REVIEW ARTICLE

Julie R. Ingelfinger, M.D., *Editor*

Behçet's Syndrome

David Saadoun, M.D., Ph.D., Bahram Bodaghi, M.D., Ph.D., and Patrice Cacoub, M.D.

From Sorbonne Universités Assistance Publique–Hôpitaux de Paris (AP-HP), Groupe Hospitalier Pitié–Salpêtrière, Département de Médecine Interne et Immunologie Clinique, Centre National de Références Maladies Autoimmunes Systémiques Rares, Centre National de Références Maladies Autoinflammatoires et Amylose Inflammatoire, Institut Hospitalo-Universitaire FOReSIGHT, Inflammation–Immunopathology–Biotherapy Department, Clinical Investigation Center in Biotherapy, and INSERM 959, Groupe Hospitalier Pitié–Salpêtrière, AP-HP (D.S., P.C.), and Sorbonne Universités AP-HP, Centre National de Références Maladies Rares en Ophtalmologie, Institut Hospitalo-Universitaire FOReSIGHT, Groupe Hospitalier Pitié–Salpêtrière, Département d'Ophtalmologie (B.B.) — all in Paris. Dr. Saadoun can be contacted at david.saadoun@aphp.fr or at Sorbonne Universités AP-HP, Groupe Hospitalier Pitié–Salpêtrière, Département de Médecine et Immunologie Clinique, F-75013, Paris, France.

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Behçet's syndrome is a chronic, multisystem, inflammatory condition with a relapsing and remitting course. This disorder has been increasingly recognized as a syndrome because it has a broad spectrum of signs and symptoms, each with distinct prognostic implications for a patient's quality of life, and is associated with substantial morbidity and even death.[1] Over the past 20 years,[2] several discoveries have reshaped our understanding of Behçet's syndrome, and it is currently classified as a primary systemic vasculitis affecting veins and arteries of any size.[3] The evolving classification of the disorder stems mainly from advances in immunogenetics, facilitated by genomewide association studies and next-generation sequencing techniques, that have led to the identification of key genetic factors.[4] In this review, we examine the most relevant and recent developments regarding the epidemiology, pathogenesis, and clinical expression of Behçet's syndrome, as well as the differential diagnosis and emerging targeted therapeutics.

Epidemiology

Historically, Behçet's syndrome occurred in regions along the ancient Silk Road. The current epidemiology varies widely according to geographic location and ethnic group. The highest prevalence is found in Turkey, with 420 cases per 100,000 persons.[5] Across Europe, a north–south gradient has emerged, with prevalence ranging from 0.3 to 4.9 cases per 100,000 persons in northern countries and 1.5 to 15.9 cases per 100,000 persons in southern regions.[6] In the United States, the reported prevalence is 5.2 cases per 100,000 persons.[7] In Dutch and German studies, the frequency of Behçet's syndrome has been higher among immigrants from high-prevalence regions than among native residents, although the rates among immigrants are lower than those in their countries of origin.[8,9] Familial aggregation of Behçet's syndrome has been reported in specific populations, particularly among patients with early-onset Behçet's syndrome.[10] The mean age at diagnosis is approximately 30 years, with the majority of patients presenting between the ages of 15 and 45 years.[6] Disease activity tends to wane with advancing age.[11,12] Although there is no difference in the incidence of Behçet's syndrome according to sex, male patients are more likely than female patients to have severe forms of the disease.[11-13]

Environmental Triggers and Genetic Features

The pathogenesis of Behçet's syndrome is poorly understood, but it is thought to develop in genetically predisposed hosts after exposure to a wide range of environmental triggers. Such exposures lead to the activation of cellular effectors and signaling pathways, potentially resulting in tissue inflammation and damage (Fig. 1). For example, microorganisms (bacteria, viruses, and their byproducts), consumption

of histamine-releasing foods (e.g., citrus fruits, nuts, and cheese), poor oral hygiene, and stress have been proposed as potential triggers.[1] There is growing evidence of alterations in the balance of gut and salivary mucosal flora in patients with Behçet's syndrome, suggesting that these imbalances may contribute to the repertoire of antigens associated with the disorder.[14,15]

Behçet's syndrome includes both autoimmune and autoinflammatory features. The first genetic association reported for Behçet's syndrome was within the class I major histocompatibility complex antigen HLA-B*51 (particularly the major subtype HLA-B*51:01).[10] Although the prevalence of HLA-B*51 varies among ethnic groups, a meta-analysis showed that Behçet's syndrome was 6 times as likely to develop in HLA-B*51 carriers.[16] Genomewide association studies[17,18] have shown an epistatic interaction between HLA-B*51 and the gene encoding endoplasmic reticulum aminopeptidase 1 (*ERAP1*; odds ratio, 4.56), which may interfere with antigen presentation and processing and lead to the activation of natural killer cells and disturbances in T-cell homeostasis. Genes implicated in types 1 and 17 helper T-cell (Th1 and Th17) polarization, such as *IL23R–IL12RB2*, *STAT4*, and *IL10*, have been found to be associated with Behçet's syndrome (odds ratio, 1.28, 1.27, and 1.45, respectively). Also reported to play a role are genes involved in regulating natural killer cell activity (*KLRC4*; odds ratio for protective effect, 0.78) and those involved in cell chemotaxis (*CCR1*, *CCR2*, and *CCR3*; odds ratio for protective effect, 0.72).[17,18] Single-nucleotide polymorphisms (SNPs) and low-frequency variants implicated in several monogenic and polygenic inflammatory disorders have also been described in association with Behçet's syndrome.[19,20] For example, *TNFAIP3* and *MEFV* are responsible for A20 haploinsufficiency and familial Mediterranean fever, respectively.[21] The importance of epigenetics in Behçet's syndrome was highlighted in a 2014 study, which showed aberrant DNA methylation in genes that regulate cytoskeletal dynamics and cell adhesion.[22] In addition, activation histone marks have been overrepresented in natural killer cells, monocytes, lymphocytes, and neutrophils from patients with Behçet's syndrome.[23]

