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REVIEW

Behçet's Disease in Children: Diagnostic and Management Challenges

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Abstract: Behçet's Disease (BD) is an inflammatory disease of unknown etiology with multisystemic involvement, being the main clinical manifestations represented by recurrent oral and genital ulcerations and uveitis. The disease has typically a chronic-relapsing course and may cause significant morbidity and mortality due to eye, vascular and neurological involvement. Although BD is more frequently diagnosed in adulthood, the disease onset can also be in pediatric age. Pediatric-onset BD is commonly featured by an incomplete clinical picture, and therefore the diagnosis represents a considerable clinical challenge for the physicians. The first classification criteria for pediatric BD, based on a scoring system, have been proposed few years ago. This work focuses on the main difficulties concerning both the diagnostic approach and the treatment of BD in pediatric age. The recommendation for the treatment of pediatric BD has been recently updated and allowed a considerable improvement of the therapeutic strategies. In particular, the use of anti-TNFα drugs as a second-line option for refractory BD, and as a first-line treatment in severe ocular and neurological involvement, has demonstrated to be effective in improving the outcome of BD patients. The knowledge about the molecular pathogenesis is progressively increasing, showing that BD shares common features with autoimmune and autoinflammatory disorders, and thus leading to the use of new biologic agents targeting the main mediators involved in the determination of BD. Anti-IL-17, anti-IL-23, anti-IL-1 and anti-IL-6 agents have shown promising results for the treatment of refractory BD in clinical trials and will represent an important alternative for the therapeutic approach to the disease.

Keywords: Behçet's disease, aphtosis, differential diagnosis, autoinflammatory diseases, autoimmunity, biologic drugs

Introduction

Behçet's Disease (BD) is an inflammatory disease characterized by multisystemic involvement and featured by a chronic, relapsing disease course; histologically it appears as a vasculitis affecting both small and large vessels, with major involvement of the veins.[1,2] The most prominent clinical manifestations of BD are recurrent oral ulcerations (ROU), genital ulcerations (GU) and ocular inflammation, but also neurological, gastrointestinal and articular involvement are reported with considerable frequency.[3]

The epidemiological distribution of BD is peculiar: the disease has a high prevalence among countries identifying the old "Silk Road", a wide area between the Mediterranean countries and the eastern Asia.[4] The higher prevalence of BD is demonstrated in Turkey and Nothern Jordan,[5–7] and is also elevated in Korea, Northern China, Iran and Israel,[3,8] while in the rest of the Europe and in the United States it is remarkably lower.[5,9] This distribution suggested the existence

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of a predisposing factor diffused among the above-mentioned geographic area.[4] In particular, it has been remarked that 50–70% of the patients suffering from BD resulted positive for the major histocompatibility allele HLA B-51.[1,10] Despite the association with HLA-B51 increases the risk of developing BD of about 6 folds compared to general population,[11] it accounts only for a small part of the genetic susceptibility to BD. Therefore, the etiology of BD is unknown, and several genetic and environmental factors seem to be implicated.[12,13] The disease is more frequently diagnosed in adulthood, with a diagnostic peak formulated between the third and the fourth decades of life; however, an onset of BD in pediatric age, before the age of 16, is reported in a percentage that varies from 4% to 26% of the patients.[1,14-16] Given its rarity in pediatric age and the latency between the disease onset and the expression of the entire clinical picture, both diagnosis and treatment of BD in children and adolescents still represent a difficult clinical challenge.

Herein, we review the current knowledge about the etiology and pathogenesis of BD and we analyze the different phenotypic manifestations of the disease in children, in order to provide some key issues useful to improve the diagnostic process and the clinical management of pediatric patients affected by BD.

Etiology and Pathogenesis: From Old to New Aspects

The etiology and the pathogenic mechanisms underlying the development of BD have been extensively studied, not least to identify targeted therapies for the disease.

An association between the disease and several non-HLA loci, mainly codifying genes involved in the immune response and in the production, function and signaling of cytokines, was identified. In particular, genome-wide association studies demonstrated the correlation between variants in the IL-10, IL-23R–IL-12RB2, ERAP1 and STAT genes and the development of BD.[17–20] In pediatric BD the rate of familial aggregation is higher than in adults.[15,21] This suggests that in pediatric age the individual genetic background might play a more pronounced role in the pathogenesis of BD, compared to adult patients, and can partly explain the difference in the clinical phenotype of adult and pediatric BD patients.

