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☐ Original Article ☐

Epidemiological Features of Adamantiades-Behçet's Disease in Germany and in Europe

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The German Registry of Adamantiades-Behçet's disease was founded in 1990 in Berlin and it provides current data on the epidemiology, the clinical manifestations and the course of the disease in Germany on a continuous basis. A total of 218 patients, including 89 German and 100 Turkish patients, had been reported to the German Registry until October 1997. One hundred and ninety-six patients fulfilled the criteria of the Behçet's disease classification tree. The prevalence of the disease evaluated in Berlin-West was 1.68/100,000 in 1989 and had risen to 2.26/100,000 by 1994. The median age of onset was 25 years (range 5 to 66 years; German-Turks, ns). Juvenile disease was recorded in 6.9% of patients. The complete clinical picture according to the criteria of the International Study Group of Behçet's Disease developed in 15.5 months. The interval between onset of the disease and diagnosis was 35 months, which was significantly longer than the duration of the development of the complete clinical picture ($p<0.0001$). The disease was diagnosed later in German (48.5 months) than in Turkish patients (25.5 months, $p=0.003$). While German patients presented an equal male-to-female ratio, a male predominance was shown in Turkish patients (M:F 2.1:1, $p=0.022$). Familial occurrence was detected in 2.0% of German and 15.9% of Turkish patients ($p=0.013$). The frequencies of major clinical manifestations were: oral ulcers 99%, skin lesions 76%, genital ulcers 75%, ocular manifestations 59%, arthritis 59%, and positive pathergy test 52%. Clinical differences between German and Turkish patients were only found in the frequency of ocular lesions (48% vs. 66%, $p=0.025$). Oral ulcers were with 72% the most common onset symptom of the disease followed by erythema nodosum (9%), uveitis (7%), arthritis (7%), genital ulcers (3%), superficial thrombophlebitis (2%) and papules/sterile pustules (2%). Uveitis and erythema nodosum as onset

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symptoms shortened the median interval to diagnosis to 1.5 and 15 months, respectively, while arthritis delayed diagnosis (43.5 months; p=0.029). A severe course developed in 25% of the patients; irreversible retinal vasculitis to blindness in 15%, sterile meningoencephalitis in 8%, severe arthritis in 5%, hemoptysis in 2%, lethal outcome in 2% and bowel perforation in 1%. The relative risk of HLA-B5-positive German natives developing the disease was 6.25 for males (p<0.001), while females showed no association of HLA-B5 with the disease. HLA-B5 was confirmed as a marker of severe prognosis. Cardiolipin autoantibodies were associated with cutaneous vasculitis and superficial thrombophlebitis was correlated with systemic vessel involvement.

Key Words: Adamantiades-Behçet's disease, Behçet's disease, epidemiology, clinical picture, prognosis, Germany, Europe

Adamantiades-Behçet's disease is a systemic inflammatory disorder with a chronic progressive course characterized by a polysymptomatic recurrent vascular reaction or vasculitis and a potentially severe prognosis (Plotkin, 1988; Kienbaum *et al.* 1993; Jorizzo *et al.* 1995; Zouboulis, 1995). Although the disease had been described as early as in the 5th century B.C. by Hippocrates (Adams, 1849), its etiology remains unknown. Diagnosis is still based on the classical clinical trials: recurrent aphthous ulcers, genital ulcerations and iritis/uveitis. Efforts for performing accurate diagnosis have led to the proposal of several sets of diagnostic criteria (Zouboulis, 1995). The disease is distributed worldwide, however it occurs endemically in the eastern mediterranean area and in Central and East Asian countries, while it is rare in northern European countries. The spread of the endemic areas along the old silk route (Ohno *et al.* 1982) and associated immunogenetic data support the hypothesis that the disease was carried through the immigration of ancient nomadic tribes. Mixture of the genetic material or transfer of an exogenous agent may have been responsible for the expansion of the disease.

