Onset signs, clinical course, prognosis, treatment and outcome of adult patients with Adamantiades-Behçet's disease in Greece

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Received on November 4, 2002; accepted in revised form on April 7, 2003.

Clin Exp Rheumatol 2003; 21 (Suppl. 30); S19-S26.

Key words: Behçet's disease, adults, onset manifestation, clinical course.

ABSTRACT

Objectives. *To examine the onset signs, clinical course, prognosis, treatment and outcome of Adamantiades-Behçet's disease in adult Greek patients during a 10-year follow-up period, and to compare the results with those of other series reported.*

Methods. *The studied population consisted of 82 adult patients (54 male and 28 female) of Greek origin. Patients filled out a standard questionnaire and were followed up regularly. The findings during the follow-up of these patients were compared with those of other series.*

Results. *The most frequent onset sign was oral aphthae, both in our patients and in those of other published series. Eye involvement, joint involvement, genital ulcers and skin lesions followed in frequency. During a 10-year follow-up differences were observed between men and women, with arthritis being more frequent in females compared to males and with an overall more severe course in males. Eye involvement occurred earlier than neurological and vascular manifestations. A few differences were found in the clinical parameters in comparison to previously reported ethnic series. HLA-B51 positive patients presented an odds ratio of 9.5, the activity index was 5.17 ± 2.56 and the mean severity score 5.96 ± 2.32. Early treatment led to improvement of the disease.*

Conclusion. *The pattern of Adamantiades-Behçet's disease in adult Greek patients provides major similarities when compared to patterns in various other national groups.*

Introduction

Adamantiades–Behçet's disease (ABD) is a rare, chronic, multisystemic inflammatory disorder with recurrent characteristics, a variable clinical course and an unknown aetiopathogenesis (1-5). It occurs endemically in Central and East Asia and in the Eastern Mediterranean area, being rather rare in Northern European countries and in the USA (6, 7). The spreading of the endemic area along the ancient Silk Route (8, 9) and associated immunogenetic data support the hypothesis that the disease was carried through the immigration of ancient nomadic tribes. Patients of any age and gender can be affected, although differences have been observed in various populations (7).

The variability and the wide spectrum of clinical features of ABD confers a great heterogeneity with regard to the disease pattern in different countries even within the same geographic area (6). Therefore, our aim was to report on the onset signs, clinical course, prognosis, treatment and outcome of the disease in adults of Greek origin, which to our knowledge has only been investigated twice in other national populations (10, 11) over a long follow-up period.

Patients and methods

Consecutive and unselected patients of Greek origin referred by ophthalmologists and general practitioners were included in the study. Our patients were adults of Greek origin from nearly all areas of Greece. All patients fulfilled the criteria of the International Study Group for Behçet's disease (ISG) (12). They were instructed to answer 58 items in a standard questionnaire and were examined clinically. All patients were followed up for 10 years and their signs and symptoms as well as spontaneous relapses were recorded. There were no drop-outs. This prospective cohort study was started in 1991 and the data were collected in October 2001.

Oral aphthous ulcers and genital ulce-

Table I. Severity of Adamantiades-Behçet's disease (14).

Mild
Oral aphthosis
Genital ulcers
Typical skin lesions (erythema nodosum, papulopustular lesions, folliculitis, leucocytoclastic vasculitis)
Arthralgia
Recurrent headaches
Epididymitis
Mild gastrointestinal symptoms (chronic diarrhoea, chronic recurrent colicky abdominal pain)
Pleuritic pains
Superficial vein thrombosis
Moderate
Arthritis
Deep vein thrombosis of the legs
Anterior uveitis
Gastrointestinal bleeding
Severe
Posterior panuveitis, retinal vasculitis
Arterial thrombosis or aneurysms
Major vein (vena cava, hepatic) thrombosis
Neurological involvement
Bowel perforation

Table II. Clinical activity index, calculated as the sum of clinical features for each patient (15, 16).

