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Invited Review

Pediatric Behçet's disease - clinical aspects and current concepts

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Abstract

Behçet's Disease was first described by a Turkish dermatologist, Hulusi Behçet, in 1937 as a triple symptom complex; aphthous stomatitis, genital ulcers, and uveitis. Today, in light of current trials and experiments, we know that the disease may have a wider involvement with a multisystemic recurrent course, causing significant morbidity and mortality. However, there are still unanswered questions, particularly about Pediatric Behçet's Disease. Although several immunological and genetic associations have been demonstrated, the real etiologic mechanism of the disease is unclear. The diagnosis is difficult due to its rarity in childhood, the lack of validation of the diagnostic criteria obtained from adult studies, and the inadequacy of large case-controlled studies. Also, the management is challenging and controversial due to the various geographic distribution of clinical spectrum. New therapeutic options under development in light of pathogenetic hypothesis seem to be promising.

Keywords: Behçet's disease, epidemiology, classification, treatment, pediatric, juvenile

Introduction

Behçet's disease (BD) is a chronic inflammatory disease that can affect any type and size of vessel, particularly the veins, and manifests with recurrent oral and/or genital ulcers, accompanied with the involvement of skin, eyes, and joints, as well as the gastrointestinal and central nervous systems. In addition to being classified in the variable-vessel vasculitis category (1), it clinically exhibits autoinflammatory properties, as well as autoimmune effects in the pathophysiology, which render the disease heterogeneous. Although BD is commonly observed in the second or third decades, the initial symptoms occur under the age of 16 years in 4%-26% of the patients (2-4). The diagnosis is difficult due to its rarity in the childhood, lack of validation of the diagnostic criteria obtained from adult studies, and inadequacy of large case-controlled studies. Further, its management is challenging and controversial due to the wide geographical distribution of the clinical spectrum and various epidemiological properties, and the presence of still unanswered questions in the pathogenesis. By providing an evaluation of BD in the light of the recent studies, we aimed to better illustrate the diagnosis and management of BD in the pediatric age group.

Definition and classification

Behçet's disease was first described in 1937 by the Turkish dermatologist Hulusi Behçet, with the triad of oral aphthous ulcers, genital ulcers, and uveitis (5). In addition to involving the mucosa and skin, the disease also has an affinity toward various-sized vessels such as large arteries and veins. Therefore, it is known as a widely distributed vasculitis with the involvement of the central nervous, gastrointestinal, and urogenital systems. In addition to its distinctive characteristic, BD is a complex condition as it may intertwine with various other conditions such as inflammatory bowel disease and immune deficiencies, as well as assume both autoimmune and autoinflammatory characters (2). The term pediatric BD (PEDBD) is used for cases diagnosed during childhood, whereas the term juvenile BD is used for those cases who have manifestations of the disease before the age of 16 years, but the diagnosis is made during adulthood (6).

Earlier, international study groups have developed classifications and diagnostic criteria. In 1969, Mason and Barnes defined oral ulcers, genital ulcers, eye and skin lesions as the major criteria, and the involvement of gastrointestinal, cardiovascular, and central nervous systems or thrombophlebitis, arthritis, and family history as the minor criteria (7). They stated that the presence of three major or two major and two minor

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criteria would suggest BD. The most commonly used is the 1990 criteria, defined by the International Study Group (ISG) with collaborations from France, Iran, Japan, Tunisia, Turkey, UK, and USA (Table 1). According to these criteria, the occurrence of oral ulcer(s) as the major criteria and two of the cutaneous and ocular findings would establish the diagnosis with 85% sensitivity and 96% specificity (8). However, the sensitivity is low, particularly in children; while the presence of an oral ulcer is essential for diagnosis, the lack of any mention regarding vascular and neurological involvements may lead to confusion in the diagnosis.

In the year 2014, the International Team for the Revision of the International Criteria for BD (ICBD), with contributions from 27 countries, developed a scoring system and proposed new criteria with higher sensitivity (9). The main differences between these criteria are that not all the criteria are evaluated with equal points and oral aphthae is not a mandatory criterion. Another important change is the addition of vascular manifestations and neurological findings to the criteria. Among these criteria, oral aphthae and genitalia ulceration were scored as 2 points; all the other criteria were scored as 1 point. A total score of 4 and above was reported for diagnosis (9). The sensitivity and specificity of these criteria in adult patients with BD have been reported as 96.1% and 88.7%, respectively (10).

