symptoms of NBD involvement within the patient population. The records of 187 patients diagnosed with BD according to the International Study Group (ISG) criteria,[3] seen in the Rheumatology clinic of the Department of Rheumatology, Tekirdag Namik Kemal University, Tekirdag, Turkiye, in the last five years (between 2019 and 2024), were retrospectively examined.

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A power analysis was conducted to determine the sample size, utilising the G*Power software, which aimed to detect statistically significant neurological involvement with 80% power and a 5% significance level. Selection criteria included patients with a confirmed diagnosis of BD based on ISG criteria, who had complete data available in records. Exclusion criteria were patients with incomplete records, those with a diagnosis of other autoimmune diseases, and those who were lost to follow-up. The gender of those with neurological involvement, areas of involvement seen on MRI, neurological symptoms, and demographics were documented. The frequency of arthritis, mucocutaneous symptoms, uveitis, vascular involvement, pathergy, and *HLA-B51* positivity were also recorded. Approval was obtained from the local ethics committee.

Continuous data were presented as mean ± standard deviation, while categorical data were expressed as frequencies and percentages. The Shapiro-Wilk's test was utilised to assess the normality of the data distribution. Statistical analyses were conducted using SPSS Statistics version 27.0. The Chi-square test was employed to evaluate the associations between categorical variables, such as gender, *HLA-B51* status, vascular involvement, and neurological involvement. Neurological involvement and other normally distributed continuous demographic and clinical characteristics were compared using an independent samples t-test. The p-values, accompanied by 95% confidence intervals (CI), were provided.

Among the total 187 patients, 101 (54%) were females and 86 (46%) were males. The average age of the patients was 43.18 ± 12.49 years (range 18-80). Among the patients diagnosed with BD, 163 had no neurological involvement, and 24 were diagnosed with NBD. The frequency of neurological involvement

was 12.8%. On average, neurological involvement appeared approximately 15.1 years after the initial diagnosis. In the NBD population, neurological findings were the presenting symptom of BD in two of the patients. The most common areas of neurological involvement were parenchymal brainstem involvement (41%-mesencephalon; n = 7, pons n = 3) and periventricular lesions (n = 6, 25%). Sinus vein thrombosis (16%) was present in all non-parenchymal involvements. Coexistence of both parenchymal and non-parenchymal involvement was not detected. Among the neurological symptoms, headache was the most common (n = 10, 41%), followed by dizziness (n = 6, 25%).

The main clinical features observed in the course of BD were also identified. Pathergy tests were performed on 100 of the patients, and 33 of them were positive. *HLA-B51* was tested in 82 of the total patients, and 23 of them were *HLA-B51* positive (28%). Clinical features and NBD presentations observed in the course of BD are summarised in Table I.

Table I: Clinical manifestations, areas of neurological involvement, and frequencies of neurological symptoms in Behcet's patients.

Clinical manifestations (n = 187)	**Behcet's disease n (%)**
Oral aphthous ulcer	187 (100)
Genital ulcer	129 (68)
Uveitis	86 (45.9)
Erythema nodosum	63 (33.6)
Arthritis	40 (21.3)
Vascular involvement	34 (18)
Neurological involvement	24 (12.8)
Neurological symptoms (n = 24)	**n (%)**
Headache	10 (41)
Dizziness	6 (25)
Limitation of eye movement	4 (16)
Limb weakness	3 (12)
Double vision	2 (8)
Speech impairment	2 (8)
Forgetfulness	2 (8)
Increased deep tendon reflexes	2 (8)
Nystagmus	1 (4)
Neurological Involvement (n = 24)	**n (%)**
Brainstem	11 (45)
Periventricular white matter	6 (25)
Sinus vein thrombosis	4 (16)
Transverse myelitis	1 (4)
Cavernous sinus thrombosis	1 (4)
Cerebellum	1 (4)
Caudate nucleus head, lentiform nucleus, internal capsule	1 (4)
Cingulate gyrus	1 (4)

Table II: Relationship between neurological involvement and gender, age, genetics, and vascular involvement.

