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Behçet's Disease: An Enigmatic Malady with Plethoric Expressions

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Abstract

Behçet's disease (BD) is a chronic, inflammatory, repetitive, debilitating systemic vasculitis with conglomerate system involvement of uncharted aetiology portrayed by the triad of oral ulcers, genital ulcers and cutaneous lesions. Behçet's disease has a universal distribution with a predominance among populace with higher prevalence of human leukocyte antigen (HLA) B5 and its split, HLA-B51, in the Mediterranean basin, the Middle East and Far East. This ailment is presently acknowledged to be a multisystem disorder with mucocutaneous, ocular, intestinal, articular, vascular, urogenital, musculoskeletal, cardiopulmonary and neurologic systems and hence bears significant organ sinisterring morbidity and mortality. The diagnosis of Behçet's disease relies on scrupulous history, identification of its emblematic clinical countenance as per the diagnostic criteria construed by the International Study Group (ISG) and examination of all pertinent systems and excluding other systemic rheumatic diseases. However, there is a lag in diagnosis because of its plethoric presentations and a dearth of specific biomarkers. The multiple organ and tissue involvement of Behçet's disease necessitates an interdisciplinary approach from various health specialities since a general and an organ-specific approach is mandatory. Prime concern is to control the active periods of the disease which is achieved by different anti-inflammatory drugs, steroids or immunomodulators.

Keywords: Behçet's disease, triple symptom complex, Adamantiades-Behçet's disease, oral ulcers, aphthous stomatitis, vasculitis, silk road disease

1. Introduction

Behçet's disease (BD) is described as a severely debilitating chronic, recurrent, multisystem vascular inflammatory disorder characterised by the triad of oral and genital ulceration and ocular lesions. This exemplary presentation would have been probably first identified by Hippocrates [1, 2]. Even though Behçet's disease was first identified by the father of medicine in the fifth century BC, there were no literature representations for this entity till 1930, and then a Greek ophthalmologist Benediktos Adamantiades presented one of his case of relapsing eye lesions associated with genital ulceration and arthritis in a 20-year-old male; since then entity has been added with a synonym "Adamantiades-Behçet's disease" [3–6]. Further to its classic expression of orogenital ulceration and ocular lesions, the conditions seem to involve the musculoskeletal system, nervous system, gastrointestinal tract, vascular beds, urogenital tract and cardiopulmonary system, so Behçet's disease have a high morbidity and mortality particularly in males with early age onset [7, 8].

The self-limiting inflammation and the relapsing episodes of clinical manifestations are the hallmark of Behçet's disease [9]. Frequency and span of regression are uncertain and show no distinguishable pattern of onset.

Although Behçet's disease has a worldwide distribution, it is more rampant in Turkish population, where the prevalence is about 421 cases per 100,000 and 13 to 20 cases per 100,000 population in China, Korea, Japan and the Middle East [10, 11]. Behçet's disease is most commonly diagnosed in the second and third decades of life especially during the reproductive years and shows a female predilection among Europeans. Behçet's disease rarely occurs prior to puberty and after the fifth decade of life. Behçet's disease developing in early age has shown to have severe clinical manifestations and mortality. Familial occurrences have been reported in various literatures but are unusual, and the aetiology of Behçet's disease remains cryptic [12–18]. The widely accepted hypothesis is that of an inappropriate inflammatory response provoked by an infectious agent in a genetically liable host [19].

Diagnosis of Behçet's disease is based on the criteria developed by the International study group (ISG) in 1990 and International Criteria for Behçet's Disease (ICBD) [20]. The ICBD was developed with the intention of bettering the ISG criteria that did not consist of nervous system, vascular and gastrointestinal involvement that are severe but rather infrequent complications of Behçet's disease. A recent study conducted in the United Kingdom has compared the efficacy of ISG and ICBD diagnostic criteria among their patients with Behçet's disease and concluded that the sensitivity was higher for ICBD than ISG criteria, but the specificity of ICBD was much lower than the ISG criteria [20–22].

Management is aimed to alleviate symptoms, resolve inflammation, restrain tissue damage, dwindle frequency and severity and avoid lethal complications. A multitude of treatment modalities have been proposed for managing Behçet's disease ranging from anti-inflammatory to immunomodulators and biologic monoclonal antibodies. Detrimental ramifications are a main concern since it requires long-term medication [8].

2. Epidemiology

Behçet's disease is observed to have a worldwide distribution. However, it is seen commonly among the inhabitants of the historic Silk Road, which was supposed to be an old trading route that linked Japan and China in the Far East to the Mediterranean Sea, including countries such as Turkey and Iran. Therefore, Behçet's disease is also known by the synonym "Silk Road disease" [23]. Behçet's disease has a highest prevalence rate in Turkey, where the estimated prevalence is about 421 per 100,000 population followed by Iran, Israel and Japan [24]. It is rarely reported in African countries and the USA [23] as well as Australia, where the prevalence remains unknown but with an annual incidence of 0.6% (**Table 1**) [25].

