

Behcet's Disease: A Multifaceted AfflictionSireesha Maram¹, T.Venkataramana Reddy¹, Hima Bindu Mylapalli^{2*}, Sudeepthi Padala³, Hemanth Kumar Vangala⁴,
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Received: 20.05.2021

Revised: 07.07.2021

Accepted: 18.07.2021

Keywords :

Behcet's disease

Inflammation

Pathergy test

Ulcers

Vasculitis

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ABSTRACT

Behcet's disease is a rare systemic vasculitic disorder characterized by a triad of symptoms that includes recurrent mouth ulcers, genital ulcers and inflammation of uvea. The prevalence of this disease tends to be high in the third or fourth decades of life. Genetic and environmental factors may influence the development and progression of this disease. In this article, the involvement of the signs and symptoms of oral, genital, dermatological, musculoskeletal, gastrointestinal, ocular, neurologic, vascular and cardiac systems were reviewed along with the diagnosis and treatment of this disease. Diagnosis is quite complex due to the lack of specific laboratory, radiological and histological findings. Hence, the diagnosis can be completely depends upon the existing clinical features of that particular individual. Pathergy test is considered as an optional diagnostic test in the diagnosis of this disease due to the differences in the evaluation and application of the test. The treatment of Behcet's disease varies with organs involved, severity of lesion and clinical manifestations associated with the patients. There is no cure for this disease and all the available treatments are mainly focused in resolving symptoms and recurrence. Since this condition is rare, the health care professionals should have regular discussions regarding the treatment goals for better therapeutic outcome and to prevent the further complications. Proper coordination and communication among the health care professionals of various departments is a prerequisite for effective therapy as this disease requires a periodic monitoring of multidisciplinary approach.

© 2021 Published by Universal Episteme Publications. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>)**Introduction**

Behcet's disease is a rare systemic vasculitis disorder characterized by a triad of symptoms that includes recurrent mouth ulcers, genital ulcers and inflammation of uvea [1-4]. Along with the oral ulcers and genital ulcers, erythema nodosum and papulopustular lesions (PPL) are the key characteristics of Behcet's disease [5-7]. Major organ systems involved in this disease includes ocular, gastrointestinal, vascular and nervous system [8-15].

Epidemiology

Behcet's disease is distributed all over the world. Its prevalence, clinical findings and genetics varies among different regions. The prevalence of this disease tends to be high in the third or fourth decades of life. Males are more prone to have this disease than females [16]. Onset of this disease in the young age is associated with increased severity [17,18]. A Meta analysis showed that the joint involvement, erythema

nodosum and genital ulcers were more frequent among the females while the ocular manifestations, folliculitis, papulopustular lesions and vascular involvement were more common among the males. Gender difference was not observed for gastrointestinal and neurological involvement [19]. Turkey has the highest incidence and prevalence among the far eastern and Mediterranean ancestries followed by Iran, Israel and Japan [20,21]. Turkish immigrants to Germany were found to have significantly lower risk of developing Behcet's disease when compared with those of Turkish origin and Turkish residents [17,22].

Etiology

The etiology of Behcet's disease is of unknown origin. Genetic and environmental factors may influence the development and progression of this disease [23,24]. Behcet's disease is not seen as Mendelian disorder due to its unclear pattern of

inheritance but it is well recognized for its genetic background showing a familial aggregation [25]. Individuals with human leukocyte antigen (HLA) B51 gene have high risk of developing Behcet's disease and have higher incidence of posterior uveitis than those individuals without this gene. Individuals with HLA B51 carrier had approximately 6 times increased risk of developing Behcet's disease. HLA B51 gene positivity was more prevalent among males and correlated with genital ulcers, ocular and skin lesions [26-28]. It has been suggested that HLA B51 does not have prognostic role, as the vascular and neurologic involvement associated with high mortality and morbidity does not differ among both HLA B51 positive and negative patients [29].

The causes of Behcet's disease include infectious agents such as herpes simplex virus, parvovirus B19 and streptococcus anguis [30-32]. Any immunological abnormalities induced by microbial pathogens might make them susceptible in individuals with HLA B51 positive gene [33-35].

