

# Invisible neuropsychiatric burden in Behçet's disease without central nervous system involvement: a phenotype-based comparison

C. Tansu Yavuz<sup>1</sup>, R. Deniz<sup>1</sup>, S. Karabulut Gök<sup>1</sup>, B. Yavuz<sup>2</sup>, C. Bes<sup>1</sup>

<sup>1</sup>Department of Rheumatology, University of Health Sciences Başakşehir Çam and Sakura City Hospital, Istanbul; <sup>2</sup>Department of Family Medicine, Istanbul University-Cerrahpaşa, Cerrahpaşa Medical Faculty, Istanbul, Turkey.

## Abstract

### Objective

Neuro-Behçet's disease (NBD) is a serious complication of Behçet's disease (BD); however, data focusing on neuropsychiatric symptoms in patients without overt neurological involvement remain limited. The burden of neuropsychiatric symptoms in non-neuro-Behçet's disease (non-NBD) across different BD phenotypes were evaluated.

### Methods

In this cross-sectional, single-centre study, 152 patients with BD were classified as mucocutaneous (mBD, n=69), ocular (oBD, n=26), vascular (vBD, n=40), or NBD (n=17); and familial mediterranean fever (FMF) patients (n=37) for autoinflammatory burden and colchicine exposure and healthy controls (HC, n=29) were included. Neuropsychiatric assessment included headache characteristics, Beck Anxiety Inventory (BAI), Beck Depression Inventory (BDI) and Mini-Mental State Examination (MMSE).

### Results

Any headache was reported in 72.5% of mBD, 69.2% of oBD, and 67.5% of vBD patients, compared with 52.9% in NBD, 64.9% in FMF, and 41.4% in HC ( $p=0.012$ ). Migraine-type headache was the most frequent subtype across groups. BAI scores did not differ significantly but tended to be higher in mBD. In contrast, depressive symptoms differed significantly ( $p=0.005$ ), with higher BDI scores in mBD (14) and vBD (13.5) compared with NBD (11), FMF (9) and HC (7). Cognitive impairment (MMSE  $\leq 23$ ) was more frequent in mBD (41.2%) and NBD (41.2%) than in vBD (15.0%), FMF (10.8%) and HC (24.1%) ( $p=0.001$ ).

### Conclusion

Neuropsychiatric manifestations represent a substantial burden in BD even in the absence of overt neurological involvement, particularly in mBD with less control of inflammation and regular follow-up. These findings support the need for routine neuropsychiatric evaluation across all BD phenotypes, extending beyond the traditional NBD framework.

### Key words

neuro-Behçet's disease, neuropsychiatric symptoms, headache, Beck Anxiety Inventory, Beck Depression Inventory, Mini-Mental State Examination

Ceren Tansu Yavuz, MD  
 Rabia Deniz, MD, PhD  
 Sezgi Karabulut Gök, MD  
 Burak Yavuz, MD  
 Cemal Bes, MD

Please address correspondence to:  
 Rabia Deniz

Department of Rheumatology,  
 Başakşehir Çam and Sakura City Hospital,  
 Başakşehir Olimpiyat Bulvarı Yolu,  
 34480 Istanbul, Turkey.  
 E-mail: dr.rabiadeniz@gmail.com

Received on April 16, 2026; accepted in  
 revised form on October 8, 2026.

© Copyright CLINICAL AND  
 EXPERIMENTAL RHEUMATOLOGY 2026.

## Introduction

Behçet's disease (BD) is a chronic, multisystem inflammatory disorder characterised by a wide spectrum of clinical manifestations, ranging from mucocutaneous lesions to severe ocular, vascular, gastrointestinal and neurological involvement (1). Among these, neurological involvement termed neuro-Behçet's disease (NBD) is traditionally regarded as the principal cause of neuropsychiatric manifestations, including cognitive impairment, mood disorders, and focal neurological deficits (2). NBD is relatively uncommon but represents one of the most severe disease manifestations due to its association with increased morbidity and long-term disability (3).

Neurological involvement is broadly classified into parenchymal and non-parenchymal forms and is collectively referred to as NBD (4). Clinical manifestations vary according to the affected central nervous system regions. Brainstem involvement may lead to pyramidal signs and cranial nerve deficits, while cerebellar lesions typically present with ataxia and impaired coordination (5). Involvement of the cerebral hemispheres may result in altered consciousness, focal neurological deficits, seizures, language disturbances, cognitive impairment, and psychiatric symptoms (6). Non-parenchymal involvement most commonly presents with intracranial hypertension, frequently associated with dural venous sinus thrombosis, leading to chronic or acute headache, papilledema, abducens nerve palsy, seizures and visual disturbances (7, 8).

While neuropsychiatric manifestations in BD are traditionally attributed to overt neurological involvement, increasing clinical evidence suggests that symptoms such as headache, mood disturbances, cognitive complaints, and reduced quality of life may also be prevalent in BD patients who do not fulfill diagnostic criteria for NBD and lack radiological evidence of central nervous system pathology (9). These symptoms are often overlooked in routine practice or attributed to nonspecific factors such as chronic inflammation, psychosocial stress, or comorbid con-

ditions, resulting in under-recognition and undertreatment.

Whether this neuropsychiatric burden reflects a disease-specific central nervous system vulnerability in BD or merely represents a nonspecific consequence of chronic systemic inflammation remains unclear. In this context, familial Mediterranean fever (FMF), a prototypical autoinflammatory disease characterised by recurrent inflammation and routine colchicine exposure, provides a valuable comparator to distinguish Behçet-specific neuropsychiatric involvement from inflammation-related effects alone.

In this context, we aimed to comprehensively evaluate neuropsychiatric manifestations in patients with BD without overt neurological involvement and compare these findings across different clinical phenotypes, patients with familial Mediterranean fever, and healthy controls. We further sought to determine whether these manifestations are more likely to reflect disease-specific features of BD rather than nonspecific consequences of chronic inflammatory disease.

## Materials and methods

### Study design and setting

This study was designed as a cross-sectional, observational investigation conducted at the Rheumatology Department of a tertiary referral centre between March 2024 and March 2025. The study protocol was approved by the local Institutional Research Ethics Committee (approval date: 13.12.2023; approval no.: 635), and all participants provided written informed consent prior to enrollment. The study was conducted in accordance with the Declaration of Helsinki.

### Participants and study groups

Consecutive adult patients ( $\geq 18$  years) fulfilling the International Study Group (ISG) criteria for BD (10) were recruited during routine outpatient visits. Patients were stratified into clinical phenotypes based on their predominant organ involvement as mucocutaneous, ocular, or vascular BD. Patients with established NBD served as a primary disease comparator group against BD-without-

## ORCID iD

C. Tansu Yavuz: 0009-0005-6641-5481  
 R. Deniz: 0000-0003-4537-894X  
 S. Karabulut Gök: 0009-0001-1113-9759  
 B. Yavuz: 0009-0002-7928-2647  
 C. Bes: 0000-0002-1730-2991

Competing interests: none declared.