Two studies conducted in Korea and Turkey in 2016 and 2017 reported the prevalence of Behçet's disease. A study conducted in Korea estimated the prevalence of Behçet's disease, and change in prevalence rate over time from the Korean health-care big data that consists of medical institution claims data concerning diagnosis, prescription medicines and surgical treatment and represents the total population. The database was reviewed for patients diagnosed to have Behçet's disease during the year 2011 and 2015. The diagnosis was based on the Korean Standard Classification of Diseases (KCD). The estimated prevalence was about 35.0 per 100,000 population which was a little more than the previously reported prevalence of 30.2 per 100,000 in Korea. The change in prevalence rate was also estimated during the time period of 2011 and 2015 and concluded that there is a creeping

Prevalence per one lakh population	Country
Turkey	421
Iran	80
Saudi Arabia	20
Iraq	17
Israel	15.2
Japan	13.5
France	7.1
USA	5.2
Sweden	4.9
Germany	2.26
Portugal	1.53
UK	0.64

Table 1.
Worldwide prevalence of Behçet's disease [24].

escalation in the annual prevalence rate between 2011 and 2015. The prevalence rate was 32.8 per 100,000 in 2011, 34.0 per 100,000 in 2012, 34.6 per 100,000 in 2013, 35.5 per 100,000 in 2014 and 35.7 per 100,000 in 2015. The prevalence would have been more since patients with milder form of the disease have not come for treatment. Females had a higher prevalence, with a female-to-male ratio of 1:0.54 in 2011 and 1:0.56 in 2015 [26].

Another study conducted in Northern Turkey showed a prevalence of Behçet's disease in 600/100,000 population who have crossed their second decade of life and is considered as the highest prevalence reported in the literature so far [27]. Nonetheless this conclusion seems to be biased since there are methodological errors. Patients were randomly selected from the 52 urban and 33 rural general practices of a city and are invited for an examination and interview by three dermatologists. As per the authors, the invited sample would well represent the whole population since all individuals are recorded in general practices. Eye examination and pathergy test were performed in suspected individuals. Individuals compatible to ISG criteria were diagnosed as Behçet's disease. However, the total number of individuals who were invited for interview was not mentioned. Authors reported that 2325 of 2428 individuals interviewed were included in the study, of which 1290 were females and 1035 were males. Symptomatic individuals may have responded to the invitation, which might have led to a higher prevalence estimate. Authors have also reported increased prevalence of Behçet's disease in females (860/100,000) compared to males (140/100,000) ($p = 0.022$) which does not correlate with the previous studies conducted in Turkey, since they concluded no significant gender predilections [27].

A recent meta-analysis that included 45 prevalence studies suggested that even though there was clearly a wide variation across countries, the overall prevalence of Behçet's disease were 10.3/100,000. The estimated prevalence was 119.8/100,000 for Turkey, 31.8/100,000 for the Middle East, 4.5/100,000 for Asia and 3.3/100,000 for Europe [28]. A meta-regression analysis showed that classification criteria, study period or reference type had hardly any effect and study design was the deciding factor for Behçet's disease prevalence in these studies. The authors have also suggested that true geographic variations and different study methods are the possible factors responsible for the large variation in Behçet's disease prevalence across countries.

Two studies conducted in Korea reported on the clinical manifestations of Behçet's disease patients according to gender [29, 30]. The first study was carried out by a rheumatology department of a university hospital in Turkey, which assessed the prevalence between male and female with Behçet's disease in a retrospective chart review of 329 patients [29]. The study included patients who fulfilled the ISG criteria. Data on demographic features of the patients, family history, age of onset, manifestations of Behçet's, positive pathergy test and HLA-B51 were retrieved from patient charts. Among the 329 patients, 199 (60.4%) were males. A family history of Behçet's disease was reported by 9.7% of the patients and a family history of oral ulcers by 22.5%. Early onset was observed in patients with a positive family history; this phenomenon is termed as genetic anticipation which had already been seen in previous studies [31]. Female patients had an early onset compared to males (23.0 vs. 25.2 years, $p < 0.05$). Eye lesions were more common among males (42.2 vs. 29.2%, $p = 0.014$). Vascular involvement was also more common among in males (44.7 vs. 15.3%, $p < 0.001$), whereas joint involvement and headache were common among women (70.0 vs. 49.2%, $p < 0.001$ for joint involvement and 60.0 vs. 36.2%, $p < 0.001$ for headache). Frequency of genital ulcers, nodular lesions, papulo-pustular lesions and nervous system involvement was similar among males and females. Pathergy test was positive in 48.7% of the patients (52.4% among male and 43.4% among female, $p = 0.316$). HLA-B51 was positive in 44.1% of Behçet's disease patients, and the frequency was lower among men, but the difference was not that significant (38.8 vs. 50.6%, $p = 0.106$). The second study was conducted in Korea, which was a retrospective chart review of 193 patients, which analysed gender, age of onset of Behçet's disease and HLA-B51 [30]. The study showed that there is an increased prevalence in females (67%), whereas other parameters like the mean age at onset, the mean disease duration, positive pathergy test and positive HLA-B51 were similar in both males and females. Genital ulcers, peripheral joint involvement and inflammatory back pain were more common in females, while skin lesions were more frequent in males. In total, major organ involvement was present in 39% of the patients (uveitis, 27%; nervous system involvement, 7%; vascular involvement, 4% and gastrointestinal involvement, 11%), with similar frequency in both the genders. When clinical findings were compared based on onset of disease, patients with late onset (>40 years) had more nervous system involvement than those with an early onset (15.9 vs. 4.2%, $p = 0.007$).