Ocular lesions	0	Normal
	1	Cells in vitreous and/or anterior chamber only
	2	Vision 50%
	3	Vision 30%
	4	Able to see a few feet
	5	Blind
Mucocutaneous lesions	1	Aphthous stomatitis
	1	Erythema nodosum
	1	Genital ulcers
Vascular involvement	1	Unilateral limb DVT and/or superficial vein thrombosis
	2	Bilateral vein thrombosis
	3	Vein thrombosis requiring bed rest
	4	Thrombosis of superior/inferior vena cava or hepatic vein
	5	Thrombosis of both superior vena cava and inferior vena cava or arterial occlusion
Arthritis	1	For each joint
Neurological involvement	2	Intracranial hypertension
	4	Multiple sclerosis-like syndrome
	5	Pyramidal and or cerebellar involvement

rations were recorded as minor, major or herpetiform lesions. Skin lesions (pseudofolliculitis and erythema nodosum-like) were reported separately. Ophthalmologists used an additional standard form to characterize the degree of activity of anterior, posterior and intermediate uveitis and of retinal vasculitis at the first examination and during the course of the disease. Lack of light perception and blindness in one or both eyes were also reported. The involvement of peripheral joints documented by a rheumatologist was noted. X-rays of the joints, CT scan or MRI of the sacroiliac joints were performed according to the clinical signs and symptoms. The pattern of joint involvement (monoarthritis, oligoarthritis, polyarthritis) was registered. Tendonitis and myositis were also reported. Doppler ultrasound and angiography were applied to confirm venous thrombosis and arterial aneurysms and obstructions.

When central nervous system (CNS) involvement was suspected from the history and the clinical examination, CT scan, cerebrospinal fluid examination and especially MRI were performed to confirm the clinical findings. The findings of the CNS were classified as brainstem involvement, hemispheric lesions and microangiopathic lesions.

Other clinical manifestations, such as pleurisy, pericarditis, intestinal and kidney involvement were also registered. The pathergy test was performed using a 20–gauge sterile needle in four locations on the forearms and the result was read 48 hours later by the same investigator (P.K.). If a papule or a pustule formed at the site of the needle prick, the test was considered positive. Serological HLA class I typing was examined by a standard microlymphocytotoxicity technique (13).

The onset sign was considered the first clinical manifestation of the disease. Adult ABD was defined when the diagnosis was established after the age of 16 years. The disease duration was estimated as the lapse time between fulfillment of the ISG criteria and the patient's last examination.

The severity of the disease was estimated according to the classification of Krause *et al.* (14) as mild, moderate and severe (Table I). A clinical activity index was calculated as the sum of clinical features for each patient according to Yazici *et al.* (15) and Fresko *et al.* (16) (Table II). Active disease was defined as the presence of clinical manifestations over the last six months.

Statistical analysis was performed using Fisher's exact test for the comparison of 2 x 2 tables and the Wilcoxon test.

Table III. Baseline characteristics of 82 adults with Adamantiades-Behçet's disease.

	male = 54	female = 28	total = 82
Mean age (yr)	40.41 ± 11.62	40.46 ± 8.82	40.39 ± 10.72
Range (yr)	22 – 74	28 - 59	27 - 74
Mean age at onset (yr)	31.6 ± 9.55	34.1 ± 7.60	35.52 ± 9.25
Range (yr)	19 – 68	21 – 49	19 - 68
Mean time from onset sign to diagnosis (yr)	5.02 ± 4.34	3.75 ± 3.44	4.54 ± 4.07
Range (yr)	1 – 20	1 – 15	1 – 20
Mean disease duration (yr)	7.67 ± 8.09	6.32 ± 7.22	7.16 ± 7.69
Range (yr)	1 – 39	1 – 32	1 – 39
Positive pathergy test (%)	44.4	39.2	42.6

Results

Eighty two adult patients (54 male and 28 female) were enrolled in this study. The mean age was 40.39 ± 10.72 years, the mean age at onset of the disease was 35.52 ± 9.25 years, the disease du-

Table IV. Onset sign in adults with Adamantiades-Behçet's disease (in %).

Initial manifestation	Shafaie *et al.*[11] n = 3051 n (%)	Krause *et al.*[10] n = 25 n (%)	Zouboulis *et al.* n = 82 n (%)	P–value Shafaie	P–value Krause
Oral aphthous ulcers	2350 (76.9)	8 (32.0)	50 (60.9)	0.0013*	0.01*
Genital ulcerations	315 (10.3)	7 (28.0)	7 (8.5)	0.7	0.02*
Skin lesions	NR	4 (16.0)	7 (8.5)	——	0.28
Ocular lesions	336 (11.0)	NR	9 (11.0)	1.0	——-
Joint involvement	213 (6.9)	5 (20.0)	8 (9.7)	0.38	0.18
Vascular involvement	NR	1 (4.0)	1 (1.2)	——	0.41
CNS	NR	NR	0	——	——
Other manifestations	263 (8.6)	NR	0	——	——

CNS: Central nervous system; NR: not reported. * Statistically significant

ration was 7.16 ± 7.69 years, and the mean lapse time from the first sign to the fulfillment of ISG criteria was 4.54 ± 4.07 years (Table III).

