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Juvenile Adamantiades-Behçet Disease

Aristeidis G. Vaiopoulos[a] Meletios A. Kanakis[c] Violetta Kapsimali[d]
Georgios Vaiopoulos[c] Phedon G. Kaklamanis[e] Christos C. Zouboulis[b]

[a]Institute of Pathology, University of Würzburg, Würzburg, and [b]Departments of Dermatology, Venereology, Allergology and Immunology, Dessau Medical Center, Dessau, Germany; [c]Institute of Experimental Physiology and [d]Department of Microbiology, Medical School, University of Athens, and [e]Athens Medical Center, Athens, Greece

Key Words
Aphthae · Childhood · Epidemiological study · Genitoanal region · Adamantiades-Behçet disease · Behçet's disease · Uveitis

Abstract
Adamantiades-Behçet disease (ABD) is a chronic, multisystemic, recurrent, inflammatory vascular disorder of unknown etiology. Patients with symptoms initially appearing at the age of 16 or less are considered as cases of juvenile-onset ABD (JABD). JABD is relatively rare compared to ABD of adults, and only case reports and case studies have been published regarding this subtype of the disease. Epidemiology, clinical features, diagnosis and treatment of JABD are discussed in this review.

Introduction

Adamantiades-Behçet disease (ABD) is a chronic, multisystemic, recurrent, inflammatory vascular disorder of unknown etiology [1, 2]. Genetic or environmental factors as well as immunological aberrations have been incriminated by various investigators for its etiopathogenesis, still without a clear outcome to date [1, 3]. It is a worldwide disease with a predilection for people living in the Far East, Middle East and the Mediterranean regions (former so-called Silk Route). ABD affects people of all ages, showing the highest prevalence of onset in the third decade of life. Both genders may be involved, though its clinical spectrum and severity display quite substantial differences between them [4, 5]. Patients with symptoms occurring up to the age of 16 are considered as cases of juvenile-onset ABD (JABD) [6, 7].

JABD is relatively rare compared to its adult counterpart (AABD). Since the publication of the first article on the pediatric disease by Mundy and Miller in 1978 [8], several case reports and case studies have been described [6, 7, 9–14]. However, reviews on this subject are rather scarce [6, 15–18].

Epidemiology

The epidemiology of JABD is difficult to estimate also because there is no formal agreement on either the age at the disease onset or the age at which the symptoms meet the older or current diagnostic and classification criteria [19, 20].

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E-Mail karger@karger.com
www.karger.com/drm

1018–8665/16/2322–0129$39.50/0

Prof. Dr. med. Prof. h.c. Dr. h.c. Christos C. Zouboulis
Departments of Dermatology, Venereology, Allergology and Immunology
Dessau Medical Center
Auenweg 38, DE–06847 Dessau (Germany)
E-Mail christos.zouboulis@klinikum-dessau.de

Table 1. Comparison of clinical features of JABD

	Kim et al. [21], 1994, Korea	Fujikawa and Suemitsu [31], 1997, Japan	Hung et al. [33], 2013, Taiwan	Davatchi et al. [29], 2010, Iran	Atmaca et al. [15], 2011, Turkey	Sungur et al. [14], 2009, Turkey	Karincaoglu et al. [7], 2008, Turkey	Vaiopoulos et al. [32], 1999, Greece	Koné-Paut et al. [30], 1998, France	Treudler et al. [6], 1999, Germany
Patients, n	40	31	20	1973 >20	110	62	83	18	65	28
Male/female ratio	0.67	0.8	1.0	1.0	0.6	1.1	0.8	2.0	1.0	1.08
Age at disease onset (mean), years	10.6	n.r.	13 (0.0–16)	n.r.	11.6±3.5	n.r.	12.3 (1–16)	10.3 (1–15)	8.4 (0–16)	<16
Clinical features, %										
Oral aphthae	100	100	100	97.8	100	100	100	100	96.0	100
Genital ulcers	82.5	58	70	64.7	82.7	55	82.0	67	70.0	82
Skin lesions	72.5	55	65	65.3	76.0	n.r.	n.r.	n.r.	92.0	89
Erythema nodosum	58.6	n.r.	n.r.	19.6	37.3	26	52.0	44	40.0	46
Pseudofolliculitis	69.0	n.r.	n.r.	57.0	39.0	32	51.0	50	58.0	70
Ocular involvement	27.5	29	20	56.1	30.9	n.r.	35.0	67	61.0	48
Vascular involvement	7.0	n.r.	n.r.	6.5	3.6	5	9.6	11	15.0	25
Joint involvement	27.5	n.r.	30	37.1	22.7	42	40.0	61	46.0	57
CNS involvement	2.5	n.r.	n.r.	10.3	3.6	13	7.2	17	36.9	21
GI lesions	5.0	n.r.	50	7.6	n.r.	n.r.	4.8	11	14.0	19
Pathergy test	n.r.	n.r.	n.r.	49.4	45.5	47	37.0	22	80.0	38
Familial incidence	22.5	n.r.	1	n.r.	12.3	42	19.0	n.r.	15.0	25