Several reports have suggested that the adaptive immune response in patients with Behçet's syndrome is mediated by CD4+ T-helper lymphocytes, which are differentiated into Th1 and Th17 cell subtypes, and diminished regulatory T-cell activity.[24-26] The Th1 response induces the production of proinflammatory cytokines (e.g., tumor necrosis factor α [TNF-α] and interferon-γ) and cytotoxic T-cell activity,[21] which involves both CD8+ T cells and natural killer cells. The Th17 response results in the production of other proinflammatory cytokines (e.g., interleukin-17 and interleukin-23) and promotes neutrophil chemotaxis.

Neutrophils constitute the main infiltrating cell type in Behçet's syndrome lesions. By producing excessive levels of reactive oxygen species and releasing neutrophil extracellular traps, neutrophils contribute to the development of a procoagulant state in Behçet's syndrome.[27,28] Examination of skin biopsy specimens from patients with Behçet's syndrome typically reveals leukocytoclastic vasculitis, neutrophilic or lymphocytic perivascular infiltrates, microvascular thrombi, or neutrophilic dermal infiltrates.

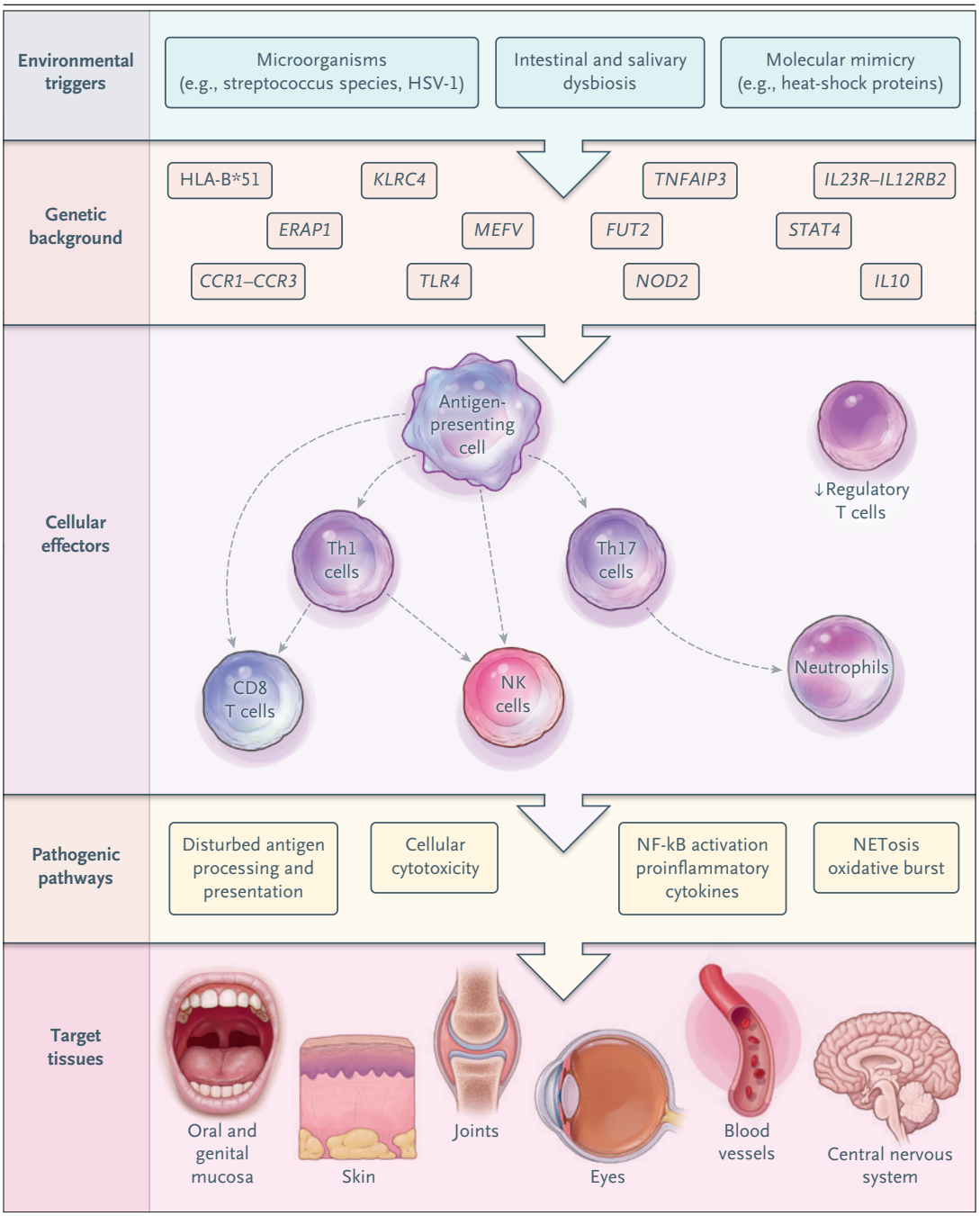
In addition, the nuclear factor κB (NF-κB) proinflammatory pathway has been reported to have a pivotal role in sensing immune responses in Behçet's syndrome. NF-κB intracellular signaling is heightened in antigen-presenting cells, neutrophils, and Th1 and Th17 cells.[24,29-31]