The role of environmental triggers for BD has also been analyzed: correlation between the development of BD and the immune response to Streptococcus sanguinis,[12,22,23] and differences in the composition of the oral and gut microbiome[24,25] have been highlighted.

The pathogenic mechanism of BD is complex and not completely elucidated; it involves multiple molecular pathways, showing common features with both autoimmune and autoinflammatory disorders.[2,12] In fact, its association with both HLA-B51 and infectious agents, such as the above mentioned as Streptococcus sanguinis, suggested that BD could be the result of an uncontrolled activation of the immune system driven by an exogenous trigger, with a mechanism of molecular mimicry.[26] On the other hand, the clinical phenotype, featured by relapsing episodes of inflammation, the high levels of pro-inflammatory cytokines and the absence of identified pathogenic autoantibodies sustain the hypothesis of BD as an autoinflammatory disease.[2] Moreover, recently it has been suggested that BD could represent a subtype of spondyloarthropathy, basing on the involvement of common molecular mechanisms between BD and this group of conditions. BD and spondyloarthropathies share multiple aspects: the association with class I MHC alleles and their interaction with endoplasmic reticulum aminopeptidase 1, the enhanced Th-17 response, and the barrier dysfunction in the involved tissues, finally determining an aberrant immune response.[12,27,28] Apart from the considerations about its inclusion in a specific category of diseases, we believe it is important to underline that BD is featured by the impairment of both innate and adaptive immunity. The relative weight of the single molecular pathways may be different in the single tissues and systems involved in the disease, thus explaining the difficulties of the treatment based on the different efficacy of the biologic agents on the heterogeneous clinical picture of the disease.

Molecular Mechanisms

Innate Immunity

Innate immune cells and soluble mediators play a key role in the pathogenesis of BD by contributing, both directly and indirectly, to the development of organ damage, trough the activation of the adaptive response. Neutrophil cell population is found in the vessels of patients with BD, determining a condition of neutrophilic vasculitis;[29] neutrophils are the main cells identified in the histologic examination of the sites involved in BD, including oral and genital mucosa and the eye.[29] The hyperactivation of neutrophils has been demonstrated by different studies, and it is partly related with HLA-B51.[30] Activated neutrophils are able to enhance chemotaxis and effector

response, with production of reactive oxygen species, phagocytosis, production of neutrophil-extracellular traps, and secretion of cytokines able to induce a Th1-mediated immune response.[31,32] Moreover, the reactive oxygen species produced by neutrophils contribute to the endothelial dysfunction and, trough modification of the fibrinogen structure, to the development of thrombosis.[32,33] Even NK cells are directly involved in the pathogenesis of BD, trough a complex modulation of other cellular components of the innate and adaptive immunity. Alterations both in number and function of peripheral NK cells, resulting in a Th1 response, have been demonstrated.[12,34] Recently, the role of γδ T-cells in BD has been investigated,[2,3] evidencing an enhanced activation of this cellular population in patients with BD.[3,35] The activation of γδ T cells is partly depending from the circulating levels of IL-1β, central in the inflammatory response, and IL-23;[36] γδ cells in turn become able to induce a TH17 immune response.[37] Therefore, γδ cells may represent one of the multiple links between the inflammation and the activation of the adaptive immunity, finally determining the effector mechanism responsible of the organ damage in BD.

Adaptive Immunity

The balance of T-cells is altered in BD, showing reduced levels of T regulatory cells (T regs) and enhanced production of TH17 and TH1 cells.[3,38] Consequently, a high Th17/T reg ratio, which influences the immune balance,[39] resulting in the potential development of autoimmunity, has been reported. This immunological pattern, characterized by the prevalence of Th17 immune response, has been observed both in patients with cutaneous involvement (folliculitis) and with uveitis.[40] Even Th22 cells, a subtype of CD4 cells, are elevated in patients with BD. Th22 cells participate in the pathogenesis of BD trough the production of TNF-α and IL-22, this pattern being associated with several autoimmune disorders.[2,41]

The role of B cells and autoantibodies in the pathogenesis of BD is controversial. Several autoantibodies have been analyzed in BD, without evidence of a conclusive correlation with the development of the disease. Anti-endothelial cells antibodies have been demonstrated in 18–50% of the patients and represent the autoantibody pattern with the most defined association with BD.[26] However, their specificity is low, as they can be detected in other vasculitides, and their pathogenic role is uncertain. A theory is that they could contribute to the development of BD activating endothelial cells, therefore increasing the production of cytokines, or initiating the inflammatory response with their cytotoxic activity.[3,8] Other antibody specificities have been detected in patients with BD, including anticardiolipin, anti-retinal and anti-*Saccharomyces cerevisiae* antibodies, but their causative role has not been demonstrated.[26]