A summary of the onset signs is presented in Table IV. Oral aphthous ulcers were the most frequent onset sign (60.9%), followed by ocular involvement (11.0%), arthritis (9.7%), genital ulcerations (8.5%), skin lesions (8.5%) and vascular involvement (1.2%). The second most frequent manifestation was genital ulcerations followed by oral aphthous ulcers and ocular involvement. The mean time elapsing between the first and second signs was 5.6 years.

The clinical features appearing during the course of the disease are presented in Table V.

Mucocutaneous lesions

Oral aphthous ulcers were of different sizes and were present as recurrent lesions in all patients. Major oral aphthous ulcers were found in 7%, minor in 85% and herpetiform in 8% of our patients. During the recurrences, the lesions were not always of the same size. They lasted for a few days to more than a week, and healed without scarring. Genital ulcerations were found in 83% of our patients, were fewer in number and usually larger than the oral aphthous ulcers and their recurrence frequency was low. They were localized in various parts of the external genitalia, lasted for a few days to more than 2 weeks, and a scar or white skin sign was noted after healing. Interestingly, both oral aphthous ulcers and genital ulcerations presented less frequent recurrences and lasted a shorter duration with time.

Skin lesions (pseudofolliculitis and erythema nodosum–like lesions) were found in 73% of our group. Pseudofolliculitis (not related to age or to corticosteroid treatment) was mostly localized on the trunk and less frequently at the extremities. It was recurrent and lasted for several days. In large lesions a scar resulted after healing. Erythema nodosum–like lesions were found in 51% of the patients and were only localized in the lower extremities. They lasted for 1 to 3 weeks and recurrences were infrequent (13%).

Ocular involvement

Ocular involvement as an onset sign was noticed in 9 patients (4 had anterior uveitis, 3 posterior and 2 retinal vasculitis). During the course of the disease unilateral or bilateral involvement and recurrences were observed. The frequency of ocular involvement was 77%. Anterior uveitis was found in 19% of our patients, posterior uveitis in 32%, intermediate uveitis in 9.5% and panuveitis in 40%. The duration of each attack depended on whether early and vigorous treatment was introduced. Lack of light perception was found in 2 patients (2.4%).

Arthritis

Arthritis was found in 60% of our patients, who presented pauciarthritis (67%), monoarthritis (29%) and polyarthritis (4%). Knees and ankles (95%) were commonly involved. The synovial fluid was mildly inflammatory. The synovial membrane (obtained from 3 patients with a Parker–Pearson needle) showed hyperplasia of the lining cells and infiltration with mononuclear cells. Recurrences were infrequently observed and each attack lasted from 1 to 3 weeks. Three patients developed a Baker cyst which ruptured in the gastrocnemious muscles. One patient suffered from persistent chronic arthritis of the right knee. He underwent synovectomy but a degree of incapacity remained. No radiological findings were observed in the affected joints except in 3 patients with aseptic necrosis of the

Table V. Comparison of clinical features during the course of Adamantiades–Behcet's disease between adult male and female patients.

Signs	Male (54) no.	Male (54) %	Female (28) no.	Female (28) %	P-value
Oral aphthous ulcers	54	100	28	100	1.0
Genital ulcerations	46	85.1	22	78.5	0.54
Skin lesions	40	74.0	20	71.4	0.80
Erythema nodosum	24	44.4	18	64.2	0.11
Ocular lesions	42	77.7	21	75.0	0.79
Joint manifestations	28	51.8	21	75.0	0.06
Vascular involvement	8	14.8	1	3.5	0.15
CNS	12	22.2	4	14.2	0.56
Epididymo-orchitis	10	18.5			
Heart signs	1	1.8	—-	—-	1.0
Kidney signs	1	1.8	—-	—-	1.0
Lung signs	1	1.8	1	3.5	1.0
GI involvement	5	9.2	1	3.5	0.66
Pathergy test	24	44.4	11	39.2	0.81

+ Suspected; GI: Gastrointestinal; CNS: central nervous system

Table VI. Time intervals between the fulfillment of the ISG criteria and the development of ocular involvement, CNS manifestations and vascular involvement.