Like the previous study, HLA-B51 positive patients had a history of early disease onset, but less nervous system (17.2 vs. 2.5%, $p = 0.02$) and gastrointestinal system (20.7 vs. 2.5%, $p = 0.01$) involvement than patients with negative HLA-B51 [32, 33].

A Japanese study conducted in 2015 analysed the change in disease phenotype over time among Behçet's disease patients treated in seven hospitals in a district in mid-Japan between 1991 and 2015. Patients fulfilled the 1987 revised diagnostic criteria of the Behçet's disease research committee; the Ministry of Health, Labour and Welfare of Japan was included in the study [34, 35]. This criterion classified the manifestations of Behçet's disease into major and minor symptoms. Major symptoms include recurrent aphthous oral ulcers, skin lesions, ocular inflammation and genital ulcers, and minor symptoms include arthritis, intestinal ulcers, epididymitis, vascular lesions and neuropsychiatric disease.

Those who have all four major symptoms during the clinical course are classified as complete, whereas those who have three major symptoms, two major and two minor symptoms, typical recurrent ocular inflammation and one or more major symptoms or typical recurrent ocular inflammation and two minor symptoms are classified as incomplete Behçet's disease. Patients were divided into three groups as group A, diagnosed before 2000; group B, diagnosed between 2000 and 2007; and group C, diagnosed after 2008. Authors observed a decrease in the number of

patients with complete disease over time, suggesting a trend for milder disease in more recent years which could be due to usage of newer medicaments and awareness about the disease. The male-to-female ratio and the age of onset of disease were not changed over time, whereas the frequency of genital ulcers and HLA-B51 positivity decreased and gastrointestinal involvement frequency increased [34, 35].

Additionally, individuals migrated from countries with high prevalence of Behçet's disease to countries with less prevalence rate were shown to have less risk of developing disease [36, 37]. Prevalence of Behçet's disease among Turkish individuals in Germany is about 21/100,000, which, although higher than that of the German population, remains inferior to prevalence in Turkey [38].

Although Behçet's disease is rare in Africans, two series have been published recently based on studies conducted in Nigeria and Dakar from the year 2007 to 2011. Based on the observation by Italian authors, the prevalence of Behçet's disease was found to be higher among immigrants when they analysed its prevalence among patients of Italian and non-Italian origin living in these areas.

A study conducted in the Netherlands estimated the prevalence of Behçet's disease in patients with diverse ethnic origins residing in the Rotterdam area showed a prevalence of 1/100,000 population among Dutch Caucasians, 39/100,000 among Moroccans and 71/100,000 among Turks, suggesting that the prevalence among Moroccans is the same as in their countries of origin [39, 40].

3. Genetics

Peculiar geographical distribution, familial aggregation, polymorphisms in genes that control immune responses and correlation with HLA-B51 class I antigen are the four factors that are considered to contribute to Behçet's disease susceptibility. Ohno in 1973 described the association of BD with HLA-B5 [39]. They demonstrated that HLA-B5 includes HLA-B51 and HLA-B52 as it has a heterogeneous composition. In major histocompatibility locus, HLA-B51 and HLA-B5701 were associated with the pathogenesis of the disease, mainly among populace alongside of ancient Silk Road. Although associations with HLA-A and HLA-C have been described, they are non-specific and require confirmation. Other MHC genes such as TNF and MHC class I genes (MICA) are under study; the exact mechanism has not been fully understood. The association with HLA-B51 appears to be important in neutrophil activation. However, the presence of HLA-B51 alone is not ample to explain the manifestations of Behçet's disease. A case series of Iranian patients showed association with HLA-B35, HLA-B51, HLA-B52 and HLA-Bw4. Supplementary studies suggest associations with HLA-B15, HLA-B27, HLA-B57 and HLA-A26 [40].