Pathophysiology

The pathogenesis of this disease can be better explained by genetics and immunology. The most closely associated genetic factors of Behcet's disease are HLA-B51 & variants in IL-10 at the IL-23-IL-XRR2 locus. In patients with genetic predisposition infectious agents show triggering factors that leads to progression of this disease.

Bacterial infections (streptococcus sanguinis), viral infections (herpes simplex virus, parvovirus B19) and abnormal auto antigens are some of the triggering factors. Eventually these triggering factors activates the innate and adaptive immune system resulting in release of numerous cytokines & chemokine's to counter balance antigen and auto antigens.

In innate immune system the primary cells involved in the pathogenesis of this disease are natural killer cells, $\gamma\delta$ T cells and neutrophils. Natural killer cells play a cytotoxic role in infected cells & tumor cells and also regulate the function of other immune cells including T cells and D cells through the secretion of cytokines. In adaptive immune system CD4⁺, T cells including Th1, Th2, Th17, Th22 & regulatory T cells and related cytokines play an important role in the pathogenesis of Behcet's disease [36].

Signs and Symptoms

a. Oral Cavity

Recurrent aphthous stomatitis is a condition in which oval or round painful ulcers occurs on the oral mucosa. It is the key characteristic sign of the Behcet's disease, which occur in 97-100% of the patients. Recurrent aphthous stomatitis is typically the early symptom seen in Behcet's disease. The appearance and localization of oral ulcers resembles the mouth ulcer. It becomes difficult to distinguish aphthous stomatitis from oral ulcers of Behcet's disease especially when it arises as an early manifestation. Usually the lesions are well defined, round and covered with yellowish pseudo membrane. These lesions may arise either single or in clusters and subsides within few weeks. The familiar sites of oral ulceration are lips, gingiva, tongue and buccal mucosa. The ulceration can also occur in palate, pharynx and tonsils.

Based on their size and shape of the lesions oral ulcers are categorized as major, minor and herpetiform ulcers [37]. Major ulcers are larger (>10mm in diameter), deeper and more painful but seen less frequently than minor ulcers. The healing process of major ulcers is very slow and often leads to scarring. Minor ulcers are smaller in size (<10mm in diameter) and well defined as multiple, isolated, shallow which heals without scarring. These are frequently observed in oral cavity. Herpetiform ulcers are small (1-2mm in diameter), pinpoint, numerous and shallow lesions which occur as clusters. These are large ragged ulcers by coalesce and can be healed with scarring [38,39]. Persistent recurrence of oral ulcers in males is the predictive factor for major organ involvement during the early stages of disease [40].

b. Genital

In Behcet's disease, the second most common clinical finding is the genital ulcer. In more than 70% of the cases, genital ulcers are common which usually begins as papules and morphologically resembles oral ulcers but they are usually deeper, larger and heals with scarring [37,41]. Genital ulcers occur commonly on groin, perinatal and perianal region. In males, the genital ulcers mostly occur on the scrotum while penile lesions are rare. In females, it mostly occurs on the vulva, vagina and cervix which might cause dyspareunia [39]. Ulcers occurring in areas such as under breast, interdigital area and axilla are called as extra genital ulcers. Almost two-third of the patients

can be observed with healing and scar formation within 10-30 days [42,43].

c. Dermatological

In Behcet's disease, about 75% of patients are suffering from skin diseases. The most common skin lesions are acneiform lesions and papulopustular lesions (PPL) occurring mostly on trunk, extremities, face and chest. PPL on legs is a key distinguishing feature in this condition. Most of these patients will suffer from nodular lesions, either in the form of erythema nodosum or superficial thrombophlebitis (STM). Erythema nodosum are red, painful nodules about 1-5 cm in diameter which are more localized on lower extremities, sacral regions and thighs. Erythema nodosum heals with post-lesional hyper pigmentation in 1-6 weeks and are more prevalent in females. Among adolescents, acneiform lesions can be distinguished from acne vulgaris by identifying on their body parts other than face [44-50].