**Table I.** Sociodemographic characteristics and lifestyle factors of patients with Behçet's disease phenotypes, familial Mediterranean fever, and healthy controls.

| Variable                   | Mucocutaneous BD (n=69) | Ocular BD (n=26) | Vascular BD (n=40) | Neuro-BD (n=17)  | FMF (n=37)       | Healthy controls (n=29) | p-value          |
|----------------------------|-------------------------|------------------|--------------------|------------------|------------------|-------------------------|------------------|
| Female sex, n (%)          | 38 (55.1)               | 13 (50.0)        | 4 (10.0)           | 5 (29.4)         | 21 (56.8)        | 14 (48.3)               | <b>&lt;0.001</b> |
| Age, years, median (range) | 33 (18–63)              | 38.5 (19–61)     | 40 (25–60)         | 41 (22–52)       | 33 (19–60)       | 45 (18–61)              | <b>0.048</b>     |
| Education level, n (%)     |                         |                  |                    |                  |                  |                         |                  |
| Illiterate                 | 3 (5.5)                 | 0                | 0                  | 0                | 0                | 0                       |                  |
| Primary                    | 28 (50.9)               | 12 (57.1)        | 9 (32.1)           | 7 (53.8)         | 14 (37.8)        | 12 (41.4)               | 0.162            |
| Secondary                  | 16 (29.1)               | 5 (23.8)         | 12 (42.9)          | 3 (23.1)         | 14 (37.8)        | 5 (17.2)                |                  |
| Higher                     | 8 (14.5)                | 4 (19.0)         | 7 (25.0)           | 3 (23.1)         | 9 (24.3)         | 12 (41.4)               |                  |
| Current smoking, n (%)     | 21 (30.4)               | 14 (53.8)        | 18 (45.0)          | 10 (58.9)        | 13 (35.1)        | 13 (44.8)               | <b>0.008</b>     |
| Current alcohol use, n (%) | 5 (7.2)                 | 8 (30.8)         | 7 (17.5)           | 1 (5.9)          | 3 (8.1)          | 3 (10.3)                | <b>0.048</b>     |
| Height, cm median (range)  | 165 (151–200)           | 168 (153–190)    | 175 (155–190)      | 171 (150–190)    | 167 (150–188)    | 164 (150–182)           | <b>0.011</b>     |
| Weight, kg median (range)  | 73 (46–140)             | 70.5 (53–113)    | 80 (50–165)        | 74 (44–105)      | 70 (52–120)      | 75 (52–110)             | 0.345            |
| BMI median (range)         | 25.8 (17.4–43.2)        | 24.1 (19.7–40.6) | 26.2 (18.7–47.7)   | 25.2 (18.2–33.1) | 24.6 (19.1–38.1) | 26.7 (21.1–38.6)        | 0.476            |

BD: Behçet's disease; FMF: familial Mediterranean fever; BMI: body mass index.

neurological-involvement groups. Patients reporting headache in the absence of objective neurological findings and compatible neuroimaging were not classified as neuro-Behçet's disease solely on the basis of headache. To strengthen internal validity and control for potential confounders related to chronic inflammation and colchicine exposure, two additional control groups were included as FMF patients followed in the same clinic, selected due to shared features such as autoinflammatory pathophysiology, early disease onset, and frequent long-term colchicine use, but without known central nervous system involvement and Healthy controls (HC) without a history of rheumatic, neurological, or psychiatric disorders.

#### *Clinical and demographic data collection*

Demographic variables, disease-related characteristics, and treatment history were recorded using structured face-to-face interviews and standardised data collection forms. Laboratory and radiological data were retrieved retrospectively from medical records when available. Disease activity was assessed based on clinical evaluation at the most recent visit and categorised as active disease or remission according to routine clinical judgment. Active BD was defined as the presence of at least one active clinical manifestation at the last study.

#### *Neuropsychiatric assessment*

All participants underwent standardised psychometric evaluation using

validated instruments administered in person under uniform conditions. Depressive symptoms were assessed using the Beck Depression Inventory (BDI), a 21-item self-report scale widely used in clinical and research settings. BDI scores were categorised as follows: 0–9 minimal or no depression, 10–18 mild depression, 19–29 moderate depression, and >30 severe depression (11). Anxiety severity was evaluated using the Beck Anxiety Inventory (BAI), a 21-item self-report instrument designed to assess somatic and cognitive symptoms of anxiety. BAI scores were interpreted as 0–21 mild anxiety, 22–35 moderate anxiety, and >36 severe anxiety (12). Global cognitive function was assessed using the Mini-Mental State Examination (MMSE). In accordance with established conventions, MMSE scores  $\leq 23$  were considered indicative of cognitive impairment (13). In addition, participants were systematically questioned regarding neuropsychiatric symptoms, including mood changes, cognitive complaints, and sleep disturbances.

#### *Headache evaluation and neurological examination*

Headache characteristics were assessed in detail, including presence, duration, frequency, localisation, temporal pattern, and headache type, based on patient self-report. A focused neurological examination was performed in all participants, including assessment of cranial nerves, motor and sensory function, reflexes, coordination, and gait.

Tandem gait and subtle cerebellar signs were specifically evaluated.

#### *Neuroimaging review*

Previously obtained cranial imaging studies (magnetic resonance imaging (MRI) or computed tomography (CT)), performed as part of routine clinical care, were reviewed when available. Imaging findings were categorised as normal or pathological. Imaging was primarily used to exclude overt neurological involvement in BD patients classified as non-NBD.

#### *Control of colchicine exposure*

Given the potential neuropsychiatric and anti-inflammatory effects of colchicine, its use was carefully documented across BD and FMF groups, including current use and duration of exposure. The inclusion of FMF patients receiving long-term colchicine allowed for partial control of medication-related effects on neuropsychiatric outcomes.