Researches focused on single-nucleotide polymorphisms (SNPs) revealed that SNP which is in the HLA-B region between HLA-B and MICA genes is responsible for the relationship between HLA-B51 and Behçet's disease. The epistatic interactions with endoplasmic reticulum-associated aminopeptidase 1 (ERAP-1) has also been studied, and the authors suggested that the interaction of ERAP-1 and HLA-B has also been consistent, and these cytokines were apparently high in the peripheral blood mononuclear cells of patients with Behçet's disease compared to the control group. Another conclusion was the unbalanced suppressor of cytokine signalling expression in patients with Behçet's disease compared to controls [41].

A Chinese study stated that the polymorphisms of NOS3/rs1799983, a nitric oxide synthase gene, were found to be associated with the disease and the involvement of CD16 and CD11c in Behçet's disease susceptibility. Mutations in the familial Mediterranean fever (MEFV) gene were suggested by a meta-analysis of 8 studies which analysed 2538 patients and 2792 healthy controls. Researches also suggested

the associations of Toll-like receptors 7 (TLR7) and other nucleic acid-sensing genes of innate immunity-like inflammatory pathways such as IFI16 (a dsDNA cytosolic sensor and mediator of the AIM2-dependent inflammatory pathway) found to influence Behçet's disease susceptibility [39]. Epigenetic studies with inverted repeat sequences (IRS) demonstrated that methylation level of IRS elements may influence the pathogenesis of the Behçet's disease. Researches were done on genes related to apoptosis, but the results were not conclusive [41].

4. Pathogenesis

A multitude of factors that indicate the interaction between environmental, innate and adaptive immunity in the development of the disease has been already discussed in the Genetics section. Various researches have studied about the role of bacterial and viral agents in the development of Behçet's disease, but the results were inconclusive. *Streptococcus sanguinis* and Herpesviridae were suspected as contributing extrinsic factors for the oral presentations in Behçet's disease; the immune response to these microorganisms and bacterial plaque ecology may be affected in Behçet's disease, leading to changes seen in the oral mucosa. However good prognosis was noticed in patients with good oral health status [41]. Recent studies in Behçet's disease patients have demonstrated peculiar dysbiosis of the gut microbial flora with a notable drop in the production of butyrate. Butyrate can initiate the differentiation of regulatory T cells (T-reg), and thus, its decrease would lead to the reduction of regulatory T-cell response and activation of immunopathological T-cell effector responses. Predisposition to insulin resistance and metabolic syndrome in patients and reduction of angiotensin 1 especially in patients with vascular involvement has been observed in other studies [42]. In an attempt to find out specific Behçet's disease antigen, a Chinese research group demonstrated high IgG reactivity to an endothelial cell autoantigen [41].

Matzinger suggested the danger model, which occurs due to a continuous autoimmune cascade resulting from signals emitted by the affected cells of the host which will override the external stimulus. T cells and other antigen-presenting cells (APC) would command the process, which would be perpetuated on a favourable genetic terrain. Damage by a non-self-entity would trigger permanent aggression by activating an uncontrolled adaptive response. Because of their similarity to other pathogenic proteins, heat shock proteins (HSP60) could be involved. This adaptive reaction to external stimuli would persist in the permanent pathogenic presence via autoantigens that would activate dendritic T cells and B cells [40]. Thus, overexpression of proinflammatory cytokines especially Th1 and Th17 and probably association with genetic susceptibility may be the contributing factor for the increased inflammatory reaction in Behçet's disease. Stimulated lymphocytes would activate neutrophils and endothelial cells, and HSPs would probably trigger innate and adaptive immune responses. Hypersensitivity to *Streptococcus sanguinis* is observed through the innate immune system. Microbial flora along with stress proteins in oral and periodontal tissues could cross-react with host tissues and stimulate the proliferation of autoreactive T-cell clones. HSPs would transfer antigenic peptides to APCs that could be identified by TLRs, triggering an endogenous signal of danger that would lead to the activation of innate and adaptive immune systems. They could also, directly or indirectly, cause increased expression of vascular endothelial growth factor by T cells, causing both endothelial cell damage and vasculitis.