The common feature of all these criteria was that all of them were defined for adult patients, and there was a lack of validation for childhood BD. The PEDBD study in 2015 aimed to define the criteria for pediatric patients by using the largest cohort (11). The goals included the determination of the subtypes for pediatric cases, defining the symptom types and chronology, comparing the criteria for this age group, and eventually presenting the criteria for PEDBD (Table 2). A positive pathergy test was not included in these criteria; in contrast to the ISG criteria, oral ulcer was deemed unnecessary. Each criterion was given equal weight, and the presence of three or more of the six criteria was required. The international PEDBD criteria, as compared to the most commonly used ISG criteria, have greater sensitivity (91.7%) and lower specificity (42.9%) (11, 12). This has been supported by various epidemiological studies (4, 12-14). In a study evaluating the performance of different classification criteria of the disease, the sensitivity and specificity of PEDBD/ISG criteria were 73.5%/52.9% and 97.7%/100%, respectively (12). Comprehensive studies, formulated by using an adequate number of control groups and large cohorts, supporting these criteria are imperatively needed.

Main Points

- Behçet's disease (BD) is a chronic inflammatory disease that can affect any type and size of vessel and manifests with recurrent oral and/or genital ulcers, accompanied with the involvement of skin, eyes, and joints, as well as the gastrointestinal and central nervous systems.
- Although BD is commonly observed in the second or third decades, the initial symptoms occur under the age of 16 years in 4%-26% of the patients.
- The settlement of the clinical picture may take years after the initial symptoms, which may be even longer in the childhood period.
- The pathergy test is a nonspecific hypersensitivity response of the skin against trauma. It is a warning sign in BD; however, it is not pathognomonic.
- The diagnosis is difficult due to its rarity in childhood, lack of validation of the diagnostic criteria obtained from adult studies, and inadequacy of large case-controlled studies.
- Its management is challenging and controversial due to the wide geographical distribution of the clinical spectrum and various epidemiological properties, and the presence of still unanswered questions in the pathogenesis.

Etiopathogenesis

The etiopathogenesis of BD is still not fully understood. The disease has overlapping pathological mechanisms with autoimmune diseases, autoinflammatory diseases, and seronegative spondyloarthropathies (MHC-I-opathy). Furthermore, in adult studies, it was shown that the disease has different clinical phenotypes and tends to go with various symptom clusters (acne/arthritis/enthesitis, etc.) (15, 16). It is understood that such differences between the subtypes of the disease probably can be attributed to different mechanisms. The main accepted opinion regarding the occurrence of this disease is that various infectious agents play the triggering role in the development of this disease in genetically predisposed ones (17).

Since this disease was first identified, microbiological agents that could cause this disease

Table 1. Criteria of the International study group for BD (8)

Recurrent Oral Ulceration (*Mandatory*)	Minor aphthous, major aphthous, or herpetiform ulceration observed by physician or patient, which recurred at least 3 times in one 12-month period
Plus 2 of:	Aphthous ulceration or scarring, observed by physician or patient
Recurrent genital ulceration Eye lesions	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, pseudo folliculitis, or papulopustular lesions; or acneiform nodules observed by physician in post adolescent patients not on corticosteroid treatment
Positive pathergy test	Read by physician at 24-48 h.

Findings applicable only in absence of other clinical explanations.

Table 2. Pediatric criteria for BD (11)

Recurrent oral aphthosis	At least three attacks/year
Genital ulceration or aphthosis	Typically with scar
Skin involvement	Necrotic folliculitis, acneiform lesions, erythema nodosum
Ocular involvement	Anterior uveitis, posterior uveitis, retinal vasculitis
Neurological signs	With the exception of isolated headaches
Vascular signs	Venous thrombosis, arterial thrombosis, arterial aneurysm.

Three or more items are needed for diagnosis.

were investigated. Lehner et al. (18, 19) suggested that there is a cross-reaction between *Streptococcus sanguinis* and certain body proteins (heat-shock proteins), and this could be the triggering factor. In addition, antibodies against *S. sanguinis* and *S. pyogenesis* have been reported more frequently in the ones with BD than those in controls (18, 20). Studies have reported that oral and intestinal microbiota may play a role in the pathogenesis of this disease. Oral bacterial diversity in patients with BD has been shown to be less than those in healthy controls (21, 22). It has been shown that cutaneous and systemic disease activation may occur after dental procedures in patients with BD (23). Intestinal microbiota studies have shown a decrease in *Roseburia* and *Subdoligranulum* species and an increase in *Bifidobacteri* species in patients with BD (21, 24, 25). The authors suggested that the effect in butyrate production associated with changes in the intestinal microbiota could trigger immunological changes (18, 25).

