Late-onset Adamantiades-Behçet's disease

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Introduction and aim of the study

Adamantiades–Behçet's disease (ABD) is a rare, multisystemic, heterog-enous, inflammatory, chronic recurrent vasculitis equally affecting both sexes[1]. The diagnosis of ABD is clinical, established more accurately with the International Criteria[2]. ABD usually manifests during the second and third decade of life[1]. Recurrent oral and genital ulcers as well as ocular, skin, and musculoskeletal manifestations are the most common clinical signs, neurologic and vascular manifestations may also occur[1]. Exacerbations and spontaneous remissions are characteristic of the disease, and the prognosis is poor in young patients. ABD after the age of 40 years, the so called late-onset disease, is not well defined. The late-onset ABD has been reported in various publications as symptoms onset after 40 years of age and subsequent fulfilment of the diagnostic criteria or the diagnosis of the disease at an age older than 40 years.

The purpose of the present study was to evaluate the prevalence and the clinical features of patients with late-onset ABD and compare them with early-onset ABD patients.

Patients and methods

A systematic review and meta-analysis was conducted in accordance with the Meta-analysis Of Observational Studies in Epidemiology (MOOSE). PubMed and Scopus databases, the bibliographies of selected articles and the abstract books of ISBD conferences published from 1990 through December 2022 were searched using the following MeSH terms and free text keywords: "Behcet's disease," "late-onset Behcet's disease" and "Behcet syndrome, aged." In addition, results in the MEDLINE database using age filters have been registered. The duplicates among bibliographic records were removed, titles and abstracts were then scrutinized by two reviewers working independently followed by scrutiny of full texts of eligible studies. Discrepancies were resolved by discussion with senior investigators. The statistical analysis was performed by using the Chi-Square Test Calculator (2023, June 14), retrieved from https://www.socscistatistics.com/tests/chisquare2/default2.aspx. Statistical signi-ficance was considered with p-values <0.05 after applying the Bonferroni correction for multiple comparisons.

Results

Twelve original investigations related to the late-onset ABD from Algeria, China, Iran, Israel, Korea, Lebanon, Morocco, Taiwan, Tunisia and Turkey (3 studies), together with own unpublished data from Greece were included in the evaluation (Table 1)[3]. Sex was predominantly male in six studies, female in three studies, equal in three studies and not reported in one study, whereas overall males represented 57% of the late-onset ABD patients (361/631). Seven studies reported age of first symptom while six studies reported age of diagnosis. Among the 8524 patients reported in comparative late-onset versus early-onset studies, only 596 patients exhibited a late onset (7%; Table 2a). Oral ulcers were present in 98% of patients, followed by genital ulcers (72%), ocular lesions (47%) and a positive pathergy test (45%; Table 1). Signs which were more common in early-onset ABD patients were genital ulcers, pseudofolliculitis, erythema nodosum and vasculitis (Table 2a). The ethnic prevalence of ocular manifestations (4 more common in early-onset ABD studies/2 more common in late-onset ABD studies), arthritis (3/3), central nervous system involvement (2/2) and positive pathergy) test (1/4) was indifferent (Table 2a). In the meta-analysis, late-onset ABD was associated with significantly lower rates of vessel involvement, such as erythema nodosum, ocular and vascular lesions (all p<0.00001; Table 2a). Despite the sex-associated differences in the occurrence of erythema nodosum, pseudofollliculitis, genital ulcers, ocular manifest-ations, vascular lesions, central nervous system, arthritis and pathergy test in different populations, no sex-associated statistical differences of clinical signs were calculated in the meta-analysis after application of the Bonferroni correction for multiple comparisons (Table 2b).

Table 1. Male/female occurrence and clinical features of late-onset Adamantiades-Behcet's disease during follow-up (in %) - NR, not reported

Country / Authors	Number of patients	Number of male / female	Oral lesions	Genital lesions	Pseudo-folliculitis	Erythema nodosum	Ocular lesions	Arthritis	Vascular lesions	CNS involvement	Positive pathergy test
Algeria / Ghembaza et al.	37	22 / 15	100	73	62	14	56	58	33	27	29
China / Zou et al.	152	73 / 79	99	77	12	36	11	10	5	2	NR
Greece / own data	21	12 / 9	100	71	24	24	62	29	29	0	43
Iran / Shahram et al.	120	63 / 57	92	48	42	18	65	28	13	3	50
Israel / Weinberger et al.	13	26 / 41	100	100	NR	18	70	NR	NR	NR	50
Korea / Ryu et al.	44	NR	98	71	41	48	27	61	7	16	33
Lebanon / Ziadé et al.	2	1/1	100	50	50	0	100	50	0	0	NR
Morocco / Zakour et al.	134	80 / 54	NR	NR	NR	NR	52	50	19	19	NR
Taiwan / Tsai et al.	7	3 / 4	100	71	NR	57	57	43	NR	0	23
Tunisia / Hamzaoui et al.	68	44 / 24	100	81	63	18	37	57	37	25	50
Turkey / Saricaoglu et al.	9	7 / 2	100	100	11	33	33	NR	11	28	56
Turkey / Sungur et al.	42	21 / 21	100	88	36	31	62	40	5	10	48
Turkey / Hazirolan et al.	26	9 / 17	100	85	50	46	54	42	0	4	39
Total	675	361 / 270	98	72	36	28	47	37	15	11	45

