Clinical Reviews in Allergy & Immunology (2021) 61:171–180
https://doi.org/10.1007/s12016-020-08809-2

Clinical Manifestations and Management of Pediatric Behçet's Disease

Ya-Chiao Hu[2] · Bor-Luen Chiang[2,3] · Yao-Hsu Yang[1,2]

Published online: 7 August 2020

Abstract
Behçet's disease (BD) is a chronic, vasculitic disorder affecting all sizes of vessels. The disease rarely onsets at childhood and an early diagnosis is often challenging. Oral ulceration and fever of unknown cause are common initial manifestations that might confuse other inflammatory disorders. The clinical manifestation pattern in pediatric BD is heterogeneous and varies in different genders, ethnicities, and geographic regions. There are also some differences in clinical presentations and prognosis between pediatric and adult BD. The disease also affects children at an extremely young age with mostly benign outcomes compared with that in older children. A limited number of studies reported issues about pediatric BD, let alone studies of children's treatments. Currently, the recommendation of the treatment in pediatric BD is according to the guideline of adult BD. The heterogeneity of clinical features makes the treatment more complicated. The main goal of the treatment is to control the inflammatory process and prevent recurrences. We will discourse the definition, epidemiology, clinical features, diagnosis, and treatment of pediatric BD in this review.

Keywords Childhood · Behçet's disease · Clinical features · Treatment

Introduction

Behçet's disease (BD) is a recurrent, multisystem, inflammatory disorder that affects all sizes of vessels. Its variety of clinical manifestations include recurrent oral and genital aphthous ulcers, skin lesions, arthritis, uveitis, thrombophlebitis, and gastrointestinal and central nervous system involvements [1, 2]. Although the age of peak onset is between the second and fourth decades of life [3], some patients had their disease onset in childhood. Since the publication of the first article on pediatric disease by Mundy and Miller in 1978 [4], awareness about BD's presence during childhood has increased gradually [5–7].

✉ Yao-Hsu Yang
yan0126@ms15.hinet.net

[1] Department of Pediatrics, National Taiwan University Hospital Hsin-Chu Branch, Jingguo Road, Hsinchu City, Taiwan

[2] Department of Pediatrics, National Taiwan University Hospital, College of Medicine, National Taiwan University, Taipei, Taiwan

[3] Department of Medical Research, National Taiwan University Hospital, Graduate Institute of Clinical Medicine, College of Medicine, National Taiwan University, Taipei, Taiwan

Definition and Classification of Pediatric BD

Since the first pediatric BD patients reported, childhood-onset or juvenile-onset BD has been described. Patients with initial symptoms at age 16 years or younger were considered as having juvenile-onset BD [6, 7]. Nevertheless, pediatric BD, or childhood BD, is used more commonly in the literature. Pediatric BD was defined if the disease was fully manifested and diagnosed up to the age of 16 years [5].

The diagnosis of BD is difficult and mainly based on clinical features. Lack of specific biomarkers for BD has led to the development of several sets of diagnostic criteria for BD. The most widely used one for adult-onset disease is the International Behçet's Study Group (ISG) criteria [8], but their sensitivity is suboptimal, especially for pediatric BD [9–11]. Other BD classification criteria developed for more robust diagnoses, either for adults and children. The International Criteria for Behçet's Disease (ICBD) was designed in 2014 (Table 1) [10]. The main changes from the previous classification are that oral ulceration and pathergy test are not mandatory. Also, the new criteria consist of vascular and neurological symptoms. It has been validated in pediatric BD patients with sensitivities that range from 70 to 80%, but specificity data are absent [12, 13]. Given the rarity and variety of clinical presentations in pediatric BD, the Pediatric Behçet's

Table 1 International classifications criteria for behçet's disease. International criteria 2014 clinical manifestations

