REUMA.PT/VASCULITIS PROTOCOL PROJECT

Formatou: Inglês (Reino Unido)

TITLE: Clinical features and predictors of neurologic and vascular manifestations in patients with Behçet's disease: analysis of the Rheumatic Diseases Portuguese Registry

1. BACKGROUND:

Behçet's disease (BD) is a multisystem inflammatory disorder of unclear aetiology that can cause an array of symptoms, including oral, gastrointestinal and genital ulcers, skin lesions, uveitis, arthritis, vascular and central nervous system manifestations. [1-5] Diagnosis is frequently established according to the clinical manifestations of the disease and the multiple existing diagnostic criteria, such as the International Criteria for Behçet´s Disease. [1]

Involvement of the central nervous system (CNS) is a potentially severe manifestation of BD. Neuro-BD (NBD) is classified according to the type of involvement into: i) parenchymal involvement which includes brainstem, hemisphere and spinal cord, and ii) myelopathy or nonparenchymal involvement which includes meningitis, intracranial hypertension and cerebral vascular thrombosis. Parenchymal involvement, particularly affecting the brainstem, seems to be the most frequent type of NBD manifestation (61%) and vascular thrombosis the most common non-parenchymal NBD lesion [2]. NBD can present with a variety of symptoms, most commonly headache, but also pyramidal signs, dysarthria, psychiatric symptoms and seizures [6,7]. The prevalence of this involvement is still uncertain. Case reports and case series have reported values ranging from 1.1% to 59.0%, depending on the diagnostic criteria used. [2,6-11].

Comentado [ES1]: What is meant by method?

Comentado [NC2R1]: 'By method used' means whether the classification is based on symptoms or imaging findings but we simplified by just using the expression "diagnostic criteria",

NBD was reported 2-8 times more often in male than in female patients and its prevalence is much higher in Middle Eastern and Far Eastern countries [2,6,11-28]. In addition, it has also been shown that the age of onset and manifestations of NBD differ between countries [2,6,9,17]. A monocentric study, including 121 patients with NBD from Tunisia, described an age of onset of neurological involvement of 29.7 years and an average disease duration before the onset of neurological manifestations of 6.4 years [2]. A retrospective study from South Korea demonstrated a later onset for these manifestations (37.6±10.6 years), which is in accordance with most data reported in the literature [6]. A consensus among studies is that patients with NBD seem to have an earlier onset of BD symptoms than patients without neurological manifestations. Moreover, in 6% of patients, neurologic-related symptoms may be the first manifestation of the disease or even precede its diagnosis [12,17,27,29]. NBD confers a poor prognosis, with high morbidity and mortality, as previously shown in a retrospective analysis of 115 patients with a 5- and 7-year event-free survival rates of 65% and 53%, respectively [30]. Three previous reports have evaluated patient and clinical characteristics that were associated

with NBD and the findings on bivariate analysis included a correlation with genital ulcers, deep vein thrombosis, arterial aneurysms and ocular involvement and a negative association with HLA-B51 positivity. [2,29,31]

As part of the neurological involvement, the peripheral nervous system may rarely be involved in BD. Its prevalence can be up to 3% among patients with BD, although these patients are often asymptomatic or have mild symptoms. Some case reports have described non-vasculitic axonal neuropathy or myopathy. [32]

Vascular involvement is another severe manifestation of BD. It can affect all vessels, regardless of their type (arterial or venous), size or location, hence being categorized under "variable vessel vasculitis" in the revised 2012 Chapel Hill nomenclature. [33-56] Venous involvement has been described as more prevalent than arterial, with lower extremity deep venous thrombosis as the most frequent vascular manifestation. [3, 54-56] Other venous manifestations include deep venous thrombosis of other distal veins, large vein thrombosis and superficial thrombophlebitis. Of note, the latter is classified as a skin lesion, not a vascular lesion, according to the Japanese criteria. [54] Arterial involvement includes dilatation or aneurysms, involving the pulmonary arteries, lower extremity arteries and the aorta. [3,53]

Besides aneurysms and pseudoaneurysms, other arterial lesions may also occur such as occlusion, stenosis or thrombosis. [3] Vascular involvement can occur in up to 51.6% of patients, being more prevalent in Maghreb countries. [34-56] The onset of vascular features in BD occurs around 5 years after diagnosis, but in 10.0-27.5% of cases it may be the initial manifestation of the disease. [3,53] It seems particularly more prevalent in males than females (ratio 4-5.6:1). [53,56] As previously shown in a Chinese retrospective study, vascular lesions are correlated with a high frequency of cardiac involvement and a low incidence of ocular lesions, genital ulcers and arthritis. [3] Large vessel involvement accounts for 40-45% of mortality in BD as vascular manifestations are the main predictors of morbimortality in BD patients. [3,53] Even after successful surgery, postoperative anastomotic aneurysms due to the recurrence of primary disease are not rare. [54]

In BD, neurologic and vascular involvements are the major causes of morbidity and mortality. [57-59] However, there is a lack of data in the literature on risk factors and prognosis for neurovascular involvement in BD. Therefore, it is important to identify possible clinical predictors for these involvements to ensure a prompt and potentially more aggressive approach in clinical practice.