Many studies have demonstrated the presence of IFN-gamma and IL-12 in peripheral blood of Behçet's disease patients suggesting involvement of TH1 cells. Elevated IL-1, IL-6, IL-18, TNF-alpha and chemokines would reflect the activation of innate

and adaptive immune systems. Neutrophils are hyperactivated with increased phagocytosis, chemotaxis, superoxide and lysosomal enzyme production. Lymphocytes have also shown abnormal functions such as clonal expansion of autoreactive T cells specific for heat shock protein 60 peptides. In addition, gamma-delta T cells are abundant in the blood and mucosal lesions of the affected individuals. Researchers have concluded that the interaction between T cells, neutrophils and antigen-presenting cells probably contributes to the pathogenesis of Behçet's disease [40].

5. Clinical presentations

Behçet's disease is a form of systemic vasculitis which affect almost all vascularized systems (**Table 2**) and is characterised by episodes of relapses and remissions [9, 43, 44].

The triad of oral aphthae, genital ulcers and ocular lesions specifies the disease pattern even though Behçet's disease has other multisystem involvement and several clinical manifestations.

Children exhibit more frequent perianal ulceration and more severe course of chorioretinitis and less frequent genital ulcers and vascular involvement [44, 45].

5.1 Eye manifestations

A meta-analysis of 18 articles which was performed by Horie et al. to assess the association between HLA-B51 and the ocular manifestations of Behçet's disease among various ethnic group studies from Middle and Far East suggested that there was a strong association between HLA-B51 expression and ocular involvement, whereas studies from North Africa and Europe showed no association [46].

Accorinti et al. investigated demographic and clinical trends of 385 Behçet's disease patients with uveitis seen over 44 years in a referral unit at Sapienza University in Rome, Italy. The cohort was divided into cohort 1, which included the patients seen from 1968 to 1992, and cohort 2 included the patients seen during 1993 and 2011. Compared to the cohort 1, the cohort 2 has more female patients, more patients with milder disease (more frequent isolated anterior uveitis, less frequent hypopyon) and more immunosuppressive use. Ocular complications such as optic atrophy, maculopathy and retinal neovascularisation and retinal detachment

Manifestation	Prevalence	Prognosis	Comments
Oral ulcers	47–83%	Favourable	Appear in all patients during the disease course
Genital ulcers	57–93%	Favourable	Lesion will leave a scar
Ocular lesions	30–70%	Poor	More frequent in males. Has high morbidity
Cutaneous lesions	38–99%	Favourable	Erythema nodosum more frequent in females
Joint involvement	45–60%	Favourable	Nondeforming and nonerosive
Cardiovascular involvement	7–49%	Poor	More frequent in males, high morbidity and mortality
Neurological involvement	5–10%	Poor	More frequent in males, high morbidity and mortality
Gastrointestinal involvement	3–26%	Poor	More frequent among Japanese

Table 2.
Manifestations of Behçet's disease.

were significantly more common in cohort 1. The visual acuity at final evaluation was better in the second cohort. When considered both the cohorts, more severe findings were observed in males. From the above findings, the authors concluded that timely and aggressive management reduces ocular complications and facilitates better prognosis [47].

Even though uveitis is the common ocular pathology in Behçet's disease, it is not a common cause of uveitis. The highest incidence of uveitis is reported by Mishima S from Japan [48], where it constitutes about 25%, but it is much rarer in other countries such as Brazil, where the incidence is 2% [49], and India, where the incidence is 1% reported by Sen DK from a study conducted in 94 Indian children [50]. The classical feature of Behçet's disease is recurrent, acute anterior uveitis associated with hypopyon. Other ocular manifestations seen in Behçet's disease include necrotizing vascular lesions involving the retina and the optic nerve. These manifestations may be unnoticed because of severity of the anterior segment reaction and commonly include macular oedema, retinal periphlebitis and periarteritis, thrombosis of the vessels and retinal or vitreous haemorrhages which are frequently observed in males with Behçet's disease [51, 52].

5.2 Oral manifestations

Recurrent oral ulcers are one of the earliest manifestations of Behçet's disease in around 47–86% of patients and are seen in almost all patients during their clinical course [53]. Other symptoms may at times take years to appear after the onset of disease. Oral ulcerative lesions usually manifest as a round- or oval-shaped ulcer with discrete erythematous border with a greyish-white pseudomembrane or a central yellowish fibrinous floor and grow rapidly from a flat ulcer to a deep sore [9]. They may occur as single ulcers or as numerous [9, 53]. Oral ulcers most commonly affect the gingival and buccal mucosa, tongue and lips yet may also appear in the soft and hard palates, pharynx and tonsils [9]. Minor ulcers which are less than 1 cm in diameter heal without scarring over a period of 1 to 2 weeks, whereas major ulcers which are more than 1 cm in diameter are more painful and heal within 2–6 weeks. Herpetiform ulcers occurring in recurrent crops of small ulcers that are 0.2–0.3 cm in diameter are painful and may coalesce to form large ulcers. Treatment is usually symptomatic, and prognosis of oral ulcerations is favourable [18, 53].