CLINICAL MANIFESTATIONS

The heterogeneous clinical features of Behçet's syndrome (Figs. 2 and 3) overlap throughout the course of the disease, with frequencies of disease-related manifestations that vary according to ethnic group.[32-35] Overall, Behçet's syndrome can be categorized on the basis of its manifestations, which affect the skin, mucosa, joints, eyes, vascular system, central nervous system, and gastrointestinal tract.[1,35]

SKIN AND MUCOSAL MANIFESTATIONS

Recurrent oral ulceration, a hallmark of Behçet's syndrome, is the most common clinical manifestation, followed by genital ulcers, papulopustular lesions, and nodular skin lesions. Up to a third of patients present with only these manifestations throughout the course of their illness.[12,35] Oral ulcers are typically both the initial and most persistent symptom in Behçet's syndrome.[35] However, distinguishing Behçet's syndrome–related oral ulcers from those in the general population



(which affect up to 60% of the population)[36,37] can be challenging. Genetic findings suggest that Behçet's-like disorders constitute a spectrum from recurrent aphthous stomatitis to PFAPA (periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis) syndrome[38] (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).

Genital ulcers may occur in Behçet's syndrome, and they form scars in approximately two thirds of cases.[39] These ulcers are larger, deeper, and longer-lasting than oral ulcers. Most appear on the scrotum or labia.[1,35] Papulopustular lesions, often described as "acne-like," can be indistinguishable from acne vulgaris both in appearance and histologic features.[40-42] Nodular lesions can be indica-

Figure 1 (facing page). Pathogenesis of Behçet's Syndrome.

Genomewide association studies performed across different populations have recently provided new pathogenetic insights into the epistatic interaction between HLA-B*51 and endoplasmic reticulum aminopeptidase 1 (*ERAP1*), type 1 and type 17 helper T-cell (Th1 and Th 17) polarization, natural killer (NK) cell activity and cell chemotaxis. Single-nucleotide polymorphisms (SNPs) that are implicated in gut microbiome misbalance or innate immunity have been reported in *FUT2*, *TLR4*, *NOD2*, and *MEFV*. An SNP in *TNFAIP3* was also identified, encoding the A20 protein that inhibits the nuclear factor κB (NF-κB) proinflammatory pathway. Heterozygous loss-of-function mutations in *TNFAIP3* lead to haploinsufficiency A20, characterized by early-onset systemic inflammation with recurrent oral, genital, and gastrointestinal ulcers that resemble Behçet's syndrome. Various microorganisms and their byproducts have been described among the environmental triggers potentially involved in Behçet's syndrome. A misbalance between gut and salivary microbiota has been increasingly reported as well. Gene–environment interactions are followed by the interaction of antigen-presenting cells with several types of immune cells. The adaptive immune response in Behçet's syndrome is mediated mainly by CD4+ T-helper lymphocytes, which are differentiated into Th1 and Th17 cell subtypes at the expense of decreased regulatory T-cell activity. Th1-driven cytotoxicity involves CD8+ T cells and NK cells, both of which may also be activated through direct class I major histocompatibility complex antigen priming. The Th17-cell response leads to neutrophil chemotaxis and activation that lead to reactive oxygen species production and release weblike structures known as neutrophil extracellular traps. Intracellular signaling through the NF-κB pathway further increases production of proinflammatory cytokines and has been shown to be enriched in several cellular effectors in Behçet's syndrome. HSV-1 denotes herpes simplex virus type 1, and NETosis program for formation of neutrophil extracellular traps.

tive of either panniculitis or superficial thrombophlebitis. Clinically, Behçet's syndrome–associated panniculitis resembles erythema nodosum, and histopathological analysis may reveal the presence of neutrophilic vasculitis.[35]

JOINT MANIFESTATIONS

Roughly half the patients with Behçet's syndrome have joint involvement, which typically manifests as nondeforming, self-limited monoarthralgia or oligoarthralgia or arthritis, primarily affecting the knees, ankles, wrists, and elbows. These joint symptoms may be accompanied by enthesopathy (inflammation of the connective tissue between bones and tendons or ligaments). A distinct cluster of symptoms comprising acne, arthritis, and enthesitis has been proposed, since acne-like lesions tend to follow these articular and periarticular manifestations, resembling peripheral spondyloarthritis.[40,41] However, involvement of the sacroiliac joint or spine is uncommon in Behçet's syndrome.[35]

OCULAR MANIFESTATIONS

The eye is the most frequently affected major organ in Behçet's syndrome, with ocular involvement occurring in approximately 50% of patients.[2,12,43] Bilateral involvement is observed in 75 to 80% of new cases with ocular manifestations, on average occurring 2 years after the onset of the initial symptoms.[12] Panuveitis is the most common presentation. Severe attacks of anterior uveitis may lead to a characteristic hypopyon (accumulation of leukocytic exudate in the anterior chamber). However, isolated anterior uveitis occurs in approximately 10% of patients.[43] Vitritis, foci of retinitis, signs of occlusive retinal vasculitis, diffuse retinal capillary leakage on angiography, and the absence of granulomatous anterior uveitis or choroiditis are suggestive of Behçet's syndrome–associated uveitis.[44,45] Certain factors, including male sex, posterior eye chamber involvement, a history of more than three attacks per year, and the presence of vitreous opacity with macular edema, are associated with a poor visual outcome.[43,46]