GI = Gastrointestinal; CNS = central nervous system; n.r. = not reported.

In several studies, the prevalence of JABD was estimated to be in the range of 2–5% of all ABD-suffering patients [4, 15, 21–23]. Indicatively, the prevalence of JABD in France has been recorded as 1/600,000 [24]. On the other hand, in Turkey the reported results vary widely: no active ABD could be detected in a population of 46,816 children [25], while JABD prevalences of less than 0.006 [26], of 0.2 [27], of 5.3 [28] and of 13.4% [7] among all ABD patients were reported in different Turkish studies. In Germany a JABD rate of 17% among 168 ABD patients was assessed, 5% of which met the International Study Group for Behçet's Disease criteria [19] under the age of 16 [6].

Sex Ratio

The sex ratio is not consistent among the existing studies. Both a male [10, 14, 21, 28–30] and a female [7, 15, 31] predominance have been registered. Overall, the male-female ratio in JABD is comparable to that in AABD [9].

Familial Incidence

The familial prevalence among patients with JABD ranges widely from 12 to 15 [7, 15, 30] to 22.5–25 [6, 21] and 42–55% [13, 14, 16].

Clinical Features of JABD

Oral Aphthous Ulcers

Recurrent oral aphthous ulcers are in 70–87% of the patients the most frequent initial symptom in JABD, followed by skin lesions in 5–15%, genital lesions in 6% and ocular findings in 5% [7, 15, 30, 32] (tables 1–3). However, during the course of the disease, oral aphthous ulcers occur in nearly all patients [7, 11, 14, 15, 21]. There have been only a few reports with recurrent oral aphtha prevalence of less than 100% incidence of recurrent aphthae [29, 30]. The number of attacks, annually, ranges from 1 to 40 [30]. Oral aphthous ulcers have a similar frequency of appearance between boys and girls. The characteristics of the lesions are generally similar to those of AABD patients.

Genital Ulcers

Recurrent genital ulcers are the second most frequent manifestation in JABD, and their frequency ranges from 58 to 94% [7, 13, 15, 21, 31, 33]. They usually leave a scar on the involved skin or mucosa [13]. Nevertheless, scarring is less frequent in JABD than in AABD patients [34]. Genital ulcers are more frequent in girls than in boys (50–61% vs. 75–96%) [15, 24]. In boys, they are mostly localized in the scrotum and pubis and rarely in the penis, whereas in girls they appear at the major labiae and rarely in the vagina [13]. Perianal and extragenital ulcers can also be observed [30, 33].

Table 2. Comparison of clinical features between males and females with JABD (%)

	Atmaca et al. [15], male/female	Kural-Seyahi et al. [27], male/female	Koné-Paut et al. [30], male/female
Patients, n	110	121	65
Country	Turkey	Turkey	France
Year of study	2011	2004	1998
Male/female ratio	0.60	1.00	1.03
Oral aphthae	100/100	100/100	96.9/96.8
Genital ulcers	61/95.7	56/75	60.6/81.2
Skin manifestations	n.r.	n.r.	90.6/93.7
Erythema nodosum	39/36.2	48/30	40/–
Pseudofolliculitis	41.5/37.7	n.r.	58/–
Ocular involvement	48.7/20.3	62.3/46.7	81.8/40.6
Athritis/joint involvement	26.8/20.3	22/21	56/–
Vasculitis	9.8/0	20.9/0	21.2/9.3
CNS involvement	9.8/0	12.9/7	12.1/18.7
Gastrointestinal	n.r.	n.r.	15.1/12.5
Pathergy test	43.9/46.4	n.r.	80/–
Family history	12.3	n.r.	n.r.

n.r. = Not reported.