5.3 Cutaneous manifestations

The most commonly seen cutaneous manifestations are erythema nodosum and pseudofolliculitis, in which erythema nodosum is manifested as painful multiple subcutaneous nodules that vary in size and colour, whereas pseudofolliculitis (pustulosis) appears as a dome-shaped sterile pustule on a round reddish edematous base that looks like acne vulgaris [54]. Although these are commonly seen on the lower extremities, it can be seen throughout the body [55]. The pathergy reaction is included in the criteria for the diagnosis of Behçet's disease. Although more than 50% of patients from Turkey and Japan had a positive pathergy test, it is rarely observed in patients from Northern Europe, the USA and Australia [56, 57]. It used to be an important diagnostic criterion for Behçet's disease; however, the frequency of the pathergy phenomenon was reported to decrease during the recent years [58]. Subcutaneous thrombophlebitis is often confused with lesions of erythema nodosum; the former is manifested as tender erythematous nodules with a linear arrangement in most case. The lesions may relocate depending on the vascular segment involved [59].

5.4 Cardiac manifestations

Cardiac involvement is a rare finding in patients with Behçet's disease. Behçet's disease affects arteries, veins as well as the heart. Cardiovascular features have been reported to affect 7–49% of patients, more frequently in males. They occur 3–16 years after the onset of Behçet's disease. Cardiac involvement in Behçet's disease patients was first described by Mirone et al. in 1958 as a case of paroxysmal fibrillation and heart block. In 1963, Oshima et al. described a case of myocardial infarction complicated by incomplete right bundle-branch block [60]. Since then different types of cardiovascular lesions, including pericarditis, atrial thrombus, complex ventricular arrhythmia, myocardial infarction, heart block and sudden death, have been reported in association with Behçet's disease [61]. Dong Soo et al. in 1998 reported a case of superior vena cava syndrome caused by Behçet's disease in a 40-year-old man with recurrent oral aphthous ulcers and skin rashes on the anterior chest wall [62].

5.5 Neurological manifestations

Neurological involvement in Behçet's disease, the neuro-Behçet's disease, occurs very rarely and only in 5–10% of patients. It is frequently seen in males [63]. It usually occurs around 5 years after the onset of the disease and is associated with long-term morbidity and mortality [9]. Neuro-Behçet's disease can be parenchymal, nonparenchymal or mixed brain disease, in which the parenchymal brain disease affects the brainstem and/or basal ganglia and is correlated with a poor prognosis, whereas nonparenchymal also known as vasculo-Behçet's disease or angio-Behçet's disease is characterised by subsets of cerebral venous thromboses, dural venous sinus thrombosis, arterial vasculitis and aseptic meningitis and comprises the most devastating symptom category of Behçet's disease with high mortality [63, 64]. A mixed parenchymal and nonparenchymal disease has also been reported but is very rare. Infrequent clinical manifestations like epilepsy, stroke, brain tumour-like neuro-Behçet's disease, acute meningeal syndrome, movement disorders, optic neuropathy, spinal cord involvement and asymptomatic and subclinical neurological involvement have also been reported [65, 66]. Meningitis, neurological deficits including motor disturbances and brainstem symptoms and psychiatric symptoms including personality changes develop in patients with neuro-Behçet's disease are considered as a classic finding [18, 63]. These symptoms are associated with disease exacerbations and gradually cause disability and unfortunately are irreversible [18]. At late stages, dementia develops in approximately one-third of patients with neuro-Behçet's disease.

5.6 Gastrointestinal manifestations

Gastrointestinal involvement was observed in 3–26% of patients and varies among different populations [38, 39]. It is much more frequent in Japan than in the Middle East and the Mediterranean region [1–3]. Mucosal inflammation and ulceration can occur anywhere in the gastrointestinal tract but typically in the ileocecal region. Other rarely involved sites include the oesophagus, ascending colon and transverse colon [18, 19, 67]. Clinical symptoms include anorexia, vomiting, dyspepsia, diarrhoea, melena, abdominal pain and, less frequently, perforation requiring surgical intervention [68]. Due to the similarity in intestinal and extraintestinal symptoms, it is tough to differentiate Behçet's disease from inflammatory bowel disease; however, the presence of granulomata can be used to confirm inflammatory bowel disease [66].

5.7 Articular manifestations

Joint involvement is common in patients with Behçet's disease seen in almost half of patients. It presents as an initial manifestation seen long before the commencement of other features of BD [55]. Erosive, non-deforming oligoarthritis typically involving the knees, ankles and wrists is seen in most of the Behçet's disease patients. Rarely, it can present as sacroiliitis or erosive arthritis. Myopathy has also been reported by Arkin in 1980 [69–72].

