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Review

Pediatric Behçet's disease

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ABSTRACT

Behçet's disease (BD) is a vasculitis that affects vessels of any size. It is more frequent along the ancient Silk Road, extending from the Far East to the Mediterranean basin. Its etiopathogenesis is complex, and both the innate and adaptive immune systems play a role in recurrent hyperinflammation. The significant association between human leukocyte antigen B-51 and BD indicated a strong genetic background in pathogenesis. Although mucocutaneous involvement is the most common finding, it may present with a broad spectrum of clinical signs and symptoms involving the ocular, vascular, musculoskeletal, neurologic, and gastrointestinal systems. Pediatric cases may present with an incomplete clinical picture of the BD, making diagnosis difficult for the physicians. Several classification criteria have been published so far. In 2015, a classification criteria set for pediatric BD (PEDBD) was established for the first time.

The treatment strategies vary depending on the severity and type of organ involvement. The treatment should be arranged with a multidisciplinary approach according to the organs involved. Also, the possibility of developing morbidity and mortality requires early diagnosis, appropriate treatment, and close follow-up. In this review, we aimed to discuss the etiopathogenesis, clinical findings, diagnostic criteria, and treatment approach of pediatric BD based on current data.

Keywords: Behçet's disease, pediatric

INTRODUCTION

Behçet's disease (BD) is a vasculitis with systemic inflammation that can affect arteries and veins of all sizes.[1] The most common clinical findings are oral and genital aphthae, skin involvement, arthritis, uveitis, and thrombophlebitis. It is known that mucocutaneous involvement is more common, especially in pediatric cases.[2] The distribution of BD in the world coincides with the historical Silk Road (area between the Mediterranean region and the Far East). The disease often occurs in young adulthood between the ages of 20 and 40; however, about one-fifth of patients have a pediatric-onset BD.[3,4] Pediatric BD differs from adult-onset BD in terms of clinical findings, treatment approach, and outcome. Considering that BD can involve many organ systems, the treatment approach should be planned with a multidisciplinary perspective for the affected organ system.[5,6]

Epidemiology

The frequency of BD varies from country to country, and Turkey has the highest prevalence in the world with 20-420/100000.[7,8] Then, the countries with the highest prevalence are the Middle Eastern countries and Saudi Arabia. The frequency was 15.9/100000 in Italy, 5.2/100000 in the USA, and 0.9/10000 in the UK.[9] The actual prevalence of BD in children is not yet known. The pediatric BD prevalence in the United Kingdom and the

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Republic of Ireland has been reported as 4.2 per million.[10] The majority of pediatric BD cases presented in the literature have been reported from Iran, Turkey, Italy, France, and England.[2,11-16]

Etiopathogenesis

Although the etiopathogenesis of BD has not been clearly clarified, it is noteworthy that it has common features of autoimmune and autoinflammatory diseases. As in autoimmune diseases, immunosuppressive agents are helpful in the treatment, autoantigen and antigen-specific T cells play a role in the pathogenesis. It resembles autoinflammatory diseases with its course with inflammatory attacks and increased neutrophil activity and interleukin 1B (IL-1B) activity during exacerbations.[17,18] Also, the absence of autoantibodies implicated in the pathogenesis of BD suggests that BD may have an autoinflammatory nature.

The disease occurs in genetically predisposed individuals, triggered by environmental factors such as infection.[19,20] Herpes simplex virus -1 (HSV-1) and streptococcus species are infectious agents clearly associated with BD.[21] Professor Hulusi Behçet is the first author to describe the relationship between BD and infectious diseases.[22] Similarities were found between Streptococcus sanguinis, a subspecies of Streptococcus species, and human proteins such as heat-shock protein.[21] Antibodies against S. sangius and S. pyogenes were higher in patients with BD compared to the control group.[23] Moreover, the first symptoms observed in the oral mucosa in most of the patients suggested to the researchers that the oral microbial flora may play a role in the pathogenesis.[24] Recent studies have shown that gut microbiota content also plays a role in the pathogenesis of BD.[25,26]

