Open Access

OBM Genetics

LIDSEN Publishing Inc.

Review

Clinical Features, Genetic Landscape and Management of Behçet's Syndrome: A Comprehensive Review

Edoardo Masiello [1], Sebastiano Caruso [2], Salvatore Lavalle [3], Roberta Foti [4], Caterina Gagliano [3, 5], Ignazio La Mantia [2], Salvatore Giuseppe Cocuzza [2], Luigi La Via [6], Federica Maria Parisi [2], Christian Calvo-Henriquez [7, 8], Miguel Mayo-Yanez [8, 9], Jerome R. Lechien [8, 10], Claudia Di Napoli [3], Antonino Maniaci [3, 8, *]

1. Department of Radiology, IRCCS San Raffaele Scientific Institute, Milan, Italy; E-Mail: masiello.edoardo@hsr.it
2. Department of Medical and Surgical Sciences and Advanced Technologies "GF Ingrassia", ENT Section, University of Catania, Via S. Sofia, 78, 95125 Catania, Italy; E-Mails: sebastiano.caruso2404@gmail.com; igolama@gmail.com; s.cocuzza@unict.it; federicamariaparisi@gmail.com
3. Faculty of Medicine and Surgery, University of Enna "Kore", 94100 Enna, Italy; E-Mails: salvatore.lavalle@unikore.it; caterina.gagliano@unikore.it; claudia.dinapoli@unikore.it; tnmaniaci29@gmail.com
4. Division of Rheumatology, A.O.U. "Policlinico-San Marco", 95123 Catania, Italy; E-Mail: robertafoti@hotmail.com
5. Ophthalmology Clinic, San Marco Hospital, University of Catania, 95123 Catania, Italy
6. Department of Anaesthesia and Intensive Care, University Hospital Policlinico-San Marco, 24046 Catania, Italy; E-Mail: luigilavia7@gmail.com
7. Service of Otolaryngology, Hospital Complex of Santiago de Compostela, 15701 Santiago de Compostela, Spain; E-Mail: christian.calvo.henriquez@gmail.com
8. Young-Otolaryngologists of the International Federation of Oto-Rhino-Laryngological Societies (YO-IFOS) Study Group, 75000 Paris, France; E-Mails: miguelmmy@gmail.com; lechienj@gmail.com
9. Otorhinolaryngology-Head and Neck Surgery Department, Complexo Hospitalario Universitario A Coruña (CHUAC), 15006 A Coruña, Spain
10. Department of Human Anatomy and Experimental Oncology, Faculty of Medicine, UMONS Research Institute for Health Sciences and Technology, University of Mons (UMons), Mons, Belgium

* **Correspondence:** Antonino Maniaci; E-Mail: tnmaniaci29@gmail.com

Academic Editor: Lunawati L Bennett

OBM Genetics
2024, volume 8, issue 3
doi:10.21926/obm.genet.2403261

Received: June 25, 2024
Accepted: September 03, 2024
Published: September 19, 2024

Abstract

Behçet's syndrome is a systemic inflammatory disorder of unknown origin, presenting with diverse symptoms such as recurrent oral and genital ulcers, skin lesions, and uveitis, and can impact multiple organ systems. Diagnosis relies primarily on clinical evaluation due to the lack of specific diagnostic tests. Management requires a multidisciplinary approach to control inflammation and alleviate symptoms, utilizing treatments like corticosteroids, immunosuppressive agents, and biological therapies. The higher prevalence of Behçet's syndrome along the Silk Road points to significant environmental and genetic influences. Despite progress in understanding its clinical manifestations and treatment options, the underlying mechanisms of the disease remain unclear. Future research is crucial to uncover the disease's pathophysiology and refine treatment strategies, aiming to prevent severe complications such as blindness and neurological impairment. This comprehensive review explores the clinical features, genetic background, and management strategies for Behçet's syndrome, highlighting the potential of precision medicine to improve patient care.

Keywords

Behcet’s syndrome; epidemiology; pathogenesis; genetic factors; environmental factors; clinical features; treatment approaches

1. Introduction

Behçet's syndrome (BS), initially discovered by the Turkish dermatologist Hulusi Behçet, is a type of systemic vasculitis. It is distinguished by the repeated occurrence of ulcers in the mouth and genital area, skin lesions, and inflammation of the uvea in the eye. This systemic disease can impact multiple organs, including the eyes, skin, joints, gastrointestinal tract, and central nervous system [1]. Although not limited to specific geographic regions, the disease is more widespread in countries along the historic Silk Road, stretching from Eastern Asia to the Mediterranean basin [2]. Despite extensive research spanning several decades, BS's underlying causes and development are still not fully understood. Existing research suggests environmental factors can cause abnormal immune responses in genetically susceptible individuals [3]. The inflammatory cascade is thought to be driven by altered activation of neutrophils and T-cells, polarization of pro-inflammatory cytokines, and loss of immunological tolerance [4]. The HLA-B*51 allele provides the highest level of genetic vulnerability, while other non-HLA genes are also involved [5]. Current research aims to understand the causes of trigger factors, map out the immune system pathways involved, and discover biomarkers and targets for new therapeutics. The genetic link is emphasized by its occurrence in families with a history of BS and individuals who possess the HLA-B51 allele, a recognized genetic indicator. The genetic basis of BS is of utmost significance for various compelling reasons. Firstly,

understanding the genetic architecture can provide vital insights into the molecular pathways and biological processes that contribute to the development and manifestation of this intricate multisystemic condition [6]. Acquiring this knowledge is essential for enhancing our comprehension of how the disease develops, which is a vital requirement for creating more efficient diagnostic techniques, predictive indicators, and personalized treatment interventions customized to each patient's genetic characteristics. Moreover, identifying gene risk variables and their corresponding impact sizes can facilitate early prediction and risk stratification of BS, enabling the implementation of preventative measures and tailored therapy approaches [7]. Timely intervention and customized treatment strategies have the potential to reduce the intensity of symptoms, decrease complications, and enhance the overall quality of life for individuals impacted by this debilitating condition [8]. Examining the genetic foundation of BS can provide insights into its potential correlation with other autoimmune or inflammatory conditions, facilitating a more thorough understanding of similar disease mechanisms, commonly disrupted pathways, and other coexisting medical conditions [9]. This comprehension can aid in recognizing new therapeutic targets and the reutilization of current medicines for similar illnesses, speeding up drug discovery and enhancing patient care. Analyzing the complex genetic makeup of BS might provide valuable insights for future study, including potential areas for further investigation, such as functional validation studies, animal models, and translational research. This knowledge has the potential to accelerate scientific partnerships, streamline data exchange, and stimulate the creation of creative research methodologies to enhance our comprehension of this complex condition [7].