5.8 Vascular manifestations

Vasculitis is one of the classic signs in Behçet's disease, and the typical finding is deep vein thrombosis. Thrombophlebitis occurs generally in the first year after onset of Behçet's disease, and relapses are frequent. Vasculitis can affect both the veins and arteries and capillaries although venous involvement is more common [55]. Venous thrombosis may occur at any site and can even involve large vessels like the inferior vena cava, the superior vena cava and the pulmonary artery. [55]. Arterial involvement is seen in 3–5% of cases [73]. Aneurysm formation is found to be the foremost manifestation, and the affected patients can be asymptomatic [74]. Vascular surgery is mandatory, but relapse is a frequent concern [55].

5.9 Pulmonary manifestations

Pulmonary manifestations are rare in patients with Behçet's disease. Haemoptysis is the only reported manifestation, but it can be massive and fatal [74].

6. Diagnostic criterion and activation markers in Behçet's disease

The diagnosis of Behçet's disease relies purely on its clinical manifestation since it lacks specific biological test, so diagnosis with clinical symptoms is challenging, especially due to non-concomitant symptoms. Hence different diagnostic criteria have been developed for the determination of Behçet's disease. In 1990, an ISG for Behçet's disease was formed by a group of researchers [21]. The International Study Group developed a set of classification criteria which is designed for research studies, which in many instances is used for diagnosing. The features were defined as the presence of specific symptoms as seen in **Table 3**. Oral ulceration along with any other two symptoms is said to be diagnostic [75]. The capability of the ISG criteria as a diagnostic tool has been questioned [56]. An international team which includes 27 countries was formed to evaluate and reassess the ISG criteria, and a new ICBBD was developed that include the major criteria consisting of oral aphthosis, genital aphthosis and ocular lesions which were each given 2 points, whereas 1 point was assigned to the skin lesion, neurological manifestation, vascular manifestation and positive pathergy test (which is optional and not included in the primary criteria due to geographic variation and its declining sensitivity and increased specificity) [58, 75]. Higher sensitivity of the ICBBD was reported as it aided in earlier diagnosis and hence earlier treatment and thereby better prognosis [75]. However, the delay between the onsets of major manifestations may be decades needs to be considered [76]. Inflammatory markers such erythrocyte sedimentation rate (ESR) and C-reactive protein have no longer been recognised as accurate or specific for the disease activity (**Table 4**).

Investigations for Behçet's disease include routine total blood count; renal, liver and bone profile; inflammatory markers, including C-reactive protein and erythrocyte sedimentation rate; urine analysis; chest X-ray; coeliac screen; stool sample; autoimmune

Recurrent oral ulcerations	Minor aphthous, major aphthous or herpetiform ulceration observed by physician or patient, which recurred at least three times in one 12-month period
Plus any two of the following	
Recurrent genital ulceration	Aphthous ulceration or scarring observed by physician or patient
Eye lesion	Anterior uveitis, posterior uveitis or cells in vitreous on slit lamp examination or retinal vasculitis observed by ophthalmologist
Skin lesions	Erythema nodosum observed by physician or patient, pseudofolliculitis or papulopustular lesions or acneiform nodules observed by physician in post adolescent patients not on corticosteroid treatment
Positive pathergy test	Read by a physician at 24–48 hours

Table 3.
The international study group criteria for Behçet's disease [21].

Symptoms	Points
Oral aphthosis	2
Genital aphthosis	2
Ocular lesion	2
Skin lesion	1
Neurological manifestation	1
Vascular manifestation	1
Positive pathergy test	1 ^b

Table 4.
International criteria for Behçet's disease [75].

screen; coagulation profile and antiphospholipid antibodies; mouth and genital ulcer swab and culture; and occasionally eye swab. Other investigations that may be required include oral biopsy and direct immunofluorescence to exclude orofacial granulomatosis and bullous dermatosis. Vulval biopsy is indicated to exclude lichen sclerosis).

Doppler studies, CT or MRI brain and spinal cord, magnetic resonance venography, computerised tomographic venography, magnetic resonance angiography, computerised tomography angiography to evaluate neurologic and vascular disease; CSF studies, electroencephalogram, electromyography, nerve conduction study, 18 F fluoro2-deoxyglucose positron emission tomography, with CT/MRI localisation (for early inflammation in large vessel vasculitis). Musculoskeletal BD—synovial fluid analysis, X-ray, ultrasound or MRI to evaluate joints. Skin biopsy and immunofluorescence for cutaneous involvement. Cardiac BD—electrocardiogram, echocardiogram in case of cardiovascular involvement chest CT to assess mediastinal diseases, fibrosing mediastinitis, aneurysms, pleural effusions, complications of venous thrombosis and collaterals. Stool sample for faecal calprotectin, endoscopy and biopsy if there is Gastrointestinal involvement. Ocular BD—optical coherence tomography, visual evoked potentials, fluorescein angiogram, Schirmer's test, intraocular fluid culture to exclude infections in Behçet's patients with ocular involvement. Cystoscopy and kidney, urinary bladder CT for urological disease [7].