	Ocular involvement	Central nervous system	Vascular involvement
Number	15	12	7
Average (in years)	2.05	4.58	9.7
	0.1	2	4
	0.2	4 x 3	6
	0.4	2 x 4	7
	0.5	3 x 5	8
	0.6	6	9
	3 x 1	12	14
	2 x 2		20
	3 x 3		
	5		
	8		
Ocular involvement as one of the ISG criteria	48		
Development of systemic manifestations before fulfillment of the ISG criteria		4	2

femoral head. Sacroiliitis was seen in 2 patients, both of whom were HLA-B27 positive and HLA-B51 negative. Recurrent entesopathy mainly of the Achilles tendon was observed in 6 patients. Myalgia of the gastrocnemious muscles was reported in 2 patients.

Vascular involvement

Vascular involvement could be detected in 11% of the patients aged 37 to 69 years (mean 50.3 years). The vascular involvement developed between the ages of 21 and 68 years (mean 38.2 years). Superficial thrombophlebitis was observed in 5 patients. Budd- Chiari syndrome was found in one patient, arterial obstruction in another patient, and anterial aneurysms of the femoral artery and of the popliteal artery in 2 patients. This latter complication was successfully treated by surgery. We did not observe any recurrences of these manifestations under treatment.

CNS involvement

The age of the patients with CNS involvement ranged from 35 to 52 years (mean 43.2 years). This manifestation was found in 19.5% of our patients but was not seen as a first manifestation of the disease. It developed 2 to 27 years after the presenting symptom (Table VI). The clinical symptoms were speech disturbance, diplopia, hemiparesis, headache and ataxia. Acute neurological symptoms developed in 6 patients. Isolated brainstem lesions were found in 8 patients, multiple periventricular white–matter lesions bilaterally in 3 and microangiopathy in 4. In one patient communication hydrocephalus developed. In 3 patients recurrences were observed 3 to 8 months apart. At the last examination 3 patients still had pyramidal signs and 2 speech disturbances. In all patients CNS involvement developed from 1 to 10 years following the ocular disease.

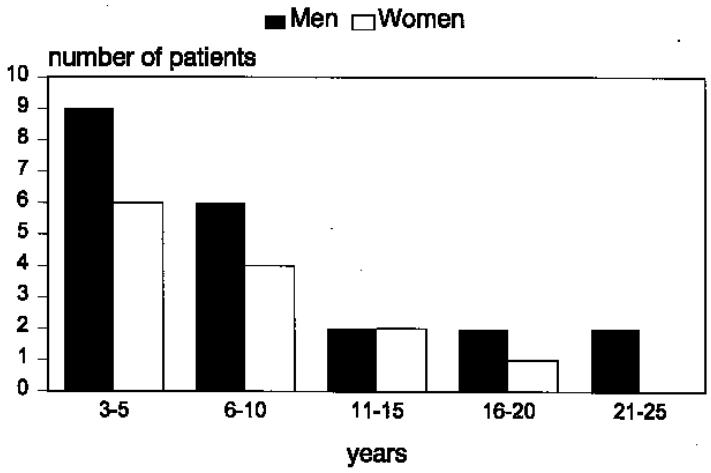

Fig. 1. Duration of the activity of Adamantiades-Behçet's disease in adult patients of Greek origin (in years).

Other manifestations

Epididymo-orchitis was observed during the follow–up period in 18.5% of our male patients. In the majority it was recurrent, affecting the same or the other testis, and lasted from a few days to nearly 2 weeks. The interval between recurrences varied from 1 to 7 years following the initial episode.

Gastrointestinal involvement (intestinal ulcers with or without perforation) was found in 6 patients (7%) among them 5 males. Four presented ulcers on colonoscopy and 2 developed intestinal perforation. More rare manifestations were pleurisy, pericarditis and glomerulonephritis.

Thirty-five patients (43%) showed a positive pathergy test.

HLA-B5 and -B27 positivity

HLA B51 was found in 76% of our patients. This rate is similar to the 79% rate of HLA-B51 positivity in 108 Greek patients reported previously (6). Since 28% of the Greek population is HLA-B51 positive, a high odds ratio of 9.5 for HLA-B51 positivity in Greek patients was calculated. HLA-B52 was found in no patient. HLA–B27 was only present in the two HLA-B51 negative patients with sacroiliitis (2.4%) leading to an odds-ratio of 0.5, since 4.72% of the Greek population is HLA-B27 positive (17).