Clustering of BD, especially in a certain geography, suggests the importance of genetic features in pathogenesis. Human leukocyte antigen (HLA) B-51, located in MHC class I, is the gene region with the most evidence for the disease.[27] Genome-wide association studies (GWAS) found that polymorphisms observed in non-HLA genes were also higher in individuals with BD.[28,29] Endoplasmic reticulum aminopeptidase 1 (ERAP1) genetic variation is one of the loci associated with BD. In addition to BD, ERAP-1 has also been shown to be associated with psoriasis and ankylosing spondylitis.[30,31] ERAP-1 polymorphism affects T-cell and natural killer cell identification.[32-35] Single nucleotide polymorphisms of interleukin 10 (IL-10) and IL-23/IL-12RB2 gene were also associated with BD in Turkish and Japanese patients.[18,36] Other genetic causes known to be associated with BD include STAT4 gene expression, which is associated with IL-17 production, and changes in the promoter region of tumor necrosis factor.[18,37]

Clinical features

Although the distribution of clinical findings varies from country to country, mucocutaneous involvement is the most common finding in pediatric BD patients.[1] Recurrent oral aphthous stomatitis is observed in almost all patients (Figure 1).[15,20,38,39] It is typically characterized by painful ulcers on the lips, tongue, and palate, and the lesions usually heal within 3-10 days. Sometimes, healing may take weeks, but scarring is not observed. While oral aphthous stomatitis was mandatory in the diagnostic criteria of BD until 2014, this requirement has been removed with the criteria of The International Criteria for Behçet's Disease (ICBD) set in 2014.[40] According to the consensus classification criteria of pediatric Behçet's disease (PEDBD), oral aphthae are accepted as diagnostic criteria if at least three attacks per year.[15] Oral ulcers can be triggered by infections, stress, fatigue, and certain foods such as eggplants, nuts, tomatoes, and hot peppers.[41]

The frequency of genital ulcers ranges from 33% to 82% in various case series (Figure 1).[42] In the results of a 10-year single-center case experience study in Turkey, the frequency of genital ulcers was 56%.[42] Genital aphthous lesions are observed more

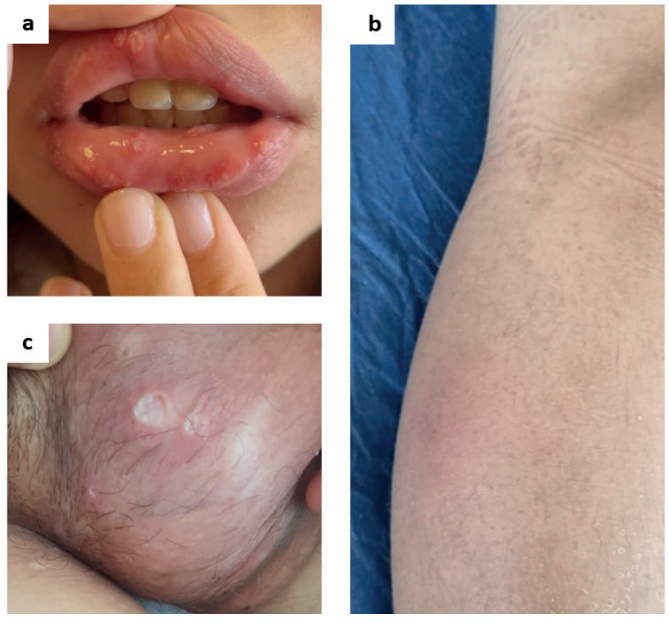

Figure 1. Some of the clinical features of Behçet's disease; Painful non-scaring recurrent oral aphthous lesions on the lips, tongue, and palate, usually healing within 3-10 days (Figure 1a), red, tender nodules called erythema nodosum, usually occur on the legs (Figure 1b), painful and deeper genital aphthous lesions, healing with scarring, and usually located in the labia major and minor in girls, and the scrotum in boys (Figure 1c).

often in girls; they are located in the labia major and minor in girls and in the scrotum in boys. Rarely, the perineal and perianal regions may be involved. Unlike oral aphthous lesions, genital ulcers are deeper, irregular, and heal with scarring.[43]

The most common skin lesions include pseudofolliculitis, papulopustular, erythema nodosum, skin rash, and acne (Figure 1). The frequency of skin involvement varies between 39% and 85% from country to country.[44] Although not specific for BD, pathergy positivity can be seen in 14.5% to 57% of patients.[11,45,46] The application of the test is the intradermal puncture of an avascular area on the anterior surface of the forearm with a sterile needle. An indurated erythematous papule or pustule that occurs after 48 hours is considered positive for the test.[47] The main underlying mechanism is the nonspecific hypersensitivity reaction to trauma.