2. KEYWORDS:

Behçet's disease; vascular involvement; aneurysms; pseudoaneurysms; neurologic involvement.

3. AIMS:

Main Hypothesis:

Based in previous works we expect to find that younger age of onset and higher systemic burden are associated with neurologic and/or vascular manifestations of BD.

3.1 Primary aim

- To identify demographic or clinical predictors of neurologic and/or vascular involvements, as poor outcome manifestations in BD patients.

  Outcomes: Presence of neurologic and/or vascular involvements (see section 4.2 "Population and inclusion criteria").

  Variables of interest: see section 4.3 "Variables to be collected"

3.2 Secondary aims

- To determine the prevalence of neurologic and vascular involvements in a Portuguese cohort of patients with BD.
- To describe and compare the demographic, clinical and treatment characteristics of patients with BD with and without neurologic involvement.
- To describe and compare the demographic, clinical and treatment characteristics of patients with BD with and without vascular involvement.
- To identify demographic or clinical predictors of neurologic involvement in BD patients.
- To identify demographic or clinical predictors of vascular involvement in BD patients.

  Outcomes: Presence of neurologic and/or vascular involvements (see section 4.2 "Population and inclusion criteria").

  Variables of interest: see section 4.3 "Variables to be collected"

4. METHODS:

4.1 Study design:

Longitudinal, multicentre study using information from the vasculitis protocol of Reuma.pt, the Rheumatic Diseases Portuguese Registry. [60]

4.2 Population and inclusion criteria:

Patients with a clinical diagnosis of BD according to their treating rheumatologist and fulfilling the 2013 International Criteria for Behçet´s Disease (ICBD 2013) will be included. All patients will have been enrolled in the Reuma.pt/Vasculitis protocol database and patients with other concomitant inflammatory systemic rheumatic diseases will be excluded.

NBD will be defined according to the International consensus recommendation (ICR) criteria for NBD diagnosis [61], as having neurological and/or psychiatric symptoms with compatible

Comentado [ES3]: If possible state your hypothesis.

Comentado [NC4R3]: Added.

Comentado [ES5]: To be sure, patients will be excluded if do not fulfill the ICBD criteria? even if the diagnosis was established by the rheumatologist?

Comentado [NC6R5]: Yes, for the sake of patient uniformity, only patients who meet the ICBD criteria will be included in the analysis. We can later perform a sensitivity analysis including those patients who do not meet the ICBD criteria.

abnormalities in magnetic resonance imaging (MRI) and/or cerebral spinal fluid (CSF), and without other possible explanation for their symptoms. BD peripheral neuropathy will be defined as neuropathic symptoms with a compatible conventional electrodiagnostic study of peripheral nerves including F latencies or a compatible nerve biopsy. Absence of objective neurological involvement (unclear symptoms, normal neurological examination, normal cerebrospinal fluid analysis, absence of neuroradiological findings) will not be considered as NBD.

Diagnosis of vascular lesions will be based on clinical assessment and computed tomography angiography, magnetic resonance angiography, positron emission tomography and/or ultrasonography.

Patients with neurologic manifestations due to vascular involvement will be classified as having NBD and will not be included in the vascular Behçet cohort.

4.3 Variables to be collected:

4.3.1 At baseline visit

Baseline visit will be defined as the visit at first clinical suspicion of BD and/or clinical diagnosis of BD.

4.3.1.1 Patient's characteristics:

- Age (continuous; years); sex (binary; male/female), ethnicity (four categories; Caucasian/African/Asian/other), country of origin (Portugal, Brazil, or any other option available on the list), smoking status (three categories; never smoked/past smoker/current smoker), cardiovascular comorbidities (hypertension, dyslipidaemia, obesity, diabetes mellitus, hypertensive/ischemic/dilated cardiomyopathy) (binary; yes/no).