Table 3. Comparison of clinical manifestations in JABD and AABD (%)

	Karincaoglu et al. [7], J/A	Kural-Seyahi et al. [27], J/A	Krause et al. [9], J/A	Vaiopoulos et al. [32], J/A	Treudler et al. [6], J/A
Patients, n	83/536	121/428	19/34	18/52	28/140
Country	Turkey	Turkey	Israel	Greece	Germany
Year	2008	2004	1999	1999	1999
Male/female ratio	0.8/1.2	1.0/n.r.	0.73/n.r.	2.0/n.r.	1.08/1.60
Oral aphthae	100/100	100/100	100/100	100/100	100/100
Genital ulcers	82/86	65/95	32/87	67/79	82/76
Skin lesions	n.r.	n.r.	90/82	n.r.	89/86
Erythema nodosum	52/43	40/62	37/27	44/42	46/43
Pseudofolliculitis	51/56	62/83	n.r.	50/46	70/58
Ocular involvement	35/30	60/47	47/47	67/75	48/67
Articular involvement	40/34	20/39	32/71 arthritis	61/52	57/64
Vascular involvement	10/11	14/21	11/26	11/6	25/28
CNS involvement	7/3	10/3	26/6	17/21	21/21
Gastrointestinal	5/1	0.8/n.r.	37/12	11/2	19/17
Epididymitis	n.r.	n.r./n.r.	n.r.	27/11	13/21
Pathergy test	37.3/38	n.r./n.r.	41/57	22/35	38/61
Family history	19/10.3	19/n.r.	37/35	n.r./n.r.	25/8

J = Juvenile; A = adult; n.r. = not reported.

Skin Lesions

The frequency of skin lesions in JABD ranges from 76 to 92% [15, 21, 29, 30]. The most frequent skin manifestations in JABD are recurrent erythema nodosum and pseudofolliculitis. The determination of a papulopustular lesion, e.g. pseudofolliculitis, as a JABD manifestation is quite a challenge. Erythema nodosum may be found in 18–20% [13, 29] to 40–59% of the JABD patients [7, 21, 24], i.e. as frequently as in AABD [6, 32]. The frequency of pseudofolliculitis ranges from 38 to 69% [11, 21] and is less frequent in JABD than in AABD [6, 7, 24]. Both erythema nodosum and pseudofolliculitis are more fre-

quent in boys than in girls [7, 15, 24]. Nonfollicular lesions, located in areas other than the face, are considered more characteristic for JABD. Palpable purpura, Sweet's syndrome, pyoderma gangrenosum-like lesions and abscesses have rarely been reported [13].

Eye Involvement

The frequency of recurrent eye involvement in JABD ranges from 7.5 to 80% [9, 12, 13, 15–17, 21, 25–30, 33, 35]. In a recent cohort of 3,382 ABD patients, only 3.3% were younger than 15 years, whereas 31% of the children had been diagnosed with ocular involvement [15]. The latter may be the initial manifestation in 20% of JABD patients [36]. In a cohort of 62 JABD patients, 80.7% developed uveitis at the end of the follow-up period [14]. Ocular involvement is more often found in AABD than JABD patients [6]. Recurrent ocular manifestations can affect either one or both eyes. Eye involvement may last for quite a few weeks. Several studies have shown that panuveitis, associated with retinal vasculitis, is the most prominent type of eye involvement [28]. The prevalence of uveitis in JABD ranges from 0.7 [37] to 14.7% [28]. Further ocular manifestations include conjunctivitis, papilledema, band keratopathy, retinal vasculitis, retinitis, papillitis, macular edema, hypopyon and ophthalmomalacia [14, 18, 30]. Posterior synechiae, cataract, glaucoma, phthisis bulbi, branch retinal vein occlusion, maculopathy [14, 38] and ultimately vision loss to blindness were also reported in 6.3–9% [6, 30, 32]. Hypopyon was reported in 11–15% of JABD patients [14, 39]. A recent relevant review including 130 JABD patients also reported ocular features, i.e. papilledema, optic atrophy, blurry vision and diplopia [17]. Eye inflammation is typically nongranulomatous and affects the anterior, the posterior or both segments [37]. The outcome of ocular manifestations in JABD is better than that in AABD [39, 40] and severe complications, particularly blindness, are less frequent in JABD than in AABD patients (9 vs. 29%) [6]. However, the JABD incidents should have been observed early enough to clarify their morbidity more accurately. Ocular disease was observed in 47–63% males and 20–47% females with JABD [9, 15, 24]. Boys experience a more severe eye involvement [15, 30, 41]. Anterior uveitis was reported more often in juvenile than in adult patients [35]. Hypopyon was reported in 9% of JABD patients [15].