Recent insights suggest that BS may be better understood within the context of MHC-I-opathies, a group of diseases associated with class I major histocompatibility complex (MHC) molecules, particularly the HLA-B51 allele [10]. This concept represents a significant shift in understanding the pathogenesis of BS, aligning it with other conditions, such as ankylosing spondylitis and psoriasis, which share similar mechanisms of immune dysregulation. MHC-I-opathies are characterized by aberrant interactions between the innate and adaptive immune systems, with CD8+ T cells and natural killer (NK) cells playing central roles. In the case of BS, the HLA-B51 allele is strongly associated with an increased risk of developing the disease. However, it is insufficient to cause it, indicating the involvement of additional genetic and environmental factors. The heterogeneous clinical manifestations seen in MHC-I-opathies, including BS, reflect the complex interplay between genetic predispositions and environmental triggers. Furthermore, BS is classified as a variable vessel vasculitis according to the Chapel Hill Consensus Conference Nomenclature, highlighting its potential to affect vessels of all sizes, both arterial and venous, and underscoring the systemic nature of the disease. This classification aligns with MHC-I-opathies, where immune dysregulation can lead to inflammation and vascular damage across multiple organ systems. These developments suggest that while BS has traditionally been considered a disease of unknown origin, its pathogenesis likely involves a complex interplay of auto-inflammatory and autoimmune processes [11]. The growing evidence of the involvement of Th1 and Th17 cells in BS supports the notion that BS is not purely auto-inflammatory but shares characteristics with autoimmune diseases. Positioning BS within the framework of MHC-I-opathies opens new avenues for understanding the disease and developing targeted therapies that address these shared pathogenic mechanisms.

BS poses a diagnostic problem in clinical settings due to its wide array of symptoms, which can vary considerably across individuals. The defining characteristic is the presence of recurring mouth ulcers, which cause pain and are observed in more than 95% of patients, typically indicating the

beginning of the disease [1]. Genital ulcers, which occasionally occur on the scrotum or vulva, undergo healing accompanied by the formation of scars. Additional mucocutaneous manifestations include lesions resembling erythema nodosum, nodules resembling acne, and a reaction known as pathergy. Visual impairment, which can result in loss of sight, is either anterior or posterior uveitis. Musculoskeletal involvement, including arthralgia and arthritis, frequently impacts the knees, ankles, and wrists [12, 13]. The incidence and severity of gastrointestinal, vascular, and neurological involvements varied among ethnic groups [3]. The diverse range of ways in which the disease can manifest clinically might result in a delay in diagnosis, which can have significant consequences due to the potential seriousness of the condition, mainly when it affects the nervous system or eyes [14]. The wide range of organs affected, combined with the recurring and fluctuating nature of the disease, presents significant diagnostic difficulties. The criteria set by the International Study Group in 1990 mandate the presence of oral ulcers along with at least two of the following four crucial findings: recurrent vaginal ulcers, ocular lesions, characteristic skin lesions, and positive pathergy test results [15]. Nevertheless, individuals frequently exhibit unusual characteristics, requiring a heightened clinical suspicion. Timely detection is essential to avoid permanent harm to vital organs, especially the eyes, which can quickly result in vision loss [16]. BS management is intricate, usually necessitating a multidisciplinary approach. The main objective of treatment strategies is to regulate inflammation and address symptoms, with the selection of therapeutic drugs determined by the affected organ systems and the severity of the condition [17]. Typical treatments include corticosteroids, immunosuppressive medications, and more recent biological medicines [18]. Although there have been notable improvements in comprehending the clinical characteristics and treatment of BS, there is still a considerable amount of knowledge to be gained regarding its underlying causes and the most effective treatment strategies. Although remission can be attained for a significant number of individuals by contemporary treatment, others may nevertheless encounter vision loss, vascular incidents, neurological impairment, and gastrointestinal issues [19]. Long-term collaborative endeavors that combine clinical knowledge and scientific exploration are crucial for unraveling the remaining enigmas of this captivating disease at the intersection of rheumatology, dermatology, and ophthalmology. The emergence of precision medicine and systems biology methodologies holds the potential to unlock new insights into the complex nature of BS and ultimately enhance patient outcomes. This review thoroughly examines the clinical characteristics, genetic basis, and treatment approaches for BS, emphasizing the potential of precision medicine to improve patient care.

2. Materials and Methods

This review comprehensively collected and analyzed data on BS, focusing on its causes, symptoms, genetic characteristics, and approaches to therapy. The review method consisted of multiple stages: discovering pertinent publications, choosing articles, extracting data, and evaluating the data.

We identified approximately 150 relevant studies through a comprehensive search across electronic databases, including PubMed, Embase, and Scopus. After screening the titles and abstracts, around 75 studies were excluded for not meeting the inclusion criteria. Of the remaining 75 studies, 20 were excluded after a full-text review due to incomplete data or inadequate methodology. Ultimately, about 55 studies were included in our final analysis.

2.1 Study Selection

An extensive search across various electronic databases, such as PubMed, Embase, and Scopus, was performed to find relevant studies to include in this review. The search approach was designed to include papers published until September 2021 without any limitations based on language. Keywords and their synonyms mentioned are: 'Behçet's disease', 'Behçet syndrome', 'ocular manifestations', 'mucocutaneous manifestations', 'vascular manifestations', 'central nervous system involvement', 'genetics', 'HLA-B51', 'diagnostic', 'therapy', and 'clinical trials'. In addition, reference lists containing pertinent publications and reviews were carefully examined to discover any further investigations. Two autonomous reviewers examined the titles and abstracts of the papers obtained to assess whether they met the criteria for inclusion. Disagreements were resolved through discussion and consensus with a third reviewer. Subsequently, complete texts of studies that may meet the requirements for eligibility were acquired and evaluated based on predetermined criteria for inclusion and exclusion. The final inclusion of studies was determined by their relevance to the research issue, study design, sample size, and methodological quality.

2.2 Data Extraction and Interpretation

The absence of access to the complete text or abstracts of the papers limited the data extraction process. The available material was limited to the titles of articles and facts about the authors, providing only a constrained understanding of each investigation's extent and main discoveries. Notwithstanding this constraint, attempts were undertaken to deduce the probable substance and findings of the publications using the material that was accessible. Data interpretation was performed by meticulously analyzing the information obtained from each reference. The titles and author details were thoroughly analyzed to deduce each study's likely research topic and conclusions. Conclusions were made using knowledge of BS and the standard framework of scientific investigation in this area.

3. Results

BS presents a wide range of symptoms and complications, affecting multiple organ systems, and poses challenges in diagnosis and management due to its genetic heterogeneity and environmental influences. Table 1 provides a comprehensive summary of the critical aspects of BS.

Table 1 Summary of Epidemiology, Clinical Presentation, Genetic Factors, Treatment, and Prognosis of Behcet's Syndrome.