VASCULAR MANIFESTATIONS

Vascular Behçet's syndrome can affect both veins and arteries of varying calibers[35] and typically follows a relapsing course.[47] Overall, the estimated 5-year cumulative risk of recurrent vascular events among patients with Behçet's syndrome is close to 40%.[48]

Superficial thrombophlebitis and deep-vein thrombosis are the most common manifestation of vascular Behçet's syndrome, occurring in 15 to 40% of cases. In patients with deep-vein thrombosis, there is a predilection for lower limb involvement, which can lead to a severe post-thrombotic syndrome. However, pulmonary embolism is rare. Thrombotic events have also been noted in several other locations, including portal or suprahepatic veins (Budd–Chiari syndrome), the superior or inferior vena cava, and cerebral sinuses.[6,48] Thrombi in Behçet's syndrome adhere to vein walls and are considered to be a hallmark of inflammation-induced thrombosis.[47]

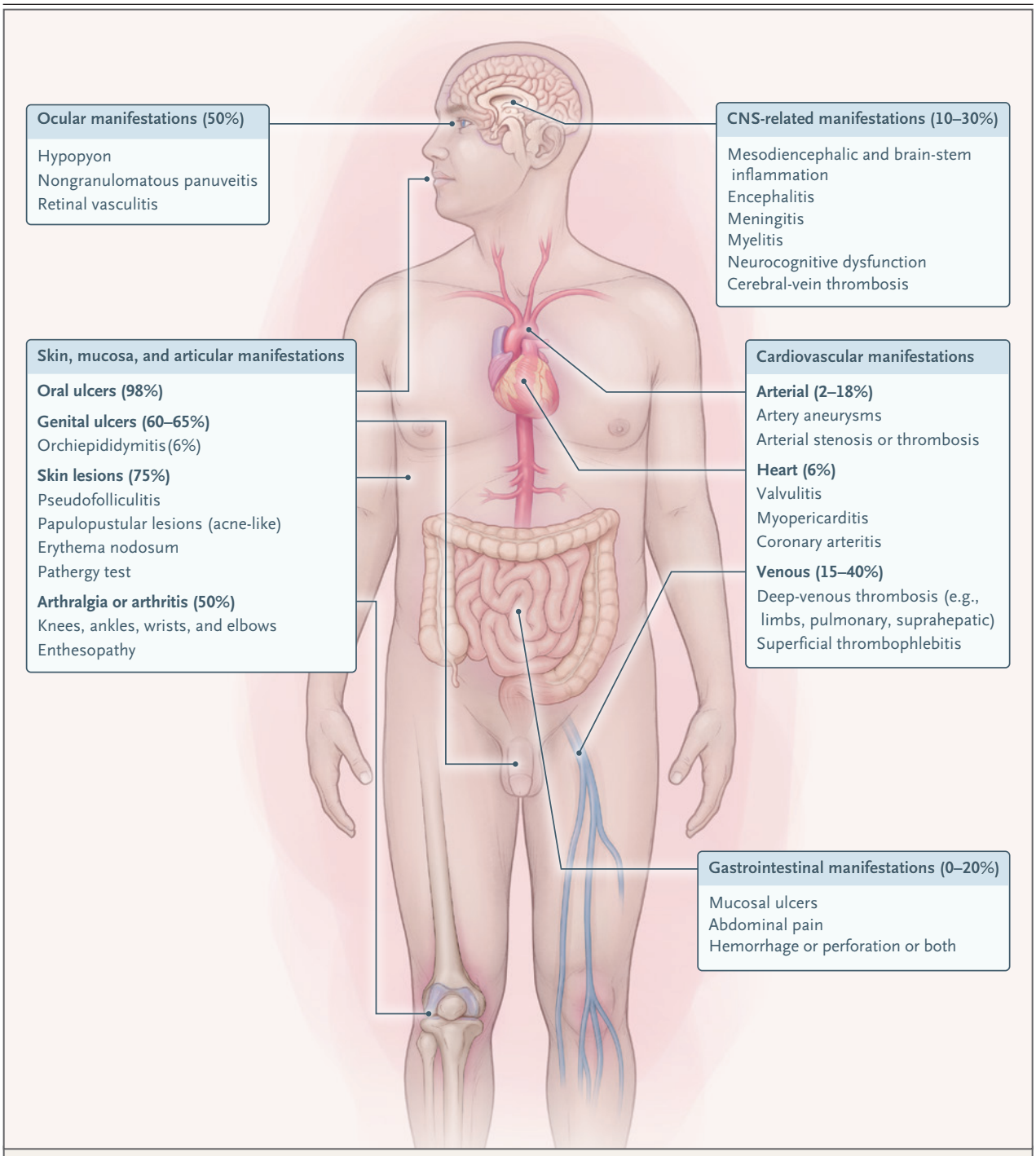


Figure 2. Affected Organs in Behçet's Syndrome.
Shown are the affected organs and the frequency of clinical manifestations in Behçet's syndrome. CNS denotes central nervous system.