Clinical manifestations	Description	Value/item
Oral aphthosis		2
Genital ulceration		2
Ocular signs	Anterior uveitis, posterior uveitis, retinal vasculitis	2
Skin lesions	Pseudofolliculitis, skin aphthosis, erythema nodosum	1
Neurological manifestation		1
Vascular signs	Arterial thrombosis, large vein thrombosis, phlebitis or superficial phlebitis	1
Positive pathergy test	(additional criteria)	1

Behçet's disease diagnosis is made if the score is ≥ 4

Disease (PEDBD) criteria (Table 2) were developed specifically for children, and they have a sensitivity of 73.5% and a specificity of 97.7% [11, 14]. Though the diagnosis of pediatric BD is challenging and often delayed, the newly developed diagnostic criteria with better sensitivity might aid in the early diagnosis and treatment in pediatric patients.

Epidemiology

BD is sometimes referred to as the Silk Route disease because of its relatively high frequency in the Middle East and Far East Asia to Japan [15, 16]. The BD incidence varies according to the geographical location, with the highest prevalence in Turkey (20–620 per 100,000 people), followed by Iran, Japan, northern China, and Korea [17]. Overall, pediatric BD represent a range from 5 to 15.5% in all BD population, based on the studies from different ethnics and geographic area [6, 9, 14, 18, 19]. In most series, boys and girls are affected with an equal frequency, and the male-to-female ratio ranged between 0.6 and 2.1. The mean age at onset of disease ranges widely, from 4.9 to 12.3 years old, in different geographic regions [6, 12, 13, 20–24].

Clinical Presentation of Pediatric Behçet's Disease

The main manifestations of pediatric BD are similar to that of adult patients, which are characterized by the heterogeneity and differ among geographic distribution. For example, gastrointestinal involvement prevails in patients from Asia, and vascular disease is more common among those from the Middle East and the eastern Mediterranean [25]. Figure 1 shows the frequencies of clinical features in pediatric BD patients from recent studies in different geographic areas. Each presentation is discussed separately in the following part.

Mucocutaneous Manifestations

As adult BD patients, recurrent oral ulceration occurred in almost all pediatric populations [26]. Though oral ulceration is no longer mandatory in the new PEDBD classification criteria, it remained the most frequent initial manifestation in 70–87% pediatric BD [6, 7, 27]. In pediatric BD, it presented as the only manifestation for an average of 3.7 years before diagnosis [20]. The painful ulcers may appear on the lips, tongue, and palate (Fig. 2a). The ulcers usually last for 3 to 10 days without scarring after healing, but significant lesions may evolve over weeks. Painful genital ulcerations are another feature of BD (Fig. 2b) and more frequently seen in girls than in boys [12, 21]. Unlike oral lesions, they usually healed with scarring over the affected area [28], but scarring is less frequent in pediatric BD than in the adult population [27]. Aphthae may appear in other regions. Skin ulceration over the perianal region (Fig. 2c) has been observed in 7–30% of patients [29, 30].

Other skin manifestations happen in 23.9–88.9% pediatric BD. The lesions vary from erythema nodosum, purpura, papulopustular lesions, or folliculitis. The most frequent skin

Table 2 Consensus classification of pediatric Behçet's disease (BD)