Cytokines

The levels of several pro-inflammatory cytokines, produced by cells of the innate immune system, have been demonstrated in patients with BD. IL-1β, IL-6 and TNF-α have an important role in the induction of the immune response in BD, and therefore represent potential therapeutic targets for the disease.[2,42,43] IL-1 and IL-6, together with IL-21 and IL-23, participate in the activation of TH-17 T cells, while TNF-α, mainly derived from the monocytic lineage, is important in the induction of autoimmunity.[2,39] High levels of TNF-α and IL-6 have been detected in the aqueous humor and in the vitreous fluid of patients with active uveitis, respectively, and their pathogenic role has been demonstrated in the development of neuro-Behcet.[42,44]

As a result of the above-mentioned alterations of the adaptive immune response, the levels of cytokines related to Th1 and Th17 activations are elevated. Serum levels of IL-17, produced by TH17 cells, IFN-γ, IL-2, IL-12 and IL-18, produced by Th1 cells, together with a reduction of IL-10, produced by T regs, have been demonstrated in patients suffering from BD.[12,45-48] This cytokine scenario underlies the complex pathogenesis and guides the future therapeutic strategy of BD.

Clinical Manifestations

Mucocutaneous Lesions

As described in Table 1, ROU is present in almost all children with BD (92–100%), similarlyto adult BD patients.[15,16,21,49-53] In most patients it represents the first manifestation (80–98%),[15,49,51] occurring at a mean age of 8–9 years.[49] ROU can precede other symptoms by years and this time frame in children is even longer than in adults. The lesions tend to be widespread and multiple, but they may also be single. Both minor and major ulcers can be observed. They involve lips, tongue, cheeks and palate and disappear without scar. The mean healing time is 10 days but major ulcers may persist for weeks.[1,14] ROU is a nonspecific sign and differential diagnosis includes a wide range of conditions, as summarized in Table 2. Increased number of ulcers (more than six at the same

Table 1 Clinical Manifestations in Pediatric and Adult BD Cohorts

			Pediatric Series						Adult Series		
Reference	**Koné-Paut[51]**	**Shahram[52]**	**Atmaca[53]**	**Karingcaoglu[15]**	**Gallizzi[16]**	**Koné-Paut[21]**	**Makmur[54]**	**Krause[55]**	**Alpsoy[1,15]**	**Makmur[54]**	**Krause[55]**
Number of patients	156	204	110	83	110	65	46	19	661	560	34
Oral aphtosis (%)	100	91.7	100	86	94.5	96	97.8	100	100	96.6	100
Genital ulcers (%)	55.1	42.2	82.7	81.9	33.6	70	73.9	31.6	58.3	75.7	88.2
Skin lesions (%)	66.6	51.5	37.3	51.8	39.6	76	21.7	89.5	44.2 (Erythema nodosum) 55.4% (pseudo folliculitis)	55.4	82.4
Pathergy positivity (%)	N/A	57	45.5	37.3	14.5	NA	NA	41.2	37.8	NA	57.1
Ocular involvement (%)	45.5	66.2	61.8	34.7	43.6	60	4.3	47.4 (anterior uveitis) 42.1 (posterior uveitis) 10.5 (retinal vasculitis)	29.2	37	Approx. 50%
Arthralgia/arthritis (%)	41	30.9	22.7	39.8	42.7	56	21.7 (arthritis)	47.4**	33.4	9.6**	17.6
Gastrointestinal involvement (%)	29.4	5.9	NA	4.8	42.7	14	21.7	36.8	1.6	4.5	11.7
Neurological involvement (%)	5*	4.4*	3.6*	7.2*	NA	15	NA	26.3	3*	NA	5.8*
Vascular involvement (%)	14.7	6.4	3.6	7.2	1.8	15	6.5	10.5	4.4	17.5	26.5

Notes: *Other than headaches. **Patients with only arthralgia are not included.
Abbreviation: NA, not available.