d. Musculoskeletal

Arthritis and arthralgia are the two common manifestations of this disease with the prevalence of around 40-70% of the cases. Erosive arthritis is quite rare among these patients, while non-erosive arthritis occur in about 50% of the patients. Non-erosive arthritis can be either monoarthritis or oligoarthritis affecting the joints such as knee, wrist, ankle and elbow. In contrast to HLA-B27 associated diseases, sarcoiditis rarely occurs in patients with this disease. Behcet's disease patients with arthritis are more prone to acne and enthesopathy, which is a feature of seronegative spondyloarthritis. PPL is the only extra-articular manifestation associated with arthritis attack [51-55].

e. Gastrointestinal

Gastrointestinal Involvement of Behcet's Disease (GIBD) results in anorexia, abdominal pain, melena and diarrhea. Due to vasculitic nature of GI tract, perforation and massive bleeding are more common affecting any part of the GI tract. Ulceration is seen typically in the terminal ileum, ascending colon and cecum. The usual shape of ulcer in GIBD is oval or round which is similar to the conditions like non steroidal anti inflammatory drugs induced enteropathy and tuberculosis. Therefore, these conditions must be ruled out before the diagnosis [56-60].

f. Ocular

Ocular involvement is more prevalent and severe in men than in women which occurs in 30-70% of the patients with this disease [61,62]. Ocular involvement might occur within the first 5 years of the disease onset. During the early stages of disease, mild ocular inflammation remains asymptomatic [63]. Chronic and recurrent anterior uveitis can lead to hypopyon due to the accumulation of white blood cells in the anterior chamber of eye. The altered neurological activity of these patients might result in scleritis, episcleritis, keratitis, conjunctival ulcers, conjunctivitis and extra ocular muscle paralysis. Intraocular inflammation may involve either anterior or posterior segment or both. The uveitis classification is important both therapeutically and prognostically as lesions affecting posterior segments are persistent in the nature and results in significant vision loss. Bilateral panuveitis with retinal vasculitis is the most common and severe form of ocular involvement [62].

g. Neurologic

The involvement of central nervous system in this disease is usually called as Neuro-Behcet's Syndrome (NBS) which can be also called as "parenchymal NBS". It is one of the most serious manifestations affecting telencephalic-diencephalic junction, brain stem and spinal cord. Among these patients with CNS disease, 70-80% might have parenchymal involvement, while the most commonly affected site is the brain stem. Patients may develop neurological symptoms such as neurologic deficits, psychiatric symptoms and meningoencephalitis after several years of disease onset. Frequent recurrence of these symptoms results in neural injury. Cerebral venous sinus thrombosis (CVST) is the second most common form of neurological manifestations which is also called as vascular NBS or extra axial NBS. It is more frequent in pediatric NBS population and occurs in 20% of patients among the adult NBS population [64,65].

h. Vascular

It occurs in about 25% of the patients with Behcet's disease and is more prevalent in male patients. Among the Asian population, superficial thrombophlebitis and deep vein thrombosis (DVT) are common among females while in case of Mediterranean countries it is vice versa.



In vascular damage, venous vessels are mostly affected than arterial vessels. The inflammation of arterial vessel due to aneurysm causes the symptoms such as acute or destructive vasculitis and bleeding. The venous vessel involvement shows extensive adherent thrombus formation without an increase of thromboembolism. This is due to an inflammation of the vessel wall. The involvement of venous and pulmonary artery begins after 5 years of disease onset and arterial involvement develops in later stages of the disease course [66].

Venous thrombosis

The first vascular event of the Behcet's disease patients in venous thrombosis is DVT on lower extremities. The characteristics that differentiate DVT due to Behcet's disease from DVT due to non-Behcet's disease include gender, age and involvement of deep proximal & superficial veins. When thrombosis occurs in inferior venacava, it causes abdominal pain and swelling of extremities. Thrombosis in superior venacava in the acute & sub-acute phase leads to dyspnea, swelling of neck, arm and face. Headache, nausea, diplopia, intracranial hypertension are the typical symptoms of cerebral venous sinus thrombosis. Complications during the chronic phase includes chylothorax, pleural effusion and sleep apnea [67,68].