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

Three of the six items are required to classify a patient as having pediatric BD

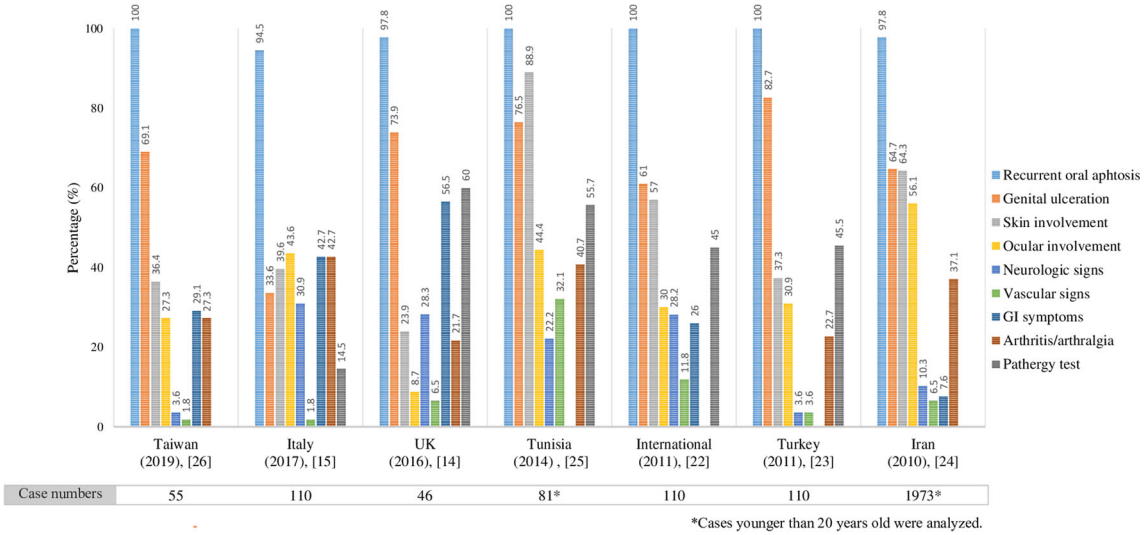

Fig. 1 Percentage of the clinical features of pediatric Behçet's disease in different geographic regions

manifestations are pseudofolliculitis and erythema nodosum, which account for 14.5–30.3% and 13.6%–18.7% of pediatric BD patients, respectively [12–14]. Pathergy phenomenon, an unusual cutaneous pustular reaction occurring 24 to 48 h after a needle puncture of the dermis, is highly characteristic. It may be observed in up to 60% of pediatric cases [12] and remained a diagnostic tool though it is not specific for BD.

Ocular Involvement

Eye lesions occurred in 27.3 to 56.1% of children with BD. It is characterized by chronic relapsing posterior and anterior uveitis with necrotizing retinal vasculitis. Unilateral or bilateral eyes might be affected, but most patients have bilateral involvement [7, 31]. The ocular symptoms were associated more with males than females in children, especially in those with posterior uveitis and retinal vasculitis [14, 20, 28, 31]. Cataract, posterior synechiae, macular edema, or maculopathy were the most common complications [7, 14, 31, 32]. Though BD only accounts for 0.3 to 10.9% of all pediatric uveitis in a variety of studies [33], physicians should consider it as one of the differential diagnoses of isolated uveitis in children since it tends to be more recurrent and sight-threatening than other endogenous uveitis. Recurrent attacks were reported in 70% of pediatric BD patients with eye involvement, and the mean number of acute exacerbations was 4.1 ± 2.7 [32]. Kramer et al. reported that a reduction of visual acuity during exacerbations happened in 68% of pediatric cases, and most of them are severe. However, 80% of the affected eyes improved after therapy [32]. In the PEDBD registry, 16.6% of patients with ocular involvement had decreased visual acuity and decreased to < 1/10 at a mean of 5 years of follow-up, and only one case had visual loss [20]. Overall, to prevent the reduction of long-term visual acuity, early diagnosis and prompt aggressive therapy remain the key point.

Vascular Disease

BD affects all types and sizes of vessels with a predominance of venous involvement. Thus, it is also classified as variable vasculitis [34]. The vascular symptoms have been incorporated in both pediatric and adult BD classification criteria recently (Tables 1 and 2). Thrombosis is the main feature of venous lesions, and the arterial lesions are characterized by aneurysm,