7. Management

The multisystem involvement in Behçet's systems alarms the requirement of a teamwork from different medical specialties such as oral medicine, ophthalmology,

Manifestations	Treatments
Mild mucocutaneous lesions	Topical steroids
Moderate to severe mucocutaneous lesions	Initial: systemic steroid, colchicine Refractory case: azathioprine, interferon α
Ocular lesions	Initial: systemic steroid + azathioprine Refractory case: first cyclosporine A + steroid + azathioprine Second interferon α +/- systemic steroid
Arthritis	(First) colchicine nonsteroidal anti-inflammatory drug, (second) azathioprine, interferon α
Vascular: deep venous thrombosis	Azathioprine, cyclosporine A, cyclophosphamide (larger vessels)
Vascular: arterial aneurysm	Cyclophosphamide + systemic steroid
Neurological	Cyclophosphamide (drug of choice)
Gastrointestinal	Systemic steroid, sulfasalazine, azathioprine

Table 5.
Suggested management options of Behçet's disease [78, 79].

Disease-modifying drugs (DMDs)	Dosage
Oral DMDs	
Azathioprine	2–3 mg/kg/day
Mycophenolate mofetil	2–3 g/day
Methotrexate	20–25 mg/week
Tacrolimus	4–8 mg/day
Ciclosporin	2–5 mg/kg/day
Sulfasalazine	2–3 g/day
Dapsone	2–3 mg/kg/day
Thalidomide (exceptional use)	50–300 mg/day
Colchicine	0.5–2 mg/day
Prednisolone	Variable dose (depending on indication and stage of treatment)
Parenteral DMDs	
Cyclophosphamide	15 mg/kg (vasculitis regimens)
Anti-TNF α inhibitors	
Infliximab	5 mg/kg at 0, 2 and 6 weeks then once every 8 weeks
Adalimumab	40 mg every 2 weeks
Etanercept	50 mg/week
Certolizumab	400 mg at 0, 2 and 4 weeks then once every 4 week
Rituximab	1 g at 0 and 2 weeks
Interferon α	Various regimens for Roferon A and pegylated interferon α 2b
Alemtuzumab	3 mg (day 1), 10 mg (day 3), 30 mg (day 5), 30 mg (day 8), 30 mg (day 10) and 30 mg (day 12)

Table 6.
Disease-modifying drugs used in Behçet's disease [7].

dermatology, rheumatology, neurology, cardiology and gastroenterology for its management. The main objective of management of Behçet's disease is to induce and maintain remission and improve the patient's quality of life, preventing irreversible damage and exacerbation of mucocutaneous and articular disease [77, 78]. Since Behçet's disease has plethoric expressions, treatment plan may vary depending on severity, organ affected, age of disease onset, disease duration and frequency of recurrences [59].

The European League Against Rheumatism (EULAR) formed a committee in 2008 to develop an evidence-based recommendation for the treatment modalities of Behçet's disease [78]. Suggestions regarding ocular and mucocutaneous diseases and arthritis are primarily evidence-based, but recommendations on neurological, vascular and gastrointestinal involvement relied on observational studies, retrospective analyses and expert opinion [78].

Treatment of Behçet's disease is mainly based on the suppression of the inflammatory attack using immunomodulatory agents such as corticosteroids, azathioprine or interferon α [78]. The primary line of management of mucocutaneous lesions in Behçet's disease is colchicine (1 mg/day). NSAID is usually sufficient for joint manifestations [54]. Clinicians should keep in mind the neurotoxicity of cyclosporine A while prescribing it to any patient with neurologic problems for treating vascular involvement and refractory eye disease [54]. Biologic agents are the only option if the disease seems to be resistant to treatments [78]. Suggested management options are summarised in **Tables 5** and **6**.

8. Conclusion

Behçet's disease is a chronic, relapsing vasculitis with multisystem involvement with considerable morbidity and mortality. There exists a delay in the diagnosis of Behçet's disease since it lacks a specific diagnostic test and biomarkers. Another area to be focussed on is to develop a more effective disease activity score. Researches are on the go to explore more about the disease's pathophysiology which may aid in early diagnosing and effective treatment planning.

Acknowledgements

We thank Prof Dr. Sobha Kuriakose, Dr. Sarika S. Kamal, Dr. Sumal V. Raj, Dr. Nithin V. S and Dr. Deena C. Thomas, Dr. Alaka Subodh and Adithi S. A for critically analysing this manuscript.

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