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DIAGNOSTIC CHALLENGES OF NEURO-BEHÇET'S DISEASE: A BRIEF SYSTEMATIC REVIEW

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SISTEMATIC REVIEW

RESUMO

Introdução: A Doença de Behçet (BD) pode evoluir com manifestações neurológicas graves, denominadas Neuro-Behçet (NB), caracterizadas por sintomas diversos e inespecíficos.

Objetivo: Analisar os principais desafios diagnósticos em NB, considerando a inespecificidade clínica, limitações dos exames complementares e lacunas nos critérios diagnósticos.

Métodos: Revisão sistemática realizada nas bases PubMed, Scopus, Web of Science e SciELO (abril–maio/2024), incluindo 22 estudos publicados entre 2013 e 2024, que abordassem aspectos diagnósticos de NB em português, inglês ou espanhol.

Resultados: Os sintomas de NB frequentemente se confundem com outras doenças neurológicas. Sintomas piramidais, cognitivos, comportamentais e esfincterianos apresentam diferentes prevalências e exigem avaliação cuidadosa para diagnóstico diferencial (Tabela 1). Alterações em exames de imagem e análise do líquido cerebrospinal (LCR) têm baixa especificidade; a atrofia cerebral crônica está associada a desfechos neurológicos piores.

Conclusão: O diagnóstico de NB continua predominantemente clínico e requer avaliação multidisciplinar. Avanços em biomarcadores, incluindo neurofilamento de cadeia leve (NFL) e proteína ácida fibrilar glial (GFAP), validação de critérios e ferramentas preditivas são necessários para identificação e tratamento precoces. Reconhecimento de características sistêmicas, como reação de patergia ou positividade para HLA-B51, pode fornecer pistas adicionais para suspeita de Doença de Behçet subjacente.

Palavras-chave: Neuro-Behçet; Doença de Behçet; Vasculite; Biomarcadores.

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ABSTRACT

Background: Neuro-Behçet's (NB) disease is a severe neurological complication of Behçet's disease (BD), characterized by diverse and nonspecific symptoms.

Objective: To analyze the main diagnostic challenges in NB, considering clinical nonspecificity, limitations of complementary tests, and gaps in diagnostic criteria.

Methods: A systematic review was conducted in PubMed, Scopus, Web of Science, and SciELO databases (April–May 2024), including 22 studies published between 2013 and 2024. Inclusion criteria encompassed studies addressing diagnostic aspects of NB in Portuguese, English, or Spanish.

Results: NB symptoms are often confused with other neurological diseases. Pyramidal, cognitive, behavioral, and sphincter symptoms vary in frequency, requiring careful differential diagnosis. MRI and cerebrospinal fluid analyses have low specificity; chronic cerebral atrophy is associated with poorer neurological outcomes.

Conclusions: Diagnosis of NB remains primarily clinical and requires multidisciplinary evaluation. Advances in biomarkers, including neurofilament light chain (NFL) and glial fibrillary acidic protein (GFAP), criteria validation, and predictive tools are needed for early identification and treatment. Recognition of systemic features such as pathergy reaction or HLA-B51 positivity may provide additional clues to support suspicion of underlying Behçet's disease.

Keywords: Neuro-Behçet's syndrome; Behçet's disease; Vasculitis; Biomarkers.

INTRODUCTION

First described by Hulusi Behçet in 1937, Behçet's disease (BD) is a chronic inflammatory disease affecting blood vessels of various sizes[8]. Its classic presentation involves oral and genital ulcerations associated with uveitis, but it has evolved into a multisystem spectrum. Among its most severe manifestations is neurological impairment, termed Neuro-Behçet's disease (NB), occurring in approximately 5–10% of patients with BD[9,10]. Diagnosing NB remains a significant challenge due to variability of neurological symptoms, absence of specific markers, and similarity to other inflammatory neurological conditions, such as multiple sclerosis and neurosarcoidosis[11]. Early identification is essential to avoid irreversible sequelae, but current diagnostic criteria are limited in terms of sensitivity and applicability[12]. This study systematically reviews literature to identify main obstacles in diagnosing NB and to inform clinical and research strategies.

METHODS

This systematic review followed PRISMA guidelines. The search was conducted between April and May 2024 in PubMed, Scopus, Web of Science, and SciELO databases using the descriptors: "Neuro-Behçet's disease," "diagnostic challenges," "Behçet's disease," "neurological involvement," and "vasculitis"[13].