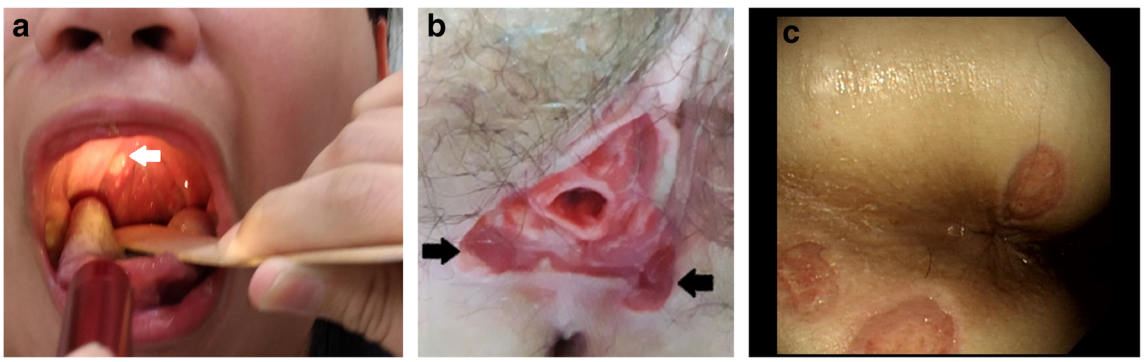

Fig. 2 The mucocutaneous lesions of pediatric Behçet's disease patients in **a** soft palate, **b** labia majora, and **c** perianal region

pseudoaneurysm, thrombosis, and stenosis. In childhood BD, 1.8 to 32.1% of patients had vascular symptoms with a male predominance fashion [35, 36]. Koné-Paut et al. reported a 7% and 12% ratio in pediatric BD with arterial and venous involvement (except cerebral venous sinus thrombosis), respectively [30]. In most children with vascular symptoms, BD was diagnosed at or following the first occurrence of vascular events [35, 36]. Like adult BD, deep vein thrombosis remains the most frequent vascular event if cerebral venous sinus thrombosis is not included [23]. Several pediatric cases with intracardiac thrombosis, arterial aneurysm/ pseudoaneurysm, pulmonary artery involvement, and Budd-Chiari syndromes have been reported [37–40]. According to the limited data due to its rarity, pediatric BD's recurrent rate of vascular events ranged from 0 to 21% [35–37, 39], which seemed to be different from the high relapse rate in adult patients [41]. In children, the possible risk factors for vascular activation include the male gender and the accumulation of thrombophilic factors such as anticardiolipin antibodies and protein C deficiency [35]. Though there is a lack of robust data in pediatric patients, the high morbidity and mortality are possibly related to pulmonary arterial involvement and Budd-Chiari syndrome in BD patients [38, 40, 42].

Central Nervous System Disease

Neurologic involvement of BD, neuro-BD (NBD), is reported in 3.6 to 30.9% of affected children. It is not common in BD patients but might result in irreversible impairment in severe NBD cases. The high frequency reported in some studies includes those who have chronic headaches, which might be isolated or related to severe NBD involvement [43]. NBD is broadly classified into two categories, including "non-parenchymal or vascular" and "parenchymal" diseases. Unlike adult patients, more of the NBD children presented with non-parenchymal diseases and cerebral venous thrombosis is the most common one [44–46]. The parenchymal presentations can be diverse but rare, including recurrent encephalomyelitis, aseptic meningitis, cranial nerve palsy, and neuropathy. Image studies such as magnetic resonance imaging (MRI) and the CSF examination can aid diagnosis. The CSF study may reveal elevated protein levels, pleocytosis containing polymorphonuclear cells and lymphocytes [1], and elevated interleukin-6 in CSF [47]. Unlike adult NBD, irreversible impairments less frequently happen in children. Mora et al. reported that 17% of children with NBD had definite sequelae in a literature review. Optic atrophy–related visual disturbances, personality changes, motor and sensory sequelae, personality change, and cognitive difficulties were reported [45]. However, the long-term consequences of schooling affected 75% of children with NBD in one study. Half of them could not attain a regular curriculum, and the others required extra assist to maintain their learning [44].