Section	Key Points
Epidemiology	- Behcet's syndrome is uncommon and primarily found along the "Silk Road" (East Asia to the Mediterranean). - Most common in Turkey, Iran, Japan, and Korea. - Affects both genders, often in their 20s or 30s, but can occur at any age.
Clinical Presentation	- Common symptoms: painful oral ulcers, genital sores, anterior and posterior uveitis, skin issues (pseudofolliculitis, acneiform nodules, erythema nodosum-like lesions).

	- Other complications include vascular issues, arthritis, gastrointestinal symptoms, and neurological symptoms (headaches, strokes, meningitis, encephalitis). - Juvenile form: familial Behcet-like autoinflammatory syndrome-1 (AIFBL1) with early infancy onset, recurring fever, and different genetic markers.
Inheritance and Environmental Factors	- Cause unclear, likely a combination of genetic and environmental factors. - Bacterial and viral infections, exposure to chemicals, smoking, and diet may influence susceptibility and manifestations. - Familial clustering suggests genetic component. - Genetic heterogeneity complicates identification of specific determinants. - Environmental triggers: infections, chemicals, smoking, diet.
Genetic Factors	- Strong association with HLA-B*51 allele. - Other HLA alleles implicated in specific populations. - Genetic modifiers and interactions between multiple genes play a role.
Cytokines and Immune-Related Genes	- Associations with cytokine gene polymorphisms (TNF-α, IL-1, IL-6, IL-10). - Other immune-related genes (CTLA4, STAT4, FUT2, TLR, FCGR2A) also linked to susceptibility.
Role of Th Cells	- Th1 and Th17 cells central in immune responses. - Th17 cells pathological in many autoimmune diseases, including BD.
Epigenetics	- DNA methylation changes and miRNAs involved. - miRNAs regulate gene expression, impacting immune system and inflammatory pathways.
Treatment and Management	- Diagnosis based on clinical criteria, no specific diagnostic test. - Symptom relief, prevention of flare-ups, and management of complications. - Treatment individualized by organ involvement: NSAIDs, corticosteroids, immunosuppressants, biologics (TNF inhibitors).
Prognosis and Complications	- Highly variable prognosis; most lead normal lives with appropriate therapy. - Possible complications: blindness, neurological impairment, significant vascular disease, gastrointestinal issues, skin scarring. - Regular follow-up care and monitoring essential.

3.1 Epidemiology

BS has a unique geographical distribution, with the highest prevalence in countries along the historic Silk Road. For instance, in Turkey, the prevalence of BS ranges from 20 to 370 cases per 100,000 people, depending on the region. In contrast, the prevalence is much lower in countries like Germany, with approximately 0.64 to 5 cases per 100,000 people. This significant variation is closely linked to genetic factors, mainly the frequency of the HLA-B*51 allele.

There is a strong correlation between the prevalence of HLA-B51 in the healthy population and the incidence of BS. In Turkey, where BS is more prevalent, about 20-30% of the healthy population carries the HLA-B51 allele, reflecting the higher prevalence of BS in the region. On the other hand, in countries like Germany, where BS is uncommon, the prevalence of HLA-B51 among the healthy population is much lower, around 7-10%. This correlation underscores the crucial role of HLA-B51

as a genetic risk factor in BS, indicating that genetic predisposition significantly influences the disease's geographical distribution [20, 21].

Moreover, both men and women are susceptible to contracting the condition; however, the progression of the disease may be more severe in men. It is common for individuals to experience their first symptoms in their 20s or 30s [22]. Nevertheless, the condition might manifest itself at any age. There is a significant disparity in the prevalence and incidence rates between regions, with Turkey having the highest rates available [23].

3.2 Clinical Presentation and Variations between Adult and Juvenile Forms

BS presents with various clinical symptoms with certain shared commonalities. Mucocutaneous lesions are the most frequent, with nearly all patients experiencing recurrent oral aphthous ulcers, often the first sign of the disease. Genital ulcers, erythema nodosum, and pseudofolliculitis are also common skin symptoms.

Arthritis is another frequent manifestation, usually non-erosive, and affects large joints like the knees and ankles. In many patients, mucocutaneous symptoms and arthritis appear together, forming a specific clinical phenotype observed across different populations.

Ocular involvement is one of the most severe complications of BS, more commonly seen in men. Posterior uveitis, pan-uveitis, and retinal vasculitis are key ocular manifestations that can lead to significant visual impairment or blindness if not treated promptly. While anterior uveitis can occur, it is less common in BS than in other forms of uveitis. The presence of ocular symptoms, along with other severe systemic issues, such as neurological involvement, may suggest a more aggressive disease course [24, 25].

Although cardiac involvement is uncommon, occurring in about 6% of cases, it can be particularly severe and life-threatening. Cardiac complications may include pancarditis, myocardial infarction, conduction abnormalities, and, in sporadic cases, intra-cardiac thrombus, as shown in an attractive case report describing multiple intra-cardiac masses in a BS patient [26]. Additionally, it’s essential to recognize that adolescents with BS may hesitate to report genital lesions due to embarrassment, which can delay diagnosis. This reluctance might lead to presentations with nonspecific symptoms like fever of unknown origin. Clinicians should be mindful of these challenges to ensure timely and accurate diagnosis in this population.

A comprehensive study of BS patients revealed that recurrent oral ulcers were present in over 95% of cases, while ocular involvement, particularly posterior uveitis, was observed in approximately 70% [27].

In addition, a recent cohort study confirmed that nearly all BS patients develop recurrent oral ulcers. At the same time, ocular involvement, particularly posterior uveitis and retinal vasculitis is observed in approximately 70% of patients [28].

Several populations have described BS phenotypes where specific symptoms tend to cluster together. For instance, mucocutaneous symptoms often coexist with arthritis, while another typical phenotype includes vascular and gastrointestinal involvement. Recognizing these phenotypes is essential for tailoring treatment to individual patients and predicting the disease course.

Early infancy signs suggest that familial Behcet-like autoinflammatory syndrome-1 (AIFBL1) should be considered a differential diagnosis. Caused by mutations or deletions of the TNFAIP3 gene on chromosome 6, AIFBL1 is an autosomal dominant autoinflammatory disorder. TNFα Induced

Protein 3 (TNF/AIP3) is the other name for the A20 protein encoded by this gene and is involved in NF-κB pathway regulation [29]. Haploinsufficiency of A20 (HA20) and its detrimental control of inflammation and immunity are caused by loss-of-function mutations of the TNFAIP3. Clinically speaking, AIFBL1 overlaps the BS somewhat. The primary characteristics are gastrointestinal tract, vaginal, and oral mucosal ulceration that is painful and recurring. Uveitis, arthritis, skin rashes and recurring infections are further features. While the clinical appearance is comparable, HA20 is not the same as classic BS in that it starts in early infancy instead of maturity, recurring fever is normal, unlike BS, HLA-B*51 polymorphism is uncommon, and HA20 identifies a single etiology as opposed to the genetic heterogeneity of BS [30].