Patients with arterial manifestations of Behçet's syndrome primarily present with aneurysms but may also have thrombotic occlusion or stenosis. The aorta and peripheral arteries are mainly affected.[6,47] Involvement of the pulmonary artery, although rare, is highly specific for Behçet's syndrome. Cardiac involvement (seen in 5% of patients), which is usually associated with vascular

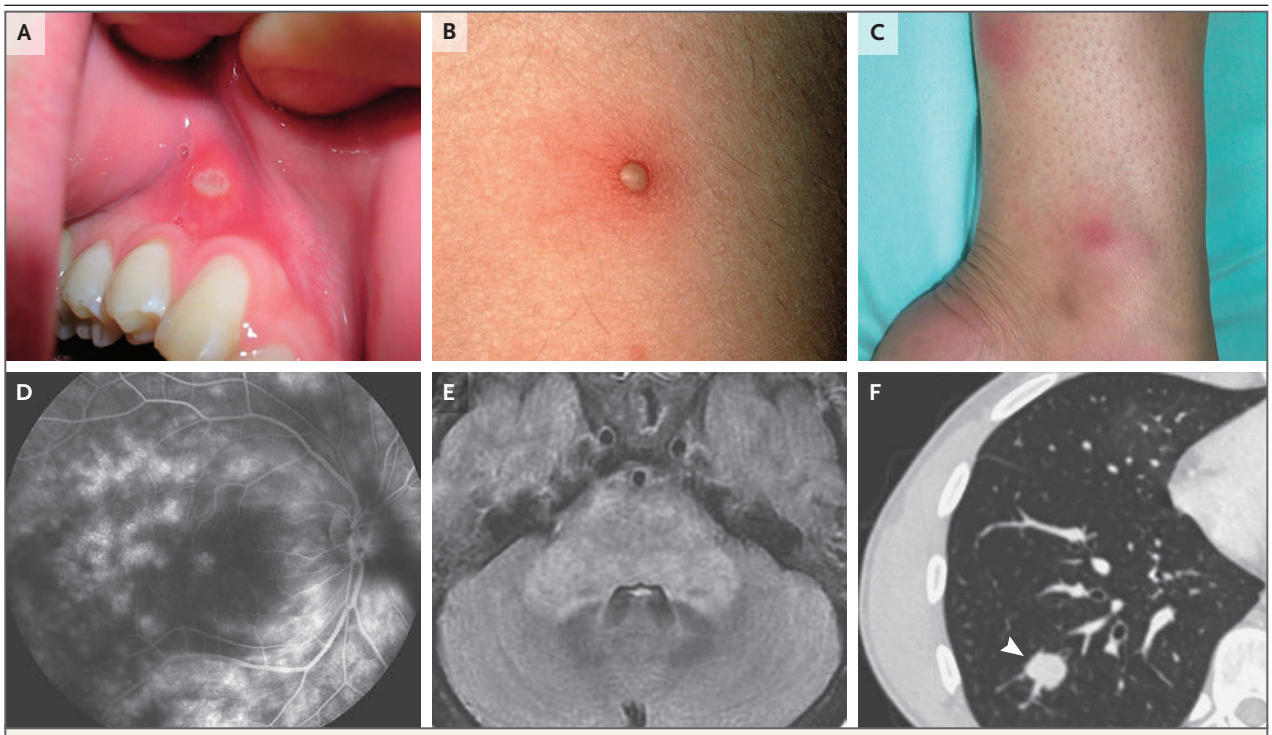


Figure 3. Clinical Manifestations of Behçet's Syndrome.

Shown are the typical features of Behçet's syndrome, including an oral ulcer (Panel A); a papulopustular lesion (Panel B); erythema nodosum (Panel C); capillary impairment and vascular leakage on retinal fluorescein angiography (Panel D); a brain-stem inflammatory lesion on a T2-weighted axial magnetic resonance imaging sequence, with an edematous, protuberant FLAIR (fluid attenuated inversion recovery) hypersignal extending to the middle cerebellar peduncles and discrete hypertrophy (Panel E); and aneurysmal dilatation of a pulmonary-artery branch (Panel F, arrowhead).

Behçet's syndrome, may entail all cardiac components and thus is associated with pericarditis, myocarditis, coronary arteritis, valvulitis, intracardiac thrombosis, and endomyocardial fibrosis.[6]

NEUROLOGIC MANIFESTATIONS

Neurologic involvement in Behçet's syndrome, which accounts for less than 30% of affected organ systems, is parenchymal (in approximately 75% of cases) or nonparenchymal (in approximately 25%).[12,49,50] The most common nonparenchymal finding is cerebral-vein thrombosis, which could be considered a vascular manifestation because of its close association with deep-vein thrombosis.[35,47,48,51] Parenchymal manifestations may occur in parallel with ocular manifestations of Behçet's syndrome, particularly in patients with posterior uveitis.[35,52] Neuro-ophthalmologic manifestations, which are present in up to 10% of patients with neurologic Behçet's syndrome, may include retrobulbar optic neuritis, papilledema, and third- and sixth-nerve palsies.[53] Parenchymal neurologic Behçet's syndrome, which may develop within 5 years after disease onset,[35] is characterized by involvement of the brain stem, particularly the mesodiencephalic junction. Magnetic resonance imaging scans with contrast enhancement show small, scattered inflammatory lesions accompanied by peripheral edema.[50,54] The main clinical symptoms are headaches, hemiparesis, and seizures, although parenchymal disease infrequently has severe manifestations such as myelitis or pseudotumor cerebri. In cases of neurologic Behçet's syndrome, progressive central nervous system damage is most often seen in patients with frequent relapses, a progressive disease course, abnormal cerebrospinal fluid results, and residual neurologic impairment during remission.[49]