Inclusion Criteria:

- Original articles, narrative or systematic reviews, and case series;
- Publications between January 2013 and April 2024;
- Languages: Portuguese, English, or Spanish;
- Studies addressing diagnostic aspects of NB.

Exclusion Criteria:

- Studies without full text available;
- Duplicate studies;
- Articles not focused on NB diagnosis.

Screening was performed by two independent reviewers; disagreements were resolved by consensus. Extracted data included year, country, study type, sample population, neurological symptoms, complementary exam findings, diagnostic criteria, and study limitations[14].

RESULTS

The initial search returned 534 articles. After excluding duplicates and applying eligibility criteria, 22 studies were included, with sample sizes ranging from 5 to 150 patients. Methodological designs included 8 case series, 5 cross-sectional studies, 6 narrative reviews, and 3 systematic reviews[15–16]. The literature selection process is illustrated in Figure 1, and the frequency of clinical symptoms and complementary exam findings is summarized in Figure 2.

Main Findings

1. Nonspecific Symptoms:

All 22 studies highlighted variability of neurological symptoms. Headache was reported in 16 articles (73%)[1–8,10–13,15–18]; hemiparesis in 15 articles (68%)[1–7,9–13,15–17]; dysarthria in 12 articles (55%)[1,4–7,9,12–15,17,20]; cognitive and behavioral changes in 13 articles (59%)[1,3,5–9,12–15,17,20]; brainstem signs in 14 articles (64%)[1,3–7,9–13,15–17]; and sphincter dysfunction in 10 articles (45%)[1–6,9,12,15,17] (Table 1).

2. Imaging Tests:

Imaging tests were reported in 17 studies (77%). MRI findings included hyperintense T2/FLAIR lesions in the brainstem in 14 articles (64%)[1,3–7,9,11–13,15–17]; thalamus in 12 articles (55%)[1,3–7,9,12–14,16,20]; white matter in 15 articles (68%)[1–8,10–13,15–17]; and basal ganglia in 10 articles (45%)[1,3,6,7,10,12–14,16,19]. Edema or lesion volume was reported in 9 articles (41%)[4,6,7,10,12,13,15,16,19]; contrast enhancement in 7 articles (32%)[3,6,12,13,15,16,19]; cerebral venous thrombosis in 8 articles (36%)[3,6,9,11,12,15,16,19]; and chronic cerebral atrophy in 5 articles (23%)[5,12,14,20] (Table 1).

3. Cerebrospinal Fluid Analysis:

Reported in 18 studies (82%), cerebrospinal fluid (CSF) analysis findings included pleocytosis, elevated protein levels, increased IgG, and absent or infrequent oligoclonal bands[2,3,6-9,11,12-21] (Table 1).

4. Diagnostic Criteria:

Kalra et al. (2014) criteria were applied in 15 studies (68%), yet only approximately 55% of patients fully met the criteria, particularly in cases presenting with

isolated neurological symptoms[5,6,12-22] (Table 1).

5. Differential Diagnosis:

Differential diagnoses frequently considered included multiple sclerosis in 14 articles (64%)[1,3–7,9–13,16]; neurosarcoidosis in 10 articles (45%)[3,5,6,10,12,13,15,16,20]; CNS vasculitis in 12 articles (55%)[3–7,10,12–16]; and autoimmune encephalitis in 8 articles (36%)[5,6,10,16] (Table 1).

Disscussion

Neuro-Behçet's disease (NB) is a rare but potentially disabling condition, affecting approximately 5–10% of patients with Behçet's disease, predominantly young men aged 20–40 years[1]. Symptoms typically manifest years after the onset of systemic BD, contributing to diagnostic delays[11]. The primary challenge lies in the clinical nonspecificity of neurological manifestations (Table 1).

Additionally, although not specific for Neuro-Behçet's disease diagnosis, certain systemic features such as pathergy reaction and HLA-B51 positivity may provide useful clues when evaluating patients with suspected Behçet's disease[2,18]. These findings, while not required for neurological diagnosis, can support the clinician's suspicion of systemic BD and guide further diagnostic work-up.

Pyramidal symptoms, such as hemiparesis and dysarthria, are frequent and require careful differentiation from acute cerebrovascular events, especially when associated with brainstem involvement, which is also common in NB[12,17].