Genetic

The genetic component of BD is one of the most frequently discussed subjects. The most important genetic predisposition factor associated with BD is human leukocyte antigen (HLA) B5 and its sub-allele HLA-B51. Menthon et al. (26) reported that individuals carrying the HLA-B5/B51 gene were 5.78 times more at risk of developing BD. HLA-B51 positivity is more common in males; genital ulcers, ocular involvement, and skin findings are reported more frequently in individuals carrying this allele (27, 28). HLA-B51 positivity has been reported between 50% and 72% of BD patients. This rate is reported to be 10%-15% in the healthy population (2, 26, 27). Due to its high incidence in the healthy population, the diagnostic value of HLA-B51 positivity is controversial and it is widely considered that it should be accepted as a supportive finding only in the presence of appropriate clinical findings.

Genetic associations between BD and various non-HLA genes, such as ERAP1, IL23 receptor (IL-23R), IL-23R/IL-12RB2, IL-10, and STAT4, have been identified with genome-wide association studies (GWAS) (18, 29, 30).

ERAP-1 is an amino peptidase expressed by the endoplasmic reticulum and is involved in the delivery of peptides to effector cells via MHC-1 molecules. If the folding required for HLA molecules to interact with the peptides is unsuitable (misfolding), inflammation may be triggered through the IL23/IL17 pathway (31, 32). It has been reported that ERAP-1 has an epistatic interaction with HLA-B51 (33). The homozygosity of ERAP1 pArg725Gln (rs7482078) has been reported to increase the BD risk by 3.78 times in HLA-B51-positive patients and 1.48 times in HLA-B51-negative patients (33). Certain ERAP1 polymorphisms have also been associated with ankylosing spondylitis and psoriatic arthritis (34-36). The misfolding of HLA-B27 in patients with ankylosing spondylitis and HLA-C*0602 in patients with psoriatic arthritis has been shown to activate the IL23/IL17 axis (31, 32). These findings are also one of the mainstays of the MHC-1-opathy concept, which suggests that BD and spondyloarthropathies such as ankylosing spondylitis and psoriatic arthritis have similar immunopathogenic bases (37).

Mutations in the FUT2 gene encoding the fucosyltransferase enzyme have been reported in the intestinal and oral epithelial cells of patients with BD. This enzyme plays an important role in bacterial symbiosis and barrier formation against pathogenic bacteria in the intestine. This mutation in patients with BD is another important support for the presence of bacterial triggering factors (21, 38, 39).

In their studies evaluating the role of epigenetic mechanisms in BD, Alipour et al. (40) emphasized the roles of DNA methylation, histone modification, and microRNAs. "Unusual" methylation in genes regulating the cytoskeletal dynamics has been shown to be effective in the pathogenesis of BD (40, 41). Further, in the recent years, many publications have shown the effects of cellular noncoding RNAs and certain specific microRNAs on immunity. In particular, changes in miR-182, miR155, miR638, and miR-4488 expressions have been shown in BD patients (42-44).

Table 3. Comparison of various pediatric BD cohorts

	Kone-Paut et al.(11)	Shahram et al.(14)	Karincaoglu et al. (3)	Gallizzi et al. (4)	Atmaca et al.(69)
Number	156	204	83	110	110
Age of first symptom (years)	7.8 ±4.3	10.5±3.4	12.2±3.5	8.3±	11.6±3.4
Oral Aphthosis (%)	100	91.7	86	94.5	100
Genital Ulcers (%)	55.1	42.2	81.9	33.6	82.7
Cutaneous Signs (%)	66.6	51.5	51.8*	39.6	37.3*
Pathergy Positivity (%)	N/A	57	37.3	14.5	45.5
Ocular Sign (%)	45.5	66.2	34.7	43.6	61.8
Joint Involvement (%)	41	30.9	39.8	42.7	22.7
Gastrointestinal Involvement (%)	29.4	5.9	4.8	42.7	N/S
Neurological Involvement (%)	59.6	4.4	7.2	N/S	3.6
Vascular Involvement (%)	14.7	6.4	7.2	1.8	3.6
Family History (%)	24.4	9.9	19	12	12.3

*Only erythema nodosum

Figure 1. World-wide epidemiology of Behçet's Disease.

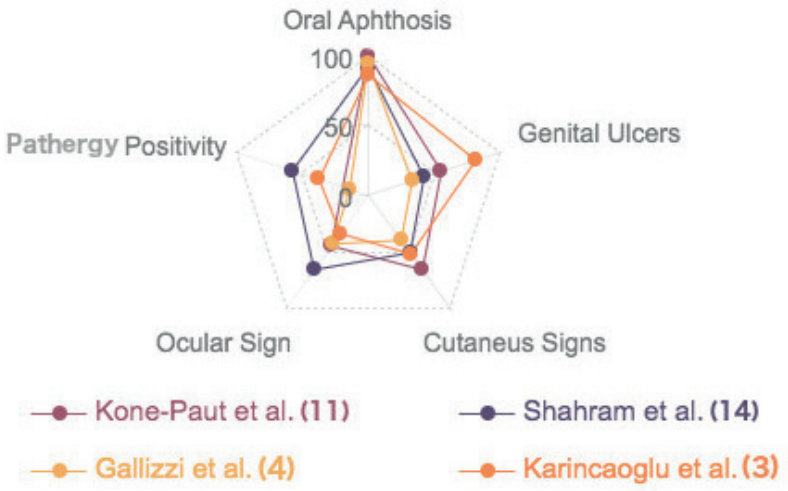

Figure 2. Frequencies of some of the clinical findings and pathergy test positivity in various pediatric Behçet's disease cohorts.