The German Registry of Adamantiades-Behçet's disease, founded in 1990 in Berlin, provides data on epidemiology, clinical manifestations and course of the disease in Germany on a continuous basis. We prefer to use the term *Adamantiades-Behçet's disease* instead of *Behçet's disease* to honour both authors who were the first to link the various symptoms into a diagnostic entity in modern times, namely Benedictos Adamantiades and Hulûsi Behçet (Adamantiades, 1931; Behçet, 1937). In this study, current epidemiological features of the disease in Germany are provided and compared with data from other European countries.

MATERIALS AND METHODS

Patients have to be permanent residents in Germany to be included in the German Registry. Until October 1997, 218 patients with Adamantiades-Behçet's disease (130 male, 88 female; 89 German, 100 Turkish and 29 of other nationalities) from Baden-Württemberg, Bayern, Berlin, Brandenburg, Hessen, Niedersachsen, Nordrhein-Westfalen, Sachsen-Anhalt, Schleswig-Holstein and Thüringen have been reported to the registry. One hundred and ninety-six patients (118 male, 60.2%; 78 female, 39.6%) were found to fulfil the criteria of the Behçet's disease classification tree (Davatchi *et al.* 1993) - which have been shown to be the most sensitive set of criteria for patients of German origin (Zouboulis, 1995) - and were further evaluated. Demographic data (prevalence of the disease, age of onset, duration of development of the complete clinical picture, interval from onset of disease to diagnosis, male-to-female ratio, familial occurrence), frequencies of clinical manifestations, onset symptoms (frequencies, association to the interval from onset to diagnosis) and prognosis of the disease and prognostic markers (HLA-B5, cardiolipin autoantibodies, clinical symptoms) were determined. In addition to the entire group, analysis was also performed for the larger ethnic groups represented, namely German (n=82, 41.8%) and Turkish (n=86, 43.9%) patients. The prevalence of the disease was

evaluated in the former West Berlin because of the previously - for epidemiological studies unique - isolated situation of the city. A retrospective evaluation was performed in the years 1984-1989, while from 1989 on the study was a prospective one. As a development of the complete clinical picture, the fulfilment of the criteria of the International Study Group for Behçet's disease (International Study Group for Behçet's disease, 1990) was determined.

Data are presented either as median values with minimum and maximum values shown in brackets or as mean values ± one standard deviation. Statistical comparisons were performed by Wilcoxon matched-pairs test, Mann-Whitney U test or Kruskal-Wallis test. Frequencies of clinical findings were compared by chi square test or 2-tailed Fisher exact test. Differences were defined as statistically significant at $p<0.05$.

RESULTS

Demographic data

The prevalence of the disease in Berlin-West was 0.65/100,000 in 1984 and had risen to 2.26/100,000 by 1994 (Table 1). The 3.5-fold increase was assessed in patients of both German and foreign origin. The prevalence in Berlin citizens of foreign origin (92% from Turkey) was 20-fold higher than that of German patients. On the other hand, the prevalence of the disease in Berlin citizens of German origin was similar to that reported from other northern European countries and from the U.S.A. (Table 2).

The median age of onset of the disease in Germany was 25 years (range 5 to 66 years; Fig. 1) being similar for patients of both German and Turkish origin (Table 3). The complete clinical picture developed by an average age of 30, also being similar for patients of German and Turkish origin (27 years, respectively). Juvenile Adamantiades-Behçet's disease (complete symptom complex developing at ≤ 16 years of age) was recorded in 6.9% of the patients. A median age of onset in the third decade of life as well as cases with early and late onset of the disease were also reported from other European countries (Table 4). The duration from onset of disease to diagnosis was 35 months (range 0-32 years) being significantly longer than the duration of development of the complete clinical picture (15.5 months; $p<0.0001$). The disease was diagnosed earlier in Turkish patients, an average 25.5 months after onset, than in German patients (48.5 months, $p=0.003$). While German patients presented an equal male-to-female ratio, a male predominance was shown in Turkish patients (M:F 2.1:1, $p=0.022$). Almost equal male-to-female ratios have also been reported in other European countries (Table 4). The familial occurrence of the disease was 15.9% in patients of Turkish origin, which was significantly higher than in German patients (2.0%; $p=0.013$).