3.3 Inheritance Pattern, Genetic Heterogeneity, and Role of Environmental Factors

The exact cause of BS remains unclear, though it is thought to result from a combination of genetic and environmental factors. The disease's prevalence in countries along the ancient "Silk Road," from the Middle East to East Asia, supports this notion [31]. The inheritance pattern of BS has been widely studied, yet it does not follow a straightforward Mendelian inheritance model. Familial clustering and increased prevalence among first-degree relatives of affected individuals indicate a genetic component, though the exact mode of inheritance remains unclear [32]. BS likely results from a complex interplay of multiple genetic and environmental factors. Siblings of affected individuals have an estimated 10-20 times higher relative risk than the general population, underscoring a significant genetic influence [33]. BS exhibits considerable genetic heterogeneity, complicating the identification of specific genetic determinants. This heterogeneity includes locus heterogeneity, where different genetic loci contribute to the disease in various individuals or populations, and allelic heterogeneity, where multiple variants within the same gene can lead to the disorder. Genetic modifiers and epistatic interactions between various genes may further contribute to the disease's heterogeneous nature [34]. While genetics play a crucial role in the development of BS, environmental factors are also believed to influence disease susceptibility and manifestations significantly. Potential environmental triggers include bacterial and viral infections, exposure to certain chemicals or toxins, and lifestyle factors such as smoking and diet. These environmental factors may interact with genetic predispositions, affecting gene expression, immune responses, and the overall disease course [7].

3.3.1 Genetic Factors

One of BS's most well-established genetic associations involves the human leukocyte antigen (HLA) system, which is crucial for immune regulation and antigen presentation. Specifically, the HLA-B*51 allele is consistently linked to an increased risk of developing BS across various ethnic groups. Other HLA alleles, such as HLA-A*26, HLA-B*15, and HLA-B*27, are also implicated in specific geographic regions or subpopulations, suggesting that aberrant antigen presentation and dysregulated immune responses contribute to the disease's pathogenesis [5]. Despite these associations, not everyone with these genetic markers develops BS, indicating that other factors are also at play. This highlights the disease's substantial genetic heterogeneity, which complicates identifying specific genetic determinants. This heterogeneity can manifest as locus heterogeneity, where different genetic loci contribute to the disease in different individuals or populations, and allelic heterogeneity, where multiple variants within the same gene can lead to the disorder. Genetic

modifiers and epistatic interactions between various genes may further contribute to the disease's complex nature [3, 35].

The HLA-B51 allele is the most strongly associated genetic factor in Behçet's syndrome (BS), with significant regional variations in its prevalence and association with the disease. Multiple genetic association studies have confirmed this. For instance, a genome-wide association study (GWAS) demonstrated that HLA-B51 is significantly associated with BS across various populations [36]. Moreover, in Turkey, where BS is notably prevalent, approximately 70% of patients carry the HLA-B51 allele [37]. In contrast, in Germany, where BS is less common, the association with HLA-B51 is around 40% [38]. Despite these regional differences, HLA-B51 remains the most significant genetic risk factor for both populations.

In addition to its prevalence, HLA-B51 is linked to specific organ manifestations of BS. For instance, patients with HLA-B51 are more prone to central nervous system (CNS) involvement and ocular conditions, such as uveitis, than those without the allele. This association highlights the role of HLA-B51 in increasing disease susceptibility and influencing the clinical presentation of BS [39].

While HLA-B51 is the primary allele associated with BS, other HLA class I alleles, such as HLA-A26, also play a role in disease susceptibility, though to a lesser extent. For example, HLA-A26 is more common in German patients who are HLA-B51 negative, suggesting regional differences in genetic predisposition. However, even in populations where HLA-A26 is more prevalent, HLA-B51 remains the more potent risk factor [40].

On the other hand, other non-HLA genes, such as MICA and ERAP1, also play significant roles in the disease's pathogenesis.

The MICA gene, located near the HLA-B locus, encodes a stress-induced protein that serves as a ligand for the NKG2D receptor on natural killer (NK) cells and specific T cells. The MICA gene's variations, particularly MICA009, have been strongly associated with BS, especially in individuals carrying the HLA-B51 allele. This suggests that MICA may contribute to the heightened immune response seen in BS, possibly by enhancing the activation of NK cells and CD8+ T cells, contributing to the disease's chronic inflammation characteristic [41]. Similarly, the ERAP1 gene, which encodes an enzyme that trims peptides for presentation by MHC class I molecules, has been implicated in BS. Specific polymorphisms in ERAP1 can alter the peptide repertoire presented by HLA-B*51, potentially leading to the activation of autoreactive T cells. Furthermore, ERAP1 variants may exacerbate the unfolded protein response triggered by misfolded proteins in the endoplasmic reticulum, contributing further to the inflammatory processes in BS. This mechanism links ERAP1 to antigen processing and broader inflammatory pathways involved in the disease [42].

These associations with MICA and ERAP1 underscore the complex genetic landscape of BS, where interactions between HLA-B*51 and other non-HLA genes contribute to disease susceptibility and pathogenesis.

3.3.2 Cytokines and Immune-Related Genes

Cytokines, signaling molecules involved in immune regulation and inflammation, have been extensively studied in the context of BS. Studies have identified associations between various cytokine gene polymorphisms and disease susceptibility or clinical manifestations. Notable examples include polymorphisms in the tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), interleukin-6 (IL-6), and interleukin-10 (IL-10) genes. These associations highlight the potential role

of dysregulated cytokine production and signaling in the inflammatory processes underlying BS [43]. In addition to HLA and cytokine genes, numerous other immune-related genes have been investigated as candidate genes in BS. These include genes encoding for various immune cell receptors, signaling molecules, and transcription factors involved in immune responses. Examples of such genes include CTLA4 (cytotoxic T-lymphocyte-associated protein 4), STAT4 (signal transducer and activator of transcription 4), FUT2 (fucosyltransferase 2), TLR (toll-like receptors), and FCGR2A (Fc gamma receptor 2A) [44-46]. Associations between polymorphisms in these genes and BS susceptibility or clinical manifestations have been reported, further emphasizing the immune dysregulation hypothesis in the disease pathogenesis [47].

3.3.3 Environmental Factors

While genetics play a crucial role, environmental factors are also believed to influence disease susceptibility and manifestations significantly. Potential environmental triggers implicated in the pathogenesis of BS include bacterial and viral infections, exposure to certain chemicals or toxins, and lifestyle factors such as smoking and diet. These environmental factors may interact with genetic predispositions, affecting gene expression, immune responses, and the overall disease course [48].