Immunological background

Behçet's disease has features that overlap with both autoimmune diseases and autoinflammatory diseases. The presence of recurrent and unprovoked episodes of inflammation and increased IL-1B levels in active patients were consistent with autoinflammatory diseases; however, the proven association with HLA-B51 and the activation of adaptive immunity are similar to autoimmune diseases (21, 45).

T lymphocytes are the main lymphocytes in the pathogenesis of BD. T lymphocytes have been shown to activate and produce inflammatory cytokines in patients. In particular, the roles of T-cell subgroups, such as γδ T cells, cytotoxic T cells, Th1, and Th17, have been emphasized in the pathogenesis of the disease (17, 46-48). Increased γδ T cells and Th17 cells and decreased T regulator (Treg) cells have been reported in the sera of BD patients (48-51).

Tulunay et al. (52) showed increased Janus kinase (JAK)/signal transducer and activator of transcription signal in the sera of patients with BD and correlated this increased signal intensity with the IL-2, IL-6, IL-17, IL-23, and INF-α levels from Th1 and Th17 cells. Another study reported increased levels of IL-21 in the serum of patients. IL-21 has a role in Th17 differentiation and can modulate Th1 and Treg cells (51). Th17 induces a neutrophil-mediated inflammatory response (17, 53). Another cytokine that plays an important role in the pathogenesis of the disease is IL-8, which is released from T lymphocytes; this cytokine is one of the main cytokines involved in leukocyte activation. Increased levels of IL-8 have been reported in the serum of patients with BD, and IL-8 levels have been shown to be correlated with the disease activity (54).

Epidemiology

The prevalence of BD varies worldwide. The disease is particularly common in communities around the Silk Road, extending from eastern Asia to the Mediterranean basin between 30 and 45 meridians (55) (Figure 1). However, due to the increasing awareness of this disease, it is better understood that this disease does not only belong to this geography and there is an increasing incidence of case reports from all over the world. In a meta-analysis in which Maldini and his colleagues evaluated the pooled prevalence of BD, the prevalence of this disease was reported to be 10.3/100000 globally, 119/100000 for Turkey, 31.8/100000 for the Middle East, 4.5/100000 for Asia, 3.3/100000 for Europe, and 3.8/100000 for North America (56, 57). The prevalence of this disease during childhood is unknown. In 4%-26% of the patients, it was reported that this disease started in the pediatric age (2-4).

In particular, studies involving immigrant communities in Western countries have shown that apart from the country of residence, ethnicity is also an important factor affecting the prevalence of this disease. The prevalence of BD was found to be higher in North African and Asian individuals living in Paris than those in European people, and this prevalence was independent of the age at which the patients migrated (58). In studies conducted in Germany and the Netherlands, the prevalence of BD among immigrants is lower than the reported frequency for the origin of immigrants, but higher than those in the German and Dutch populations (21, 59, 60).

Several studies have shown that the frequency of clinical findings of BD varies according to geographical regions. It has been reported that the involvement of the gastrointestinal system is more frequent and vascular findings and ocular involvement are less common in patients with Northern European origin than patients in endemic areas (21, 61, 62). In a recent PEDBD cohort, higher frequencies of articular findings, gastrointestinal involvement, and neurological symptoms were reported in European patients. In addition, necrotic folliculitis, acneiform lesions, and pseudofolliculitis were commonly detected in non-European patients (11).

PEDBD is seen equally in both the sexes, but the frequency of clinical findings varies between the genders. Severe uveitis and vascular diseases are more common in boys, while genital aphthae and erythema nodosum are more common in girls (6, 63, 64).

Clinical manifestations

BD is characterized by relapses and remissions. The distribution of clinical signs differs according to age, sex, and ethnic background. Mucocutaneous signs, as well as eye and joint involvement, are seen in the early stages, whereas the involvement of the gastrointestinal system, central nervous system, and large vessels often occur late in the course (65). The settlement of the clinical picture may take years after the occurrence of the initial symptoms, which may be even longer in childhood BD. The symptoms often limit themselves with a recurrent episodic course. However, ocular involvement is one of the most common causes of morbidity and may progress to blindness (66, 67). Neurological involvement, large-vessel involvement, and gastrointestinal involvement may be life-threatening (67). The risk of complications and mortality are greater in males at ages younger than 25 years (68). Geographic variability of the clinical symptoms is a prominent and challenging characteristic of this illness. There are no laboratory findings that demonstrate a good correlation with the clinical findings. The clinical criteria constitute the basis for classification and diagnosis. Clinical findings of various PEDBD cohorts are shown in Table 3 and Figure 2.