Table 2 Differential Diagnosis of Patients with BD According to Clinical Manifestations

Recurrent Oral Ulcerations	Ocular Involvement
Idiopathic aphtosis Infections (HSV, HIV)	Juvenile idiopathic arthritis (JIA)
Nutritional deficiencies (Vitamins B1, B2, B6, B12 Folate, Iron, Zinc)	Reactive arthritis
Cyclic neutropenia	Vogt-Koyanagi-Harada syndrome,
Erythema multiforme	Idiopathic intermediate uveitis (pars planitis)
Inflammatory bowel disease (Ulcerative colitis Chron's diseases)	Tubulointerstitial nephritis and uveitis syndrome
Celiac disease	Crohn's disease
Systemic lupus erythematosus	Cogan Syndrome
Reactive arthritis	Sarcoidosis
Autoinflammatory diseases (PFAPA, Familial Mediterranean fever, Hyperimmunoglobulinemia D)	**Vascular involvement**
Genital ulcerations	Antiphospholipid syndrome
Infections (HSV, HIV, syphilis)	Thrombophilia
Erythema multiforme	Takayatsu's arteritis
Gastrointestinal involvement	hypertension (CNS
Inflammatory bowel disease (Ulcerative colitis Chron's diseases)	lymphomas, intracranial neoplasia)
Neurological involvement	CNS sarcoidosis
Multiple sclerosis	CNS tuberculosis
CNS vasculitis	Other causes of CVS thrombosis (e.g. mastoiditis)
Stroke	
Idiopathic and secondary intracranial	

Abbreviations: HSV, herpes simplex virus; HIV, human immunodeficiency virus; PFAPA, periodic fever aphtas pharyngitis and cervical adenopathies; CNS, central nervous system; CVS, cerebral venous sinus.

time), concurrent variation in size from that of herpetiform to major ulcers, diffuse erythematous surrounds and involvement of soft palate and oropharynx have been suggested to differentiate BD from conventional RAS.[54,55]

Although GU are reported to be less common than in adults (33–83% in children compared to 60–90% in adults),[15,16,49-51,53] they are still the second-most common finding after ROU. In the pediatric populations, females have a higher rate of GU than males.[52] GU are generally deeper and larger than oral ulcers, recur less frequently and can have a scarring tendency. They are typically located on the vulva and on the scrotum. Differential diagnosis includes HSV infection, erythema multiforme, fixed drug eruption, sexually transmitted diseases (syphilis and HIV infection).[54] Skin aphthae over the perineal region have been described in 7% of children and should be differentiated from anal aphtosis that can be found in IBD.[21]

As in adult-onset disease, cutaneous lesions are very frequent in pediatric BD (40–90%). They appear later than OU, at a mean age of 10–13 years.[16,21,49,50] Skin lesions may occur as erythema nodosum-like lesions, papulopustular lesions, folliculitis, superficial thrombophlebitis and cutaneous vasculitic lesions. The acne-like lesions are not only limited to the typical areas of acne (face and upper part of the trunk) but can also be found on lower limbs. Necrotic folliculitis and acne-like lesions are more common in males while erythema nodosum in females.[49] The positivity of the pathergy reaction varies according to geographic distribution, being reported in 20–60% of the pediatric patients suffering from BD.[15,16,21,49-51,53] However, it has been removed from the pediatric BD classification criteria[51] and is no longer mandatory to define BD.

Musculoskeletal Involvement

The reported prevalence of joint involvement in pediatric population is slightly lower than in adults (30–40% vs 45–50%).[15,16,21,49-51,53,56] Arthritis is typically recurrent, nonerosive and does not cause any deformity; knee and ankle are the most commonly involved joints. In the Pediatric Behçet's disease (PEDBD) study, the rate of the axial involvement rate is reported to be 16.67% and the peripheral arthritis 47.44%.[49] Enthesopathy may be observed while sacroiliac involvement is rare.

Eye Involvement

Around 30–70% of children suffer from uveitis.[15,16,21,49-53] Atmaca et al found a similar rate of eye involvement in children and adults,[51] while Koné-Paut et al reported that eye involvement in children is less frequent than in adults, but associated with worse prognosis.[21] Uveitis is nearly two folds more frequent in males presenting with severe course.[49,57,58] Eye involvement may lead to severe vision loss in 25% of cases.[59] In most cases, ocular involvement occurs 2–4 years after disease onset,[51] but in 10–20% of patients it represents the initial manifestation.[49] The inflammation is typically nongranulomatous, accompanied by necrotizing obstructive vasculitis and affects anterior or posterior segment or both.[60] The ocular disease may start unilaterally but bilateral posterior uveitis with retinal vasculitis is the most typical feature of ocular-BD. Involvement of the posterior segment is the most serious ocular manifestation and patients usually have a painless decrease in visual acuity.[14,61] The most frequent posterior-segment complication is the macular edema which can either resolve with appropriate treatment or result in chronic structural changes such as scarring, atrophy, or formation of macular holes.