4.3.1.2 Disease characteristics:

- Date (year) **at diagnosis** (continuous, years); Date (year) **at first manifestation** (continuous, years).
- **Clinical characteristics** (all binary, defined as once a feature always a feature): 1. CONSTITUTIONAL (syncope/lipothymia; fatigue; nocturnal sweating; fever; lymphadenopathy; weight loss≥2kg); 2. MUSCULOSKELETAL (arthralgia; morning stiffness; myalgia; arthritis); 3. CUTANEOUS (maculopapular rash; reticular livedo; cutaneous nodules; gangrene; ulcers; urticaria); 4. OPHTALMOLOGIC (amaurosis fugax; sudden loss of vision; blurred vision; optic nevritis; scleritis or episcleritis; uveitis; retinal exsudate; retinal haemorrhages; retinal artery or vein thrombosis); 5. PULMONAR (dyspnoea; dry cough; productive cough; minor haemoptysis; major haemoptysis / alveolar haemorrhage; thoracalgia; lung nodules or cavities; infiltrate); 6. CARDIOVASCULAR (angina; upper limb claudication; lower limb claudication; pulseless extremities; Raynaud phenomenon; heart failure; cardiomyopathy; pericarditis; stroke); 7. GASTROINTESTINAL (abdominal pain;

abdominal pain after meals; diarrhoea; bloody diarrhoea; gastrointestinal bleeding; dysphagia; oral ulcers; peritonitis; acute or chronic pancreatitis; colitis; mesenteric ischemia); 8. GENITOURINARY (genital ulcers); 10. NEUROLOGIC (seizures; ischemic transitory attack; photophobia; new persistent headache; cranial nerve palsy; meningitis; cerebral vascular attack; spine lesion; mononeuritis multiplex with motor involvement; motor neuropathy; sensory neuropathy; confusion).

4.3.2 At last visit

Last visit will be defined as the last visit before data extraction.

4.3.2.1 Disease characteristics:

- **Classification criteria** (all binary, defined as once a feature always a feature; with date [year] for each feature): ISG 1990 criteria (recurrent oral ulcers; recurrent genital ulcers; ocular lesions; cutaneous lesions; pathergy test); ICBD 2006/2013 (genital ulcers; ocular lesions; oral ulcers; cutaneous lesions; neurological manifestations; vascular lesions; pathergy).

The following data will be retrieved from the data inputted in the classification criteria:

* **first criteria manifestation** of BD and **first non-oral ulcer criteria manifestation** of BD, date (year) and age at symptom onset (continuous; years).

* date (year) and age at **NBD diagnosis** (continuous, years), symptom duration until neurologic event (continuous; years): calculated as the difference between the date of NBD diagnosis and the date of symptom onset.

* date (year) and age at **vascular manifestations** (continuous; years), symptom duration until vascular event (continuous; years): calculated as the difference between the date of vascular manifestation diagnosis and the date of symptom onset.

- **Immunology/Genetics** (binary, defined as once a feature always a feature): HLA B51.
- **Clinical characteristics** (all binary, defined as once a feature always a feature): 1. CONSTITUTIONAL (syncope/lipothymia; fatigue; nocturnal sweating; fever; lymphadenopathy; weight loss≥2kg); 2. MUSCULOSKELETAL (arthralgia; morning stiffness; myalgia; arthritis); 3. CUTANEOUS (maculopapular rash; reticular livedo; cutaneous nodules; gangrene; ulcers; urticaria); 4. OPHTALMOLOGIC (amaurosis fugax; sudden loss of vision; blurred vision; optic nevritis; scleritis or episcleritis; uveitis; retinal exsudate; retinal haemorrhages; retinal artery or vein thrombosis); 5. PULMONAR (dyspnoea; dry cough; productive cough; minor haemoptysis; major haemoptysis / alveolar haemorrhage; thoracalgia; lung nodules or cavities; infiltrate); 6. CARDIOVASCULAR (angina; upper limb claudication; lower limb claudication; pulseless extremities; Raynaud phenomenon; heart failure; cardiomyopathy; pericarditis; stroke); 7. GASTROINTESTINAL (abdominal pain;

abdominal pain after meals; diarrhoea; bloody diarrhoea; gastrointestinal bleeding; dysphagia; oral ulcers; peritonitis; acute or chronic pancreatitis; colitis; mesenteric ischemia); 8. GENITOURINARY (genital ulcers); 10. NEUROLOGIC (seizures; ischemic transitory attack; photophobia; new persistent headache; cranial nerve palsy; meningitis; cerebral vascular attack; spine lesion; mononeuritis multiplex with motor involvement; motor neuropathy; sensory neuropathy; confusion).