#### *Statistical analysis*

Statistical analyses were performed using IBM SPSS Statistics version 31.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as median (minimum–maximum) for non-normally distributed data. Categorical variables were presented as number (percentage). Group comparisons were conducted using the chi-square test for categorical variables. For continuous variables, the independent samples of multiple groups Kruskal Wallis test were applied as appropriate. A two-sid-

**Table II.** Disease-related characteristics according to Behçet's disease phenotypes.

| Variable                                    | Mucocutaneous BD<br>(n=69) | Ocular BD<br>(n=26) | Vascular BD<br>(n=40) | Neuro-BD<br>(n=17) | p-value          |
|---------------------------------------------|----------------------------|---------------------|-----------------------|--------------------|------------------|
| Age at diagnosis, years, median (range)     | 30 (13–62)                 | 27 (18–45)          | 31 (15–51)            | 29 (17–46)         | <b>&lt;0.001</b> |
| Disease duration, years, median (range)     | 2 (0–30)                   | 4 (0–36)            | 5.5 (0–28)            | 6 (0–32)           | <b>0.002</b>     |
| Age at symptom onset, years, median (range) | 22 (9–58)                  | 22 (10–42)          | 25 (10–48)            | 24 (12–39)         | <b>&lt;0.001</b> |
| Active disease, n (%)                       | 10 (14.5)                  | 2 (7.7)             | 8 (20.0)              | 1 (5.9)            | 0.356            |
| HLA-B51 n (%)                               |                            |                     |                       |                    |                  |
| Negative                                    | 4 (5.8)                    | 3 (11.5)            | 10 (25.0)             | 0                  |                  |
| Positive                                    | 17 (24.6)                  | 3 (11.5)            | 9 (22.5)              | 5 (29.4)           | <b>&lt;0.001</b> |
| Unknown                                     | 48 (69.6)                  | 20 (76.9)           | 21 (52.5)             | 12 (70.6)          |                  |

BD: Behçet's disease.

**Table III.** Frequency of clinical manifestations across study groups.

| Manifestation n (%)         | Mucocutaneous BD<br>(n=69) | Ocular BD<br>(n=26) | Vascular BD<br>(n=40) | Neuro-BD<br>(n=17) | FMF<br>(n=37) | Healthy controls<br>(n=29) | p-value          |
|-----------------------------|----------------------------|---------------------|-----------------------|--------------------|---------------|----------------------------|------------------|
| Oral aphthae                | 68 (98.1)                  | 24 (92.3)           | 37 (92.5)             | 14 (82.4)          | 13 (35.1)     | 5 (17.2)                   | <b>&lt;0.001</b> |
| Genital ulcers              | 54 (78.3)                  | 18 (69.2)           | 26 (65.0)             | 11 (64.7)          | 1 (2.7)       | 0                          | <b>&lt;0.001</b> |
| Arthralgia                  | 60 (87.0)                  | 23 (88.5)           | 31 (77.5)             | 11 (64.7)          | 30 (81.1)     | 15 (51.7)                  | <b>0.004</b>     |
| Folliculitis                | 48 (42.9)                  | 12 (46.2)           | 27 (67.5)             | 11 (64.7)          | 11 (29.7)     | 3 (10.3)                   | <b>&lt;0.001</b> |
| Anterior uveitis            | 0                          | 20 (76.9)           | 3 (7.5)               | 3 (17.6)           | 0             | 0                          | <b>&lt;0.001</b> |
| Posterior/pan uveitis       | 0                          | 21 (80.8)           | 7 (17.5)              | 6 (35.3)           | 0             | 0                          | <b>&lt;0.001</b> |
| Deep vein thrombosis        | 0                          | 1 (3.8)             | 29 (78.4)             | 7 (41.2)           | 0             | 0                          | <b>&lt;0.001</b> |
| Thrombophlebitis            | 1 (1.4)                    | 1 (3.8)             | 8 (20.0)              | 2 (11.8)           | 0             | 0                          | <b>&lt;0.001</b> |
| Pulmonary artery thrombosis | 0                          | 0                   | 31 (77.5)             | 1 (5.9)            | 1 (2.7)       | 0                          | <b>&lt;0.001</b> |
| Arthritis                   | 26 (37.7)                  | 9 (34.6)            | 15 (37.5)             | 7 (41.2)           | 18 (48.6)     | 0                          | <b>0.006</b>     |
| Erythema nodosum            | 36 (52.2)                  | 15 (57.7)           | 21 (52.5)             | 9 (52.9)           | 1 (2.7)       | 0                          | <b>&lt;0.001</b> |
| Paranchymal neuro-Behçet    | 0                          | 0                   | 0                     | 8 (7.1)            | 0             | 0                          | <b>&lt;0.001</b> |
| Papilledema                 | 1 (1.4)                    | 0                   | 1 (2.5)               | 3 (17.6)           | 0             | 0                          | <b>&lt;0.001</b> |
| Dural sinus thrombosis      | 0                          | 0                   | 0                     | 9 (52.9)           | 0             | 0                          | <b>&lt;0.001</b> |
| Visceral thrombosis         | 0                          | 0                   | 4 (10.0)              | 1 (5.9)            | 0             | 0                          | <b>0.009</b>     |
| Pulmonary artery aneurysm   | 0                          | 0                   | 6 (15.0)              | 1 (5.9)            | 0             | 0                          | <b>&lt;0.001</b> |

BD: Behçet's disease; FMF: familial Mediterranean fever.

ed  $p$ -value  $<0.05$  was considered statistically significant.

## Results

### Study population and socio-demographic characteristics

A total of 218 participants were included in the study, comprising 135 patients with BD without neurological involvement, 17 patients with NBD, 37 patients with FMF, and 29 healthy controls. Among BD patients without neurological involvement, clinical phenotypes were classified as mucocutaneous ( $n=69$ ), ocular ( $n=26$ ), and vascular ( $n=40$ ).

Sociodemographic characteristics differed significantly across study groups (Table I). Female sex predominated in mucocutaneous BD (55.1%), ocular BD (50.0%), FMF (56.8%) and healthy controls (48.3%), whereas vascular BD showed a marked male predominance (10.0% female;  $p<0.001$ ). Median age was lowest in mucocutaneous BD and

FMF (33 years each) and highest in healthy controls (45 years), with a statistically significant difference across groups ( $p=0.048$ ).

Educational attainment did not differ significantly between groups ( $p=0.162$ ); however, lower education levels were more frequently observed among BD phenotypes compared with healthy controls. Current smoking was most prevalent in NBD (58.9%), ocular BD (53.8%), and vascular BD (45.0%), with significant intergroup variation ( $p=0.008$ ). Current alcohol use was more common in ocular BD (30.8%) than in other groups ( $p=0.048$ ). Height differed significantly across groups correlated with male dominance ( $p=0.011$ ), whereas body weight and body mass index were comparable (Table I).

### Disease-related characteristics of Behçet's disease phenotypes

Disease-related characteristics according to BD phenotypes are summarised

in Table II. Age at diagnosis and age at symptom onset differed significantly across phenotypes, with earlier onset observed in mucocutaneous and ocular BD and later onset in vascular BD and NBD ( $p<0.001$  for both). Median disease duration increased progressively from mucocutaneous BD (2 years) to NBD (6 years) ( $p=0.002$ ).

The proportion of patients with clinically active disease at the time of assessment was low across all phenotypes and did not differ significantly ( $p=0.356$ ). HLA-B51 status varied significantly between phenotypes ( $p<0.001$ ), with the highest positivity rate observed in NBD (29.4%) and vascular BD (22.5%), while a substantial proportion of patients had unknown HLA-B51 status.