Repeated episodes of posterior-segment flare-ups can result in end-stage ocular BD characterized by blindness with a clinical picture of optic atrophy, vascular attenuation, and diffuse retinal atrophy.[60] The main symptoms of anterior uveitis are blurred vision, redness, periorbital or global pain, photophobia, and tearing. Slit-lamp exam may disclose conjunctival injection and hypopyon. Thanks to new therapeutic strategies the prognosis of eye involvement has improved in recent years.[61] The differential diagnosis of a patient with inflammatory eye disease includes several conditions, as idiopathic juvenile arthritis (AIG), reactive arthritis, Vogt -Koyanagi-Harada syndrome, idiopathic intermediate uveitis (pars planitis), tubulointerstitial nephritis and uveitis syndrome, and Cogan Syndrome.[61]

Neurological Involvement

Both in children and adults the reported prevalence of neurologic involvement varies greatly according to studies. Neurologic manifestations occur in 5.3% to 59%[62,63] of adult cases and in 3.6–36% of pediatric patients.[15,16,21] In children the mean age at presentation is 11–12 years, with a male gender prevalence of 2–3:1.[62,63] Neuro-Behçet disease (NB) affects predominantly the central nervous system (CNS), whereas the peripheral nervous system is rarely involved. Two major forms can be distinguished: the parenchymal and the vascular form. Clinical findings of parenchymal NB include headache, hemiplegia, cranial nerve palsies, aseptic meningitis, meningoencephalitis and neuropsychiatric disturbances. Vascular involvement has a better prognosis than the parenchymal form and is more common in children. The main manifestations of the vascular form include cerebral venous thrombosis (CVS) and pseudotumor cerebri.[1,14,15] The neurological features of BD are non-

specific; when they represent the first manifestations of BD, the differential diagnosis could be extremely difficult. Differential diagnosis includes multiple sclerosis, other CNS vasculitis, stroke, idiopathic and secondary causes of intracranial hypertension (CNS lymphomas, intracranial neoplasia), neuro-sarcoidosis, CNS-tuberculosis, other causes of CVS (eg, mastoiditis).[63–65]

Vascular Involvement

Vascular manifestations are reported in 5–40% of adults[66,67] and 2–20% of children.[15,16,21,49,50,52] The mean age at their onset is 11 years and a male prevalence has been observed.[49,51] BD may affect any type and size of vessel, but venous involvement is prominent. The inflammation, as previously discussed, is predominantly driven by neutrophils, and thrombosis is secondary to the inflammatory process. Superficial venous thrombosis (SVT) and deep vein thrombosis (DVT) of the lower limbs are the most frequent vascular manifestations of BD. However, DVT can occur in atypical sites such as inferior and superior vena cava, suprahepatic veins (causing Budd-Chiari syndrome), portal vein, cerebral sinuses and right ventricle.[68] Although less common, arterial involvement is a typical feature of BD. Pulmonary artery aneurysm is an important cause of mortality and morbidity. Arterial aneurism is the most common arterial finding, but occlusion and stenosis of aorta, femoral and pulmonary vessels may also be observed.[26]

Gastrointestinal Involvement

Gastrointestinal (GI) involvement is reported to be more common in children than in adults (4–40% vs 2–12%).[15,16,21,49-53] The mean age at onset of GI symptoms is 8.9 years, as reported by the PEDBD.[49] The most common manifestations are abdominal pain, nausea, vomiting, dyspepsia, diarrhea and gastrointestinal bleeding. Mucosal inflammation and ulcers can occur throughout the GI tract, more frequently in the ileocecal region. Deep aphthous and necrotic ulcerations may lead to abscess and perforation requiring surgery.[1,14] Differential diagnosis should include IBD, in particular Chron's Disease.

Miscellaneous Manifestations

Nearly half of pediatric BD patients have recurrent fevers.[49] As in adult patients, fever can be associated with vascular and neurological disease but in children it can also be observed in association with attacks of oral aphtosis. This clinical presentation resembles PFAPA syndrome,[69] which occurs frequently in childhood and should be considered in the differential diagnosis.