- **Thrombotic manifestations** (all binary, defined as once a feature always a feature; with date [year]): arterial thrombosis, venous thrombosis, small vessel thrombosis.

4.3.2.2 Complementary exams:

- **Neurological system** (open text or uploaded at the imaging screens): brain MRI; spine MRI; needle electromyography; nerve biopsy - necrotizing vasculitis, non-necrotizing vasculitis, organized vascular occlusion with recanalization, organized haemorrhage, focal proliferation of small vessels (binary, yes/no); other findings (open text). CSF characteristics will be written in the 'Other' section of the 'Imagiology' section of Reuma.pt/vasculitis protocol.
- **Vascular system** (open text or uploaded at the imaging screens): CT (computed tomography) scan; angioCT scan; ultrasonography and/or doppler ultrasonography; MRI; angioMRI; PET scan; angiography.

4.3.2.3 Current treatment:

- **Medical treatment** (binary; yes/no): colchicine; non-steroidal anti-inflammatory drugs (specify); oral glucocorticoids; pulse glucocorticoid therapy; conventional disease-modifying antirheumatic drugs (DMARDs) – azathioprine, cyclosporine, methotrexate, mycophenolate mofetil, sulfasalazine, tacrolimus, other (specify); biological DMARDs – TNFα (specify), IL-6 (specify) or IL1 (specify) blockers or other (specify); JAK inhibitor (specify); interferon-α (INF-α); immunomodulatory therapy: cyclophosphamide; anticoagulant agents; antiplatelet therapy.
- **Surgical** (vascular intervention) **treatment** (binary; yes/no): peripheral artery angioplasty; coronary angioplasty; vascular bypass; dissection repair; peripheral artery stent placement; coronary stent placement; aneurysm resection; cardiac valve replacement; other (specify, open text).

4.4 Statistical analysis:

The data will be analysed descriptively and presented as mean ± standard deviation for continuous and normal variables, as median (interquartile range) for continuous non-normal variables, and as absolute and relative frequencies for categorical variables. In order to identify demographic and/or clinical variables associated with the presence of neurological and/or

Formatou: Inglês (Reino Unido)

Formatou: Inglês (Reino Unido)

vascular involvement in BD, chi-squared, Fisher's exact, Mann-Whitney, or *t*-tests will be performed, as appropriate. Logistic multivariable analysis will be performed to identify independent associations with NBD and VBD. The statistical analysis will be performed with SPSS version 29.0.2.0 (IBM), and statistical significance will be set at $p<0.05$.

After an initial data extraction, we will attempt to make a second call to the centers with missing data to complete the missing data, and the analysis will be performed only after the second data extraction.

Formatou: Inglês (Reino Unido)

5. EXPECTED RESULTS AND STUDY LIMITATIONS:

We expect to include between 150 and 300 patients diagnosed with BD who also fulfil the inclusion criteria; 23-46 patients with neurological and/or vascular involvement (estimation based on data obtained in an exploratory monocentric study). We expect to identify demographic and clinical associations and potential predictors of neurologic and/or vascular involvement in BD.

Despite our strategy to minimize recall bias, residual bias will always be an issue. Among other reasons for that, information contained in electronic records, other than Reuma.pt, may also be incomplete and biased. However, by cross-checking multiple sources of information we believe we will be able to limit recall bias to a significant extent.

6. ETHICS:

Reuma.pt has been approved by the Comissão Nacional de Proteção de Dados (CNPD) and by all the participating Ethics Commissions, and all participants have also signed an informed consent form (attached to this protocol) authorising the use of their data for clinical research.

This study was submitted for evaluation by the ethics committee of Centro Académico de Medicina de Lisboa (CAML) and approved with the reference number 259/24. This study will be conducted according to the 2024 revision of the World Medical Association's Declaration of Helsinki, Finland, and the International Guidelines for Ethical Review of Epidemiological Studies. Data protection will be assured by data encryption according to the Portuguese law (Law n.67/98 de 26th of October) and according to National Committee for Data Protection deliberation n.227/2007, which provided guidelines to the processing of personal data carried out under scientific clinical research.

Coauthorship policy: We accept one co-author per center for every 20 patients with Behçet's disease entered into the study. Centers contributing fewer than 20 patients may still designate a co-author if at least one patient of interest is included (a patient with Behçet's disease with neurological and/or vascular involvement).