Gastrointestinal Involvement

The frequency of GI involvement in pediatric BD ranged from 4.8 to 56.5% in various reports [6, 12, 13, 20–24], based on different definitions of GI involvement in BD. It is characterized by exacerbations and remissions. Patients may present various symptoms, such as nausea, diarrhea, abdominal pain, ulceration of the ileum, cecum, and colon, melena, or hematochezia [48]. Terminal ileum or the ileocecal region is the most frequently affected location (Fig. 3) [49, 50]. Endoscopy, computed tomography (CT), and magnetic resonance (MR) enterography are tools for the diagnosis. Deep aphthous and necrotic ulceration may lead to abscesses and perforation requiring surgery [51]. According to the PEDBD study, 40.3% of patients in the study had GI symptoms, mostly isolated abdominal pain or discomfort. Digestive aphthae and bleeding occurred in 4.49% and 2.56% patients, respectively. Perforation was rare and occurred in one case only [14].

Gastrointestinal (GI) involvement of BD is a challenging situation since the symptoms were usually non-specific, and it raises the possibility of a diagnosis of inflammatory bowel disease (IBD) under the absence of other BD manifestation. The two diseases share similar abdominal symptoms and extra-intestinal manifestations. The appearance of ulcerative lesions under endoscopy and the absence of non-caseating granuloma from histologic findings may distinguish each other [52, 53]. Also, patients with Crohn diseases may present with anal complications such as stricture, fistula, and abscess formation because of the transmural mucosal involvement, but these features are rare in BD [48].

Arthritis/Arthralgia

Oligo- or polyarthritis occurs in 20 to 50% of the children with BD [13, 14]. Peripheral arthritis occurred more frequently. Knees, ankles, elbows, and wrists were the commonly affected joints [14]. The course is recurrent, but the disease rarely results in joint destruction or functional disability.

Differences Between Pediatric BD and Adult BD

Though the spectrum of clinical presentation of pediatric BD is similar to that of adult BD, a higher familial aggregation is found in pediatric patients [6, 54]. A significantly higher rate of relatives affected by BD was reported in pediatric BD (12.3%) than the adult BD (2.2%) in a 572 patient–based retrospective study [54]. Moreover, the frequencies of some features are different between the two groups. Mucocutaneous lesions were the most commonly reported manifestation in both groups. Almost all pediatric BD patients presented recurrent oral ulcers, but only one-third of adult BD patients had an

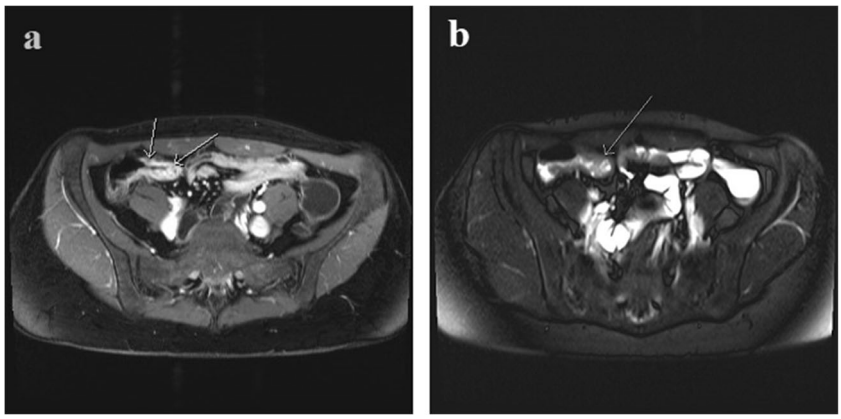

Fig. 3 Magnetic resonance enterography of the pediatric Behçet's disease patient with abdominal pain and frequent bloody stool showing active inflammation over terminal ileum, with **a** wall thick edema and **b** increased enhancement

initial presentation of oral ulcers [55]. However, genital ulcers were more common in adult BD patients [5, 6]. Children with BD present more non-specific gastrointestinal symptoms, central nervous system involvement [6], and arthralgia than the adult [5]. Also, the children with uveitis tend to have more acute exacerbations than adults though the visual outcome is similar in the two populations [32]. In general, the outcome of BD was much better in the children group. The BD severity scores and activity index were lower in children with BD than adults [5, 55]. Table 3 summarizes the comparisons between pediatric and adult BD.