Activity of the disease, activity index, severity score, and prognosis

The mean activity index was 5.17 ±

2.56, (range 2-19) and the mean severity score was 5.96 ± 2.32 (range 2-11). Active disease was present in 34 patients (41.5%), 21 male and 13 female (duration range of active disease 3-24 years for men and 3-20 years for women) (Fig. 1). After 3-5 years, 36 patients (44%) had active disease. The disease duration was between 6 and 10 years in ten patients (29%), between 11-15 years in four patients (12%), between 16 to 20 years three patients (9%), and between 21 to 25 years in two patients (6%).

Two patients died from unrelated causes, possibly from smoking and medications received (cancer of the lung and cancer of the kidney). Forty-eight patients (76%) developed ocular involvement before (onset or second criterion) or with the fulfillment of the ISG criteria, whereas 15 (24%) 0.1-8 years after the fulfillment (average 2.05 years) (Table VI). Blindness was observed in seven patients (8.5%) of whom six patients were blind in one eye and one was blind in both eyes. Twelve patients developed CNS involvement 2 to 12 years (average 4.58 years) after the fulfillment of the ISG criteria (75%), and four before (25%). Among these 16 patients, five (31.3%) presented persistent signs due to a previous involvement of the CNS (pyramidal signs or speech disturbances). Finally vascular lesions occurred 4 to 20 years (average 9.7 years) after the fulfillment of the ISG criteria in seven patients (77.8%), and in two before (22.2%). Among these nine patients, four (80%) developed severe vascular manifestations (Budd–Chiari syndrome, arterial aneurysms and obstruction).

Gender differences

Table V summarizes the clinical manifestations in adult male and female patients. All 4 patients with severe vascular manifestations (Budd–Chiari syndrome, arterial aneurysms and obstruction) and all 5 patients with severe CNS involvement and clinical findings at the most recent examination were male. Anterior uveitis and intermediate uveitis were noted more frequently in women than in men, while panuveitis and posterior uveitis were more frequent in men than in women. No light perception was found in 2 men. Six of the 7 patients who developed blindness were

Table VII. Clinical features in adults during the course of Adamantiades-Behcet's disease in four series.

Symptoms	Shafaie *et al.*[11] (Iran) n= 3051 n (%)	Pivetti-Pezzi *et al.*[18] (Italy) n = 122 n (%)	Krause *et al.*[14] (Israel) n = 34 n (%)	Zouboulis *et al.* (Greece) n = 82 n (%)	P-value compared to Iran	Italy	Israel
Oral aphthous ulcers	2933 (96.1)	120 (98.4)	34 (100)	82 (100)	0.07	0.52	1.00
Genital ulcerations	1984 (65.1)	89 (73.0)	30 (88.2)	68 (82.9)	< 0.01*	0.13	0.58
Skin lesions	2270 (74.4)	107 (87.7)	28 (82.4)	60 (73.1)	0.80	0.01*	0.35
Erythema nodosum	703 (23.0)	NR	9 (26.5)	42 (51.2)	< 0.01*	—-	0.05*
Ocular lesions	1782 (58.4)	93 (76.2)	21 (61.8)	63 (76.8)	< 0.01*	1.00	0.11
Joint manifestations	1265 (41.4)	91 (74.6)	24 (70.6)	49 (59.7)	< 0.01*	0.03*	0.30
Vascular involvement	280 (9.2)	30 (24.6)	9 (26.5)	9 (10.9)	0.56	0.02*	0.05*
Central nervous system	98 (3.2)	20) (16.4	2 (5.8)	16 (19.5)	0.01*	0.58	0.09
Epididymo-orchitis	NR	16 (17.4)	NR	10 (18.5)	—-	1.00	—-
Heart signs	NR	NR	NR	1 (1.2)	—-	—-	—-
Kidney signs	NR	NR	NR	1 (1.2)	—-	—-	—-
Lung signs	NR	NR	NR	2 (2.4)	—-	—-	—-
Gastrointestinal involvement	NR	36 (29.5)	4 (11.7)	6 (7.3)	—-	< 0.01*	0.48
Pathergy test	1861 (61.1)	NR	19 (55.9)	35 (42.6)	< 0.01*	—-	0.22

* P ≤ 0.05

male, among them the patient who was blind in both eyes. Among other signs, a trend for more common joint manifestations in females was calculated (75% compared to 52%, P = 0.06). The pathergy test was positive in 44.4% of the men and in 39.2% of the women (NS).