Formatou: Inglês (Reino Unido)

7. TIMELINE:

	Mar.-Apr. 2025	Jun. 2025	Aug. 2025	Sep.-Dec. 2025	Jan. 2026
Reuma.pt submission					
Call for data collection					
Data collection					
Database analysis					
Identifying missing information / outliers and performing database corrections / 2nd call for data					
Abstract submission for congresses			CPR, ACR		EULAR
Paper draft / submission					

ACR: American College of Rheumatology Convergence; CPR: Congresso Português de Reumatologia; EULAR: Annual European Congress of Rheumatology

8. FUNDING AND CONFLICTS OF INTERESTS:

The authors have no disclosures to report.

Authors:

Margarida Lucas Rocha[1,2]: study design, protocol development, database management, statistical analysis, interpretation and discussion of results, preparation and revision of communications and scientific articles.

Roberto Pereira da Costa[2]: study design, protocol development, database management, statistical analysis, interpretation and discussion of results, preparation and revision of communications and scientific articles.

Ana Teodósio Chícharo[1,2]: study design, protocol development, database management, statistical analysis, interpretation and discussion of results, preparation and revision of communications and scientific articles.

Inês Sopa[2]: study design, protocol development, database management, statistical analysis, interpretation and discussion of results, preparation and revision of communications and scientific articles.

Joana Martins Martinho[2,3]: study design, protocol development, database management, statistical analysis, interpretation and discussion of results, preparation and revision of communications and scientific articles.

Carla Macieira[2]: protocol development, interpretation and discussion of results, preparation and revision of communications and scientific articles.

Cristina Ponte[2,3]: protocol development, interpretation and discussion of results, preparation and revision of communications and scientific articles.

Nikita Khmelinskii[2,3]: study conception and design, protocol development, database management, statistical analysis, interpretation and discussion of results, preparation and revision of communications and scientific articles.

1. Rheumatology Department, Unidade Local de Saúde do Algarve, Faro, Portugal
2. Rheumatology Department, Unidade Local de Saúde Santa Maria, Centro Académico de Medicina de Lisboa, Lisboa, Portugal
3. Rheumatology Research Unit, Faculdade de Medicina, Universidade de Lisboa, Centro Académico de Medicina de Lisboa, Lisboa, Portugal

9. BIBLIOGRAPHY:

1. International Team for the Revision of the International Criteria for Behçet's Disease (ITR-ICBD). The International Criteria for Behçet's Disease (ICBD): a collaborative study of 27 countries on the sensitivity and specificity of the new criteria. J Eur Acad Dermatol Venereol. 2014 Mar;28(3):338-47. doi: 10.1111/jdv.12107.
2. Houman MH, Bellakhal S, Ben Salem T, et al. Characteristics of neurological manifestations of Behçet's disease: a retrospective monocentric study in Tunisia. Clin Neurol Neurosurg. 2013 Oct;115(10):2015-8. doi: 10.1016/j.clineuro.2013.06.009.
3. Fei Y, Li X, Lin S, Song X, et al. Major vascular involvement in Behçet's disease: a retrospective study of 796 patients. Clin Rheumatol. 2013 Jun;32(6):845-52. doi: 10.1007/s10067-013-2205-7.
4. Sakane T, Takeno M, Suzuki N, Inaba G. Behçet's disease. N Engl J Med. 1999 Oct 21;341(17):1284-91. doi: 10.1056/NEJM199910213411707.
5. Verity DH, Wallace GR, Vaughan RW, Stanford MR. Behçet's disease: from Hippocrates to the third millennium. Br J Ophthalmol. 2003 Sep;87(9):1175-83. doi: 10.1136/bjo.87.9.1175.
6. Kim SW, Kim TG, Oh J, et al. Clinical and Radiographic Characteristics of Neuro-Behçet's Disease in South Korea. J Clin Neurol. 2019 Oct;15(4):429-437. doi: 10.3988/jcn.2019.15.4.429.
7. Noel N, Drier A, Wechsler B, et al. Manifestations neurologiques de la maladie de Behçet [Neurological manifestations of Behçet's disease]. Rev Med Interne. 2014 Feb;35(2):112-20. French. doi: 10.1016/j.revmed.2013.10.332.