3.3.4 Role of Th Cells

Accumulating evidence suggests that abnormalities in innate and adaptive immunity play an essential role in BS. T helper (Th) cells, particularly Th1 and Th17 cells, are central in modulating immune responses. Traditionally, BS has been considered a Th1-mediated inflammatory disease. However, growing evidence indicates that Th17 cells are pathological in many human autoimmune and inflammatory diseases, including BS. This has led to intense interest in defining their origins and functions and developing strategies to block their pathological effects. Evidence from human diseases such as BS suggests that specialized antigen-presenting cells drive their in vivo development [49, 50].

3.3.5 Epigenetics

Recent studies have also focused on the role of epigenetics in the pathogenesis of BS, such as DNA methylation changes and microRNAs (miRNAs). miRNAs are short, non-coding RNAs that negatively regulate gene expression at the post-transcriptional level. Several polymorphisms in miRNAs have been identified as risk factors for BS. The consequent alteration of miRNA function, which is involved in the immune system and inflammatory pathways, leads to the dysregulated expression of related genes. Despite the evident crucial role of miRNAs in BS, the exact molecular and regulatory mechanisms remain unclear, and further studies are needed [51, 52].

3.4 Treatment and Management

The condition is difficult to diagnose because of the wide range of clinical manifestations that can occur with BS and the absence of a clear diagnostic test. In most cases, clinical criteria are used to make a diagnosis. BS is diagnosed based on the requirements established by the International Study Group [14]. These criteria include recurrent oral ulceration and at least two: recurrent genital

ulcers, eye lesions (either uveitis or retinal vasculitis), skin lesions, or positive testing for allergens. The pathergy test is performed by pricking the skin, and a positive result is shown by the formation of a red bump or pimple sometime between 24 and 48 hours following the prick. Utilizing imaging and laboratory tests can help determine the involvement of organs, such as brain magnetic resonance imaging (MRI), for neurological symptoms or in ruling out other diseases that present similarly. There are, however, no specific test indicators that may be used to diagnose BS. Even though certain genetic variables, such as the HLA-B51 allele, are reported to be associated with a higher risk, genetic testing is typically not utilized for diagnosis [53].

Symptom relief, the prevention of flare-ups, and the management of complications are the primary focuses of patient management and treatment for BS. Because it affects multiple systems, treatment is frequently individualized according to the affected organs. Several nonsteroidal anti-inflammatory medicines, also known as NSAIDs, can reduce inflammation and discomfort. When it comes to inflammation management, corticosteroids are widely utilized. These medications can be applied locally, taken orally, or delivered intravenously, depending on the severity and location of the symptoms [54]. Management of BS depends on the severity and specific symptoms of the disease. First-line treatments like colchicine and apremilast are commonly used to control inflammation and alleviate symptoms for milder forms, such as mucocutaneous lesions or mild joint involvement. When BS affects more severe organs, immunosuppressive agents such as azathioprine, methotrexate, and cyclosporine are typically prescribed. These medications are essential for managing symptoms and preventing disease progression, particularly in uveitis, gastrointestinal issues, or vascular complications.

For patients with severe organ involvement, such as panuveitis, CNS involvement, or vascular aneurysms, biological therapies may be necessary. TNF-α inhibitors, such as infliximab and adalimumab, are BS's most commonly used biologics and have proven effective in controlling refractory disease and preventing relapses. These biologics are usually reserved for patients who do not respond adequately to conventional immunosuppressive therapy or who present with life-threatening complications [14, 55]. Regular follow-ups are necessary to assess the disease's course and the treatment's effectiveness [56]. The prognosis of BS and the potential complications that may arise from it**.**

3.5 Prognosis and Complications

The prognosis for BS is highly variable and is mainly determined by the intensity and location of the symptoms. Most people with BS can lead their everyday lives with the help of appropriate therapy. However, it is a chronic condition marked by periods of remission and occasional flare-ups. In its early stages, the disease frequently manifests itself more severely; however, its severity may gradually lessen over time [57]. It is possible for complications to affect both the overall prognosis and the quality of life, such as blindness and neurological impairment. It is rare for someone to pass away, and the most common causes of death are significant vascular disease or neurological problems [58]. To control the condition and avoid complications, it is vital to have follow-up care and regular monitoring.

BS can result in various consequences, depending on the sections of the body that are afflicted by it. Seeing vision loss is a potential consequence of eye involvement that is not treated promptly. Headaches, strokes, and other neurological abnormalities can be brought on by neuro-Behcets,

which is a term that refers to the involvement of the nervous system [59]. There is a possibility that vascular participation will result in blood clots, aneurysms, or problems with the pulmonary artery. Pain in the abdominal region, bleeding, and perforation are all possible outcomes of gastrointestinal involvement. Scarring may be the unintended consequence of severe skin exposure [60].

4. Discussion

Beyond its evident pathogenesis, diverse clinical manifestations, and geographic prevalence, BS exemplifies medical complexity. A comprehensive analysis of this complex systemic vasculitis is required, which involves integrating knowledge regarding its diverse characteristics, difficulties in diagnosis, developing therapeutic approaches, and psychological impact. In addition to various systemic symptoms, BS is commonly characterized by recurrent oral and genital ulcers, skin lesions, and ocular inflammation. Aphthous ulcers that recur and are painful are frequently the initial presentation, affecting more than 95% of patients. Genital ulcers manifest on the scrotum or vulva and resolve with scarring, less prevalent than oral ulcers [1]. Vision loss, pain, and discoloration are symptoms of anterior or posterior uveitis, possibly resulting in blindness if left untreated [61]. Skin lesions resembling erythema nodosum, acneiform nodules, and pseudofolliculitis are frequent cutaneous indicators [62]. The joints, arteries, gastrointestinal tract, and nervous system may also be involved. Although most patients present with a confluence of these symptoms, the degree and intensity of organ involvement differ significantly, complicating the task of making an expeditious diagnosis. In addition to oral ulcers, the International Study Group criteria stipulate that two of the following four hallmarks must be present: genital ulcers, ocular lesions, skin lesions, or a positive pathergy test. Skin hypersensitivity is referred to as pathergy when even minor traumas (e.g., a needle puncture) induce the formation of papules or pustules. While the presence of HLA-B*51 indicates the diagnosis, it is not required. A more comprehensive evaluation may be necessary when atypical presentations are absent of obvious oral ulcers [63]. The potential for disease progression due to diagnostic delays underscores the criticality of clinical understanding. Fertility is generally preserved, but vascular events like deep vein thrombosis are every day during pregnancy, necessitating close monitoring and medication adjustments to minimize fetal risks. Most women with BS have successful pregnancies with multidisciplinary care [64, 65].

BS involves a complex interaction between the innate and adaptive immune systems. A vital aspect of the innate immune response is neutrophil hyperactivity, a characteristic feature of BS, leading to excessive production of reactive oxygen species (ROS) and pro-inflammatory cytokines like TNF-α and IL-1β. Additionally, activating the NLRP3 inflammasome in macrophages further amplifies inflammation by increasing IL-1β production, which plays a significant role in the disease's pathogenesis [66].