Extreme Age in Pediatric BD: Neonatal Behçet's Disease

Neonatal BD is rare, and the symptoms occurred at or shortly after birth. Only a few cases were reported in the literature. Most cases had a maternal history of BD, and the mothers were symptomatic during pregnancy [56–60]. This suggested that transplacental passage of pathogenic maternal antibodies. However, some reports have been made without a history of maternal symptoms, which makes the role of the maternal antibodies uncertain [61, 62].

In prior reports, the most common presentations in neonatal BD were recurrent oral ulcers and skin manifestations, including pustular lesions and erythema nodosum. Half of the cases presented recurrent genital ulcers [62]. Almost all neonatal BD cases had a benign disease course, and the symptoms resolved within 9 weeks of age spontaneously or after a short course of prednisolone [62]. Nevertheless, a fatal case has been reported. Sunila Jog et al. reported a rare neonatal BD patient with neurological manifestation, which may present as a catastrophe in adult BD patients. The patient got seizure on the 6th day of life with consequent cerebral ischemic infarcts and hemorrhage. The death occurred after withdrawal life support on day 9 [56]. Though neonatal BD is rare, it should be considered as a differential diagnosis of recurrent oral and genital ulcers at such extreme age of life.

Treatments in Pediatric BD

Specific treatment guidelines for pediatric BD are currently not available. The current treatments of BD are based on the 2018 update of the EULAR recommendation [63]. The EULAR recommendations suggest that therapeutic strategies of BD should be individualized according to age and gender, the type and severity of organ involvement, and a patient's

Table 3 Comparisons of characteristics between pediatric and adult Behçet's disease

	Pediatric BD	Adult BD
Gender distribution	Similar prevalence in male and female	
Familial aggregation	More relevant	No strong association
Oral aphthous	The initial presentation of nearly all patients	The initial presentation of 1/3 patients
Ocular involvement	More common; More episodes of acute exacerbations	Less common
Other presentations	More GI symptoms and CNS involvement	More genital ulcerations
Disease severity and outcome	Lower severity scores and activity index; better outcome	More severe disease status

BD Behçet's disease, *CNS* central nerves system

preferences. Figure 4 depicted the first- and second-line treatment choice of BD based on symptoms in different organs. The goal of treatment is to suppress inflammatory exacerbations and recurrences to prevent irreversible organ damage.

Mucocutaneous and joint involvements are common presentations in BD, but they rarely cause permanent damage. Topical measures such as steroids are the choice of treatment of oral and genital ulcers. Colchicine should be tried first for the prevention of acute arthritis and recurrent mucocutaneous lesions [63, 64]. However, for patients with chronic symptoms, high severity index or organ involvement related to a poor prognosis, such as eye, vessels, central nervous system, and gastrointestinal tract, a more aggressive and diverse therapy should be considered. High-dose corticosteroid is efficient for acute exacerbations, especially in BD patients with vascular involvement, refractory/severe gastrointestinal involvement, and NBD. Nevertheless, long-term use of corticosteroids should be avoided, and a combination of immunosuppressants such as azathioprine, cyclophosphamide, or cyclosporine-A is recommended [63].

Though BD is primarily considered a type 1 T helper and type 17 T helper–mediated inflammatory disease [2], recent evidence revealed the autoinflammatory nature in its pathogenesis [65, 66]. An elevation of IL-1, IL-6, and TNF-α, the major pro-inflammatory cytokines related to innate immunity, was found in serum [65] and aqueous humor [67] of BD patients. Based on emerging evidence, different kinds of biologics become another treatment choice. Anti-tumor necrosis factor (TNF)-alpha therapy is useful for patients with refractory, severe BD, and especially for those with ocular [68, 69], central nervous system [69], and gastrointestinal [69–71] involvements, with a symptom-improving rate ranging from 43.5 to 67.7%. However, the data of anti-TNF-alpha therapy in pediatric BD is limited. The efficacy of anti-TNF-alpha therapy has been described only in the context of small patient series or case reports [72–74]. Table 4 listed the characteristics of pediatric BD cases who received anti-TNF-alpha therapy in previous studies. According to our experience in a single medical center in the past 20 years, anti-TNF alpha therapy is safe and effective in pediatric BD patients with refractory disease courses. The corticosteroid and immunosuppressive drug-sparing effects were especially prominent [24]. More and more studies evaluate biologics other than anti-TNF-alpha therapy in BD, such as interleukin (IL)-1 inhibitors, tocilizumab, rituximab, alemtuzumab, and ustekinumab [78].