Mucocutaneous lesions

Recurrent mucocutaneous lesions mostly occur during the initial phase of this disease. Oral ulcers are the most common type of mucocutaneous lesions, seen in 96%-100% of the patients (2, 3, 64, 69, 70). They can emerge years before other signs. Recurrent oral ulceration is generally nonspecific, and a differential diagnosis includes numerous conditions such as herpes simplex virus, inflammatory bowel disease, celiac disease, nutritional deficiencies,

PFAPA, HIDS, and SLE (71). Morphological distinction is often impossible. Therefore, in the absence of other components, diagnosing BD is very difficult. The oral ulcerations in BD may occur as painful circular lesions with sharp and erythematous borders, located around the tongue or on the oropharyngeal and buccal mucosas (71, 72). Although the lesions tend to be widespread and multiple, they may be single and appear to be herpetiform or necrotic (71). The average healing time is 10 days, with some lesions persisting for weeks. Lesions heal without scarring. Main and Chamberlain reported that an increased number of ulcers, concurrent variations in size from herpetiform to major aphthous, diffuse erythematous surrounds, and involvements of soft palate and oropharynx may be useful to recognize the oral ulcers of BD (72). Several studies have investigated the effects of environmental changes on the recurrence of oral ulcers. In the questionnaire-based study from Turkey, patients reported stress and fatigue as the most common triggering factors (73). Further, several publications have reported that nutrients from eggplants, nuts, tomatoes, and hot peppers, as well as seasonal changes (particularly winter and autumn), are triggering factors for oral ulcers (74, 75).

Genital ulcers occur in 57%-93% of the patients (71, 76). Frequently affected sites are the scrotum in males and labia major and minor in females (76). Perineal and perianal areas may also be involved (6). Although genital ulcers morphologically resemble oral ulcers, they may be deeper and have irregular borders, often healing with scarring. Kitaichi et al. (77) advocated that genital ulcers are less common in children. In a study involving 110 children diagnosed with BD, Atmaca et al. (69 supported this data. Krause et al. (70) compared juvenile- and adult-onset BD patients; they found that in contrast to other mucocutaneous findings, genital ulcers were less common in children (30/34 vs. 6/19). Although genital ulcers are less common than adults, the analysis of BD patients under the age of 16 years from various geographical areas revealed that genital ulcers were still the second-most common finding after oral ulcers, with a frequency between 55% and 83% (3, 11, 64, 69, 70).

Skin involvement is seen in 38%-99% of the patients (76). The mean age at occurrence is 13 years (6). Skin lesions may occur as erythema nodosum-like lesions, papulopustular lesions, folliculitis, superficial thrombophlebitis, and cutaneous vasculitic lesions. Histologically, skin lesions are characterized by vasculitis and thrombosis. Early phases demonstrate leukocytoclastic vasculitis, and late phases show a predominance of lymphocytes. Acne-like lesions, in contrast to adolescent acne, are more common in the face, extremities, and the trunk (71).

The pathergy test consists of an intradermal puncture on the skin with a 20-gauge or smaller needle, 5 mm obliquely into the patient's flexor aspect of the avascular forearm skin under sterile conditions. It is considered positive when an indurated erythematous small papule or pustule forms within 48 h. The test is a nonspecific hypersensitivity response of the skin against trauma. However, it is not related to the involvement of a specific organ or disease activity. It is a warning sign in BD; however, it is not pathognomonic. The test positivity ranges between 40% and 80% due to geography- and population-based differences (69). Therefore, it has not been included in the newly proposed PEDBD classification criteria (11).

Musculoskeletal involvement

Articular symptoms are seen in 45%-60% of adults (71) and 20%-40% of children (2). They may occur during the initial phase (16.5%) (71). The knee and ankle are the most commonly involved joints; the elbow and wrist may be affected, too. The condition is nonerosive and does not cause any deformity. On the basis of the two studies with the same number of patients with BD, joint involvement was seen in 42.7% of the patients in Gallizzi et al. (4) cohort and 20.7% in Atmaca et al. (69) cohort. According to the PEDBD study, joint complaints were positive in 50% (78/156) of the patients diagnosed certainly with BD. The axial involvement rate was 16.67% (26/156), and the peripheral arthritis rate was 47.44% (74/156) (11). Enthesopathy may be seen, while sacroiliac involvement is rare, and there is a weak association with HLA-B27. PEDBD study reported an association with HLA-B27 spondyloarthropathy (2%) (11).