### Clinical manifestations and organ involvement

The frequency of clinical manifestations across study groups is shown in Table III. Oral aphthae and genital ul-

**Table IV.** Headache prevalence and neurological findings across study groups.

| Variable n (%)                    | Mucocutaneous BD (n=69) | Ocular BD (n=26) | Vascular BD (n=40) | Neuro-BD (n=17) | FMF (n=37) | Healthy controls (n=29) | p-value      |
|-----------------------------------|-------------------------|------------------|--------------------|-----------------|------------|-------------------------|--------------|
| Any headache                      | 50 (72.5)               | 18 (69.2)        | 27 (67.5)          | 9 (52.9)        | 24 (64.9)  | 12 (41.4)               | <b>0.012</b> |
| <b>Type of headache</b>           |                         |                  |                    |                 |            |                         |              |
| Migraine-type headache            | 20 (40.0)               | 5 (27.8)         | 13 (48.1)          | 4 (40.0)        | 12 (63.2)  | 7 (70.0)                | 0.162        |
| Cluster-type headache             | 2 (4.0)                 | 0                | 1 (3.7)            | 1 (10.0)        | 1 (5.3)    | 1 (10.0)                | 0.797        |
| Tension-type headache             | 7 (14.0)                | 2 (11.1)         | 3 (11.1)           | 1 (10.0)        | 2 (10.5)   | 1 (10.0)                | 0.997        |
| Non-specific headache             | 21 (42.0)               | 11 (61.1)        | 10 (37.0)          | 4 (40.0)        | 4 (21.0)   | 1 (10.0)                | 0.073        |
| <b>Localisation of headache</b>   |                         |                  |                    |                 |            |                         |              |
| Right hemicranial                 | 2 (4.0)                 | 2 (11.1)         | 3 (11.1)           | 2 (20.0)        | 0          | 2 (20.0)                | 0.224        |
| Left hemicranial                  | 4 (8.0)                 | 1 (5.6)          | 0                  | 0               | 0          | 1 (10.0)                | 0.427        |
| Bilateral                         | 44 (88.0)               | 15 (83.3)        | 24 (89.9)          | 8 (80.0)        | 19 (100)   | 7 (70.0)                | 0.642        |
| Frontal                           | 30 (60.0)               | 8 (44.4)         | 17 (63.0)          | 6 (60.0)        | 13 (68.4)  | 3 (30.0)                | 0.314        |
| Temporal                          | 5 (10.0)                | 6 (33.3)         | 4 (14.8)           | 1 (10.0)        | 3 (15.8)   | 4 (40.0)                | 0.106        |
| Occipital                         | 14 (28.0)               | 4 (22.2)         | 6 (22.2)           | 5 (50.0)        | 5 (26.3)   | 5 (50.0)                | 0.378        |
| <b>Rhythm of headache</b>         |                         |                  |                    |                 |            |                         |              |
| Daytime                           | 20 (40.0)               | 6 (33.3)         | 11 (40.7)          | 3 (30.0)        | 5 (26.3)   | 2 (20.0)                | 0.748        |
| Night-time                        | 14 (28.0)               | 5 (27.8)         | 6 (22.2)           | 2 (20.0)        | 3 (15.8)   | 2 (20.0)                | 0.912        |
| Both                              | 16 (32.0)               | 7 (38.9)         | 10 (37.0)          | 5 (50.0)        | 11 (57.9)  | 6 (60.0)                | 0.311        |
| <b>Onset of headache</b>          |                         |                  |                    |                 |            |                         |              |
| Before diagnosis of BD            | 35 (70.0)               | 14 (77.8)        | 18 (66.7)          | 6 (60.0)        | N/A        | N/A                     |              |
| After diagnosis of BD             | 15 (30.0)               | 4 (22.2)         | 9 (33.3)           | 4 (40.0)        | N/A        | N/A                     | 0.765        |
| Pattern of headache onset         |                         |                  |                    |                 |            |                         |              |
| Abrupt onset                      | 15 (30.0)               | 4 (22.2)         | 10 (37.0)          | 5 (55.6)        | 9 (52.9)   | 4 (40.0)                |              |
| Gradual                           | 35 (70.0)               | 14 (77.8)        | 17 (63.0)          | 4 (44.4)        | 8 (47.1)   | 6 (60.0)                | 0.290        |
| <b>Change in headache pattern</b> |                         |                  |                    |                 |            |                         |              |
| Yes                               | 29 (58.0)               | 10 (55.6)        | 14 (51.9)          | 7 (70.0)        | 4 (21.1)   | 2 (20.0)                | <b>0.023</b> |

Percentages for headache characteristics (type, localisation, rhythm, onset and pattern) were calculated among participants reporting headache.

BD: Behçet's disease; FMF: familial Mediterranean fever.

cers were highly prevalent in all BD phenotypes but were uncommon in FMF and healthy controls ( $p<0.001$  for both). Arthralgia was frequent across inflammatory disease groups, affecting 64.7–88.5% of BD phenotypes and 81.1% of FMF patients, compared with 51.7% of healthy controls ( $p=0.004$ ). Ocular involvement was restricted to ocular BD and NBD, while vascular manifestations such as deep vein thrombosis, pulmonary artery thrombosis, and pulmonary artery aneurysm were predominantly observed in vascular BD and, to a lesser extent, NBD (all  $p<0.001$ ). Parenchymal NBD, dural sinus thrombosis, and papilledema were confined almost exclusively to the NBD group (Table III).

#### Headache characteristics and neuropathic findings

Headache was common across all inflammatory disease groups (Table IV). The prevalence of any headache ranged from 52.9% in NBD to 72.5% in mucocutaneous BD and was significantly higher in BD phenotypes and FMF compared with healthy controls (41.4%,  $p=0.012$ ).

Migraine-type headache was the most frequently reported subtype; however, its distribution did not differ significantly across groups ( $p=0.162$ ) and highest prevalence were noted in FMF (63.2%) and healthy controls (70.0%). Cluster-type and tension-type headaches were infrequent and similarly distributed among groups ( $p=0.797$  and  $p=0.997$ , respectively).

Headache localisation, including laterality and regional distribution (frontal, temporal, occipital), as well as headache rhythm (day-time, night-time, or both), did not differ significantly between groups (all  $p>0.05$ ). The timing of headache onset in relation to BD diagnosis was comparable across BD phenotypes ( $p=0.765$ ), and the pattern of onset showed no significant group differences ( $p=0.290$ ). In contrast, a change in headache pattern over time was reported more frequently in BD phenotypes and NBD than in FMF and healthy controls ( $p=0.023$ ).