After mucocutaneous lesions, the most frequently involved organ is the eye.[11,48] Eye involvement occurs approximately 2-3 years after the onset of BD, but it is observed simultaneously with the diagnosis in about 10%-20% of cases. Common eye symptoms include blurred vision, photophobia, redness, epiphora, and periorbital pain; eye manifestations include anterior uveitis, posterior uveitis, panuveitis, and retinal vasculitis. Bilateral eye involvement is more common; males have an increased risk for eye involvement compared to females.[49,50] While anterior uveitis is prominent in the younger age group, the incidence of panuveitis increases with older age.[51] It progresses with recurrent attacks in more than half of pediatric BD patients.[52] Vision loss may develop due to recurrent attacks and secondary complications (such as cataract, posterior synechiae, macular edema, and maculopathy).[50-52] Ocular involvement in BD is one of the most important causes of morbidity.

Musculoskeletal complaints are present in 20% to 63% of pediatric BD patients.[12,41,42] Peripheral joints such as the knee, ankle, elbow, and wrist are more affected than axial joints. Joint involvement is non-erosive and non-destructive.

Although neurological involvement is less common in pediatric patients (3.6%-30%) than in adults, it occurs especially during puberty.[48] Neurological manifestations can be grouped into two categories: parenchymal form and non-parenchymal vascular form. The non-parenchymal vascular form is more common in children, and cerebral venous sinus thrombosis is reported as the most frequent central nervous system manifestation.[53] The parenchymal lesions are mainly located at the mesodiencephalic junction and the brainstem.[54] Of note, neurological manifestations may present as encephalomyelitis or aseptic meningitis.

Vascular involvement affects vessels of any size, and the frequency of involvement varies between 5 and 20% in children with BD.[55] Venous thrombosis of the lower extremities is the most common vascular manifestation of BD but can be seen in other sites such as the portal vein and the suprahepatic vein.[55,56] Stenosis, occlusions, or especially aneurysms can be seen in the arterial system.

Gastrointestinal findings are more common in children than adults.[57] Gastrointestinal system involvement should be suspected in BD patients with complaints such as diarrhea, gastrointestinal bleeding, and abdominal pain, and it should be differentiated from inflammatory bowel disease. Rare manifestations such as cardiac complications and renal involvement have also been reported.[58,59]

BD may present a broad spectrum of clinical signs and symptoms involving multiple systems. Of note, pediatric cases may present with an incomplete clinical picture of the BD, and it may take time for the typical phenotype to develop. Therefore, it is important to maintain a high clinical index of suspicion for diagnosis.

Classification criteria

The heterogeneity of the disease makes it difficult to define a diagnosis or classification set for BD. Many efforts have been made to develop more precise diagnostic and/or classification criteria in adults, and many criteria have been proposed (Table 1). The most widely used criterion is the International Study Group (ISG) criteria proposed in 1990.[60] In 2014, the International Criteria for BD (ICBD) was published by a team from 27 countries, which was found to be more sensitive than the ISG criteria.[40] Vascular and neurological findings are included in the ICBD criteria. The PEDBD criteria, the first pediatric criteria, is based on a large cohort of BD patients, including European and non-European countries (Table 1).[15] Batu et al. evaluated the performances of PEDBD and ISG criteria in children with BD and found that PEDBD criteria showed better sensitivity than ISG criteria (52.9% vs. 73.5%).[61] However, expert opinion remains the gold standard for diagnosis.

Treatment

Our knowledge of treatment is largely based on the experience of adults due to the lack of controlled studies in pediatric BD. The goal of treatment is to reduce inflammatory flares and relapses and prevent irreversible tissue damage. The treatment strategies vary depending on the severity and type of organ involvement. Topical corticosteroids and colchicine are widely used for mucocutaneous manifestations. Colchicine use was associated with a reduced incidence of genital ulcers, erythema

Table 1. The most widely used classification criteria in adults and pediatric BD patients

Pediatric Behçet's Disease Criteria[15] (Three of the following criteria are required to classify a child to have BD)		**International Study Group (ISG) criteria**[60]	**International Criteria for BD (ICBD)** (scoring 4 points required)[40]
Recurrent oral aphthosis	At least 3/year	**Recurrent oral ulceration** **Plus, two of the following signs** Recurrent genital ulcer Eye lesions Skin lesions Pathergy test	Oral aphthosis (2 points) Genital aphthosis (2 points) Ocular lesions (2 points) Skin lesions (1 point) Neurological manifestations (1 point) Vascular manifestations (1 point) Positive pathergy test (1 point)
Genital ulceration	Typically with a scar		
Skin features	Acneiform lesions, necrotic folliculitis, erythema nodosum		
Ocular involvement	Anterior and/or posterior uveitis, retinal vasculitis		
Neurological signs	With the exception of headache		
Vascular involvement	Venous thrombosis, arterial thrombosis, arterial aneurysm		