GASTROINTESTINAL MANIFESTATIONS

The prevalence of gastrointestinal involvement in Behçet's syndrome varies substantially across ethnic groups, with rates below 5% in Europe and the Middle East and up to 20% in East Asia;

Table 1. Classification Criteria for Behçet's Syndrome.*

Variable	ISG 1990	ICBD 2014
Criteria	Recurrent oral ulceration† Ocular lesions Skin lesions Positive pathergy test	Recurrent oral ulceration (2 points) Genital ulceration (2 points) Ocular lesions (2 points) Skin lesions (1 point) Vascular manifestations (1 point) Neurologic manifestations (1 point) Positive pathergy test (1 point)‡
Criteria or score needed for classification	Recurrent oral ulceration plus 2 other criteria	≥4 points
Sensitivity of criteria — %	81–85	94–95
Specificity of criteria — %	96	91–92

* The two most commonly used classifications for Behçet's syndrome are the International Study Group for Behçet's Disease (ISG) classification and the International Criteria for Behçet's Disease (ICBD). A diagnosis of Behçet's syndrome is still possible even if not all the criteria are met. Recurrent oral ulceration is defined as minor, major, or herpetiform oral aphthous ulcers observed by a physician or patient, recurring at least 3 times over a 1-year period; genital ulceration, as genital ulcers or scarring observed by a physician or patient; skin lesions, as erythema nodosum, pseudofolliculitis, or papulopustular lesions observed by a physician or patient or acneiform nodules observed by a physician in a postadolescent patient not receiving glucocorticoids; ocular lesions, as anterior or posterior uveitis, cells in the vitreous on slit-lamp examination, or retinal vasculitis observed by an ophthalmologist; and vascular lesion, as arterial or venous thrombosis or superficial phlebitis. Neurologic manifestations are not specified. A pathergy test is performed with at least three skin punctures, and a positive reaction is indicated by a papular reaction that is at least 2 mm in diameter and surrounded by erythema or the development of a pustule reaction within 24 to 48 hours. In current clinical practice, venous or arterial Doppler is performed when deep-vein thrombosis or peripheral arterial aneurysms are suspected. Computed tomographic angiography is recommended for cases of pulmonary-artery or aorta involvement. Cerebral magnetic resonance imaging and lumbar puncture should be considered in a patient with persistent headaches or the appearance of neurologic symptoms.

† Recurrent oral ulceration is a mandatory criterion in the 1990 ISG classification (i.e., the presence of any of the other criterion must be accompanied by recurrent oral ulceration for a diagnosis of Behçet's syndrome).

‡ The pathergy test is optional in the ICBD classification.

no differences in prevalence according to sex have been reported.[32,33,35] Gastrointestinal ulcerations may occur throughout the gastrointestinal tract, leading to a range of clinical manifestations from mild to severe, including abdominal pain, diarrhea, and gastrointestinal bleeding. These symptoms may be difficult to distinguish from those found in patients with inflammatory bowel diseases.[55]

DIAGNOSIS

Behçet's syndrome lacks pathognomonic biologic or histologic diagnostic features. The prevalence of HLA-B51 carriage varies according to ethnic group, and the relatively high occurrence of HLA-B51 in the general population limits its usefulness as a diagnostic tool.[1,6] The most widely used classification criteria for Behçet's syndrome were developed in 1990[56] and revised in 2014[57] (Table 1). However, it is important to exercise caution when applying these criteria in clinical practice, since none of them can be used to conclusively confirm or rule out Behçet's syndrome. Moreover, severe manifestations can occur in isolation as an initial presentation. Therefore, the fulfillment of all these criteria should not be mandatory for the establishment of a therapeutic strategy.

Ultimately, the diagnosis of Behçet's syndrome is largely based on the patient's clinical presentation and imaging findings,[32,34] given the broad spectrum of disorders in the differential diagnosis (Table 2). Clinical indicators that strongly suggest Behçet's syndrome may aid in the diagnosis. These indicators include genital scarring and the distinctive eye or major vascular involvement mentioned above, as well as neurologic lesions that extend from the basal ganglia to the brain stem.[1] A specific 10-item algorithm with a high odds ratio for the diagnosis of Behçet's syndrome–related uveitis has recently been reported by ophthalmologic experts.[45]

PROGNOSIS

Major organ involvement in Behçet's syndrome is predictive of both illness severity and death. Young men with Behçet's syndrome often have a rela-

Table 2. Clinical Manifestations and Differential Diagnosis of Behçet's Syndrome.*

Manifestation	Alternative Diagnoses
Skin, mucosal, and articular	
Oral ulcers	Nutritional deficiencies (e.g., iron, zinc, folate, and vitamins B_1, B_6, and B_{12}); HIV or herpes virus infections; recurrent aphthous stomatitis, PFAPA; pemphigus, lichen planus; relapsing polychondritis, MAGIC syndrome; celiac disease; inflammatory bowel diseases; spondyloarthropathies; systemic lupus erythematosus; neutropenia; mevalonate kinase deficiency
Genital ulcers	Herpes simplex virus infection and STDs; inflammatory bowel diseases; A20 haploinsufficiency; MAGIC syndrome; mevalonate kinase deficiency
Erythema nodosum	Bacterial infection (e.g., streptococcus species); tuberculosis, leprosy, yersiniosis; drugs (e.g., oral contraceptives, penicillins, and sulfonamides); inflammatory bowel diseases; Takayasu's arteritis; sarcoidosis; cancers
Oligoarthritis	Spondyloarthropathies; inflammatory bowel diseases
Ocular	
Uveitis	Infections (e.g., herpes virus infection, CMV infection, tuberculosis, and syphilis); sarcoidosis; multiple sclerosis; B27-associated uveitis (acute anterior uveitis); Vogt–Koyanagi–Harada syndrome
Vascular	
Deep-vein thrombosis	Antiphospholipid syndrome; inflammatory bowel diseases; connective-tissue diseases; myeloproliferative diseases; inherited thrombophilias
Artery aneurysms	Infections; Takayasu's arteritis; relapsing polychondritis
Central nervous system	
Inflammatory parenchymal lesions	Infections (e.g., tuberculosis, herpes, and listeriosis); primary central nervous system lymphoma; multiple sclerosis; sarcoidosis; histiocytosis
Gastrointestinal	
Gastrointestinal ulcers	Inflammatory bowel disease; NSAID toxicity; infectious colitis

