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# BEHÇET'S SYNDROME: DEMOGRAPHIC PROFILE, CLINICAL MANIFESTATIONS AND LABORATORY FINDINGS - A LITERATURE REVIEW

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Behçet's syndrome (DS) is a systemic vasculitis characterized by acute and recurrent inflammation in blood vessels of different sizes. **Objective:** The current article aimed to provide an updated overview of DS, including its clinical characteristics, associated genetic and environmental factors, diagnostic challenges and potential complications. **Methodology:** This is a literature review that consisted of a comprehensive search of scientific articles in the PubMed, Lilacs and Medline databases, from 2013 to 2022. Relevant studies were selected that addressed the clinical, etiological and diagnostic aspects of DS. The exclusion method included articles unrelated to DS, studies with different populations or that did not meet the inclusion criteria. **Results:** This article demonstrated that DS is associated with genetic factors, especially the HLA-B51 allele, and environmental factors such as infections. The most common initial symptoms are recurrent oral and genital ulcers, ocular manifestations, abdominal symptoms and skin lesions. The diagnosis of DS can be challenging due to the variety of clinical manifestations and the overlapping of symptoms with other diseases, such as Crohn's disease and herpes. In addition, DS can cause serious complications, including vascular compromise, such as thrombosis and thrombophlebitis, and involvement of the central nervous system, with high associated mortality rates. **Conclusion:** This survey emphasizes the importance of an early and accurate diagnosis of DS in order to avoid irreversible and fatal complications. Although the etiology of DS is still not completely understood, the identification of associated genetic and environmental factors can help in the development of more efficient diagnostic strategies.

**Keywords:** Triple Symptom Complex, Behcet's Syndrome, Systemic Vasculitis.

## GENERAL CONCEPT OF BEHÇET'S SYNDROME

Behçet's syndrome (BS) is described as a systemic, recurrent vasculitis, with constant acute inflammation and localized injuries in small, medium and large vessels.[1] It includes characteristic symptoms such as mucocutaneous lesions, oral and genital ulcers, joint and ocular involvement, which can intensify and compromise the central nervous system, whose evolution is potentially dangerous and, when affected, has a high mortality rate.[2] Furthermore, manifestations of BS are possibly linked to the genetic factor of the human leukocyte antigen allele B51 (HLA-B51), present in some carrier individuals and when associated with exposure to environmental factors exemplified in infections, the presentation of the disease results.[3]

## EPIDEMIOLOGY

Known as Silk Road disease, due to its higher incidence in countries that are located in the Far East to the West, research indicates that it usually occurs in individuals aged between 30 and 40 years.4 Likewise, the expression of BS varies according to with the region in which it is located, since in Turkey there is a higher prevalence of cases, but infrequently found in the West.5 The results show that the distribution is similar between the sexes, however it varies according to the region, the prevalence in Japan and in Korea they are women, whereas men are often associated with BS in countries that border the Middle East to the Mediterranean.[4,5]

This misunderstood factor disfavors a diagnostic criterion worldwide, due to multiple evidence that varies its expression according to the region affected in the body and geographic location, due to migration, being found in regions where there is greater migration of people from countries in that BS is more present, having data similar to the places of origin.[6]

The numbers vary according to the location and heterogeneity of the studies, however, in general parameters, the occurrences of mucocutaneous manifestations are the most characteristic and present in BS, seen in more than 95% of the cases, followed by ocular and joint symptoms with 93%, HLA-B51 positive in 48%, genital aphthous in 10%, uveitis in 8.6%, retinal vasculitis in 0.3% and below neurological complications.[4,6]