nodosum, and arthritis.[62-64] Short-term systemic corticosteroids, avoiding long-term use, may also help severe ulcer healing. In addition, immunosuppressive agents such as azathioprine or tumor necrosis factor-alpha inhibitors (TNFis) can be used in patients with mucocutaneous manifestations who do not respond to colchicine treatment.[55,65] In a randomized controlled study, apremilast, a phosphodiesterase four inhibitor, was also effective in reducing BD-associated oral ulcers.[66]

Collaboration with an ophthalmologist is essential for close follow-up, as uveitis can cause permanent vision damage. Azathioprine is widely used in children with ocular BD.[63] TNFis also have been reported to show a significant effect in patients with a poor response to conventional immunosuppressants.[41,67] In the European League Against Rheumatism (EULAR) recommendations, for posterior segment involvement of ocular BD, the use of azathioprine, cyclosporine-A, interferon-alpha (IFN-α), or TNFis are stated, whereas high-dose glucocorticoids, infliximab, or IFN-α was recommended for sight-threatening uveitis.[68]

As for the treatment of other manifestations, dosing strategies of systemic corticosteroids, usually chosen as initial therapy, are adjusted according to the severity of organ involvement.[69] Treatment with 5-aminosalicylic acid (5-ASA) preparations or azathioprine has been suggested for patients with gastrointestinal involvement and TNFis for patients with severe and/or resistant disease.[68] Furthermore, corticosteroids, azathioprine, cyclophosphamide, and IFN-α are used in the treatment of nervous system involvement and vasculitis, and TNFis are recommended in refractory cases.[41,70] In a study involving severe and/or refractory BD, the efficacy of TNFis treatment was demonstrated in 96.3%, 88%, 70%, 77.8%, 92.3%, and 66.7% of patients with severe and/or refractory ocular, mucocutaneous, joint, gastrointestinal manifestations, central nervous system manifestations, and cardiovascular manifestations, respectively.[71]

Prognosis

The clinical course of BD tends to follow a chronic course characterized by exacerbations and remission. The disease is usually more severe in patients with early-onset BD and male gender.[5,72] It can cause significant morbidity and mortality due to mostly ocular, vascular, and neurological involvement. Ocular involvement has been reported to be the leading cause of morbidity in BD due to the risk of visual loss.[73] Pulmonary artery aneurysm is also a significant cause of mortality and morbidity in BD.[74] In a study of 817 BD patients, including children and adults, the mortality rate was reported to be five percent. Younger age (15–25 years), male gender, arterial involvement, and increased number of flares were identified as risk factors for death. Major vessel involvement, especially arterial aneurysm, and Budd-Chiari syndrome was the cause of death in 43.9% of the patients.[75]

Comparison of pediatric and adult-onset BD

The clinical manifestations of BD vary not only from patient to patient but also according to age groups. Several differences exist between adult and pediatric BD. Pediatric cases usually present with an incomplete clinical picture, and the time from symptom onset to full-blown disease may be prolonged. As for clinical manifestations, pediatric BD patients were reported to

have more common neurologic involvement, gastrointestinal involvement, and family history of BD, and less frequent ocular manifestations.[44,46] Another study also revealed that articular features and a familiar predisposition for BD were more common in the pediatric cohort, while venous vascular events were more frequently observed in the adult group.[76] In addition, differences in treatment approach were also reported. Both traditional and biological disease-modifying antirheumatic drugs (DMARD) use was reported to be more common in the adult group, whereas pediatric patients more frequently received no treatment or corticosteroid monotherapy.[76]

CONCLUSION

BD is a systemic vasculitis characterized by multisystemic, relapsing, and remitting inflammatory disorder with a chronic course. The observed heterogeneity in clinical presentation makes the accurate diagnosis difficult. Given the morbidity and mortality risk in BD, early diagnosis and effective treatment are essential. Further research targeting pediatric BD's management and treatment strategies is necessary to provide a better prognosis.

Author contribution

Concept: ÜKA, YB; Design: ÜKA, YB; Data Collection or Processing: ÜKA, YB; Analysis or Interpretation: ÜKA, YB; Literature Search: ÜKA, YB; Writing: ÜKA, YB. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

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