Pulmonary artery

It is the most harmful manifestation of this disease with high mortality and morbidity. Its involvement results in aneurysm or thrombosis. Isolated pulmonary artery thrombosis and pulmonary artery aneurysm shows similar clinical features irrespective of *in situ* thrombosis. Pulmonary artery aneurysm shows symptoms of hemoptysis and dyspnea while these are less observed in pulmonary artery thrombosis. About 90% of Behcet's disease patients with pulmonary artery involvement suffer from pulmonary parenchymal diseases such as nodules and cavities. Pulmonary artery aneurysms and pulmonary artery thrombosis respond quite efficiently with immunosuppressive therapy. Some patients suffer from complicated recurrent hemoptysis due to bronchial artery enlargement [69-71].

Peripheral artery

Peripheral arterial involvement is quite less frequent than pulmonary artery due to the structural similarities between venous vessel and pulmonary arteries. The abdominal aorta and arteries of lower

extremities are most commonly affected while the upper limb, cerebral and visceral arteries are affected to a lesser extent. The initial symptoms vary based on the involved artery. The peripheral artery aneurysms can be detected quite easily as pulsatile painful mass [72,73].

i. Cardiac

In Behcet's disease, cardiac involvement is rare. It is precise and definite as intra cardiac thrombosis, pericarditis, myocarditis, endomyocardial fibrosis, vascular disease, coronary arteritis and endocarditis. Intra cardiac thrombosis is rare and strongly related with vascular involvement. The most common initial symptoms include fever, hemoptysis, chest pain and dyspnea. Intra cardiac thrombosis typically arises in the right ventricles or atrium and its clinical features varies from asymptomatic to acute coronary syndrome. Sinus vascular aneurysms and aortic root involvement leads to complications such as acute or chronic aortic insufficiency [74-77].

Diagnosis

The diagnosis of this disease is quite complex due to the lack of specific laboratory, radiological and histological findings. Hence, the diagnosis of this disease completely depends upon the existing clinical features of that particular individual. The diagnostic and classification criteria of Behcet's disease were introduced after studying the involvement of different organs and organ systems [78,79]. The International study group criteria consider five key characteristic features in the diagnosis of this disease. These characteristics include oral aphthous, genital aphthous, skin lesions, ocular manifestations and positive pathergy test. According to this criteria, the presence of oral aphthous is mandatory. Among the other four characters, at least two characteristics are necessary to classify the individual as Behcet's disease patient [80-85]. The criteria was revised by International study group and designed as International classification of Behcet's disease. In addition to the five characteristic features of International study group, vascular manifestations was added to the International classification of Behcet's disease as the vascular manifestations were taken into consideration in the diagnostic criteria before the advent of International study group criteria. Therefore, International classification of Behcet's disease considers six characteristic features that include oral aphthous, genital aphthous, skin lesions,



positive pathergy test, ocular and vascular manifestations. In the International classification of Behcet's disease criteria, each characteristic feature was provided with an individual scoring. Since genital aphthous and oral aphthous have significant diagnostic value, they are given two points each while the other four characteristics were given one point each. If an individual scores ≥ 3 points, then he/she can be diagnosed as Behcet's disease [86,87]. The recently revised version of International classification of Behcet's disease criteria is highly sensitive compared to the older criteria which are widely accepted. The older version was reported with a sensitivity of 77.9% while the revised version was reported with 97.9% sensitivity [78].