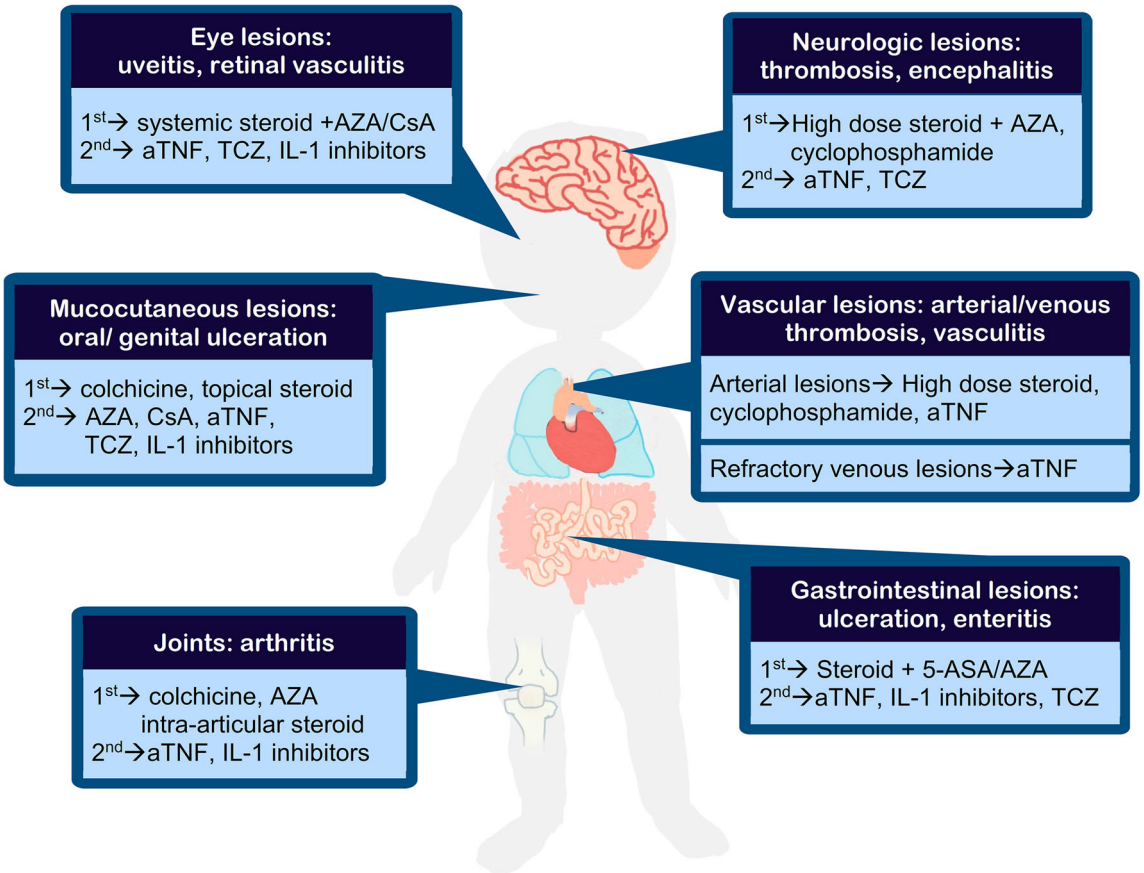

Fig. 4 The recommended first- and second-line treatments of pediatric Behçet's disease according to different organ involvement. AZA, azathioprine; CsA, cyclosporine; 5-ASA, mesalazine; aTNF, anti-tumor necrosis factor alpha therapy; TCZ, tocilizumab; IL-1 inhibitors, interleukin-1 inhibitors