Joint Involvement

The reported arthritis prevalence in JABD varies widely, though in most cases arthralgia and not arthritis occurs. The articular involvement is recurrent, lasts for a few days or weeks and leaves no permanent lesions or joint deformities [18, 32]. Recurrent arthritis is much less common in JABD that in AABD [6, 9, 32]. Arthritis in JABD is usually an oligoarthritis, which rarely leads to polyarthritis [30]. It manifests at the lower extremities, knees, ankles (rarely elbows), small joints of the fingers and more rarely the sternoclavicular joint [13, 30, 33].

Neurological Manifestations

The prevalence of nervous system involvement in JABD patients ranges from 2.5 to 44% [7, 9, 11, 14, 16, 21, 32, 42]. Neurological symptoms may be the first manifestations of ABD in children [43]. The JABD clinical types are identical to those of AABD. In the former, 14% of the patients exhibit a parenchymal neuro-ABD, 35% a nonparenchymal one and the rest a mixed type [17, 44, 45]. A severe neurological deficit may occur in the parenchymal type. The main clinical manifestations of nonparenchymal involvement with dural sinus thrombosis include headache, nausea, diplopia, subacute hemorrhage and cerebral vasculitis [17]. Other features pertaining to this type are hypertension and seizures while neuropsychotic manifestations are uncommon [46]. The dural sinus thrombosis is more common in JABD patients than in AABD ones whereas the parenchymal type is more common in adults [11, 47, 48]. In a study with 40 JABD patients, 12 of them presented neurological findings (i.e. 5 with cerebral venous thrombosis, 1 with peripheral neuropathy, 1 with transverse myelitis and 1 with psychiatric disturbance) [42]. Rare manifestations include brainstem dysfunction, myelopathy and meningoencephalitis [46]. Recurrent pyramidal signs and diffuse vasculitis have also been reported [32]. The peripheral nervous system can rarely be affected in JABD [30, 42].

Vascular Manifestations

The prevalence of vascular manifestations in JABD ranges from 3.6 to 21% [11, 15, 49]. All vessels can be involved, and recurrent aneurysms, stenosis and thrombosis have, thus, been described [29, 49, 50]. Accordingly, pulmonary artery aneurysms (24%), abdominal aortic aneurysms, aneurysms in the common carotid artery, vena cava thrombosis (18%), Budd-Chiari syndrome (6%), superficial thrombophlebitis (18%), deep vein thrombosis of the lower extremities (37%), thrombosis of the iliac and femoral arteries and superior sagittal and sinus thrombosis have been reported [24, 30, 34, 51, 52]. It should be noted that the pulmonary artery involvement

is crucial for prognosis [18]. JABD patients exhibit less frequently vascular involvement than AABD patients (10.5 vs. 26.5%) [9], and boys develop venous thrombosis more frequently than girls [30]. The vascular involvement (vasculitis) in ABD is due to vascular inflammation, dysregulation of a number of coagulation factors, elevated levels of IgG anticardiolipin antibodies and factor V Leiden mutation [51, 53].

Intestinal Manifestations

A variety of gastrointestinal symptoms have been reported by several investigators. Hemorrhage and perforation are the most frequent manifestations. The prevalence of gastrointestinal involvement in JABD ranges from 5 to 50% [11, 33]. Intestinal disease was reported to be more common in JABD than in AABD in Turkey [34]. The intestinal ulcerations in JABD are rare, localized, round and very limited compared to Crohn's disease [54]. The ulcers are localized in the terminal ileum or in the ileocecal region, in the colon and anus [33]. The intestinal involvement is probably more frequent in JABD than in AABD [9].