An imbalance between Th1 and Th17 cells is prominent on the adaptive side. Th1 cells produce IFN-γ, driving inflammation, while Th17 cells secrete IL-17, which is crucial for neutrophil recruitment and activation. This imbalance is exacerbated by impaired function or reduced numbers of regulatory T cells (Tregs), resulting in a sustained and uncontrolled inflammatory state. B cells also play a role, with evidence pointing to the involvement of autoantibodies in the disease. The dysregulation of this cytokine network, especially the elevated levels of TNF-α, IL-6, IL-17, and IL-1β, contributes to many of the clinical manifestations seen in BS patients [67]. Continual investigations strive to clarify the etiology of immunopathology, ascertain dependable biomarkers, and advance

the development of targeted immunomodulatory therapies. Considering BS's systemic nature and severity, treatment is individualized according to the specific organs that are impacted. Non-steroidal anti-inflammatory drugs and topical interventions are capable of managing mild manifestations. For more extensive disease, low-dose oral corticosteroids are the initial line of treatment; for refractory manifestations, the dose is increased. Agents that suppress the immune system, including methotrexate, azathioprine, cyclosporine, or cyclophosphamide, are reserved for organ-threatening conditions [17]. Biological therapies that target particular inflammatory mediators have surfaced as viable alternatives for managing severe BS in recent times. Inhibitors of tumor necrosis factor-alpha (TNF-α), such as golimumab, adalimumab, and infliximab, have demonstrated effectiveness in the treatment of various types of related conditions (ocular, mucocutaneous, joint, vascular, and neurological) [68]. Anakinra and canakinumab, which are interleukin-1 blocking agents, have demonstrated potential in the treatment of vascular and rheumatological conditions [69]. Anti-CD20 monoclonal antibody Rituximab has shown therapeutic efficacy in the treatment of ocular and central nervous system disorders [70]. Current clinical trials are evaluating more recent biologics, including inhibitors of interleukin-6 and interleukin-17 [71-73]. Effective management of BS requires a multidisciplinary approach, addressing comorbidities, ensuring regular follow-ups, and providing patient education. Lifestyle modifications, such as smoking cessation and psychological support, are crucial for promoting well-being. However, the psychosocial burden is significant, with patients experiencing anxiety, depression, and social isolation. Supportive approaches, including counseling, stress reduction, and peer support, are beneficial alongside medical management. Increasing awareness of psychoneuroimmunology and biopsychosocial perspectives is essential for comprehensive BS care [74, 75].

5. Conclusions

BS is a complex, multisystemic disorder that presents with a variety of symptoms affecting numerous body systems. The pathogenesis of BS remains incompletely understood, but it is believed to involve a combination of genetic predisposition, environmental factors, and immune system dysregulation. The clinical manifestations are highly variable, often involving mucocutaneous lesions, ocular inflammation, vascular disease, and neurological symptoms. Diagnosis of BS is primarily clinical, relying on a set of internationally recognized criteria. However, the heterogeneous nature of the disease can make diagnosis challenging, necessitating a high index of suspicion and thorough patient evaluation. Advances in genetic research and immunology are gradually providing more insights into disease mechanisms, which may lead to more targeted and effective treatments in the future. Current treatment strategies for BS aim to manage symptoms and prevent serious complications. These strategies typically involve a combination of immunosuppressive agents, biologics, and supportive care tailored to the individual patient's needs. Despite these treatments, managing BS remains challenging due to its unpredictable course and potential for severe complications. Ongoing research and clinical trials are essential to better understand the underlying mechanisms of BS and develop new, more effective treatments. Multidisciplinary care approaches and patient education are crucial in managing this complex condition and improving patient outcomes. Future advances in personalized medicine and biologic therapies hold promise for more effective and tailored management of BS.

Author Contributions

All authors contributed equally to conceptualization, writing and visualization of the article.

Funding

This research received no external funding.

Competing Interests

The authors have declared that no competing interests exist.

Data Availability Statement

No new data were created or analyzed in this study. Data sharing is not applicable to this article.

References

1. Sakane T, Takeno M, Suzuki N, Inaba G. Behçet's disease. N Engl J Med. 1999; 341: 1284-1291.
2. Watts RA, Hatemi G, Burns JC, Mohammad AJ. Global epidemiology of vasculitis. Nat Rev Rheumatol. 2022; 18: 22-34.
3. Alipour S, Nouri M, Sakhinia E, Samadi N, Roshanravan N, Ghavami A, et al. Epigenetic alterations in chronic disease focusing on Behçet's disease. Biomed Pharmacother. 2017; 91: 526-533.
4. Kulaber A, Tugal-Tutkun I, Yentür SP, Akman-Demir G, Kaneko F, Gül A, et al. Pro-inflammatory cellular immune response in Behçet's disease. Rheumatol Int. 2007; 27: 1113-1118.
5. Khoshbakht S, Başkurt D, Vural A, Vural S. Behçet's disease: A comprehensive review on the role of HLA-B* 51, antigen presentation, and inflammatory cascade. Int J Mol Sci. 2023; 24: 16382.
6. Davatchi F, Chams-Davatchi C, Shams H, Shahram F, Nadji A, et al. Behcet's disease: Epidemiology, clinical manifestations, and diagnosis. Expert Rev Clin Immunol. 2017; 13: 57-65.
7. Ortiz-Fernández L, Sawalha AH. Genetics of Behcet's disease: Functional genetic analysis and estimating disease heritability. Front Med. 2021; 8: 625710.
8. Esatoglu SN, Ozguler Y, Hatemi G. Disease and treatment-specific complications of Behçet syndrome. Curr Rheumatol Rep. 2024; 26: 1-11.
9. de Chambrun MP, Wechsler B, Geri G, Cacoub P, Saadoun D. New insights into the pathogenesis of Behcet's disease. Autoimmun Rev. 2012; 11: 687-698.
10. Mahmoudi M, Aslani S, Meguro A, Akhtari M, Fatahi Y, Mizuki N, et al. A comprehensive overview on the genetics of Behçet's disease. Int Rev Immunol. 2022; 41: 84-106.
11. Mattioli I, Bettiol A, Saruhan-Direskeneli G, Direskeneli H, Emmi G. Pathogenesis of Behçet's syndrome: Genetic, environmental and immunological factors. Front Med. 2021; 8: 713052.
12. Verity DH, Marr JE, Ohno S, Wallace GR, Stanford MR. Behçet's disease, the Silk Road and HLA-B51: Historical and geographical perspectives. Tissue Antigens. 1999; 54: 213-220.
13. Nakamura K, Tsunemi Y, Kaneko F, Alpsoy E. Mucocutaneous manifestations of Behçet's disease. Front Med. 2021; 7: 613432.