Eye involvement

The eye is one of the most commonly involved organs, being affected in 30%-70% of the cases, and it is the most significant cause of morbidity (71). It often occurs 2-3 years after the onset of the disease; however, in 10%-20% of the patients, it is present from the onset (78). Studies that have compared eye involvement in BD in children versus adults have found controversial results. Certain studies have reported that pediatric eye involvement occurs less commonly and at a later phase (6). It has also been reported that BD is not a common cause of pediatric uveitis, even in countries with a high prevalence of this disease (77). Some others have reported that eye involvement may be more common in children (79, 80). In a cohort of 110 patients from 16 Italian pediatric rheumatologic centers, Gallizzi et al. (4) found that eye involvement was the second-most common (43.6%) clinical finding after oral ulcers. In a cohort of Iranian patients with BD who have been diagnosed in childhood, ocular involvement was more frequent (62%) and more severe as compared to those in the other reports (14).

Krause et al. (70) advocated that frequency and morbidity were not associated with age. Atmaca et al. (69) found that the eye involvement rates were similar between children and adults (30.9% and 29.1%, respectively). Koné-Paut et al. (6) reported that eye involvement in children was less frequent than adults; however, they had a worse prognosis, particularly in males.

Patients may present with blurred vision, photophobia, redness, epiphora, and periorbital pain (81). Typically, it is a chronic, bilateral nongranulomatous inflammatory condition that shows flare-ups and can present with panuveitis by the involvement of the anterior or posterior segments or both (65, 71). Anterior uveitis with hypopyon, where the inflammatory exudate forms a visible layer in the anterior chamber, is a significant sign of the disease (71). Laghmari et al. (82) reported that hypopyon is a rare finding, and Atmaca et al. (69) found a 9% incidence in a larger series of patients. In addition to smooth-layered hypopyon, superficial retinal infiltrate with retinal hemorrhages and branch retinal vein occlusion with vitreous haze are important indications in differential diagnoses (83). Iridocyclitis, keratitis, episcleritis, scleritis, vitritis, vitreous hemorrhage, optic neuritis, cataract, glaucoma, and retinal detachment can be other manifestations of eye involvement in BD. Newer and more intense treatment strategies in the recent years have improved the prognosis process and enabled a decreased risk of vision loss when compared with the situation in the 1990s (84, 85).

Neurological involvement

Neurological involvement is seen in 5.3%-59% of adults (86-89) and 3.6%-36% of pediatric patients (3, 4, 6, 69, 90). Manifestations usually present during puberty; however, earlier emergence is also possible (91). BD predominantly involves the central nervous system, whereas the peripheral nervous system is rarely affected (89). Parenchymal lesions are distributed in the brain stem, spinal cord, basal ganglia, and cerebral white matter, and they lead to the clinical picture of the Neuro-BD (88). This clinical con-

dition is progressive and involves acute onset and relapses. Headache, hemiplegia, cranial nerve palsies, aseptic meningitis, meningoencephalitis, psychosis, and cognitive dysfunctions are among the clinical findings. Multiple sclerosis is considered in the differential diagnosis (87).

Cerebral venous thrombosis and pseudotumor cerebri are related to the nonparenchymal vascular form. Parenchymal lesions are more common in adults, whereas nonparenchymal lesions are more common in children and have a better prognosis (3, 70). However, there are geographical differences, and studies from France, Israel, and Saudi Arabia have reported the predominance of parenchymal lesions in children (65).

Vascular involvement

The rate of vascular involvement ranges within 5%-40% of adults (92-94) and 1.8%-21% of children (3, 4, 6, 69, 90), depending on the source-reference center. Venous involvement, presenting with superficial or deep vein thrombosis in the lower extremities, is the most common type of vascular involvement. Superficial thrombophlebitis appears as a sensitive erythematous elevation, which is transient and migratory. Deep vein thrombosis can be seen in various sites, particularly in bigger vessels including iliofemoral, superior or inferior vena cava, or on unusual localizations such as dural sinus thrombosis (headache, papilledema, intracranial hypertension), hepatic veins (Budd-Chiari syndrome), or inferior vena cava with pulmonary aneurysms (Hughes-Stovin syndrome) (95).

Arterial involvement is seen in 3%-12% of the patients (95, 96). However, when asymptomatic cases diagnosed during autopsy are taken into consideration, it may rise up to 33% (95). Pulmonary artery aneurysm is the most common cause of morbidity and mortality. Although arterial aneurysm is an expected consequence, occlusion or stenosis of the aorta, femoral, and pulmonary vessels may occur (96). Pulmonary embolism is not expected. Male sex and young age are the risk factors for vascular complications (68, 93).