Neuropathic symptoms were frequently reported across inflammatory disease groups but did not differ significantly (Supplementary Table S1) ( $p=0.177$ ). The majority of neuropathic symptoms

were symmetrically distributed across all groups ( $p=0.525$ ). Distal involvement of the lower extremities was the most common localisation pattern, with no significant intergroup differences. Electromyography (EMG) findings, performed in selected patients, demonstrated heterogeneous patterns including mononeuritis multiplex, sensorineural injury and polyradiculopathy; however, EMG results did not differ significantly across groups ( $p=0.553$ ).

#### Treatment exposure and ancillary investigations

Treatment exposure during overall follow-up and at the study visit is detailed in Supplementary Tables S2 and S3. Colchicine use was highly prevalent among BD and FMF patients, particularly in FMF (97.3% during follow-up). Immunosuppressive and biologic agents were more frequently used in ocular BD, vascular BD, and NBD. Neuroimaging utilisation and findings are summarised in Supplementary Table S4. Pathological cranial MRI and MR venography findings were observed almost exclusively in NBD patients. Detailed neurological examination

**Table V.** Psychometric assessment outcomes across Behçet's disease phenotypes and control groups.

| Measure                       | Mucocutaneous<br>BD (n=69) | Ocular BD<br>(n=26) | Vascular BD<br>(n=40) | Neuro-BD<br>(n=17) | FMF<br>(n=37) | Healthy controls<br>(n=29) | p-value      |
|-------------------------------|----------------------------|---------------------|-----------------------|--------------------|---------------|----------------------------|--------------|
| Beck Anxiety Score            |                            |                     |                       |                    |               |                            |              |
| Mild                          | 47 (70.1)                  | 21 (80.8)           | 28 (75.7)             | 15 (88.2)          | 30 (81.1)     | 22 (78.6)                  | 0.369        |
| Moderate                      | 16 (23.2)                  | 2 (7.7)             | 7 (18.9)              | 1 (5.9)            | 5 (13.5)      | 6 (21.4)                   |              |
| Severe                        | 4 (6.0)                    | 3 (11.5)            | 2 (5.4)               | 1 (5.9)            | 2 (5.4)       | 0                          |              |
| BAI score, median (range)     | 14 (0-49)                  | 12 (1-48)           | 13 (0-39)             | 12 (2-50)          | 11 (0-43)     | 6.5 (0-29)                 | <b>0.093</b> |
| Beck Depression Score         |                            |                     |                       |                    |               |                            |              |
| None-minimal                  | 20 (29.9)                  | 11 (42.3)           | 14 (36.8)             | 6 (35.3)           | 20 (54.1)     | 20 (54.1)                  | <b>0.041</b> |
| Mild-moderate                 | 23 (34.3)                  | 6 (23.1)            | 12 (31.6)             | 7 (41.2)           | 13 (35.1)     | 13 (35.1)                  |              |
| Moderate                      | 17 (25.4)                  | 6 (23.1)            | 11 (28.9)             | 4 (23.5)           | 3 (8.1)       | 3 (8.1)                    |              |
| Severe                        | 7 (10.4)                   | 3 (11.5)            | 1 (2.6)               | 0                  | 1 (2.7)       | 1 (2.7)                    | <b>0.005</b> |
| BDI score, median (range)     | 14 (0-46)                  | 11 (0-45)           | 13.5 (0-39)           | 11 (2-28)          | 9 (1-54)      | 7 (0-27)                   |              |
| Mini Mental State Examination |                            |                     |                       |                    |               |                            |              |
| Components, median (range)    |                            |                     |                       |                    |               |                            |              |
| Orientation                   | 10 (5-10)                  | 10 (8-10)           | 10 (3-10)             | 10 (8-10)          | 10 (8-10)     | 10 (8-10)                  | 0.268        |
| Record-Memory                 | 3 (1-3)                    | 3 (2-3)             | 3 (0-3)               | 3 (3-3)            | 3 (3-3)       | 3 (3-3)                    | 0.449        |
| Attention-Calculation         | 1 (0-5)                    | 1 (0-5)             | 3.5 (0-5)             | 1 (0-5)            | 3 (0-5)       | 2 (0-5)                    | <b>0.020</b> |
| Recall                        | 2 (0-3)                    | 2 (0-3)             | 2 (0-3)               | 2 (0-3)            | 2 (0-3)       | 2 (1-3)                    | 0.130        |
| Language                      | 8 (5-9)                    | 8 (5-9)             | 8 (6-9)               | 8 (7-9)            | 9 (7-9)       | 9 (6-9)                    | 0.257        |
| Low MMSE (≤23), n (%)         | 28 (41.2)                  | 10 (38.5)           | 6 (15.0)              | 7 (41.2)           | 4 (10.8)      | 7 (24.1)                   | <b>0.001</b> |
| Normal MMSE (>23, n (%))      | 40 (58.8)                  | 16 (61.5)           | 34 (85.0)             | 10 (58.8)          | 33 (89.2)     | 22 (75.9)                  | <b>0.004</b> |
| MMSE Score, median (range)    | 24 (16-30)                 | 24 (18-29)          | 25 (22-30)            | 24 (21-30)         | 27 (21-30)    | 25 (20-30)                 |              |

BD: Behçet's disease; FMF: familial Mediterranean fever; BDI: Beck Depression Inventory; BAI: Beck Anxiety Inventory; MMSE: Mini-Mental State Examination.

findings were presented in Supplementary Table S5, with most abnormalities confined to NBD and vascular BD.

#### Psychometric assessment outcomes

Psychometric assessment results are presented in Table V. Anxiety severity, assessed by BAI, did not differ significantly across groups in terms of categorical distribution or median scores ( $p=0.369$  and  $p=0.093$ , respectively).

In contrast, depressive symptoms showed significant intergroup differences. Moderate-to-severe depression was most frequent in mucocutaneous BD (35.8%) and NBD (23.5%), while severe depression was uncommon in FMF and healthy controls ( $p=0.041$ ). Median BDI scores were significantly higher in BD phenotypes compared with controls ( $p=0.005$ ).

Cognitive performance also differed across groups. Low MMSE scores ( $\leq 23$ ) were observed in 41.2% of mucocutaneous BD and NBD patients and in 38.5% of ocular BD patients, compared with 10.8% of FMF patients and 24.1% of healthy controls ( $p=0.001$ ). Median total MMSE scores were lowest in BD phenotypes and NBD and high-

est in FMF patients ( $p=0.004$ ). Among MMSE subdomains, attention and calculation scores differed significantly across groups ( $p=0.020$ ), whereas other components were comparable.

#### Discussion

In this study, we comprehensively evaluated neuropsychiatric manifestations in patients with BD without overt neurological involvement and compared them with NBD, FMF, and healthy controls. These findings should be interpreted within the context of the evolving understanding of BD as a heterogeneous multisystem disease, in which recent advances have further emphasised phenotype-specific clinical characteristics, disease assessment, immunopathogenesis, and individualised management strategies (14). Our findings demonstrate that neuropsychiatric symptoms, particularly depression, cognitive impairment, and headache, constitute a substantial burden not only in NBD but also in BD patients lacking formal neurological involvement, revealing the need to reconsider the conventional organ-based perception of neuropsychiatric morbidity in BD.