Clinical manifestations

Oral aphthous ulcers, genital ulcerations, skin lesions, ocular lesions and arthropathy were the most

Table 1. Prevalence of Adamantiades-Behçet's disease in Berlin-West

	1984		1989		1994	
	P / I	PR	P / I	PR	P / I	PR
All patients	14/2,147,943	0.65	37/2,202,734	1.68	49/2,170,411	2.26
German	3/1,903,856	0.16	8/1,915,405	0.42	10/1,817,211	0.55
Foreign	11/ 244,117	4.51	29/ 287,329	10.09	39/ 353,200	11.04
Turkish			26/ 125,297	20.75		
Male	9/1,003,317	0.90	16/1,048,675	1.52	23/1,034,649	2.22
Female	5/1,144,656	0.44	21/1,154,059	1.82	26/1,135,762	2.29

P=patients, I=inhabitants, PR=patients per 100,000 inhabitants

Table 2. Distribution of Adamantiades-Behçet's disease in Europe

Land	Year	Prevalence per 100,000 inhabitants
Sweden (Ek and Hedfors, 1993)	1993	1.18
Great Britain (Dinning, 1987)	1987	0.50
Yorkshire (Chamberlain, 1977)	1977	0.64
Scotland (Jankowski *et al.* 1992)	1992	0.27
Germany - Berlin (Zouboulis *et al.* this work)	1994	2.26
Germans	1994	0.55
Turks	1989	20.75
Portugal (Crespo *et al.* 1993)	1993	1.53
Italy (Pivetti-Pezzi, 1988)	1988	2.50
For comparison		
Turkey		
Anatolia (Yurdakul *et al.* 1988)	1988	370
European part (Demirhindi *et al.* 1981)	1981	80
Iran (Gharibdoost *et al.* 1993)	1992	100
Japan (Nakae *et al.* 1993)	1991	13.50
USA (Chamberlain, 1979)	1979	0.12
Olmsted County, MN (O'Duffy, 1978)	1978	0.33

Table 3. Demographic data on Adamantiades-Behçet's disease in Germany

	All patients n=196	German n=82	Turkish n=86	Significance	German male n=41	German female n=41	Significance
Age of onset, y (range, y)	25 (5-66)	24.5 (5-66)	25 (7-58)	ns	22 (9-66)	30.5 (5-55)	ns (p=0.076)
Age of complete clinical picture, y (range, y)	30 (10-67)	27 (11-67)	27 (10-58)	ns	25 (11-67)	35.5 (13-55)	p=0.003
Onset with ≤ 16 years of age	17.6%	24.4%	14.6%	ns	23.1%	25.6%	ns
Juvenile disease	6.9%	8.9%	6.6%	ns	13.0%	4.5%	ns
Male-to-female ratio	1.51:1	1:1	2.07:1	p=0.022			
Familial occurrence	10.1%	2.0%	15.9%	p=0.013	0%	4.2%	ns

y=years

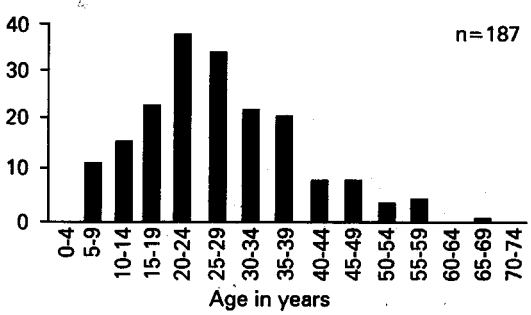

Fig. 1. Distribution of the age of onset of the disease in the German Registry.