In the study by Seyahi et al. (65), vascular involvement was seen in 15% (17/61) of the patients, all of whom were males. Large-vessel involvement was seen in the form of pulmonary artery aneurysm (4/17, 24%), vena cava thrombosis (3/17, 18%), Budd-Chiari syndrome (1/17, 6%), deep vein thrombosis of the lower extremities (6/17, 35%), and superficial vein thrombosis (3/17, 18%).

Gastrointestinal involvement

Gastrointestinal system involvement differs between various populations. The lowest frequencies have been reported in Turkey (2.8%), India (3.4%), and Saudi Arabia (4%); moderate frequencies in China (10%) and Taiwan (32%); and the highest frequencies in the United Kingdom (38%-53%) and Japan (50%-60%) (97). Intestinal involvement was reported to be more common in juvenile patients as compared to adults (65, 70). In the juvenile cohort of Krause et al. (70), the gastrointestinal symptom frequency was 36.8%. Studies performed involving the same age group and different populations revealed frequencies between 4.8% and 14.0% (3, 6, 90). The gastrointestinal symptoms emerge 4.5-6 years after the onset of oral ulcers (98). The most common symptoms include abdominal pain, nausea, vomiting, dyspepsia, diarrhea, and gastrointestinal bleeding (71). Mucosal inflammation and ulcers can occur throughout the gastrointestinal tract, more frequently in the ileocecal region, less frequently in the colon, and sparing the rectum. Endoscopic and colonoscopic examinations are important to differentiate this illness from Crohn's disease. A study of 235 patients with Crohn's disease and intestinal BD revealed that round ulcer, focal single/focal multiple distribution of ulceration, fewer than six ulcers, absence of cobblestone appearance, or aphthous lesions were the most predictive symptoms of BD on colonoscopy in a multivariate analysis (99).

Another form, presenting with mesenteric artery involvement and leading to intestinal ischemia and infarction, is also present (97). Budd-Chiari syndrome is rare, but a serious and mortal condition. Twenty out of 43 patients (47%) diagnosed with disease-related Budd-Chiari syndrome died at the end of a 10-month follow-up period (IQR: 5-33) (100).

Management

BD is a multisystemic illness, with symptoms depending on the age, sex, and ethnic origin. The first step in the approach to this heterogeneous disease is to determine the treatment goals. The primary goals should be to manage the inflammatory flare-ups, which are the typical characteristic of this disease, as well as prevent irreversible organ damage (101). The type of the involved organ and level of damage, as well as the patient's age, sex, and treatment preferences should be taken into consideration. Since this disease affects different systems, the treatment certainly requires a multidisciplinary approach. Newer treatment recommendations have been proposed in the light of this approach (102).

Topical treatment

Topical corticosteroids (triamcinolone acetonide cream) are recommended as the initial treatment for isolated oral aphthae and genital ulcers (103). Topical sucralfate can be used in combination with or as an alternative to topical corticosteroids. Topical corticosteroids are also useful for the treatment of anterior uveitis (104).

Colchicine

Colchicine is an antiinflammatory plant alkaloid that inhibits neutrophil migration by interfering with microtubule formation (81). Colchicine should be the first choice for the prevention of recurrent mucocutaneous lesions with a daily dosage of 1-2 mg in divided doses (102, 105). In a randomized trial of 116 patients comparing colchicine versus placebo, colchicine therapy was associated with significant healing on the genital ulcers and erythema nodosum, particularly among women (106). The efficacy of colchicine for the treatment of arthritis associated with the disease was evaluated in the same trial and was found to be associated with a significant decrease in the number of arthritic joints after two years of follow-up (106).

Systemic corticosteroids

Corticosteroids are commonly used to treat clinical manifestations of the disease as a monotherapy or in combination with immunosuppressant drugs. Corticosteroids can be in the form of oral prednisolone (1 mg/kg/day) or intravenous methylprednisolone pulses (1 g/day for 3 days) (81). Systemic glucocorticoids are preferred for oral aphthae and genital ulcers resistant to topical therapy or dermal lesions unresponsive to colchicine treatment. Most patients with posterior uveal segment involvement or retinal vasculitis require systemic corticosteroids depending on the severity of ocular inflammation (101, 107). Systemic, high-dose glucocorticoids are used for the rapid suppression of inflammation during acute attacks (102). However, glucocorticoids are not recommended to be used alone in patients with posterior uveitis. Because of its potential side-effects, a combined therapy is preferred to reduce the frequency of relapses and to diminish the dose of corticosteroids (81, 101, 102).