Consistent with previous literature, we observed significant differences in age at diagnosis, age at symptom onset, and disease duration across BD clinical phenotypes (15). Patients with mucocutaneous and ocular involvement were diagnosed at a younger age compared with vascular and neurological phenotypes, and symptom onset occurred significantly earlier in these groups. These findings suggest that the clinical expression of BD strongly influences diagnostic timing, likely reflecting differences in symptom visibility and clinical awareness. Ocular involvement, in particular, may prompt earlier medical attention due to its acute and potentially vision-threatening presentation. Similarly, disease duration differed markedly between phenotypes, with the longest median duration observed in neurological and vascular BD, probably due to the increased morbidity and mortality of these phenotypes resulted in stricter follow-up and patient compliance (16-18).

An important sociodemographic observation in our cohort was that all illiterate individuals were confined to the mucocutaneous BD group, where-

as higher education levels were most prevalent among healthy controls. Although education level did not statistically differ across all groups, this distribution suggests that lower educational attainment may influence disease recognition, health literacy, and access to care, particularly for manifestations perceived as 'benign' such as recurrent oral ulcers. Lower education has previously been linked to poorer chronic disease management and health outcomes, potentially through reduced self-care capacity and delayed healthcare utilisation (19-22). These factors may also contribute indirectly to increased neuropsychiatric vulnerability through psychosocial stressors and reduced coping resources.

Neuroimaging utilisation differed significantly between groups, with cranial MRI and MR venography predominantly performed in neurological and vascular BD, as expected. MRI findings were most frequently pathological in NBD, supporting its role as the gold standard for detecting central nervous system involvement, particularly parenchymal lesions (7, 23). MR venography abnormalities were restricted to NBD, highlighting its diagnostic value when cerebral venous thrombosis is clinically suspected (3).

Recent MRI-based evidence further supports a cautious interpretation of neurological symptoms in BD. Talarico et al. demonstrated that incidental white matter abnormalities in patients without active neurological involvement were generally infrequent, mild, predominantly subcortical, and largely age-related rather than disease-related (24). Moreover, these lesions were not associated with headache or disease activity, suggesting that incidental MRI abnormalities should not directly be interpreted as evidence of subclinical neuro-Behçet's disease. In this context, our findings indicate that neuropsychiatric manifestations may occur even in the absence of overt CNS involvement or corresponding structural MRI abnormalities, emphasising that not all neurological symptoms necessarily reflect active neuro-Behçet's disease.

Peripheral nervous system involvement, assessed by electromyography,

was rare and scattered across phenotypes. Although NBD is primarily characterised by central nervous system involvement, peripheral neuropathy has been sporadically reported and remains a possible but uncommon manifestation (8).

Headache was common across all BD phenotypes, irrespective of neurological involvement, and migraine was the predominant subtype. This aligns with prior studies indicating that headache in BD often resembles primary headache disorders and lacks specificity for NBD (25). Therefore, although headache is the most common neurological symptom reported in BD, it should not be considered sufficient for the diagnosis of neuro-Behçet's disease in the absence of objective neurological findings and supportive neuroimaging. Similarly, mild neurological examination abnormalities (e.g. tandem gait difficulty) were observed beyond NBD, reinforcing that 'soft signs' may occur in systemic inflammatory contexts and should prompt careful clinical correlation rather than a direct attribution to NBD.

A key finding of our study is the dissociation between anxiety and depression across clinical groups. Despite the presence of highest score in mucocutaneous BD group, anxiety levels were comparable among BD phenotypes and FMF but highly lower in healthy controls, suggesting that anxiety may represent a nonspecific response to chronic disease. In contrast, depressive symptoms were significantly more prevalent and severe in BD, clustering in mucocutaneous and neurological phenotypes. Depression has been consistently linked to impaired quality of life in BD and may be driven by chronic inflammation, pain, fatigue, relapses, and psychosocial burden caused by stigma related to visible mucocutaneous lesions, pain, fatigue, and functional limitations (26-28). This divergence of higher depression signal compared to anxiety signal across BD groups and may reflect contextual factors such as coping, social support, disease phase, and treatment status at assessment (29, 30).

Whether psychiatric manifestations in BD represent a primary disease-

related phenomenon or a secondary consequence of chronic systemic illness remains a matter of ongoing debate. Talarico et al. demonstrated that psychiatric disorders, particularly bipolar disorders, were associated with disease activity but were not related to neurological involvement, suggesting that neuropsychiatric manifestations may constitute an intrinsic component of BD rather than merely reflecting chronic disease burden or impaired quality of life. Our findings are consistent with this concept, as depressive symptoms and cognitive impairment were observed even in patients without overt neurological involvement, supporting the notion that neuropsychiatric manifestations may extend beyond the conventional neuro-Behçet spectrum while acknowledging that psychosocial factors and chronic disease burden may also contribute (31).

The most clinically actionable finding is the unexpectedly high proportion of low MMSE ( $\leq 23$ ) not only in NBD but also in mucocutaneous BD and ocular BD, while vascular BD showed comparatively lower rates despite greater systemic severity and longer disease duration. While cognitive impairment in NBD is well recognised (32, 33), its presence in non-neurological BD suggests potential contributions from systemic inflammation, endothelial dysfunction, or indirect neuroimmune mechanisms as emphasised in literature (34-37). These findings emphasise that cognitive screening may be clinically relevant across all BD phenotypes, not solely in those with overt neurological involvement. This pattern and prominence of lower results in mucocutaneous group supports the concept that cognitive dysfunction in BD is not merely a proxy of 'major organ burden', but may reflect phenotype-specific mechanisms, including subclinical neuroinflammation, cumulative inflammatory exposure, and psychosocial impact that is not captured by routine organ-based disease stratification, and also sociocultural dynamics. Also, preservation of cognitive functions in FMF group add even better results compared to healthy controls, suggest that longer duration of systemic inflammation and colchicine

exposure are not the single mechanism of this cognitive impairment. Importantly, the MMSE is a screening tool and may underestimate subtle executive and processing-speed deficits; nevertheless, the magnitude of impairment in several BD subgroups in our cohort suggests a signal that is unlikely to be explained solely by measurement noise. One of the major strengths of our study is the inclusion of FMF as an autoinflammatory disease control together with the evaluation of colchicine exposure. FMF shares chronic autoinflammatory mechanisms, recurrent inflammatory episodes, and long-term colchicine exposure with BD, while lacking primary CNS involvement, thereby providing an appropriate comparator to distinguish neuropsychiatric manifestations that may be specific to BD from those attributable to chronic systemic inflammation or its treatment. Although both BD and FMF groups demonstrated high cumulative colchicine exposure, with even longer disease duration and colchicine use in the FMF group, cognitive impairment and depressive symptoms were more pronounced across BD phenotypes. These findings suggest that chronic systemic inflammation and colchicine exposure alone are unlikely to fully explain the observed neuropsychiatric burden in BD, supporting the contribution of disease-specific mechanisms such as vasculitic biology, endothelial dysfunction, cytokine-driven neuroimmune cross-talk, and disease-specific psychosocial stressors. At the same time, treatment heterogeneity, particularly the greater use of immunosuppressive and biologic therapies in ocular, vascular, and neuro-Behçet phenotypes, may have attenuated symptom burden in these groups and should be considered when interpreting between-group differences.