Other manifestations that have been reported in BD are pulmonary parenchymal lesions (nodules and cavities), pleural effusions, pericarditis, myocarditis and glomerulonephritis.[70–72]

Disease Course and Prognosis

BD onset is usually insidious, but acute life-threatening manifestations may represent the first symptom. Disease course is typically recurrent and unpredictable. Unlike adults, in whom symptoms usually decrease after a mean follow up of ten years, in children the disease often remains active and new symptoms appear over time.[1] Younger patients and men

generally have a more severe disease, showing an increasing frequency both of mortality and morbidity related to eye, vascular and neurologic disease.[73]

Diagnostic Approach

The diagnosis of BD relies substantially on the clinical features, but no specific symptoms and signs are described. The spectrum of the differential diagnosis is extremely wide, including autoimmune and autoinflammatory diseases. In children the diagnosis is even more challenging due to the long time interval between disease onset and the development of a clinical picture compatible with the BD diagnostic criteria. Consequently, the time to diagnosis is generally longer in pediatric patients (between 2 and 5 years) than in adults.[15,49,53] The majority of children observed at the presentation of the disease have few suggestive symptoms to satisfy any BD classification criteria and the diagnosis is based on the physician's expertise. In these cases, a diagnosis of "partial" BD is usually performed. Therefore, a detailed history and a systemic examination are recommended in the evaluation of a child suffering from oral and/or genital ulcers (the most typical BD presentation in children) together with a long critical monitoring during follow-up (Table 2). Until a few years ago the most commonly used criteria were the 1990 International Classification Criteria for BD defined by the International Study Group (ISG).[74] According to these criteria, the diagnosis could be established by the concurrent presence of two of the following findings in addition to ROU (mandatory criterion): GU, skin lesions, ocular involvement and pathergy test positivity. These criteria displayed a sensitivity of 85% and a specificity of 96%.[75] The relatively low sensitivity is explained by the high significance attributed to ROU, which can be absent only in 5% of the patients. In the year 2014, the International Team for the Revision of the International Criteria for BD (ICBD) proposed new criteria based on a scoring system, in order to increase the sensitivity of the previous ones.[76] The new classification considered ROU as not mandatory criterion for the diagnosis, included vascular and neurologic findings, whereas pathergy test positivity was defined as an optional criterion. The sensitivity of these criteria is 93.9% and the specificity as 92.1% in adult patients.[75] Both these criteria have been defined for adult patients and are not validated for pediatric BD. In 2015 the PEDBD study aimed to establish the criteria for pediatric patients using the largest cohort to date (Table 3).[49] In contrast to the ISG criteria, ROU are not mandatory and pathergy test is not included. A recent study reported that PEDBD criteria show a greater sensitivity (73,5% vs 52.9%) but a lower specificity (97,7% vs 100%) than ISG criteria. The better sensitivity of PEDBD is particularly important in the pediatric area since it allows an early diagnosis.[77]

Table 3 Consensus Classification of Pediatric Behçet Disease

Item	Description	Value/ Item
Recurrent oral aphtosis	At least three attacks/year	1
Genital ulceration and aphtosis	Typically with scar	1
Skin involvement	Necrotic folliculitis, acneiform lesions, erythema nodosum	1
Ocular involvement Neurological signs	Anterior uveitis, posterior uveitis, retinal vasculitis With the exception of isolated headaches	1 1
Vascular signs	Venous thrombosis, arterial thrombosis, arterial aneurysm	1

Note: Three of six items are required to classify a patient as having pediatric Behçet disease. Data from Kone-Paut et al.[49]

Therapeutic Strategies: From Old to New Drugs

The clinical phenotype and the system involved by the disease strongly influence the therapeutic strategies in adult and pediatric BD.[78] The progressive knowledge of the pathogenic mechanisms underlying BD resulted in a considerable improvement in the disease management, with the introduction of new biologic drugs and an optimization of the use of conventional immunosuppressive agents.[78,79] Table 4 summarizes the current recommendations[78] and promising therapeutic strategies for the treatment of BD focusing on the different approaches suggested for the single disease manifestations. In this regard, it is important to remark that the clinical trials on BD are mostly directed to adult patients. Therefore, the recommendations for the treatment of BD in pediatric age are often derived from the guidelines used in the adult population.