14. Hatemi G, Christensen R, Bang D, Bodaghi B, Celik AF, Fortune F, et al. 2018 update of the EULAR recommendations for the management of Behçet's syndrome. Ann Rheum Dis. 2018; 77: 808-818.
15. Disease ISGfBs. Criteria for diagnosis of Behcet's disease. International Study Group for Behcet's Disease. Lancet. 1990; 335: 1078-1080.
16. Torgutalp M, Eroğlu DŞ, Sezer SE, Yayla ME, Karataş G, Özel EM, et al. Patient characteristics in Behçet's syndrome and their associations with major organ involvement: A single-centre experience of 2118 cases. Scand J Rheumatol. 2022; 51: 50-58.
17. Alpsoy E, Leccese P, Emmi G, Ohno S. Treatment of Behçet's disease: An algorithmic multidisciplinary approach. Front Med. 2021; 8: 624795.
18. Scherrer MA, Rocha VB, Garcia LC. Behcet's disease: Review with emphasis on dermatological aspects. An Bras Dermatol. 2017; 92: 452-464.
19. Alibaz-Oner F, Direskeneli H. Advances in the treatment of Behcet's disease. Curr Rheumatol Rep. 2021; 23: 47.
20. Torgutalp M, Eroglu DS, Sezer S, Yayla ME, Karatas G, Yurteri EU, et al. Analysis of vascular involvement in 460 patients with Behçet's syndrome: Clinical characteristics and associated factors. Joint Bone Spine. 2022; 89: 105277.
21. Yazici Y, Hatemi G, Bodaghi B, Cheon JH, Suzuki N, Ambrose N, et al. Behçet syndrome. Nat Rev Dis Primers. 2021; 7: 67.
22. Bonitsis NG, Luong Nguyen LB, LaValley MP, Papoutsis N, Altenburg A, Koetter I, et al. Gender-specific differences in Adamantiades–Behçet's disease manifestations: An analysis of the German registry and meta-analysis of data from the literature. Rheumatology. 2015; 54: 121-133.
23. Leccese P, Alpsoy E. Behçet's disease: An overview of etiopathogenesis. Front Immunol. 2019; 10: 1067.
24. Sconfienza LM, Albano D, Messina C, Gitto S, Guarrella V, Perfetti C, et al. Ultrasound-guided percutaneous tenotomy of the long head of biceps tendon in patients with symptomatic complete rotator cuff tear: *In vivo* non-controlled prospective study. J Clin Med. 2020; 9: 2114.
25. Hatemi G, Silman A, Bang D, Bodaghi B, Chamberlain AM, Gul A, et al. EULAR recommendations for the management of Behçet disease. Ann Rheum Dis. 2008; 67: 1656-1662.
26. Ramoğlu MG, Atalay S, Uçar T, Fitoz S, Özçakar ZB, Çiftçi E, et al. Multiple intra-cardiac masses: A life-threatening complication of Behçet's disease. Echocardiography. 2020; 37: 1077-1079.
27. Ruiz N, Rivera-Rosales R, Cedillo J, Luna-Rivero C, Flores-Suárez LF. Unusual cause of intestinal perforation in granulomatosis with polyangiitis (Wegener's). Int J Rheum Dis. 2017; 20: 1014-1021.
28. Alpsoy E, Donmez LE, Onder ME, Gunasti S, Usta AY, Karincaoglu Y, et al. Clinical features and natural course of Behçet's disease in 661 cases: A multicentre study. Br J Dermatol. 2007; 157: 901-906.
29. Tsuchida N, Kirino Y, Soejima Y, Onodera M, Arai K, Tamura E, et al. Haploinsufficiency of A20 caused by a novel nonsense variant or entire deletion of TNFAIP3 is clinically distinct from Behçet's disease. Arthritis Res Ther. 2019; 21: 137.
30. Berteau F, Rouviere B, Delluc A, Nau A, Le Berre R, Sarrabay G, et al. Autosomic dominant familial Behçet disease and haploinsufficiency A20: A review of the literature. Autoimmun Rev. 2018; 17: 809-815.

31. Kilian NC, Sawalha AH. Behçet's disease in the United States: A single center descriptive and comparative study. Eur J Rheumatol. 2017; 4: 239-244.
32. Tezcan ME. No family clustering in Behçet's syndrome. Balk Med J. 2019; 36: 145.
33. Ahn HS, Kim HJ, Kazmi SZ, Kang T, Jun JB, Kang MJ, et al. Familial risk of Behçet's disease among first-degree relatives: A population-based aggregation study in Korea. Rheumatology. 2021; 60: 2697-2705.
34. Okubo M, Sumitomo S, Tsuchida Y, Nagafuchi Y, Takeshima Y, Yanaoka H, et al. Transcriptome analysis of immune cells from Behçet's syndrome patients: The importance of IL-17-producing cells and antigen-presenting cells in the pathogenesis of Behçet's syndrome. Arthritis Res Ther. 2022; 24: 186.
35. Farhadi J, Nouri M, Sakhinia E, Samadi N, Babaloo Z, Alipour S, et al. Epigenetics and Behçet's disease: DNA methylation specially highlighted. Iran J Allergy Asthma Immunol. 2019; 18: 462-472.
36. Remmers EF, Cosan F, Kirino Y, Ombrello MJ, Abaci N, Satorius C, et al. Genome-wide association study identifies variants in the MHC class I, IL10, and IL23R-IL12RB2 regions associated with Behcet's disease. Nat Genet. 2010; 42: 698-702.
37. Lavalle S, Caruso S, Foti R, Gagliano C, Cocuzza S, La Via L, et al. Behçet's Disease, Pathogenesis, Clinical Features, and Treatment Approaches: A Comprehensive Review. Medicina (Kaunas). 2024; 60: 562.
38. Bergamo S, di Meo N, Stinco G, Bonin S, Trevisini S, Trevisan G. Adamantiades-Behçet Disease at the Beginning of the Silk Route: North-East Italian Experience. Acta Dermatovenerol Croat. 2017; 25: 295-297.
39. Mizuki N, Ota M, Katsuyama Y, Yabuki K, Ando H, Goto K, et al. Association analysis between the MIC-A and HLA-B alleles in Japanese patients with Behçet's disease. Arthritis Rheum. 1999; 42: 1961-1966.
40. Morton LT, Situnayake D, Wallace GR. Genetics of Behçet's disease. Curr Opin Rheumatol. 2016; 28: 39-44.
41. Sugita S, Kawazoe Y, Imai A, Yamada Y, Horie S, Mochizuki M. Inhibition of Th17 differentiation by anti-TNF-alpha therapy in uveitis patients with Behcet's disease. Arthritis Res Ther. 2012; 14: R99.
42. Kanoni S, Masca NG, Stirrups KE, Varga TV, Warren HR, Scott RA, et al. Analysis with the exome array identifies multiple new independent variants in lipid loci. Hum Mol Genet. 2016; 25: 4094-4106.
43. Tong B, Liu X, Xiao J, Su G. Immunopathogenesis of Behcet's disease. Front Immunol. 2019; 10: 665.
44. Fei Y, Webb R, Cobb BL, Direskeneli H, Saruhan-Direskeneli G, Sawalha AH. Identification of novel genetic susceptibility loci for Behcet's disease using a genome-wide association study. Arthritis Res Ther. 2009; 11: R66.
45. Chen S, Li H, Zhan H, Zeng X, Yuan H, Li Y. Identification of novel genes in Behcet's disease using integrated bioinformatic analysis. Immunol Res. 2022; 70: 461-468.
46. Perazzio SF, Andrade LE, De Souza AW. Understanding Behçet's disease in the context of innate immunity activation. Front Immunol. 2020; 11: 586558.
47. Deng Y, Zhu W, Zhou X. Immune regulatory genes are major genetic factors to Behcet disease: Systematic review. Open Rheumatol J. 2018; 12: 70.