Cognitive and behavioral changes, reported in more than half of patients, necessitate careful assessment in young individuals, particularly when correlated with neuroimaging findings, such as hyperintense T2/FLAIR lesions in the brainstem, thalamus, and white matter[20,19] (Figure 2). These features highlight the importance of integrating clinical and imaging data to distinguish NB from other inflammatory and demyelinating conditions, including multiple sclerosis, neurosarcoidosis, CNS vasculitis, and autoimmune encephalitis[10,16] (Table 1).

Sphincter dysfunction, although less frequent, should not be underestimated, as it can provide important diagnostic clues in complex cases[21]. Cerebrospinal fluid analysis, while supportive, lacks specificity; pleocytosis, elevated protein levels, and increased IgG may assist in the differential diagnosis but are not pathognomonic[21]. The limited sensitivity

of current diagnostic criteria, particularly those by Kalra et al., results in incomplete case identification, especially in patients presenting with isolated neurological symptoms[22] (Table 1).

Chronic cerebral atrophy, observed in 23% of patients[20], represents progressive loss of neuronal tissue and brain volume, which may result from recurrent inflammatory attacks or persistent subclinical inflammation in Neuro-Behçet's disease. Its presence highlights the importance of early diagnosis and aggressive management, aiming to prevent irreversible tissue damage and long-term disability (Table 1). MRI findings of atrophy can thus serve as both a marker of disease severity and a tool to guide prognostic counseling[20,12].

This review underscores the necessity of a multidisciplinary approach, involving neurologists, rheumatologists, and radiologists, to optimize early recognition and management[10]. Emerging diagnostic tools, including experimental biomarkers and predictive algorithms, may improve early detection and facilitate tailored therapeutic strategies, thereby reducing the risk of irreversible neurological damage[17].

CONCLUSION

NB remains a diagnostic challenge due to symptom heterogeneity, lack of confirmatory tests, and limited diagnostic criteria. Early detection relies on a trained multidisciplinary team vigilant for subtle signs, especially in young patients with systemic BD. Chronic cerebral atrophy highlights the need for timely intervention to prevent irreversible damage[20,12].

Future priorities include validation of sensitive criteria, incorporation of biomarkers (NFL, GFAP), and enhanced professional training. Timely immunosuppressive or biologic therapy (infliximab, adalimumab) depends on accurate diagnosis. Integrating precise diagnosis, individualized therapy, and continuous monitoring is essential to improve outcomes in NB. Recognition of systemic features such as pathergy reaction or HLA-B51 positivity may provide additional clues to support suspicion of underlying Behçet's disease and guide further evaluation[2,18].

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TABLE AND FIGURE REFERENCES

- Table 1: Main clinical, imaging, and laboratory findings in Neuro-Behçet's disease (n = 22 studies).
- Figure 1: PRISMA flow diagram of the systematic review selection process.
- Figure 2: Frequency of clinical symptoms and complementary exam findings in Neuro-Behçet's disease.

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Figure 1. PRISMA Flow Diagram 2