The mean activity index was similar for male and female patients, being 5.44 ± 2.94 [95% confidence intervals (CI) 0.38–1.98] for males and 4.64 ± 1.50 [95% CI 0.17-1.78] for females. In contrast, the mean severity score for males was higher, *i.e.* 6.35 ± 2.51 [95% CI 0.09 –2.19] than for females 5.21 ± 1.68 [95% CI 0.21-2.07] (two–tailed t-test, P=0.017). These findings indicate that the disease runs a more severe course in men and affects the vital organs.

Treatment and outcome

Treatment was administered depending on the organ involved and the activity of the disease. Monotherapy was administered in 31 patients [38%, 5 colchicine, 11 corticosteroids, 7 cyclosporine A, 2 methotrexate and 6 NSAIDS]. Combination therapy was given to 44 patients (54%, 12 corticosteroids + colchicine, 11 corticosteroids + azathioprine, 6 corticosteroids + cyclosporine A, 1 corticosteroids + thalidomide, 8 cyclosporine A + azathioprine, 3 cyclosporine A + azathioprine + anti-tumor necrosis factor (TNF)-α, 1 pulse methylprednisolone + pulse cyclophosphamide, 2 anticoagulants + cyclophosphamide). In 7 patients showing complete remission for over a year, treatment was discontinued without recurrence of the disease (8.5%).

In the past, small doses of corticosteroids combined with azathioprine + chlorambucil have been given to patients with sight-threatening eye disease. In 3 patients resistant to this regime anti-TNF-α was added with rapid and excellent results. Lack of light perception and blindness were observed in patients who in the past had not been given aggressive treatment with combination drugs. Pulse cyclophosphamide + pulse methylprednisolone were administered for severe CNS involvement. Following the third pulse of cyclophosphamide the clinical features and the MRI findings subsided considerably. Non–steroidal anti-inflammatory drugs with colchicine or methotrexate prevented recurrences in patients with recurrent arthritis. One of our patients with aseptic necrosis of the femoral head underwent surgical treatment. Mucocutaneous lesions have been treated with local application of corticosteroids or with colchicine + corticosteroids. In rare cases cyclosporine A was also added for this manifestation. One patient was treated with thalidomide with excellent results. Anticoagulants and immunosuppressive drugs were used for vascular involvement with good results and no recurrence. In 2 patients with arterial aneurysms, surgical treatment was performed with satisfactory results.

Comparison of our findings with those in the literature

Table IV shows that oral aphthous ulcers were found as the onset sign more frequently in the series of Shafaie *et al.* (11) and less frequently in patients studied by Krause *et al.* (10) compared with our series. In addition, genital ulcerations were a more frequent onset sign in the patients reported by Krause *et al.* (10) than in our patients and those by Shafaie *et al.* (11).

The frequency of clinical features during the course of the disease in adult Iranian (11), Italian (18), Israeli (14), and Greek patients are presented in Table VII. Genital ulcerations, ocular lesions, joint involvement and CNS manifestations were less frequent in the Iranian series. Erythema nodosum was less frequent in both Iranian and Israeli patients. Skin lesions and joint involvement were more frequent in the Italian patients, vascular involvement more frequent in Italian and Israeli patients and pathergy test was more often positive in Iranian patients.

Discussion

The present study presents the first thorough investigation of the clinical features of ABD in adult patients of Greek origin. The prevalence of ABD in Greece is not known since exact epidemiological studies have not been carried out. In a limited study from North Greece the incidence was approximately 4/100,000 (19). However, this study does not represent other areas of Greece since there is a mixed population (native Greeks and refugees of Greek origin) in this province. In the present study a male predominance was demonstrated which is a common finding in Arab populations only (6). In most countries an approximate 1:1 male-to-female ratio is currently recorded (6, 7). Familial occurrence of the disease was observed in two sisters, while various rates have been reported from other nations (7).

Since we applied the ISG criteria (12) to enroll the patients in the study, 100% of our patients presented with recurrent oral aphthous ulcers. The second most frequent manifestation in our patients was genital ulcerations followed by ocular involvement and skin lesions. Similar to other studies the most common onset sign was aphthous ulcers. The mean time of 5.6 years that elapsed between onset and the second sign in our patients seems to be rather long compared to other national group studies (6, 7). Interestingly, vascular manifestations and a high rate of ocular involvement as onset sign, already seen in Iranians (11), was detected in Greek patients, a finding indicating that many Greek patients are possibly prone to develop a severe course of ABD (20).