* For the assessment of cutaneous, mucosal, and articular manifestations, the following diagnostic approaches can be considered to rule out differential diagnoses, depending on the context: clinical presentation, laboratory tests (i.e., hemogram, C-reactive protein, iron, zinc, folate, and vitamin B_1, B_6, and B_{12}), immunologic tests (antidesmoglein antibodies, antitransglutaminase antibodies, antinuclear antibodies, HLA-B27, and angiotensin-converting enzyme), local infectious sampling, and serologic tests for infections or skin biopsy. For the assessment of uveitis, the following methods may be used: ophthalmologic presentation and, depending on the context, laboratory tests (hemogram and C-reactive protein), immunologic tests (HLA-B27 and angiotensin-converting enzyme), serologic tests for infections, chest computed tomography, and magnetic resonance imaging (MRI) of the central nervous system. For vascular manifestations, the diagnostic approach may involve the clinical presentation, vascular imaging, and, depending on the context, an investigation for thrombophilias (e.g., antiphospholipid antibodies, antinuclear antibodies, myeloproliferative syndrome, and inherited factors), serologic tests for infections and blood cultures. For central nervous system involvement, the diagnostic workup may include the clinical presentation, MRI of the central nervous system, and, depending on the context, serologic tests for infections, blood cultures, and lumbar puncture. CMV denotes cytomegalovirus, MAGIC mouth and genital ulcers with inflamed cartilage, NSAID nonsteroidal antiinflammatory drug, PFAPA periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis, and STD sexually transmitted disease.

tively large disease burden and appear to be most likely to have severe manifestations among persons with the disorder.[12,13,35] Male sex is associated with an increased risk of death (hazard ratio, 4.94).[13] Other findings associated with death are arterial involvement (hazard ratio, 2.51) and a high frequency of flares (hazard ratio, 2.37).[13] The most worrisome complication of ocular Behçet's syndrome is the loss of useful vision, which was estimated to occur in 25% of cases over a 10-year period, before the use of immunosuppressive therapy became widespread.[43] However, the advent of newer therapies has reduced this risk to an estimated 13%.[58]

Neurologic Behçet's syndrome can lead to disability or death, particularly when parenchymal involvement is present. Estimates vary, but the risk of severe disability or death ranges from approximately 25% at 7 years[59] to as high as 60% at 10 years.[50] Vascular Behçet's syndrome is the leading cause of death, which is mainly due to arterial aneurysms (e.g., aortic or pulmonary) and Budd–

Chiari syndrome.[12,13] In cases of venous thrombosis, poor recanalization and a lack of immunosuppressive treatment options are major predictive factors for relapse. In two large, long-term cohort studies, the estimated overall mortality was 5% over 7.7 years and 9.8% over 20 years of the follow-up.[12,13] Irrespective of a given patient's clinical phenotype, Behçet's syndrome has a substantial effect on quality of life, adversely affecting both physical functioning and psychological well-being.[60]

TREATMENT

Given the heterogeneous clinical manifestations of Behçet's syndrome and the variable disease course among patients, individualized, multidisciplinary treatment is warranted.[61] The overall goal is prompt control of inflammation in order to prevent relapses and irreversible organ damage. However, there are no standardized outcome measures for assessing activity in patients with Behçet's syndrome, and both end points and definitions of remission vary among clinical trials.[62]

Assessment of the therapeutic response is based on a set of clinical, biologic, and radiologic elements. In practice, clinicians should assess the treatment response for each disease manifestation. The goals of treatment are to reduce the number, duration, and frequency of mucocutaneous lesions; reduce joint pain and swelling; control ocular inflammation and ensure visual acuity with regular ophthalmologic examinations; control vascular inflammation and prevent new vascular lesions and the post-thrombotic syndrome; and control neurologic inflammation and prevent new nervous system inflammatory lesions, thrombosis, and neurologic sequelae. Measurement of serum C-reactive protein levels and the use of comparative imaging are valuable supplementary tools for assessing the effectiveness of each treatment.

Data regarding the appropriate duration of immunosuppressive therapy in patients with Behçet's syndrome are limited. Consequently, the decision to escalate or deescalate treatment depends on the severity of the clinical presentation and the presence or absence of factors associated with a poor prognosis. Most randomized, controlled trials (RCTs) involving patients with Behçet's syndrome have focused on those with cutaneous, mucosal, and articular manifestations or ocular manifestations. For the management of nonsevere manifestations, first-line treatment strategies include topical antiinflammatory therapy and the use of colchicine. For major organ manifestations and refractory conditions,[63,64] glucocorticoids and synthetic or biologic immunosuppressive agents are generally used (Table S2).