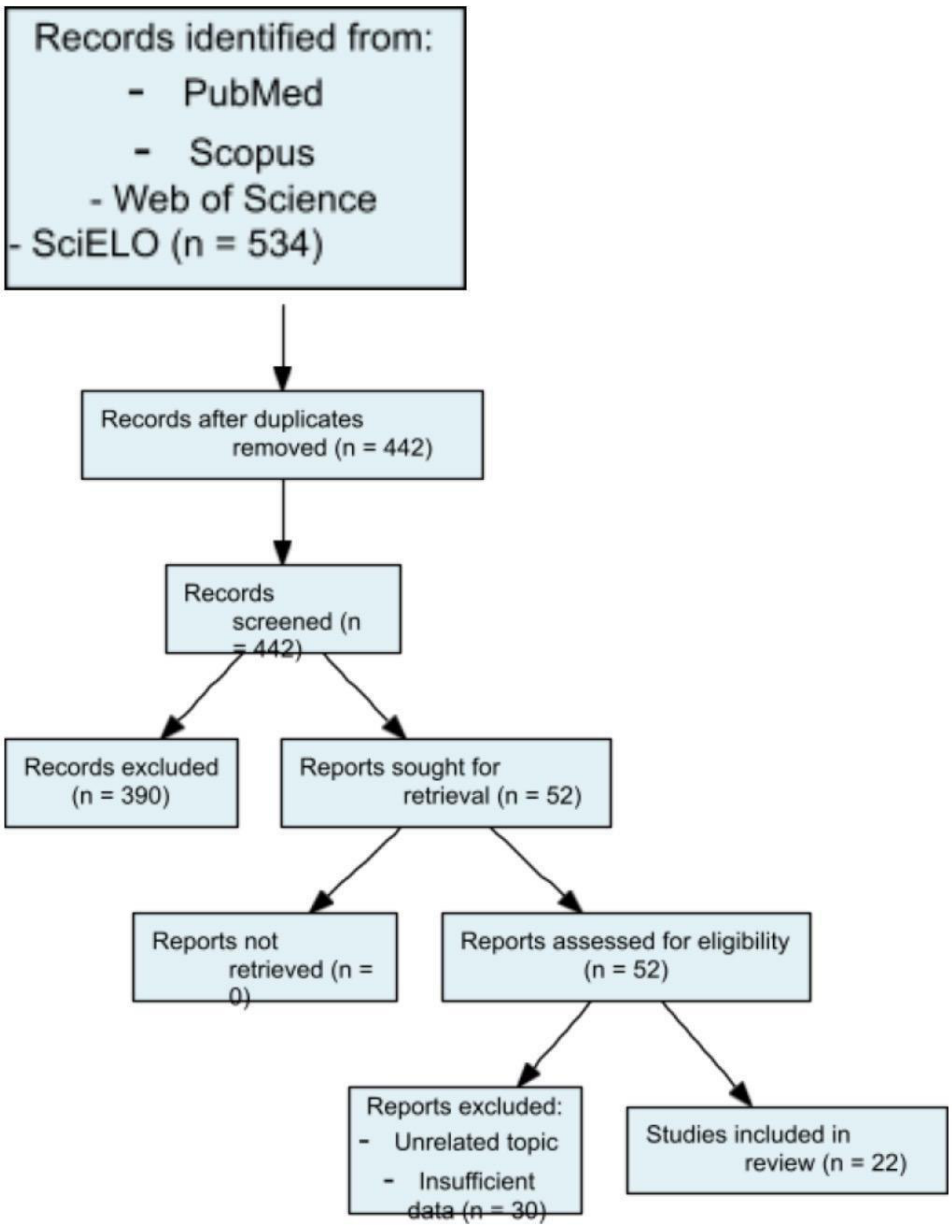

Figure 2. Results Graph

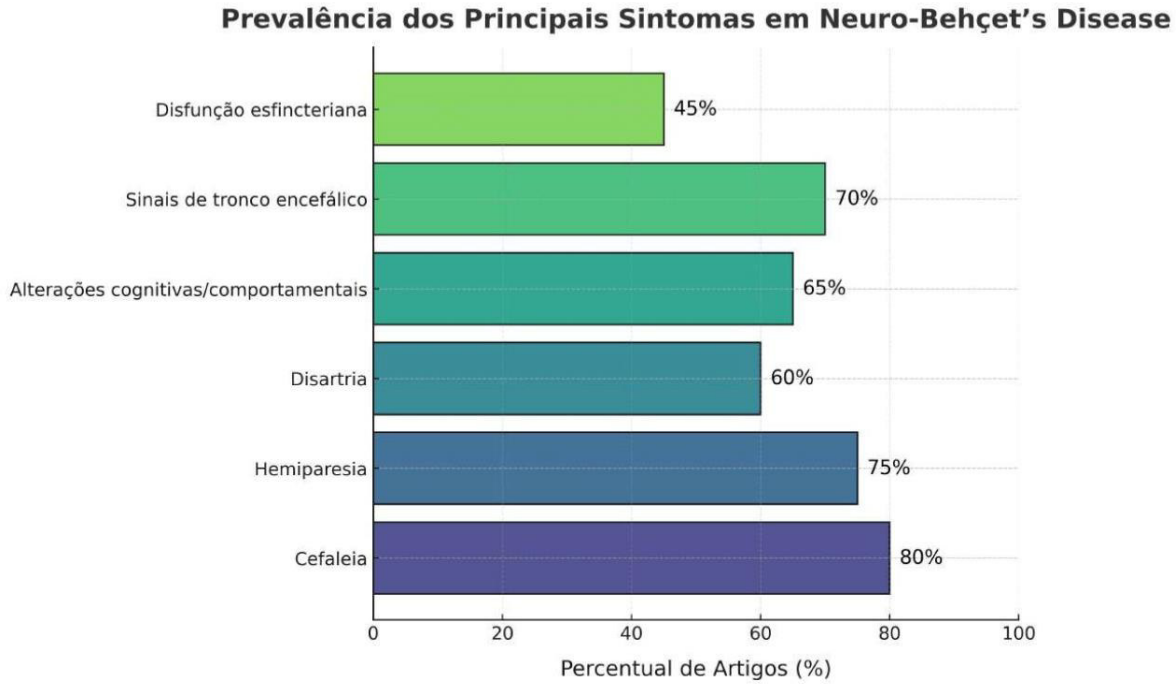

Table 1 – Characteristics of the Included Studies on Neuro-Behçet's Disease

Author and Year	Gender (% Male)	Main Symptoms	CSF Findings	Differential Diagnosis
Al-Fahad (1999)[1]	70%	Hemiparesis, Headache, Dysarthria	Pleocytosis and elevated protein	Multiple sclerosis
Borhani-Haghighi et al. (2013)[2]	60%	Headache, Cognitive impairment, Pyramidal signs	Increased protein	Neurosarcoidosis
Borhani-Haghighi, Pourmand & Nikseresht (2005)[3]	63%	Hemiparesis, Ataxia, Headache	Normal	Multiple sclerosis
Hentati et al. (1993)[4]	65%	Hemiparesis, Headache, Ataxia	Normal	Not specified
Kalra et al. (2014)[5]	60%	Paresthesia, Hemiparesis, Sphincter dysfunction	Increased IgG, absent oligoclonal bands	Multiple sclerosis, autoimmune encephalitis

Miller, Venna & Siva (2014)[6]	55%	Headache, Brainstem signs, Dysarthria	Pleocytosis and elevated protein	Autoimmune encephalitis, vasculitis
Saadoun et al. (2018a)[7]	72%	Dysarthria, Cognitive impairment, Headache	Mild pleocytosis	Neurosarcoidosis, CNS vasculitis
Saadoun et al. (2018b)[8]	68%	Cognitive impairment, Dysarthria, Pyramidal signs	Increased protein, absent oligoclonal bands	Autoimmune encephalitis
Saip, Akman-Demir & Siva (2014)[9]	50%	Hemiparesis, Brainstem signs, Dysarthria	Pleocytosis	CNS vasculitis