Conventional Immunosuppressive Agents

Corticosteroids represent a valid option during both the acute phase and disease relapses and are used to treat a wide range

Table 4 Recommended Therapies for the Major Clinical Manifestations of BD

Clinical Manifestations	First Line	Second Line	Other Options
Mucocutaneous involvement	Topical corticosteroids Colchicine (prevention)	AZA IFNα Etanercept Infliximab Adalimumab	Apremilast* MTX Anakinra Canakinumab Ustekinumab Secukinumab Thalidomide
Arthritis	Intra-articular steroids Colchicine	Low-dose steroids AZA IFNα Infliximab Adalimumab	Secukinumab
Eye involvement	Corticosteroids** AZA Cyclosporine (Infliximab)# (Adalimumab)#	Infliximab Adalimumab IFNα	Intravitreal steroids*** MTX Anakinra Canakinumab Tocilizumab Rituximab
Neuro-Behçet	Corticosteroids AZA Anticoagulation**** (Infliximab)# (Adalimumab)#	Infliximab Adalimumab	MMF MTX Tocilizumab Rituximab
Arterial involvement	Corticosteroids Cyclophosphamide*****	Infliximab Adalimumab	Surgery/Stenting
GI involvement	Corticosteroids 5-ASA AZA	Infliximab Adalimumab	Thalidomide

Notes: *Recurrent oral ulcers; **posterior uveitis; ***acute exacerbation in one eye, ****deep Venous Thrombosis; *****arterial aneurysms; #first-line treatment in severe cases.
Abbreviations: 5-ASA, 5-aminosalicylate; AZA, azathioprine; IFNα, interferon-α; GI, gastrointestinal; MMF, mycophenolate mofetil; MTX, methotrexate.

of BD manifestations. The administration of topical corticosteroids has reported to be effective in the treatment of mucocutaneous manifestations and of monoarthritis, through infiltrative arthrocentesis.[80] Systemic corticosteroids, frequently in combination with other immunosuppressive agents, are recommended for patients presenting with posterior uveitis, acute DVT, cerebral venous thrombosis, arterial involvement and severe gastrointestinal involvement.[26,78] The use of colchicine is recommended as a preventive therapy to limit the recurrence of mucocutaneous manifestations, and as a first-line treatment for patients with arthritis.[78,81] This drug is effective in reducing the frequency of genital ulcer exacerbations, while the efficacy on oral ulcers is controversial, since studies have shown conflicting results.[82] Among immunosuppressive agents, azathioprine (AZA) is the most widely used drug, with the aim of sparing the administration of corticosteroid therapy. AZA is effective in patients with severe mucocutaneous manifestations, arthritis, active uveitis, DVT, CNS and gastrointestinal involvement.[1,63,78,83,84] Cyclosporine, an agent with demonstrated efficacy in patients with uveitis and DVT, should be avoided in case of both active and inactive CNS involvement,[78] as its administration has been linked to an increased risk of developing manifestations of neuro-Behçet.[26,85] Cyclophosphamide is a therapeutic option for patients with severe vascular involvement,[1,86] and is recommended in case of extended DVT, involving large vessels, and arterial aneurysms, in combination with corticosteroids.[78] Methotrexate can be used in patients with ocular and mucocutaneous involvement, or in a combination

Table 5 Molecular Targets and Treatment Options

Target	Clinical Significance	Drugs
TNF-α	Pro-inflammatory cytokine, mainly produced by monocytes.	Infliximab (chimeric anti-TNF-α antibody) Adalimumab (human anti-TNF-α antibody) Etanercept (soluble TNF-α receptor) Golimumab (human anti-TNF-α antibody)
IL-1	Pro-inflammatory cytokine, mainly produced by monocytes and dendritic cells.	Anakinra (IL-1 receptor antagonist) Canakinumab (human anti-IL-1antibody) Gevokizumab (humanized anti-IL-1 antibody)
IL-6	Pro-inflammatory cytokine, produced by macrophages and T cells.	Tocilizumab (humanized anti-IL-6antibody)
IL-17	Cytokine produced by Th-17 cells. Uveitogenic activity.	Secukinumab (human anti-IL-17A antibody)
IL-23	Cytokine with inflammatory properties, including the induction of Th-17 response.	Ustekinumab (human anti-IL-12/IL-23 antibody)
CD20	Expressed by B-lymphocytes. Targeted in B-mediated diseases, including lymphomas and autoantibody-mediated pathologies.	Rituximab (chimeric anti-CD20 antibody)
CD25	Component of the IL-2 receptor. Its activation promotes the differentiation and proliferation of T cells.	Daclizumab (humanized anti-CD25 antibody)
CD52	Expressed by mature lymphocytes. Targeting CD52 causes lymphocyte depletion.	Alemtuzumab (humanized anti-CD52 antibody)

therapy for neuro-Behçet,[26] while mycophenolate mofetil represents an alternative in the treatment of CNS involvement,[87] but showed poor results on mucocutaneous manifestations.[88] The use of thalidomide, despite its effectiveness in mucocutaneous and gastrointestinal involvement, is strongly limited by the low safety profile and the adverse effects.[26]