Orcheoepididymitis

The prevalence of orcheoepididymitis in JABD is reported to range from 5 to 27% [6, 29, 32, 55]. The frequency of genitourinary symptoms in JABD is altogether similar to that in AABD [6, 32]. The orcheoepididymitis is usually unilateral [32].

Neonatal ABD

Only a few reports on neonatal ABD (4 boys and 5 girls) were extracted from the literature [56–62]. The disease started at birth [56, 57], at the age of 5 days [58], 10 days [59] or 2 weeks [60]. ABD-diseased mothers, aged from 28 to 38 years, were reported in 8 out of 9 cases (3 male and 5 female children) [56–59, 61, 62]. Other children in those families were healthy. Oral ulcers and skin lesions were found in all neonates, 3 of whom further developed genital ulcers and gastrointestinal manifestations, and 4 of them showed fever. The symptoms subsided within 3–9 weeks. Neurological manifestations were reported in a 34-week neonate of a diseased mother and were suspected to be ABD-related; death occurred on the 9th day [63]. A transient incident in a neonatal girl with ABD of a diseased mother has also been described [64]. On day 1 of life, the neonate presented papulopustular lesions of the labia and perineum.

Table 4. Current treatment options in JABD

Clinical features of JABD	Treatment
Oral aphthous ulcers	Topical corticosteroid cream, sucralfate, colchicine
Genital ulcers	Topical corticosteroid cream
Skin manifestations	Colchicine, corticosteroids, azathioprine
Joint involvement	NSAIDs, colchicine, in refractory cases: azathioprine, anti-TNF-α agents
Ocular manifestations	Topical and systemic corticosteroids, azathioprine, anti-TNF-α agents
CNS manifestations	Cyclosporine A, intravenous corticosteroids, cyclophosphamide, anti-TNF-α agents
Gastrointestinal manifestations	Sulfasalazine, thalidomide
Vascular manifestations	Anticoagulants (contraindicated when there is the possibility of a coexisting pulmonary arterial aneurysm), immunosuppressives

Pathergy Test

A positive pathergy test has been observed in 14–80% of patients with JABD [13, 30, 32, 65]. In most studies the prevalence of the pathergy test ranged from 40 to 50% [14, 15, 29]. From 6 ABD neonatal cases with reported pathergy test results, 2 had a positive reaction (33%). The positive pathergy test was found equally likely in both genders. There exists no difference in the prevalence of a positive pathergy test among JABD and AABD cases [7].

Diagnosis

Specific features of the disease may not exist at the same time, thus rendering the diagnosis of JABD quite difficult. Consequently, a long time lapse may be necessary before the appearance of any characteristic clinical features that would allow a solid diagnosis [6, 65, 66]. In such cases, diagnosis can only be made by an exclusion approach, using the current international criteria [20] as well as those for specific organ involvement [45].

Treatment

As in AABD, mortality rates in JABD are more prominent for males. The armamentarium for JABD treatment is similar, to some extent, to that of AABD (table 4) [67–70]. The most frequently prescribed systemic therapy in East/South Asian JABD patients is corticosteroids (42.2%), followed by cyclophosphamide (20.0%), methotrexate (18.9%), colchicine (13.3%), azathioprine (8.9%), cyclosporine A (8.1%) and interferon-α (1.5%) [71]. Three quarters of the patients were treated with drug combinations. JABD patients in Turkey were treated with colchicine, corticosteroids, cyclosporine A and azathioprine [15]. Treatment with anticoagulants is not widely accepted [72] although these are administered in thrombosis of the central nervous system [45]. Anticoagulants are clearly contraindicated in coexisting pulmonary arterial aneurysm, which may lead to fatal hemorrhage. In selected cases, immunosuppressive drugs, biological agents and thalidomide could be effective [69, 73–78]. In addition, there is an increasing interest in the results pending regarding the effectiveness of anti-IL-6 and various anti-IL-1 agents.

It is evident that the pediatric community needs to design multicenter studies on the use of new treatments, including biological agents, in JABD.

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Statement of Ethics

No EC approval was required.

Disclosure Statement

The authors declare no conflict of interest.

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