common features of the disease in patients of the German Registry (Fig. 2, 3). Papules and sterile pustules as well as erythema nodosum were the most common skin lesions (Fig. 4). A positive pathergy test was detected in approximately one-half of the patients. A comparison of the frequencies of clinical features among patients of German origin and native patients from other European countries revealed higher rates of ocular lesions in south-eastern European patients (Italian and Greek) compared to south-western as well as northern European patients, while all further manifestations were overall similar(Table

Table 4. Demographic data on Adamantiades-Behçet's disease in Europe

Country	Number of patients	Age of onset, y median (range)/mean ± SD	Male:Female
Russia (Prokaeva *et al.* 1997)	25	24.7 ± 12.9	0.56 : 1
Sweden (Ek and Hedfors, 1993)	5	33.0 (19-48)	0.67 : 1
Scotland (Jankowski *et al.* 1992)	15		0.36 : 1
England (Chamberlain, 1977; Davies *et al.* 1984; Binder *et al.* 1987)	53	24.7 (10-61)	0.96 : 1
Ireland (Kilmartin *et al.* 1997)	24	20.8 ± 7.5	1.40 : 1
Germany (Zouboulis *et al.* this work)	82	24.5 (5-66)	1.00 : 1
Portugal (Crespo, 1996)	241	25.7 ± 11.1	1.01 : 1
Spain (Torras *et al.* 1982; Fernández Miranda *et al.* 1983)	31	26.0 (15-48)	1.38 : 1
France (Wechsler *et al.* 1988; Roux *et al.* 1989)	126	28.5 (2-64)	1.57 : 1
Italy (Valesini *et al.* 1991)	155	25.0 (5-53)	2.44 : 1
Greece (Vaiopoulos *et al.* 1997)	63	29.0 (5-67)	1.42 : 1

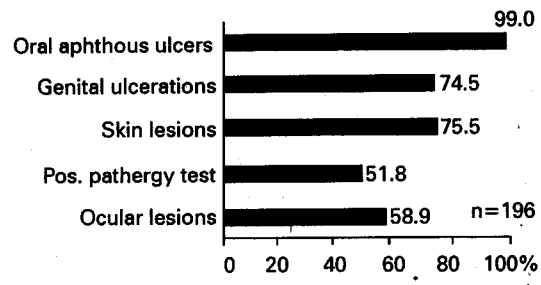

Fig. 2. Frequencies of the major clinical features of the disease in patients of the German Registry.

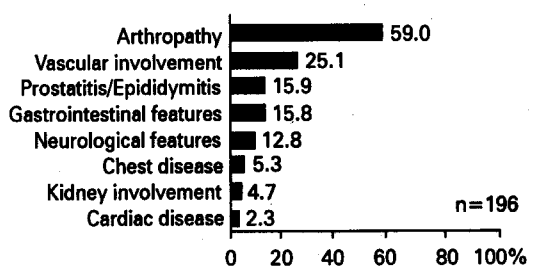

Fig. 3. Frequencies of the minor clinical features of the disease in patients of the German Registry.

5). The only significant difference between patients of German and Turkish origin in Germany was also found in the frequency of ocular lesions, where German patients (47.6%) presented a lower rate of involvement than Turkish patients (66.3%; p=0.025). Trends were also assessed in the frequencies of genital ulcers (81.7% vs. 68.6%; ns, p=0.050), superficial thrombophlebitis (7.6% vs. 17.6%; ns, p=0.054) and blindness (7.7% vs. 17.3%; ns, p=0.087).

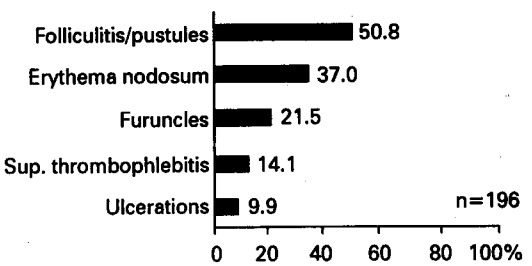

Fig. 4. Frequencies of the skin lesions in patients of the German Registry.