Table 2. A. Clinical features of late-onset versus early-onset Adamantiades-Behcet's disease (in %), B. Clinical features of males and females in late-onset Adamantiades-Behcet's disease (in %) - NR, not reported

A

Country / Authors	Algeria / Ghembaza et al.		China / Zou et al.		Greece / own data		Iran / Shahram et al.		Israel / Weinberger et al.		Korea / Ryu et al.		Morocco / Zakour et al.		Taiwan / Tsai et al.		Tunisia / Hamzaoui et al.		Cumulative patients n (rate in %)		p
Onset	Late	Early	Late	Early	Late	Early	Late	Early	Late	Early	Late	Early	Late	Early	Late	Early	Late	Early	Late	Early	
Number of patients	37	40	152	638	21	201	120	5073	13	54	44	144	134	1398	7	18	68	362	7 (596/ 8524)	93 (7928/ 8524)	
Genital lesions	74	67	77	77	71	66	48	NR	10	90	80	87	NR	NR	71	67	81	77	75 (255)	77 (1118)	0.40
Pseudofolliculitis	62	55	12	24	NR	NR	42	NR	NR	NR	77	47	52	NR	NR	NR	63	84	50 (118)	46 (547)	0.31
Erythema nodosum	14	11	36	42	24	36	18	NR	15	38	48	54	NR	NR	7	78	18	19	**23** (80)	**31** (448)	**<0.00001**
Ocular lesions	56	73	11	21	62	66	65	NR	70	55	27	28	52	61	57	28	37	44	**36** (171)	**48** (1383)	**<0.00001**
Arthritis	58	53	10	13	29	38	28	NR	NR	NR	65	65	50	43	43	39	57	41	39 (179)	37 (1030)	0.44
Vascular lesions	33	20	5	9	29	10	13	NR	NR	NR	7	4	19	23	NR	NR	37	32	**17** (79)	**19** (529)	**<0.00001**
CNS involvement	27	18	2	3	0	17	3	NR	NR	NR	16	4	11	18	0	6	25	22	11 (52)	14 (399)	0.08
+ pathergy test	29	47	NR	NR	42	28	50	NR	50	40	33	28	NR	NR	29	28	50	56	41 (78)	42 (345)	0.79

B

Country / Authors	China / Zou et al.		Taiwan / Tsai et al.		Greece / own data		Cumulative data		p
Number of patients	152		7		21		180		
Sex	Male	Female	Male	Female	Male	Female	Male	Female	
Number of patients	73	79	3	4	12	9	88	92	
Genital lesions	70	84	66	75	83	56	72	80	0.16
Pseudofolliculitis	14	10	NR	NR	33	11	16	10	0.23
Erythema nodosum	27	44	66	55	10	33	26	43	0.015
Ocular lesions	7	11	100	25	50	78	16	18	0.65
Arthritis	4	15	33	55	25	33	8	18	0.047
Vascular lesions	8	3	NR	NR	8	56	8	8	0.95
CNS involvement	4	0	NR	NR	0	0	4	0	-
Positive pathergy test	NR	NR	NR	NR	25	67	25	57	0.06

Discussion

The definition of early-onset and late-onset ABD and the clinical characteristics differ among studies, which may partially explain the conflicting results reported[4]. Juvenile disease is with 2–21% in different populations less frequent[5] and late-onset ABD is with 7%, as shown in this study, even less common. Late-onset ABD exhibits with 57% a slight androtropism, with recurrent oral ulcers, genital ulcers, ocular lesions and a positive pathergy test as clinical signs with a prevalence of ≥45%. It is associated with significantly lower rates of vessel involvement, such as erythema nodosum, ocular and vascular lesions. A lower frequency of erythema nodosum has been reported in adults than in children (27% vs. 37%),16 and in our study, an even lower frequency was calculated in late-onset than in early-onset ABD (23% vs. 31%) indicating an inverse association of erythema nodosum as ABD clinical sign with age. The gradual frequency of erythema nodosum with age probably might explain the wide range of this sign reported in different ABD studies (15–78%)[1]. Since the frequency of ocular and vascular lesions has been associated with the occurrence of erythema nodosum[4], it should be expected that the frequency of ocular and vascular lesions might also vary in different studies (29–100%)[4] and might be less frequent in late-onset ABD, as found in our study. Vascular lesions are not common in ABD but they are usually accompanied with severe complications. Their frequency in early-onset ABD ranged from 3.5% to 32% while in patients with late-onset ABD it ranged from 5.3% to 37%[4]. Overall, major vascular complications tend to occur in patients with a younger age at onset. Aside from age at onset, sex is one of the major prognostic factors for ABD, because men experience more often a vascular involvement[5]. However, no statistical difference between the early- and late-onset ABD in terms of sex was detected. This is in line with previous and our results, which did not detect any sex-associated symptomatology in the late-onset disease.

In conclusion, late-onset ABD might occur predominantly in males with a milder course in comparison with early-onset ABD, especially regarding a vessel involvement.

References

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