## CLINICAL AND LABORATORY MANIFESTATIONS

BS is considered a vasculitis of vessels of different sizes, its involvement is due to the inflammation process, whose clinical symptom varies depending on the location.[7] It is often associated with venous events, however, it rarely affects the arterial system and, when affected, has a poor prognosis.[8] To be considered SB vasculitis, it must have the diagnosis of exclusion of other diseases that can lead to venous thrombosis and have different histological and clinical characteristics, not have a high risk of atherosclerosis, without granulomatous inflammatory lesions found and with preserved elastic fibers in the vessel walls, inflammatory infiltrate with lymphocytes and neutrophils and perivascular histology, so it is called neutrophilic perivasculitis.[9] Venous thrombosis (VT) is found in about ⅓ of the cases, with bilateral characteristics, with superficial venous thrombosis and deep venous thrombosis being the most assiduous among the vascular manifestations; however, thrombosis can progress and convert into portal thrombosis, thrombosis cerebral vein, intracardiac thrombosis.[10] In addition, we can have vascular complications with the final location in the lungs, such as pulmonary embolisms and aneurysms in the pulmonary

artery circulation.[11]

In the nervous system, cognitive alterations, impaired late recall and, rarely, cerebral embolism were observed, with headache being the most frequent neurological manifestation.[11,17]

In the gastrointestinal system, the most reported symptoms are epigastric abdominal pain and dyspepsia, however, as they involve several organs of the alimentary tract, occurrences in the esophagus, stomach, pancreas and intestine are reported.[12]

Rare complications include Dieulafoy lesions and gastric non-Hodgkin's lymphoma, acute pancreatitis, multiple esophageal and ileocecal ulcers, descending esophageal varices, stenosis, abscess formation, fistula, perforation, infarction, and intestinal ischemia.[12]

The optical system is one of the most affected in BS, which can lead to total and irreversible blindness, however, uveal symptoms are the most common, being found in more than half of patients with BS, making uveitis the most typical and with initial signs demonstrated by ophthalmia, photophobia, flying flies, amaurosis and anopsia.[13] Anterior and posterior uveitis and panuveitis are non-granulomatous acute intraocular inflammations related to retinal vasculitis, other inflammations such as scleritis, keratitis, keratoconjunctivitis, episcleritis, optic neuritis and orbitopathy may be present in BS.[13] However, complications may result from ocular recurrences, resulting in macular edema, posterior synechiae, retinal detachment, cataracts, ocular hypertension, macular pucker membrane optic atrophy, glaucoma and retinal hemorrhages.[14]

The histopathological trait established in BS is the infiltration of neutrophils and monocytes in the perivascular region, caused by the autoimmune response and hyperactivity of neutrophils that play a role in the regulation of the inflammatory process.[15]

That said, the thickness of the venous wall of the lower limbs (VWT) is constantly reported in BS, the elevation demonstrates a sign of iterative venous inflammation with predisposition to VT, thus, VWT is used as an inflammatory marker, having the count as a parameter of procalcitonin, mean platelet volume, erythrocyte sedimentation rate, monocyte-lymphocyte ratio, red blood cell distribution amplitude, erythrocyte sedimentation rate, and C-reactive protein.[16]

There are still no biological markers that characterize BS to define the presence and severity, using only clinical findings as a diagnosis, however, an increase in interleukin 2, 6, 8 and 12 was observed, in addition to interferon gamma, adenosine, antistreptolysin and deaminase indicating disease activity.[16,17]

## DIAGNOSIS

Currently, 17 sets of diagnostic criteria for BS are found in different countries where they differ in the methodology for confirming the disease, the most used and with the greatest sensitivity being the Behçet's Disease International Study Group (ISG), developed in 1990 by Turkey, Iran, France, Tunisia, United States, Japan and United Kingdom.[18] The ISG consists of a table with clinical and laboratory findings in which there is confirmation of BS when there is oral aphthous disease present for at least 3 times within a period of 12 months, in addition to two more manifestations, among them: genital, ocular lesions and/or skin lesions and a positive pathergy test.[18,19] In addition to serum inflammation measurements, it is recommended to count antinuclear antibodies and antineutrophil cytoplasmic antibodies, human leukocyte antigen B51, and syphilis serology for diagnosis of exclusion.[19]