Onset symptoms of the disease

Skin and mucosal lesions represented 86% of the onset features of the disease (Fig. 5). Oral aphthous ulcers were found as onset symptoms in the majority of patients, followed by erythema nodosum, which was a more frequent onset symptom in male (11.9%) than in female patients (3.9%; p=0.023). The disease presented more often with ocular lesions in male (9.2%) than in female patients (2.6%). Females more often developed arthropathy as an onset symptom (11.8%) than males (2.8%). The high prevalence of

Table 5. Clinical findings of Adamantiades-Behçet's disease in European patients (%)

Nationality Number of patients	Russian[a] 25	English[b] 46	German[c] 82	Portuguese[d] 142	Spanish[e] 38	French[f] 133	Italian[g] 141	Greek[h] 63
Oral aphthous ulcers	100	100	99	100	100	98	100	98
Genital ulcerations	80	71	82	79	91	65	74	73
Skin lesions	84	81	75	69	73	71	78	66
Folliculitis/sterile pustules			45	49	41	48		
Erythema nodosum	78		39	42	29	39	25	
Ulcerations			11	3		4		
Superf. thrombophlebitis	8		8	29	10	4		
Positive pathergy test	52	32	49	47	12	44		28
Ocular lesions	44	52	48	47	35	58	92	69
Arthropathy	84	55	64	73	62	77	65	55
Neurological features	12	48	16	13	17	32	12	17
Vascular involvement	16	10	17	19	19	37	17	19
Gastrointestinal features	60	19	20	15	5	14	19	
Prostatitis-Epididymitis*	44	28	22			2	7	7
Chest disease	8		9		17	5	4	1.5
Kidney involvement	0	10	5			3	8	3
Cardiac disease	0	6	3	5		2		3

* Male

[a] Prokaeva *et al.* 1997; [b] Chamberlain, 1977; Davies *et al.* 1984; [c] Zouboulis *et al.* this work; [d] Pinto *et al.* 1991; de Jesus *et al.* 1997a; Vaz Patto *et al.* 1997b; [e] Torras *et al.* 1982; Fernández Miranda *et al.* 1983; Quecedo Estebanez *et al.* 1995; [f] Wechsler *et al.* 1988; Roux *et al.* 1989; [g] Pivetti-Pezzi, 1988; [h] Vaiopoulos *et al.* 1997

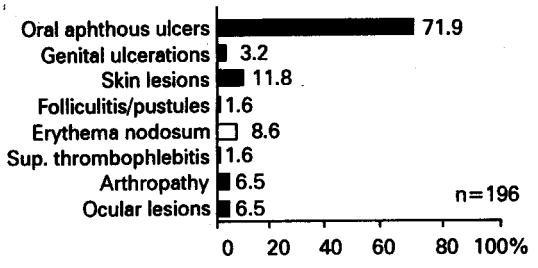

Fig. 5. Onset symptoms in patients of the German Registry.

oral aphthous ulcers as an onset symptom in German patients was compatible with reports on several groups of native patients (Table 6). Uveitis and erythema nodosum as onset symptoms shortened the median interval to diagnosis in contrast to arthritis, which delayed identification of the disease (p=0.029; Fig. 6).

Prognosis of the disease and prognostic markers

A severe course developed in 25% of patients, mainly manifested by decreased visual capacity to blindness and sterile meningoencephalitis (Fig. 7). All three patients of the German Registry who died from complications of their disease were of German origin.