8. Sahin Eroglu D, Torgutalp M, Yucesan C, et al. Prognostic factors for relapse and poor outcome in neuro-Behçet's syndrome: results from a clinical long-term follow-up of a single centre. J Neurol. 2022 Apr;269(4):2046-2054. doi: 10.1007/s00415-021-10787-0.
9. Peño IC, De las Heras Revilla V, Carbonell BP, et al. Neurobehçet disease: clinical and demographic characteristics. Eur J Neurol. 2012 Sep;19(9):1224-7. doi: 10.1111/j.1468-1331.2012.03706.x.
10. Tursen U, Gurler A, Boyvat A. Evaluation of clinical findings according to sex in 2313 Turkish patients with Behçet's disease. Int J Dermatol. 2003 May;42(5):346-51. doi: 10.1046/j.1365-4362.2003.01741.x.
11. Farah S, Al-Shubaili A, Montaser A, et al. Behçet's syndrome: a report of 41 patients with emphasis on neurological manifestations. J Neurol Neurosurg Psychiatry. 1998 Mar;64(3):382-4. doi: 10.1136/jnnp.64.3.382.
12. Al-Fahad SA, Al-Araji AH. Neuro-Behcet's disease in Iraq: a study of 40 patients. J Neurol Sci. 1999 Nov 30;170(2):105-11. doi: 10.1016/s0022-510x(99)00165-3.
13. Hentati F, Fredj M, Gharbi N, Hamida M. Clinical and biological aspects of neuro-Behçet's in Tunisia. In: Wechsler B, Godeau P, eds. Behçet's disease. Amsterdam: Elsevier. 1993;415-8.
14. Bohlega S, AlKawi MZ, Omer S, et al. Neuro-Behçet's: clinical syndromes and prognosis. In: Wechsler B, Godeau P, eds. Behçet's disease. Amsterdam: Elsevier. 1993;429-33.
15. Nakamura Y, Takahashi M, Ueyama K, et al. Magnetic resonance imaging and brain-stem auditory evoked potentials in neuro-Behçet's disease. J Neurol. 1994 Jul;241(8):481-6. doi: 10.1007/BF00919709.
16. Kidd D, Steuer A, Denman AM, Rudge P. Neurological complications in Behçet's syndrome. Brain. 1999 Nov;122:2183-94. doi: 10.1093/brain/122.11.2183.
17. Akman-Demir G, Serdaroglu P, Tasçi B. Clinical patterns of neurological involvement in Behçet's disease: evaluation of 200 patients. The Neuro-Behçet Study Group. Brain. 1999 Nov;122:2171-82. doi: 10.1093/brain/122.11.2171
18. Siva A, Kantarci OH, Saip S, et al. Behçet's disease: diagnostic and prognostic aspects of neurological involvement. J Neurol. 2001 Feb;248(2):95-103. doi: 10.1007/s004150170242.
19. Lee SH, Yoon PH, Park SJ, Kim DI. MRI findings in neuro-behçet's disease. Clin Radiol. 2001 Jun;56(6):485-94. doi: 10.1053/crad.2000.0675.
20. Yücesan C, Isikay CT, Ozay E, Aydin N, Mutluer N. The clinical involvement patterns of neuro-Behçet's disease. Eur J Neurol. 2001 Jan;8(1):92. doi: 10.1046/j.1468-1331.2001.00177.x.
21. Lannuzel A, Lamaury I, Charpentier D, Caparros-Lefebvre D. Neurological manifestations of Behçet's disease in a Caribbean population: clinical and imaging findings. J Neurol. 2002 Apr;249(4):410-8. doi: 10.1007/s004150200031.