Biologic Drugs and New Perspectives

Since their introduction, biologic drugs (mainly IFN-α and anti-TNFα) have markedly improved the management of patients suffering from BD. The first biological agent introduced for BD was IFN-alpha, for its well-known immunomodulatory properties. This cytokine is effective in inducing remission in patients affected by BD, with the best efficacy in those with severe uveitis.[89]

Based on the pathogenesis and, particularly, on the cytokine profiles of patients with BD, new biologic agents have been proposed for the treatment of BD (Table 5). As for conventional treatments, most of the studies are performed on adult patients with BD, and subsequently the drugs are used in pediatric population. The experience with the single agents in pediatric age is limited, mostly deriving from isolated case reports and series.[16,90-92] Anti-TNFα agents have been used in a wide range of severe manifestations of BD, including uveitis, NB, gastrointestinal involvement, arthritis vascular and mucocutaneous manifestations.[78,93] In particular, infliximab and adalimumab have been shown to be effective in patients with uveitis and severe GI disease,[83,94-96] while randomized studies demonstrated the efficacy of etanercept on mucocutaneous involvement.[97]

The anti-IL-1 agents anakinra and canakinumab have been successfully used in adult and pediatric age for the treatment of refractory uveitis, retinal vasculitis and mucocutaneous manifestations, while gevokizumab showed conflicting results on ocular manifestations.[16,92,98,99]

The anti-IL-6 agent tocilizumab currently represents a valid therapeutic option for refractory BD, with a significant effect in patients with uveitis and promising effects on CNS involvement.[93,100,101] However, it is known that this drug has scarce efficacy on mucocutaneous manifestations of BD,[102] and that cases of drug-related cutaneous flares are reported.[103,104] The recognized crucial role of the Th17-mediated immune response led to the introduction in the BD therapy of the anti-IL-17 drug secukinumab, whose efficacy has been demonstrated in preliminary studies for the treatment of mucocutaneous and articular manifestations, while its role in the management of uveitis is controversial.[102,105] The anti-IL-12/IL-23 agent ustekinumab represents a promising therapeutic option, despite literature reports limited experience, mainly on patients with refractory oral ulcers.[106,107] Beyond cytokine blockade, lymphocyte-directed treatments have been studies in BD. Alemtuzumab, an anti-CD52 agent, has been successfully used in patients

with refractory BD, taking advantage of the lymphocyte depletion deriving from its administrations.[108] However, the safety profile and the clinical applicability of this drug have yet to be defined.[102] The ant-CD25 antibody daclizumab has been proposed for the treatment of refractory uveitis, for its effect of inhibition of the IL-2 signaling on T cells, but its use showed conflicting results.[102,109] Despite the role of B-cells and autoantibodies has been shown not to be prominent in BD, the use of B-targeted therapies has been proposed, focusing on the vascular manifestations of the disease, as this condition may be associated with anti-endothelial autoantibodies. The anti-CD20 monoclonal antibody rituximab has proven to be effective in patients with retinal vasculitis, NB and uveitis, but the small number of patients evaluated is not sufficient to provide conclusions.[102,110-112] Finally, apremilast, an inhibitor of phosphodiesterase 4, active on multiple mechanisms of the innate and adaptive immunity (including Th1 and Th17) represents a promising agent for the treatment of patients suffering from OU.[113]

Conclusion

BD is a heterogeneous disease, with multiform clinical presentation. In pediatric age the clinical picture may be frequently incomplete; therefore, differential diagnosis of BD is complex, and the latency between disease onset and the definitive diagnosis is common. The recent introduction of diagnostic criteria for BD in pediatric age will help to improve the diagnostic sensibility in this peculiar subpopulation of patients. The advances in the comprehension of the pathogenesis of BD allowed a significant improvement in the disease management, with the introduction of targeted therapies aiming to optimize the therapeutic approach of adult and pediatric patients suffering from BD.

Disclosure

The authors report no conflicts of interest in this work.

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