Variables	**Neurological involvement**	**p-value**
Age (years)	48 ± 9.18	0.054
Duration of disease	15.09 ± 7.10	0.319
Gender	**n (%)**	0.289
Female	9 (38)	
Male	15 (62)	
Genetic	**n (%)**	>0.99
HLA-B51	5 (20)	
Vascular involvement	**n (%)**	0.006
	12 (50)	

**p-values were determined by Chi-square test and independent sample t-test.*

The average age of those with neurological involvement was 48 ± 9.18 years, and the average age at BD diagnosis was 15.09 ± 7.10 years. Among those without neurological involvement, the average age was 42.6 ± 13.6 years and the average age at BD diagnosis was 13.05 ± 9.2 years. No statistically significant relationship was found between neurological involvement and age or the year of BD diagnosis. Among those with neurological involvement, 15 (62%) were men and 9 (38%) were women, while among those without neurological involvement, 92 (56%) were women and 71 (44%) were men. No significant relationship was found between gender and neurological involvement. While 18 Behcet patients without neurological involvement (11%) tested positive for *HLA-B51*, a higher proportion of those with neurological involvement, 5 out of 24 (20%), were also *HLA-B51* positive. No statistically significant relationship was found between *HLA-B51* positivity and neurological involvement ($p > 0.05$).

While 12 (50%) out of 24 Behcet's patients with neurological involvement had vascular involvement, 22 (13%) patients without neurological involvement exhibited vascular involvement. A statistically significant relationship was observed between vascular involvement and neurological involvement ($p < 0.05$, with 95% CI). These findings are summarised in Table II.

It was observed that there was no statistically significant relationship between oral aphthous ulcers, genital aphthosis, pathergy positivity, uveitis, erythema nodosum, and arthritis and neurological involvement ($p > 0.99$, 0.9, 0.98, 0.24, 0.68, and 0.55, respectively).

The neurological involvement of BD was first described in Berlin in 1941. It has been a subject of emphasis since that year, with numerous case reports and NBD series available in the literature. In this study, patients with NBD constituted 12.8% of the population, which is within the wide range reported in the literature. In studies in the literature, the frequency of NBD is reported to range from as low as 1.3% to as high as 59%.[4] This broad range suggests a lack of consensus in the field and raises questions about the accuracy of the reported frequencies. Male gender has been associated with severe BD and early symptom onset. Although no statistically significant relationship was found between neurological involvement and gender in this study, a male predominance was observed in the course of NBD, similar to the general results in the literature.

In BD, the neurological findings typically appear three to six years after the onset of systemic symptoms, according to the literature.[5] In this population, neurological involvement appeared, on average, approximately fifteen years after the initial diagnosis. This situation highlights that NBD can develop over a wide range of years following the onset of Behcet's disease, emphasising the importance for clinicians to remain vigilant in recognising symptoms.

In the current study, the most common symptom in the course of NBD was headache, consistent with the literature. For this

reason, it is suggested that, especially in geographical regions where BD is common, young male patients presenting with headache and accompanying neurological symptoms should also be evaluated for BD.[6] A significant relationship was found between vascular involvement and neurological involvement. Therefore, it is recommended that clinicians suspect that extracranial thrombosis may occur in patients diagnosed with BD who have cranial sinus thrombosis and resort to imaging methods if necessary.

This study has several limitations. First and foremost, it was a retrospective and epidemiological study. Secondly, the relatively small sample size poses another significant limitation. Larger, prospective studies are needed to validate current findings and provide more robust evidence. After the frequency and morbidity associated with NBD are more clearly defined, it will be crucial for rheumatologists and neurologists to collaborate closely.

The study presents some novel findings that address a gap in the literature regarding the relationship between NBD, vascular involvement, gender, duration of disease, and *HLA-B51*. By investigating these complex interactions, this research may provide valuable insights into how *HLA-B51* and vascular complications impact NBD.

PATIENTS' CONSENT:
Informed consent was obtained from all patients to publish the data concerning this article.

COMPETING INTEREST:
The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
DBG: Data collection, idea, writing, and statistical analysis
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