To assist in the investigation of BS, there is a detailed anamnesis that includes the

systems most affected by the disease, such as the vascular, optical, gastrointestinal and neurological systems.[19] In addition, physical examinations are necessary, which include arterial, joint and dermatological health, as well as imaging investigation if complications are suspected, including chest X-ray and tomography to exclude aneurysms, abdominal ultrasound to analyze whether there is thrombosis of the vena cava and also hepatosplenomegaly, magnetic resonance imaging of the central nervous system, angiography, cerebrospinal fluid puncture and colonoscopy.[18,19]

## DIFFERENTIAL DIAGNOSIS

In dermatological diseases, ulcerations that resemble BS may appear, such as Stevens-Johnson syndrome, pemphigus, bullous pemphigoid, sapho syndrome and lichen planus.[20] On the other hand, manifestations that affect joints and present aphthous ulcerations can be confused with other rheumatological diseases such as systemic lupus erythematosus, familial Mediterranean fever, rheumatoid arthritis, non-deforming arthritis, PAPA syndrome, Blau syndrome, Muckle-Wells syndrome, cinc and spondyloarthritis.[21] However, when they reach the gastrointestinal system, they can be linked to other diseases such as celiac, Crohn's, inflammatory bowel disease and ulcerative colitis.[21] With inflammatory or hematological changes, cyclic neutropenia, hyperimmunoglobulinemia D with periodic fever syndrome, infectious diseases with positivity for herpes simplex virus or human immunodeficiency virus.[20,21]

## TREATMENT

The most applied first-line treatment is the use of glucocorticoids (GC), as they induce remission and recurrence of new lesions when administered in low doses, orally or topically, in cases of joint and mild skin involvement.[22] Together, they associate non-steroidal anti-inflammatory drugs (NSAIDs) or colchicine, which can also be used alone due to its tolerability, safety and when combined, they did not obtain an increase in the potential for malignancy and infection.[22,23] For oral ulcers, the effectiveness of apremilast, an oral phosphodiesterase-4 inhibitor, has been proven by the Food and Drug Administration (FDA), but for recurrent ulcers, azathioprine is still used. (AZA).[23] Cyclosporine E, mycophenolate mofetil (MMF) and ASA are recommended for mild cases, when there is ocular involvement, prevention of iterative uveitis and visual protection.[22] For mild consequences of the gastrointestinal system, 5-aminosalicylic acid (ASA) with or without the addition of GC is available as an alternative therapeutic resource.[22,23]

Thus, diseases that affect major organs are treated with long-term immunosuppression.[24] But when they do not respond to more conventional treatments or the complications caused by BS worsen, they use immunobiological inhibitors of gamma tumor necrosis factor such as IFX (infliximab) or ADA (adalimumab), and also interleukin inhibitors such as secukinumab and ustekinumab or GC pulses for a week as more aggressive forms of treatment.24 For cases of intolerance to the drugs already mentioned, they apply interleukin 1 inhibitors such as anakinra (ANA) or canakinumab (CANA).[22,25]

## CONCLUSION

Behcet's syndrome (BS) is a systemic vasculitis characterized by recurrent acute inflammation affecting blood vessels of different sizes. This disease exhibits a wide variety of clinical manifestations, such as mucocutaneous lesions, oral and genital ulcers, joint and ocular involvement, as well as possible complications in the central nervous

system. A similar distribution between sexes is observed in the demographic profile of BS, although there are variations according to geographic region, being more prevalent in countries that extend from the Far East to the Mediterranean. The HLA-B51 allele is considered a genetic factor associated with the disease. The diagnosis of BS is established based on clinical and laboratory criteria, with the set of criteria from the Behcet's Disease International Study Group (ISG) being widely used. Treatment consists of the administration of glucocorticoids, non-steroidal anti-inflammatory drugs and immunosuppressants, and immunobiologicals may be used in serious situations or when the patient does not respond to conventional treatments. It is essential to understand in detail the demographic, clinical and laboratory profile of patients with BS in order to make an accurate diagnosis and provide adequate management of the disease.

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