Collectively, these findings argue for a pragmatic approach. First a routine screening for depression and cognitive complaints in BD clinics, accepting a low threshold for targeted neurocognitive evaluation when MMSE is low or functional concerns emerge, and multidisciplinary management integrating rheumatology, psychiatry/psychology, and when indicated neurology may

improve patient outcomes. Given that treatment recommendations for BD primarily focus on organ-threatening manifestations, structured neuropsychiatric assessment may represent an under-recognised 'care gap' that affects quality of life and functional outcomes. Several limitations should be acknowledged. First, smaller size of subgroups and the single-centre and cross-sectional design precludes causal inference and does not capture longitudinal fluctuations in neuropsychiatric symptoms relative to inflammatory activity. Second, neuropsychiatric outcomes were assessed using screening instruments (BDI, BAI, MMSE) rather than structured psychiatric interviews or comprehensive neuropsychological batteries; therefore, diagnostic specificity is limited and subtle cognitive phenotypes may be misclassified. Third, although education level did not statistically differ across groups, residual confounding by education and cognitive reserve may influence MMSE-based comparisons, particularly when groups differ in sex distribution and age structure (*e.g.* older healthy controls). In addition, the relatively high proportion of healthy controls with MMSE scores below the predefined cut-off should be interpreted cautiously, as MMSE is a screening rather than a diagnostic instrument, the healthy control group was relatively small (corresponding to only seven individuals), and controls were recruited from hospital staff and patients' relatives rather than through population-based sampling. Fourth, neuroimaging was not uniformly performed across all participants; thus, silent neurological findings in non-NBD groups could not be systematically excluded. Finally, treatment exposure varied substantially by phenotype, and medication effects including corticosteroid-related mood or cognitive effects cannot be fully disentangled from disease-related mechanisms in this design.

In this large, phenotype-stratified cohort study, we show that neuropsychiatric manifestations, including headache, cognitive impairment, and depressive symptoms, represent a substantial burden in patients with BD even in the absence of overt neurological involve-

ment. These findings indicate that a broad spectrum of neuropsychiatric symptoms may occur in patients who do not meet diagnostic criteria for NBD, supporting the value of systematic neuropsychiatric evaluation across phenotypes. Symptoms were more frequent in patients with mucocutaneous disease without radiologic evidence of neurological pathology, potentially reflecting differences in socioeconomic factors, health literacy, and treatment adherence. In contrast, more intensive immunosuppressive treatment and closer follow-up in patients with major organ involvement may contribute to better control of subclinical inflammation and preservation of neurocognitive function. Also, better results in FMF group despite longer duration of chronic inflammation may support the BD-driven specific neurocognitive impairment regardless of BD phenotype. Overall, recognising and addressing neuropsychiatric symptoms across all BD phenotypes may improve quality of life and reduce long-term healthcare burden.

#### Take home messages

- Cognitive and mood symptoms are common in Behçet's patients without neurological involvement.
- Mucocutaneous Behçet's patients showed unexpectedly high rates of migraine, depression, and low MMSE scores.
- Fewer neuropsychiatric symptoms in FMF support disease-specific CNS vulnerability in BD beyond chronic systemic inflammation.

#### References

1. GUL A: Pathogenesis of Behçet's disease: autoinflammatory features and beyond. *Semin Immunopathol* 2015; 37(4): 413-18. <https://doi.org/10.1007/s00281-015-0502-8>
2. UYGUNOGLU U, SIVA A: Behçet's syndrome and nervous system involvement. *Curr Neurol Neurosci Rep* 2018; 18(7): 35. <https://doi.org/10.1097/bor.0000000000000562>
3. SIVA A, SAIP S: The spectrum of nervous system involvement in Behçet's syndrome and its differential diagnosis. *J Neurol* 2009; 256(4): 513-29. <https://doi.org/10.1007/s00415-009-0145-6>
4. KIDD D, STEUER A, DENMAN AM, RUDGE P: Neurological complications in Behçet's syndrome. *Brain* 1999; 122 (Pt 11): 2183-94. <https://doi.org/10.1093/brain/122.11.2183>