Azathioprine

Azathioprine has been successfully used for select patients with persistent arthritis and refractory mucocutaneous lesions. Moreover, it is one of the most effective treatment options in BD with more severe disease manifestations, such as inflammatory eye disease (102). The recommended dose is 2.5 mg/kg/day. In a trial of 73 patients with BD, patients were randomized to receive either azathioprine or placebo

and followed-up for two years. Patients on azathioprine had fewer episodes of new or recurrent eye diseases. It was also associated with less frequent oral and genital ulcers and arthritis (108). In a study involving 157 consecutive patients treated with azathioprine for severe uveitis (active posterior uveitis or panuveitis) due to BD, 51.6% were complete responders and 41.4% were partial responders (109). Azathioprine therapy may also be the preferable treatment regimen for patients with gastrointestinal and neurological involvements. Systemic glucocorticoids are recommended to be used in combination with azathioprine or other systemic immunosuppressives (101, 102).

Cyclosporine A

Cyclosporine A is an effective option for severe ocular manifestations as well as refractory mucocutaneous lesions (103). It is currently recommended at a dose of 3 to 5 mg/kg/day due to its side-effects of hypertension, renal failure, and neurological problems (81, 110). Because of its neurotoxicity, cyclosporine is not recommended in patients suffering from neurological diseases (111). In a randomized trial involving 96 patients, cyclosporine (10 mg/kg per day in divided doses) was more effective than colchicine in the management of oral and genital ulcers as well as other skin lesions (112).

Cyclophosphamide

Cyclophosphamide is used for life-threatening conditions such as PAI, Budd-Chiari syndrome, peripheral arterial aneurysms/occlusions, and parenchymal neurological involvement in patients with BD (102, 105). These manifestations should be managed with aggressive medical treatment; high-dose glucocorticoids and monthly cyclophosphamide pulses followed by maintenance therapy with azathioprine should be initiated (102). Cyclophosphamide orally (2 mg/kg/day) or intravenously (750 to 1 g/m^2 every 4 weeks) can also be used.

Antitumor necrosis factor (Anti-TNF) (Etanercept, Infliximab, and Adalimumab)

TNF-blocking agents (anti-TNF), such as infliximab, etanercept, and adalimumab, have been reported to show an important therapeutic advance for patients with severe disease and resistant to standard immunosuppressive regimens, as well as for those patients with contraindications or intolerance to such treatments (102, 105). These biological agents are found to be very useful in controlling symptoms and recurrences, as well as significantly decreasing the required daily dose of corticosteroids (107, 113). Anti-TNF-α agents, particularly infliximab, have been reported to be very effective in the treatment of intraocular inflammation associated with BD (113-115). A multicenter observational study including 164 patients with BD-related uveitis who were treated with infliximab (5 mg/kg/infusion) for more than one year concluded that infliximab significantly reduced the frequency of ocular attacks and improved visual acuity (115). Uveitis relapsed in 59.1% of all the patients after initiating treatment with infliximab. However, 90% of relapses were controlled by increasing the doses of topical corticosteroids and shortening the interval of infliximab infusion (115). In a multicenter retrospective study involving 40 select patients, adalimumab has been found to be highly effective and safe for the treatment of BD-related uveitis, providing long-term control over ocular inflammation (116).

Anti-TNF agents are recommended in severe nervous system involvements as the first line or in refractory patients (102). They could be considered in cases of refractory venous thrombosis or arterial involvement (102). In a large retrospective study, it was shown that adalimumab-based regimens were more effective and rapid than disease-modifying antirheumatic drugs in inducing the resolution of venous thrombosis in BS patients, allowing the reduction of steroid exposure (117). Infliximab and adalimumab were also found to be well tolerated and effective therapy strategies for patients with moderate-to-severe intestinal BD (118).

Interferon α (IFN-α)

IFN-α is a naturally occurring cytokine that has immunomodulatory properties. In a systematic review of 32 original articles and four select abstracts including 338 patients treated with IFN-α-2a or IFN-α-2b, partial remissions have been recorded in patients with mucocutaneous symptoms (119). IFN-α has been found to be effective in resistant posterior uveitis, providing long-term remissions with the preservation of visual acuity (119).

Other treatment options

Biological and nonbiological agents such as anakinra, canakinumab, tocilizumab, ustekinumab, secukinumab, apremilast, and mycophenolate mofetil have been applied for the mucocutaneous lesions and refractory organ manifestations of BD, but controlled evidence is not available until now (120-125). Further studies are needed to better understand their efficiency and prove their safety.

Conclusion

BD is a rare but complex disease occurring in childhood, requiring a multidisciplinary approach in collaboration with pediatricians, rheumatologists, dermatologists, ophthalmologists, neurologists, gastroenterologists, and other specialists, when necessary. Multicenter, placebo-controlled, standardized studies that involve large patient series, utilize clinical scores, and have long-term follow-up are needed to better understand the nature of this disease. New therapeutic options under development in the light of pathogenetic hypothesis can be promising.

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