Twenty-three of 64 German patients (35.9%) were HLA-B5-positive vs. 196 of 1415 controls (14%; p<0.001). HLA-B5-positive individuals of German origin as well as from other northern European countries, presented a lower relative risk to develop the disease compared to southern Europeans (Table 7), especially patients from south-eastern European countries (Fig. 8). HLA-B5-positivity was found to be associated with a poorer prognosis in patients of the German Registry: Ocular manifestations (85.8% vs. 46.3%, p=0.027), vascular involvement (31.3% vs. 13.0%, p=0.008), superficial thrombophlebitis (18.3% vs. 3.0%, p=0.003) and cutaneous lesions (87.8% vs. 64.2%, p<0.001) were more frequent in HLA-B5-positive patients than in HLA-B5-negative ones. In addition, HLA-B5-positive patients developed the complete clinical picture earlier (26 years of age) than HLA-B5-negative patients (33 years; p=0.017).

Table 6. Onset symptoms of Adamantiades-Behçet's disease in patient groups of European origin (%)

Nationality Number of patients	English[a] 39	German[b] 82	Portuguese[c] 241	Spanish[d] 22	French[e] 133	Italian[f] 51	Greek[g] 63
Oral aphthous ulcers	59	74	78	58	61	22	60
Genital ulcerations	5	2.7		3	2		7
Skin lesions	26	12.4		18	8	12	7
Folliculitis/sterile pustules		1.4					
Erythema nodosum		9.6		14			
Superf. thrombophlebitis		1.4		5	2		1.6
Ocular lesions	5	1.4		18	9	13	11
Arthropathy	8	9.6		5	24		10
Neurological features					9	1	
More than one symptom						49	

[a] Chamberlain, 1977; Davies *et al.* 1984; [b] Zouboulis *et al.* this work; [c] Crespo, 1996; [d] Fernández Miranda *et al.* 1983; [e] Wechsler *et al.* 1988; Roux *et al.* 1989; [f] Pivetti-Pezzi *et al.* 1985; [g] Vaiopoulos *et al.* 1997

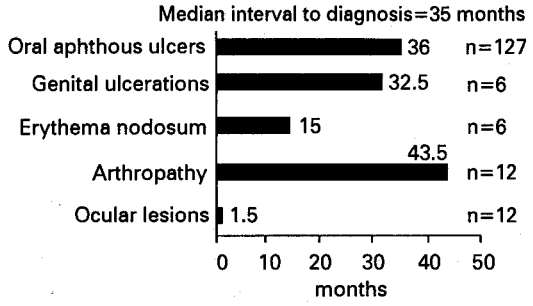

Fig. 6. Influence of the kind of onset symptom on the interval from onset symptom to diagnosis.

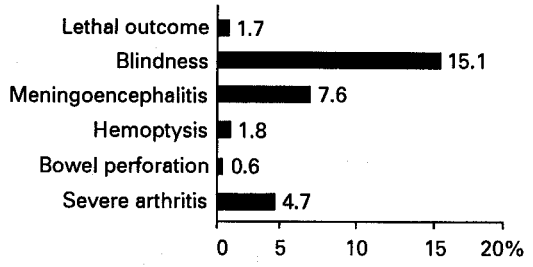

Fig. 7. Severe course of the disease in patients of the German Registry.

Interestingly, 47.1% (16/34) of the German male patients were HLA-B5-positive compared to 12.4% (86/691) of controls (Zouboulis *et al.* 1993a) ($p<0.001$, relative risk=6.25) but only 23.3% (7/30) of German female patients versus 15% (110/735) of controls (ns). German male patients showed a tendency toward on an earlier onset of the disease (average 22 years of age) compared to German female patients (30.5 years), developed the complete clinical picture significantly earlier (25 years of age compared to 35.5 years for German female patients, $p=0.003$; Table 3) and presented an overall more severe course with ocular lesions (61.3% vs. 34.4%, $p=0.032$), blindness (13.9% vs. 0%) and vascular involvement (32.5% vs. 2.4%, $p<0.001$). In comparison, Turkish patients, who were 74.6% (53/71) HLA-B5-positive versus 31% (83/268) of controls (Müftüoglu *et al.* 1981) ($p<0.001$, relative risk= 6.56) with similar occurrences between genders, did not present any gender-associated differences during the course of the disease.