22. Sbaï A, Wechsler B, Duhaut P, et al. Neuro-Behçet's disease (isolated cerebral thrombophlebitis excluded). Clinical pattern, prognostic factors, treatment and long term follow-up. Adv Exp Med Biol. 2003;528:371-6. doi: 10.1007/0-306-48382-3_75.
23. Al-Araji A, Sharquie K, Al-Rawi Z. Prevalence and patterns of neurological involvement in Behcet's disease: a prospective study from Iraq. J Neurol Neurosurg Psychiatry. 2003 May;74(5):608-13. doi: 10.1136/jnnp.74.5.608.
24. Turker H, Terzi M, Bayrak O, et al. Visual evoked potentials in differential diagnosis of multiple sclerosis and neurobehcet's disease. Tohoku J Exp Med. 2008 Oct;216(2):109-16. doi: 10.1620/tjem.216.109.
25. Borhani-Haghighi A, Samangooie S, Ashjazadeh N, et al. A. Neurological manifestations of Behçet's disease. Saudi Med J. 2006 Oct;27(10):1542-6.
26. Lo Monaco A, La Corte R, Caniatti L, Borrelli M, Trotta F. Neurological involvement in North Italian patients with Behçet disease. Rheumatol Int. 2006 Oct;26(12):1113-9. doi: 10.1007/s00296-006-0149-9.
27. Barros R, Santos E, Moreira B, et al. Clinical characterization and pattern of neurological involvement of Behçet's disease in fifteen Portuguese patients. Clin Exp Rheumatol. 2007;24(Suppl 42):S31.
28. Joseph FG, Scolding NJ. Neuro-Behçet's disease in Caucasians: a study of 22 patients. Eur J Neurol. 2007 Feb;14(2):174-80. doi: 10.1111/j.1468-1331.2006.01613.x.
29. Houman MH, Neffati H, Braham A, et al. Behçet's disease in Tunisia. Demographic, clinical and genetic aspects in 260 patients. Clin Exp Rheumatol. 2007 Jul-Aug;25(4 Suppl 45):S58-64.
30. Noel N, Bernard R, Wechsler B, et al. Long-term outcome of neuro-Behçet's disease. Arthritis Rheumatol. 2014 May;66(5):1306-14. doi: 10.1002/art.38351.
31. Ideguchi H, Suda A, Takeno M, et al. Neurological manifestations of Behçet's disease in Japan: a study of 54 patients. J Neurol. 2010 Jun;257(6):1012-20. doi: 10.1007/s00415-010-5454-2.
32. Atasoy HT, Tunc TO, Unal AE, et al. Peripheral nervous system involvement in patients with Behçet disease. Neurologist. 2007 Jul;13(4):225-30. doi: 10.1097/NRL.0b013e31805778d1.
33. Jennette JC. Overview of the 2012 revised International Chapel Hill Consensus Conference nomenclature of vasculitides. Clin Exp Nephrol. 2013 Oct;17(5):603-606. doi: 10.1007/s10157-013-0869-6.
34. Bang D, Lee JH, Lee ES, et al. Epidemiologic and clinical survey of Behcet's disease in Korea: the first multicenter study. J Korean Med Sci. 2001 Oct;16(5):615-8. doi: 10.3346/jkms.2001.16.5.615.

35. Davatchi F, Shahram F, Chams-Davatchi C et al. Behcet's disease in Iran: analysis of 6500 cases. Int J Rheum Dis. 2010 Oct;13(4):367-73. doi: 10.1111/j.1756-185X.2010.01549.x.
36. Zhang Z, Peng J, Hou X, et al. Clinical manifestations of Behcet's disease in Chinese patients. APLAR J Rheumatol. 2006;9:244–7.
37. deguchi H, Suda A, Takeno M, Ueda A, Ohno S, Ishigatsubo Y. Characteristics of vascular involvement in Behçet's disease in Japan: a retrospective cohort study. Clin Exp Rheumatol. 2011 Jul-Aug;29(4 Suppl 67):S47-53.
38. Ko GY, Byun JY, Choi BG, Cho SH. The vascular manifestations of Behçet's disease: angiographic and CT findings. Br J Radiol. 2000 Dec;73(876):1270-4. doi: 10.1259/bjr.73.876.11205670.
39. Düzgün N, Ateş A, Aydintuğ OT, Demir O, Olmez U. Characteristics of vascular involvement in Behçet's disease. Scand J Rheumatol. 2006 Jan-Feb;35(1):65-8. doi: 10.1080/03009740500255761.
40. Tohmé A, Aoun N, El-Rassi B, Ghayad E. Vascular manifestations of Behçet's disease. Eighteen cases among 140 patients. Joint Bone Spine. 2003 Sep;70(5):384-9. doi: 10.1016/s1297-319x(03)00076-9.
41. Sarica-Kucukoglu R, Akdag-Kose A, Kayaball M, et al. Vascular involvement in Behçet's disease: a retrospective analysis of 2319 cases. Int J Dermatol. 2006 Aug;45(8):919-21. doi: 10.1111/j.1365-4632.2006.02832.x.
42. al-Dalaan AN, al Balaa SR, el Ramahi K, et al. Behçet's disease in Saudi Arabia. J Rheumatol. 1994 Apr;21(4):658-61.
43. Altenburg A, Papoutsis N, Orawa H, Martus P, Krause L, Zouboulis CC. Epidemiologie und Klinik des Morbus Adamantiades-Behçet in Deutschland -- Aktuelle pathogenetische Konzepte und therapeutische Möglichkeiten [Epidemiology and clinical manifestations of Adamantiades-Behçet disease in Germany -- current pathogenetic concepts and therapeutic possibilities]. J Dtsch Dermatol Ges. 2006 Jan;4(1):49-64; quiz 65-6. German. doi: 10.1111/j.1610-0387.2006.05841.x.
44. Seaman G, Pearce R. Disease manifestation in a population drawn from the UK Behcet's Syndrome Society. In: Hamza M, eds. Behcet's Disease. PUB ADHOUA, Tunisia, 1997;196-9.
45. Sharqui K, Al-Araji A, Al-Rawi Z. Behcet's disease in Iraqi patients. A prospective study from a newly established multidiscipline Behcet's disease clinic. In: Bang D, Lee E, Lee S, eds. Behcet's disease. Design Mecca, Seoul, 2000;60-3.
46. Assaad-Khalil S, Kamel F, Ismail E. Starting regional registry for patients with Behcet's disease in North-West Nile Delta region in Egypt. In: Hamza M, eds. Behcet's Disease. PUB ADHOUA, Tunisia, 1997;173-6.