CUTANEOUS, MUCOSAL, AND ARTICULAR INVOLVEMENT

The first-line systemic treatment for cutaneous, mucosal, and articular manifestations of Behçet's syndrome is colchicine, which is used to prevent the recurrence of mucocutaneous and joint lesions.[61] Patients who have recurrent manifestations may also benefit from topical medication, including the use of topical glucocorticoids, antiinflammatory mouthwashes, and intraarticular glucocorticoid injections. Apremilast, a phosphodiesterase 4 inhibitor, is a small-molecule immunomodulatory drug that has been approved by the Food and Drug Administration (FDA) for the treatment of refractory oral ulcers in Behçet's syndrome,[65] and it is currently considered as second-line therapy for this condition. Other RCTs investigating various agents for the treatment of refractory Behçet's syndrome have shown positive results, particularly in managing ulcerations. These trials have evaluated medications such as azathioprine, thalidomide, interferon alfa, and etanercept, which may offer alternative treatment options.[63] Another promising target is ustekinumab, an inhibitor of interleukin-12 and interleukin-23, which has shown efficacy in an open-label trial for treating oral ulcers that are refractory to colchicine in patients with Behçet's syndrome.[66]

MAJOR ORGAN INVOLVEMENT

A close collaboration with ophthalmologists is essential for the effective management of ocular Behçet's syndrome. Posterior segment involvement warrants a combination of glucocorticoids and systemic immunosuppressants, an approach that is substantiated by RCTs evaluating the use of azathioprine, interferon alfa, TNF inhibitors, or cyclosporine.[61] In head-to-head comparison trials, cyclosporine was inferior to both interferon alfa and the TNF inhibitor infliximab.[64] In cases of acute sight-threatening uveitis, the use of treatment regimens containing infliximab or interferon alfa are in accordance with European guide-

lines.[64] Adalimumab, a TNF inhibitor, recently received FDA approval for the treatment of noninfectious uveitis on the basis of the results of RCTs that included a small number of patients with Behçet's syndrome. The efficacy and safety of adalimumab in treating Behçet's syndrome have been further supported by meta-analyses of observational data.[67] Isolated anterior uveitis is typically managed with topical therapy, although systemic immunosuppressants may be considered in patients with poor prognostic factors, such as young male patients and patients with recurrent uveitis.[61]

The management of deep-vein thromboses in patients with Behçet's syndrome primarily involves the use of immunosuppressants; the role of anticoagulants remains a subject of debate.[1] The choice of treatment depends on the site of venous involvement and whether the patient presents with an acute or chronic thrombosis. Treatment options include mainly glucocorticoids, sometimes in combination with conventional immunosuppressants, such as cyclophosphamide, azathioprine, or biologic agents (e.g., TNF inhibitors).[27,61,68] Arterial involvement in Behçet's syndrome usually warrants the use of high-dose glucocorticoids combined with azathioprine, cyclophosphamide, or a TNF inhibitor as induction therapy.[61] Regardless of the type of vascular procedure and whether it is endovascular or open surgery, preemptive immunosuppressive treatment appears to be essential for preventing postoperative complications such as prosthetic thrombosis or anastomotic dehiscence.[69] In addition, it is important in this context to address cardiovascular risk factors.

Acute neuroparenchymal Behçet's syndrome should be managed with high-dose glucocorticoids together with an immunosuppressive agent, such as azathioprine or cyclophosphamide.[61] In one study, patients with severe neuroparenchymal Behçet's syndrome who were treated with cyclophosphamide tended to have longer event-free survival than those who received other disease-modifying antirheumatic drugs, such as azathioprine or methotrexate.[59] Case series provide support for the use of a TNF inhibitor as a first-line treatment in cases of severe or refractory neurologic Behçet's syndrome.[64]

Managing the relatively uncommon gastrointestinal involvement in Behçet's syndrome is challenging because of the limited available evidence.[64] First-line therapy generally includes the use of glucocorticoids, together with 5-aminosalicylic acid derivatives for mild disease, whereas azathioprine is recommended for those with moderate to severe manifestations. TNF inhibitors or thalidomide can be used in refractory gastrointestinal cases.[64] In cases leading to emergency surgery (e.g., perforation), concomitant immunosuppressive therapy is recommended, since it appears to reduce the risk of adverse postoperative outcomes.[61]

Unfortunately, high-level evidence is lacking regarding the appropriate induction immunosuppressive therapy for major organ involvement in Behçet's syndrome, particularly severe or refractory life-threatening cases.[64] The choice of treatment regimens usually comes down to a decision between cyclophosphamide and a TNF inhibitor.[61,64,70-72] TNF inhibitors are reshaping the approach to treatment for ocular Behçet's syndrome by reducing the risk of blindness,[58] and they hold promise as a potential solution for the treatment of severe Behçet's syndrome overall. The results of a head-to-head trial comparing infliximab and cyclophosphamide (ClinicalTrials.gov number, NCT03371095) are awaited. An emerging option for patients with refractory major organ involvement is tocilizumab, an interleukin-6–receptor inhibitor.[73]

CONCLUSIONS

The care of patients with Behçet's syndrome has improved substantially in the past few decades as a result of advances in immunogenetics, syndrome recognition, and targeted therapeutic approaches. However, unmet needs that warrant further research include standardized outcome measures in clinical trials, better diagnostic tools, identification of reliable markers for disease activity, evaluation of biologic therapeutic strategies, the determination of the appropriate duration of immunosuppressive therapy, and clarification of the role of anticoagulant therapy in managing venous thrombosis.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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