48. Bettiol A, Emmi G, Mattioli I, Prisco D. Etiopathogenesis of Behçet's syndrome: The role of infectious, genetic, and immunological environmental factors. Transl Autoimmun. 2023; 6: 475-485.
49. Nanke Y, Yago T, Kotake S. The role of Th17 cells in the pathogenesis of Behcet's disease. J Clin Med. 2017; 6: 74.
50. Hu D, Guan JL. The roles of immune cells in Behçet's disease. Adv Rheumatol. 2023; 63: 49.
51. Gu F, Huang X, Huang W, Zhao M, Zheng H, Wang Y, et al. The role of miRNAs in Behçet's disease. Front Immunol. 2023; 14: 1249826.
52. Salmaninejad A, Gowhari A, Hosseini S, Aslani S, Yousefi M, Bahrami T, et al. Genetics and immunodysfunction underlying Behçet's disease and immunomodulant treatment approaches. J Immunotoxicol. 2017; 14: 137-151.
53. Yenmis G, Sabancelebi S, Atak E, Yalinkilic SB, Soydas T, Sadikoglu T. Association of IL-23R and IL-10 variations with Behçet disease: A genetic analysis study. Immunol Res. 2024; 72: 293-298.
54. Karadag O, Bolek EC. Management of Behcet's syndrome. Rheumatology. 2020; 59: iii108- iii117.
55. Yazici H, Fresko I, Yurdakul S. Behçet's syndrome: Disease manifestations, management, and advances in treatment. Nat Clin Pract Rheumatol. 2007; 3: 148-155.
56. Alibaz-Oner F, Sawalha AH, Direskeneli H. Management of Behçet's disease. Curr Opin Rheumatol. 2018; 30: 238-242.
57. Zeidan MJ, Saadoun D, Garrido M, Klatzmann D, Six A, Cacoub P. Behçet's disease physiopathology: A contemporary review. Autoimmun Highlights. 2016; 7: 4.
58. Caruso P, Moretti R. Focus on neuro-Behçet's disease: A review. Neurol India. 2018; 66: 1619-1628.
59. Kidd DP. Neurological involvement by Behçet's syndrome: Clinical features, diagnosis, treatment and outcome. Pract Neurol. 2023; 23: 386-400.
60. Kiafar M, Faezi ST, Kasaeian A, Baghdadi A, Kakaei S, Mousavi SA, et al. Diagnosis of Behçet's disease: Clinical characteristics, diagnostic criteria, and differential diagnoses. BMC Rheumatol. 2021; 5: 2.
61. Greco A, De Virgilio A, Ralli M, Ciofalo A, Mancini P, Attanasio G, et al. Behçet's disease: New insights into pathophysiology, clinical features and treatment options. Autoimmun Rev. 2018; 17: 567-575.
62. Vural S, Boyvat A. The skin in Behçet's disease: Mucocutaneous findings and differential diagnosis. JEADV Clin Pract. 2022; 1: 11-20.
63. Martineau M, Haskard DO, Nelson-Piercy C. Behçet's syndrome in pregnancy. Obstet Med. 2010; 3: 2-7.
64. Iskender C, Yasar O, Kaymak O, Yaman ST, Uygur D, Danisman N. Behçet's disease and pregnancy: A retrospective analysis of course of disease and pregnancy outcome. J Obstet Gynaecol Res. 2014; 40: 1598-1602.
65. van der Houwen T, van Laar J. Behçet's disease, and the role of TNF-α and TNF-α blockers. Int J Mol Sci. 2020; 21: 3072.
66. Bettiol A, Prisco D, Emmi G. Behçet: The syndrome. Rheumatology (Oxford). 2020; 59: iii101-iii107.
67. Takeuchi M, Kastner DL, Remmers EF. The immunogenetics of Behçet's disease: A comprehensive review. J Autoimmun. 2015; 64: 137-148.

68. Ozguler Y, Hatemi G. Management of Behçet's syndrome. Curr Opin Rheumatol. 2016; 28: 45-50.
69. Fabiani C, Vitale A, Emmi G, Lopalco G, Vannozzi L, Guerriero S, et al. Interleukin (IL)-1 inhibition with anakinra and canakinumab in Behçet's disease-related uveitis: A multicenter retrospective observational study. Clin Rheumatol. 2017; 36: 191-197.
70. Garcia-Estrada C, Casallas-Vanegas A, Zabala-Angeles I, Gomez-Figueroa E, Rivas-Alonso V, Flores-Rivera J. Rituximab as an effective therapeutic option in refractory Neuro-Behçet syndrome. J Neuroimmunol. 2020; 346: 577308.
71. Eshwar V, Kamath A. Assessment of safety profile of secukinumab in real-world scenario using United States food and drug administration adverse event reporting system database. Sci Rep. 2024; 14: 1222.
72. Nikolai LO, Egeberg A, Isufi D, Rasmussen MK, Bryld LE, Ajgeiy KK, et al. Response to interleukin-17A inhibitors according to prior biologic exposures: A Danish nationwide study. Acta Derm Venereol. 2023; 103: 12616.
73. Țiburcă L, Bembea M, Zaha DC, Jurca AD, Vesa CM, Rațiu IA, et al. The treatment with interleukin 17 inhibitors and immune-mediated inflammatory diseases. Curr Issues Mol Biol. 2022; 44: 1851-1866.
74. Sweeting F, Arden-Close E. The impact of Behcet's disease on intimate relationships in women: A qualitative study. Chronic Illn. 2022; 18: 255-267.
75. El Hasbani G, Uthman I, Jawad S, Jawad AS. The psychological impact of Behçet's disease. Musculoskelet Care. 2022; 20: 742-757.