Nineteen of 44 patients evaluated (43.2%) had elevated levels of circulating cardiolipin autoantibodies, 6 of the IgG isotype (13.6%), 11 of the IgM isotype (25%) and 2 had both isotypes (4.5%). In positive patients moderate increases were assessed; mean IgG levels were 14.46 ± 5.14 GLP/ml (normal values <10 GLP/ml) and mean IgM levels were 19.95 ± 9.34 MLP/ml (normal values <6 GLP/ml). Cardiolipin autoantibodies, especially of the IgM type, were associated with the presence of erythema nodosum (72.2% with positive levels vs. 28% with negative levels, $p=0.004$) and cutaneous vasculitis (88.2% with positive levels vs. 37.5% with negative levels, $p=0.001$).

Erythema nodosum was a prognostic factor for

Table 7. Frequency of HLA-B5 antigen in patient groups of European origin and relative risk (RR) for Adamantiades-Behçet's disease

Country	Patients		Controls		RR
	n	HLA-B5+ in %	n	HLA-B5+ in %	
Russia[a]	19	37	150	15	3.2
Great Britain[b]	107	25	2032	9	3.3
Ireland[c]	24	25	96	3	6.3
Germany[d]					
German	64	36	1415	14	3.5
Turks	71	75	268	31	6.6
Switzerland[e]	8	38		17	3.0
Portugal[f]	77	31	135	24	1.5
Spain[g]	43	49	452	21	3.6
France[h]	105	51	591	13	6.7
Italy[i]	57	75	304	22	10.9
Greece[j]	108	79	583	28	9.7

[a] Prokaeva *et al.* 1997; [b] Jung *et al.* 1976; Chamberlain, 1977; Crews *et al.* 1979; Lehner *et al.* 1982; [c] Kilmartin *et al.* 1997; [d] Zouboulis *et al.* this work; [e] Rosselet *et al.* 1976; [f] de Jesus *et al.* 1997a; Vaz Patto *et al.* 1997a; [g] Fernández Miranda *et al.* 1983; Sanchez Burson *et al.* 1992; [h] Godeau *et al.* 1976; Wechsler *et al.* 1988; Roux *et al.* 1989; [i] Okuyama *et al.* 1984; Balboni *et al.* 1992; [j] Psilas *et al.* 1979; Palimeris *et al.* 1980; Zervas *et al.* 1988; Messini *et al.* 1997

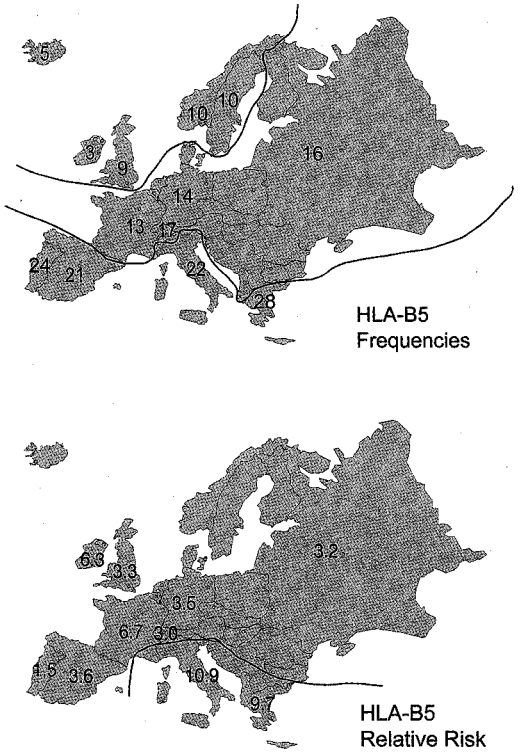

Fig. 8. (a) Distribution of the HLA-B5 antigen in natives of Europe (Ryder et al. 1978; Kilmartin et al. 1997; Zouboulis et al. 1997) and (b) relative risk for the development of the disease in several European countries.