47. Madanat W, Fayyad F, Zureikat H, et al. Analysis of 150 patients with Behcet's disease from Jordan. In: Bang D, Lee E, Lee S, eds. Behcet's disease. Design Mecca, Seoul, 2000;941-4.
48. Calamia KT, Mazlumzadeh M, Balbanova M, et al. Clinical characteristics of United States patients with Behcet's disease. In: Bang D, Lee E, Lee S, eds. Behcet's disease. Design Mecca, Seoul, 2000;48-51.
49. Benamour S, Naji T, Echchilali K, et al. Study of 1034 cases of Behcet's disease. Clin Exp Rheumatol. 2006;24(Suppl 42):S13.
50. B'chir Hamzaoui S, Harmel A, Bouslama K, et al. La maladie de Behçet en Tunisie. Etude clinique de 519 cas [Behçet's disease in Tunisia. Clinical study of 519 cases]. Rev Med Interne. 2006 Oct;27(10):742-50. French. doi: 10.1016/j.revmed.2006.07.019.
51. Valesini G, Pivetti Pezzi P, Catarinelli G, et al. Clinical manifestations of Behcet's disease in Italy: study of 155 patients at Rome University. In: O'Duffy JD, Kokmen E, eds. Behcet's Disease Basic and Clinical Aspects. Marcel Decker Inc, New York, 1991;279-89.
52. de Souza-Ramalho P, DAlmeida MF, Freitas JP, et al. Incidence and clinical aspects of Behcet's disease in Portugal. In: O'Duffy JD, Kokmen E, eds. Behcet's disease basic and clinical aspects. Marcel Decker, New York, 1991;291-8.
53. Tazi Mezalek Z, Khibri H, El Fari S, et al. Les complications vasculaires de la maladie de Behçet [Vascular manifestations of Behcet's disease]. Rev Med Interne. 2023;44(2):72-8. French. doi: 10.1016/j.revmed.2022.11.011.
54. Ishibashi H. What Is Vascular Behçet's Disease? Ann Vasc Dis. 2018;11(1):52-6. doi: 10.3400/avd.ra.18-00002.
55. Kotsis T, Moulakakis KG, Mylonas S, Andrikopoulos V. Vascular manifestations of Behcet's disease: report of a case and review of the literature. *Phlebology*. 2011;26(6):249-253. doi:10.1258/phleb.2010.010024
56. Alibaz-Oner F, Direskeneli H. Management of vascular Behçet's disease. Int J Rheum Dis. 2019 Jan;22 Suppl 1:105-108. doi: 10.1111/1756-185X.13298.
57. Hochberg MC, Gravallese EM, Smolen JS, van der Heijde D, Weinblatt ME, Weisman MH. Rheumatology. 8th ed. Elsevier. 2022;1451-52.
58. Firestein GS, Budd RC, Gabriel SE, McInnes IB, O'Dell JR. Firestein & Kelley's Textbook of Rheumatology. 11th ed. Elsevier. 2020; pp. 2003-9.
59. Mendes D, Correia M, Barbedo M, et al. Behçet's disease--a contemporary review. J Autoimmun. 2009 May-Jun;32(3-4):178-88. doi: 10.1016/j.jaut.2009.02.011.
60. Ponte C, Khmelinskii N, Teixeira V, et al. Reuma.pt/vasculitis - the Portuguese vasculitis registry. Orphanet J Rare Dis. 2020 May 5;15(1):110. doi: 10.1186/s13023-020-01381-0.

61. Kalra S, Silman A, Akman-Demir G, et al. Diagnosis and management of Neuro-Behçet's disease: international consensus recommendations. J Neurol. 2014 Sep;261(9):1662-76. doi: 10.1007/s00415-013-7209-3.