Pathergy phenomenon is a nonspecific cutaneous, hypersensitivity response, characterized by formation of erythematous induration at the trauma site with a papule formation at centre. It is performed by applying three needle pricks to a hairless site on the flexor of each forearm. The forearm must be wiped with alcohol and 20G needles are inserted in an oblique or perpendicular angle. The skin is observed after 48 hours. The formation of palpable erythematous papule or pustule of approximately 1-2mm size at the insertion point of at least one of the needle prick site indicates positive result [88,89]. Pathergy phenomenon may also develop in areas apart from skin such as trauma or injury, might cause an exaggerated inflammatory response in Behcet's disease patients. Vascular surgery, intraocular injections, dental procedures and venipuncture are the few known triggering factors of pathergy phenomenon [90]. The incidence of positivity of test varies depending on gender, genetic factor, thickness & type of needle application method, number of punctures and disease activity. Pathergy test is considered as an optional diagnostic test in the diagnosis of this disease due to the differences in the evaluation and application of the test [91-93].

Treatment

In Behcet's disease, the treatment regimen can be individualized because the clinical manifestations and severity of the disease varies from patient to patient. The impairment of mucocutaneous and joint involvement results in diminished quality of life, while ocular, gastrointestinal, neurological damage and vasculitis can result in organ damage which might lead to death. The main objectives of the treatment are

to prevent the damage during acute attack by suppressing the inflammation reaction and to prevent relapses by using immune suppressants [5,6]. The treatment of Behcet's disease varies with organs involved, severity of lesion and clinical manifestations associated with the patients [17].

Antiseptics, mouth washes, sucralfate suspensions, corticosteroid gels, topical lidocaine or triamcinolone acetonide injection are used to treat oral ulcers. By using topical antiseptics and mild corticosteroids, genital ulcers can be treated. In case of severe disease condition, systemic therapy is recommended which includes, oral corticosteroids, colchicine, thalidomide, azathioprine, interferon- α and anti-tumor necrosis factor- α [94]. Patients with recurrent arthritis can be treated with azathioprine, anti-tumor necrosis factor and interferon- α . Other treatment alternatives include non-steroidal anti-inflammatory drugs and intra articular corticosteroid injections. Non-steroidal anti-inflammatory drugs are usually excluded in patients with gastrointestinal ulcerations and hypersensitivity.

Behcet's disease patients suffering from posterior uveitis either with or without retinal vasculitis should be treated with immunosuppressive agents. Treatment of severe acute attacks, include systemic and intravitreal corticosteroids [95]. Immunosuppressive agents show better efficacy in reducing the relapse rate of venous thrombosis (VT) when compared with anticoagulation therapy alone. The drugs of choice in treating venous thrombosis are azathioprine and interferon- α while anti-tumor necrosis factors can be recommended for the resistant cases. No evidence supports the efficacy of anticoagulation therapy in prevention of thrombosis relapse due to the Behcet's disease. In patients with severe vascular involvement such as peripheral arterial involvement and pulmonary artery aneurysm, cyclophosphamide along with a high dose of corticosteroids can be recommended. These patients are advised to undergo surgery if they have pulmonary artery aneurysm along with compromised immune system [96].

The treatment options of gastrointestinal involvement of Behcet's disease (GIBD) are similar to that of inflammatory bowel disease that includes glucocorticoids, azathioprine, salazopyrine and 5-aminosalicylic acid derivatives [97]. In case of neuro Behcet's disease, high dose methylprednisolone pulse

therapy can be recommended for 7-10 days and then the dose is tapered for about 3-6 months depending upon the severity of the disease. Azathioprine and infliximab are used to suppress the immune system thereby preventing the further relapses [98].

Ultimately, Behcet's disease is a chronic, relapsing, inflammatory disorder with the potential to affect many organs and organ systems causing considerable morbidity and mortality. The diagnosis of this disease depends mainly on thorough medical history and clinical evaluation, as the manifestations varies among the patients and may emerge at any point in the course of the disease. There is no cure for this disease and all the available treatments are mainly focused in resolving the symptoms and recurrence. Since this condition is rare, the health care professionals should have regular discussions regarding the treatment goals for better therapeutic outcome and to prevent the further complications. Proper coordination and communication among the health care professionals of various departments is a prerequisite for the effective therapy as this disease requires a periodic monitoring of multidisciplinary approach.

Conflict of Interest: None

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