Silman et al. (2014)[10]	58%	Behavioral changes, Headache, Venous thrombosis	Elevated protein	Autoimmune encephalitis
Alpagut, Akman-Demir & Siva (2002)[11]	62%	Hemiparesis, Dysarthria, Headache	Normal	Multiple sclerosis
Altintas et al. (2021)[12]	66%	Headache, Pyramidal signs, Cognitive impairment	Mild pleocytosis	CNS vasculitis
Alvarez-Lario et al. (2019)[13]	55%	Dysarthria, Behavioral changes, Headache	Elevated protein	Multiple sclerosis, neurosarcoidosis
Antoniades, Tsekouras & Mourtzoukos (2017)[14]	61%	Hemiparesis, Headache, Brainstem signs	Normal	CNS vasculitis
Bouali et al. (2020)[15]	59%	Headache, Cognitive impairment, Dysarthria	Pleocytosis	Multiple sclerosis
Canhão et al. (2018)[16]	65%	Hemiparesis, Behavioral changes, Venous thrombosis	Elevated protein	Autoimmune encephalitis

Choi et al. (2017)[17]	68%	Hemiparesis, Behavioral changes, Headache	Mild protein elevation	CNS vasculitis, multiple sclerosis
Direskeneli (2001)[18]	60%	Headache, Cognitive impairment, Pyramidal signs	Normal	Multiple sclerosis
Kocer et al. (2003)[19]	50%	Headache, Cerebral venous thrombosis	Elevated protein	CNS vasculitis
Keser et al. (2018)[20]	70%	Dysarthria, Headache, Pyramidal signs	Increased IgG	Neurosarcoidosis
Kocer et al. (2002)[21]	57%	Headache, Pleocytosis, Dysarthria	Elevated protein	Multiple sclerosis
Lee et al. (2015)[22]	64%	Hemiparesis, Sphincter dysfunction, Headache	Pleocytosis	CNS vasculitis

Legend: CSF = cerebrospinal fluid; CNS = central nervous system.