Despite the differences in the frequencies of certain clinical signs, there were many similarities in the data of the previously published national studies on ABD patients (11,14,18) and the present study. Erythema nodosum was observed at a higher frequency in our patients compared with other series. In the patients reported by Pivetti–Pezzi *et al.* (18) diffuse uveitis was found in a higher frequency (76%) than in our Greek patients, while hypopyon iritis was also seen in the Italian patients (18%) but in none of the Greeks. In the Iranian group studied by Shafaie *et al.* (11) anterior and posterior uveitis were found in a higher frequency (45% and 46%, respectively). These investigators also reported retinal vasculitis (31%). However, they do not separate panuveitis from involvement of other parts

of the eye. In the Israeli series of Krause *et al.* (14) the most frequent finding was anterior uveitis (47%) and the least frequent posterior uveitis (9%). These authors also report retinal vasculitis at a rate of 6%. Blindness was found in a small percentage of our patients compared to those of Pivetti–Pezzi *et al.* (18) who reported 29% of the patients with visual acuity lower than 0.1.

The most frequent joint manifestation in our patients was recurrent pauciarthritis (67%), a finding not mentioned by the other groups (11,14,18). Aseptic bone necrosis is also not reported in these three series, although this may be attributed to long-term corticosteroid administration and not to the disease itself (21). However, this complication has also been reported in patients with ABD not on corticosteroid treatment (22). Six of our patients presented with Achilles tendonitis, which was also described by other investigators (23).

Gastrointestinal involvement was found in a lower frequency in our patients compared with other series and there was a statistically significant difference between our results and those of Pivetti–Pezzi *et al.* (18). This difference may be due to the fact that in our study only patients with intestinal ulcers were included.

Budd–Chiari syndrome, arterial aneurysms and occlusion, and CNS involvement are well-known complications of ABD (2, 24-27). Other less frequent manifestations are heart, kidney and lung involvement. A positive pathergy test was less frequent in our group than those reported in other studies.

Positive pathergy test was seen less frequently in our patients compared to the Iranian series. The positivity of this test depends on the method used, the origin of the group studied, the activity of the disease, the treatment, and other factors.

The rates of HLA-B51 positive patients and controls are similar in Italian, Israeli, Iranian, and Greek patients, as previously described (7). Similarly, the odds ratios are equally high. Although the association of HLA-B51 with a more severe disease course in ABD has been controversially discussed (8, 28), current epidemiological studies detected HLA-B51 positivity to be the third major factor for a severe prognosis after male gender and a systemic manifestation as the onset sign (20). HLA-B27 was not increased in our patients.

The activity index and severity score were similar to those reported by Krause *et al.* (14), with the average severity score being slightly higher in the latter study. In our series and that of other investigators (5, 7) the activity of the disease tends to decline with time. The mean severity score was higher in men compared to women, with a statistically significant difference. Similar findings have currently been reported from Germany (20). However, gender had no effect on the clinical course according to other authors (29). In addition vital organ involvement (ocular, CNS, vascular involvement) was more frequent and more severe in men than in women. Generally, eye involvement was an early systemic manifestation when compared to CNS and vascular features. Increased mortality was reported in young male patients of Turkish origin (30), while the two deaths in our series were due to unrelated causes. Although ABD has rarely been reported in association with malignant diseases, the possibility of increased malignancies, most of them lymphoid and hematological but also solid tumors, during the course of ABD has recently been discussed (31).

Treatment included a variety of compounds applied as monotherapy or in combination. In resistant cases of ocular involvement anti–TNF-α was added to immunosuppressive drugs (32).

A open question is whether ABD belongs to the wide spectrum of the autoimmune diseases, or to the spondyloarthropathies or to the vasculitides. The present data exclude the thesis of this condition being a pure autoimmune disease (33) or spondyloarthropathy. Sacroiliitis was found in nearly the same frequency as in the general population and thus ABD does not belong to the spondyloarthropathy group (34). Clinical and histopathological findings support the view that ABD belongs to the vasculitides. However, further studies are needed in order to gain insight into the process of the pathogenetic mechanisms of the disease.

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