Table 4 Review of reported cases with pediatric Behçet's disease receiving anti-tumor necrosis factor alpha therapy in the literature

Case	Sex	Age at diagnosis	Age at aTNF	aTNF	Major organ involvement	Efficacy	Side effect	Reference
1	Female	13	15	IFX	Intestinal lesion	(+)	None	Saulsbury et al. (2003), USA [72]
2	Male	nr	12	IFX	Budd-Chiari syndrome	(−)	None	Seyahi et al. (2007), Turkey [40]
3	Male	15	15	IFX	Budd-Chiari syndrome	(−)	None	
4	Female	13	15	IFX	Ocular lesion	(+)	None	Evereklioglu et al. (2007), Turkey [75]
5	Female	10	11	ETN	Ocular lesion	(+)	Fever	Cantarini et al. (2009), Italy [76]
6	Female	9	13	ETN	Cutaneous lesion	(+)	Bacterial endocarditis	
7	Male	12	14	ETN	Cutaneous lesion	(+)	None	
8	Female	11	13	ETN	Cutaneous lesion	(+)	Fatigue	
9	Male	8	18	IFX	Intestinal lesion	(+)	None	Kaneko et al. (2010), Japan [73]
10	Female	4	9	ETN	Cutaneous lesion	(+)	None	
11	Female	10	12	ADA	Central nervous system	(+)	None	Robinson et al. (2010), USA [77]
12	Female	5	5	IFX	Intestinal lesion	nr*	Infusion reaction	Watanabe et al. (2013), Japan [74]
				ETN		(+)	None	
13	Female	8	15	ETN	Intestinal lesion	(+)	Herpes zoster	Hu et al. (2019), Taiwan [24]
14	Female	11	14	ETN	Intestinal lesion	(+)	None	
15	Female	13	20	ADA	Ocular lesion	(+)	None	
16	Male	2	3	ETN	Intestinal lesion	(+)	Recurrent sinusitis	
17	Male	7	13	ADA	Ocular lesion	(−)	None	
18	Male	3	18	ETN	Central nervous system	(+)	None	

aTNF anti-tumor necrosis factor alpha therapy, *ETN* etanercept, *ADA* adalimumab, *IFX* infliximab *nr* not reported

*IFX in this case was discontinued due to drug infusion reaction

Among them, IL-1 inhibitors are mostly studied. IL-1, especially IL-1β, is crucial for host defense responses to infection and injury [79]. Previous studies proved the association between IL-1 and several inflammatory diseases, such as type I diabetes mellitus, systemic-onset juvenile idiopathic arthritis, and familial Mediterranean fever disease [79, 80]. Many studies reported IL-1 inhibitors as an effective and safe choice in adult BD patients, which responded to mucosal involvement, ocular lesions, enteritis, and arthritis in some cases [81]. Some publications describe the use of tocilizumab in BD patients with refractory mucosal involvement, NBD, uveitis, and enteritis [81–84]. However, the effectiveness of the treatment varied and there were limited numbers of patients reported. As evidence of the pathogenesis underlying BD continues to emerge, more therapeutic options become available for BD. Large-scale trials investigating the treatment of pediatric BD patients, especially the use of biologics, are necessary to enable the development of more effective and safe treatments.

Conclusions

Although the awareness of pediatric BD has been mentioned recently, the diagnosis and treatments of the disease in children remain challenging because of its rarity and diverse presentations. The new classification criteria for pediatric patients may aid in identifying these patients more promptly. Overall, the prognosis of pediatric BD is better than the adult group. However, there are still some children suffering from a refractory course or severe disease entity. Along with more understanding of the disease mechanisms, more treatment options, such as anti-TNF-alpha therapy, have shown effectiveness in adult BD. However, there is still the need for more reliable evidence of the efficacy and safety of these drugs in pediatric BD.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethics Approval Not applicable.

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