5. HIROHATA S: Histopathology of central nervous system lesions in Behçet's disease. *J Neurol Sci* 2008; 267(1-2): 41-47. <https://doi.org/10.1016/j.jns.2007.09.041>
6. AL-ARAJI A, SHARQUIE K, AL-RAWI Z: Prevalence and patterns of neurological involvement in Behçet's disease: a prospective study from Iraq. *J Neurol Neurosurg Psychiatry* 2003; 74(5): 608-13. <https://doi.org/10.1136/jnnp.74.5.608>
7. AKMAN-DEMIR G, SERDAROGLU P, TASCI B: Clinical patterns of neurological involvement in Behçet's disease: evaluation of 200 patients. The Neuro-Behçet Study Group. *Brain* 1999; 122 (Pt 11): 2171-82. <https://doi.org/10.1093/brain/122.11.2171>
8. BORHANI HAGHIGHI A, POURMAND R, NIKSERESHT AR: Neuro-Behçet disease. A review. *Neurologist* 2005; 11(2): 80-9. <https://doi.org/10.1097/01.nrl.0000156343.16797.c4>
9. FISHER CA, BERNARD C: A systematic review of neurocognitive functioning in Behçet's disease. *Neuropsychol Rev* 2019; 29(4): 498-521. <https://doi.org/10.1007/s11065-019-09416-5>
10. Criteria for diagnosis of Behçet's disease. International Study Group for Behçet's Disease. *Lancet* 1990; 335(8697): 1078-80.
11. BECK AT, WARD CH, MENDELSON M, MOCK J, ERBAUGH J: An inventory for measuring depression. *Arch Gen Psychiatry* 1961; 4: 561-71. <https://doi.org/10.1001/archpsyc.1961.01710120031004>
12. BECK AT, EPSTEIN N, BROWN G, STEER RA: An inventory for measuring clinical anxiety: psychometric properties. *J Consult Clin Psychol* 1988; 56(6): 893-97. <https://doi.org/10.1037//0022-006x.56.6.893>
13. FOLSTEIN MF, FOLSTEIN SE, MCHUGH PR: "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975; 12(3): 189-98. [https://doi.org/10.1016/0022-3956\(75\)90026-6](https://doi.org/10.1016/0022-3956(75)90026-6)
14. HATEMI G, SEYAHİ E, FRESKO I, TALARICO R, UCAR D, HAMURYUDAN V: Behçet's syndrome: one year in review 2025. *Clin Exp Rheumatol* 2025; 43(10): 1699-708. <https://doi.org/10.55563/clinexprheumatol/8xuim0>
15. KURAL-SEYAHİ E, FRESKO I, SEYAHİ N *et al.*: The long-term mortality and morbidity of Behçet syndrome: a 2-decade outcome survey of 387 patients followed at a dedicated center. *Medicine* (Baltimore) 2003; 82(1): 60-76. <https://doi.org/10.1097/00005792-200301000-00006>
16. MCHUGH J: Different phenotypes identified for Behçet syndrome. *Nat Rev Rheumatol* 2021; 17(4): 188. <https://doi.org/10.1038/s41584-021-00587-1>
17. GUL A: Behçet's disease as an autoinflammatory disorder. *Curr Drug Targets Inflamm Allergy* 2005; 4(1): 81-83. <https://doi.org/10.2174/1568010053622894>
18. HATEMI G, CHRISTENSEN R, BANG D *et al.*: 2018 update of the EULAR recommendations for the management of Behçet's syndrome. *Ann Rheum Dis* 2018; 77(6): 808-18. <https://doi.org/10.1136/annrheumdis-2018-213225>
19. ATAY IM, ERTURAN I, DEMIRDAS A, YAMAN GB, YUREKLI VA: The impact of personality on quality of life and disease activity in patients with Behçet's disease: a pilot study. *Compr Psychiatry* 2014; 55(3): 511-17. <https://doi.org/10.1016/j.comppsy.2013.11.008>
20. MELIKOGLU M, MELIKOGLU MA: What affects the quality of life in patients with Behçet's disease? *Acta Reumatol Port* 2014; 39(1): 46-53.
21. MUMCU G, LEHIMCI F, FIDAN O *et al.*: The assessment of work productivity and activity impairment in Behçet's disease. *Turk J Med Sci* 2017; 47(2): 535-41. <https://doi.org/10.3906/sag-1603-161>
22. NUTBEAM D: The evolving concept of health literacy. *Soc Sci Med* 2008; 67(12): 2072-8. <https://doi.org/10.1016/j.socscimed.2008.09.050>
23. ALBAYRAM S, SAIP S, HASIOGLU ZI *et al.*: Evaluation of parenchymal Neuro-Behçet disease by using susceptibility-weighted imaging. *AJNR Am J Neuroradiol* 2011; 32(6): 1050-55. <https://doi.org/10.3174/ajnr.a2477>
24. TALARICO R, DI CIANNI F, CALZONI T, LORENZONI V, COSOTTINI M, MOSCA M: White matter abnormalities in an MRI-based study in Behçet's syndrome: incidental findings or clinically relevant? *Rheumatology* (Oxford) 2026; 65(2). <https://doi.org/10.1093/rheumatology/keag051>
25. AYKUTLU E, BAYKAN B, AKMAN-DEMIR G, TOPÇULAR B, ERTAS M: Headache in Behçet's disease. *Cephalalgia* 2006; 26(2): 180-86. <https://doi.org/10.1111/j.1468-2982.2005.01017.x>
26. DURSUN R, UGUZ F, KAYA N, SAVAS CILLI A, ENDOGRU H: Psychiatric disorders in patients with Behçet's disease. *Int J Psychiatry Clin Pract* 2007; 11(1): 16-20. <https://doi.org/10.1080/13651500600811438>
27. UGUZ F, DURSUN R, KAYA N, CILLI AS: Quality of life in patients with Behçet's disease: the impact of major depression. *Gen Hosp Psychiatry* 2007; 29(1): 21-24. <https://doi.org/10.1016/j.genhosppsych.2006.10.001>
28. TALARICO R, PALAGINI L, D'ASCANIO A *et al.*: Epidemiology and management of neuropsychiatric disorders in Behçet's syndrome. *CNS Drugs* 2015; 29(3): 189-96. <https://doi.org/10.1007/s40263-015-0228-0>
29. ATAY IM, ERTURAN I: The impact of coping strategies in Behçet's disease: a case-control study. *Niger J Clin Pract* 2020; 23(5): 680-85. [https://doi.org/10.4103/njcp.njcp\\_84\\_19](https://doi.org/10.4103/njcp.njcp_84_19)
30. KARLIDAG R, UNAL S, EVEREKLIOGLU C, SIPAHI B, ER H, YOLOGLU S: Stressful life events, anxiety, depression and coping mechanisms in patients with Behçet's disease. *J Eur Acad Dermatol Venereol* 2003; 17(6): 670-75. <https://doi.org/10.1046/j.1468-3083.2003.00760.x>
31. TALARICO R, PALAGINI L, ELEFANTE E *et al.*: Behçet's syndrome and psychiatric involvement: is it a primary or secondary feature of the disease? *Clin Exp Rheumatol* 2018; 36 (Suppl. 115): S125-28.
32. SIVA A, ALTINTAS A, SAIP S: Behçet's syndrome and the nervous system. *Curr Opin Neurol* 2004; 17(3): 347-57. <https://doi.org/10.1097/00019052-200406000-00017>
33. GUNDUZ T, EMIR O, KURTUNCU M *et al.*: Cognitive impairment in neuro-Behçet's disease and multiple sclerosis: a comparative study. *Int J Neurosci* 2012; 122(11): 650-56. <https://doi.org/10.3109/00207454.2012.704454>
34. ALTUNKAYNAK Y, USTA S, ERTEM DH, KOKSAL A, DIRICAN AC, BAYBAS S: Cognitive functioning and silent neurological manifestations in Behçet's disease with ocular involvement. *Noro Psikiyatr Ars* 2019; 56(3): 173-7. <https://doi.org/10.5152/npa.2017.19406>
35. CAVACO S, DA SILVA AM, PINTO P *et al.*: Cognitive functioning in Behçet's disease. *Ann NY Acad Sci* 2009; 1173: 217-26. <https://doi.org/10.1111/j.1749-6632.2009.04670.x>
36. MONASTERO R, CAMARDA C, PIPIA C *et al.*: Cognitive impairment in Behçet's disease patients without overt neurological involvement. *J Neurol Sci* 2004; 220(1-2): 99-104. <https://doi.org/10.1016/j.jns.2004.02.021>
37. GRECO A, DE VIRGILIO A, RALLI M *et al.*: Behçet's disease: New insights into pathophysiology, clinical features and treatment options. *Autoimmun Rev* 2018; 17(6): 567-75. <https://doi.org/10.1016/j.autrev.2017.12.006>