the development of superficial thrombophlebitis (p=0.03). From patients with erythema nodosum (n=67), 22.4% developed superficial thrombophlebitis compared to 10.5% of patients without erythema nodosum (n=114). On the other hand, superficial thrombophlebitis, ocular lesions and gender were risk factors for the development of systemic vessel involvement (100% with thrombophlebitis vs. 11.5% without, p<0.0001; 32.3% with ocular lesions vs. 17.4% without, p=0.03; 34.2% of male vs. 11.5% of female patients, p=0.0004).

DISCUSSION

Adamantiades-Behçet's disease is a rather rare disorder in native citizens of Germany and of the other European countries, however, at least in Germany, there is a continuous increase in diagnosed cases. In contrast, the prevalence of the disease in German citizens of Turkish origin is high, although it is 5-fold lower than the prevalence determined in the European part of Turkey and 18-fold lower than in Anatolia (Demirhindi *et al.* 1981; Yurdakul *et al.* 1988). This markedly different prevalence of the disease in Turks dependent on the geographic area

of residence, in association with similar data reported from Japan and Hawaii for individuals of Japanese origin (Hirohata *et al.* 1975; Ohno *et al.* 1979), lead to the suggestion of an unknown environmental factor possibly influencing the development or onset of the disease.

The rate of German patients with the onset symptom occurring under the age of 16 reported in this study (24%) is markedly higher than the rates reported from Brazil (17%; Barra *et al.* 1991), Korea (8%; Kim *et al.* 1988), Morocco (7%; Benamour *et al.* 1997) and Tunisia (2%; Hamza, 1993). Juvenile disease was also more common in patients of German origin (9%) than in Turkish (6%; Gürler *et al.* 1997), Iranian (3%, Shafaie *et al.* 1997), Moroccan (3%; Benamour *et al.* 1997), Tunisian (2%; Hamza, 1993) and Japanese patients (2%; Maeda and Nakae, 1977). These observations are important in association with the better prognosis reported for German patients than for patients from endemic areas (Zouboulis, 1996) and also the better prognosis detected in juvenile than in adult patients (Treudler *et al.* 1997).

The delay of diagnosis in German patients compared to those of Turkish origin may be due to the still common medical opinion in western Europe that Adamantiades-Behçet's disease is an eastern mediterranean disorder.

In contrast to the classical Japanese and Turkish reports of an androtropism, more recent epidemiological studies registered an approximately 1:1 male-to-female ratio in Japan, Korea, China, Iran, Turkey, Brazil and Europe (Zouboulis *et al.* 1997). An androtropism is still observed in some countries around the eastern mediterranean area (Saudi Arabia, Israel, Egypt, Morocco, Greece and Italy). In contrast, gynaecotropism was evident in most northern European countries.

The familial occurrence in patients of German origin was as low as in other European countries, namely Greece (0%; Constantinidou, 1991), Italy (0.7-2.7%; Sensi and Baricordi, 1986; Pivetti-Pezzi, 1988), Great Britain (3.6%; Mason and Barnes, 1969), Spain (4.5%; Fernández Miranda *et al.* 1983) and Portugal (2.6%; de Souza-Ramalho *et al.* 1991). In contrast, familial occurrence was high in patients of Turkish origin in Germany, as in patients from endemic geographic areas (11.9-13.4% in Israel, Korea and Tunisia; Kim *et al.* 1988; Arber *et al.* 1991; Makni *et al.* 1997).

The high frequencies of oral aphthous ulcers, genital ulcerations, skin and ocular lesions in European patients and their almost exclusive occurrence as onset symptoms confirmed the importance of these clinical features for diagnosis. Highly recurrent oral aphthosis, the most frequent onset symptom, is a warning signal for Adamantiades Behçet's disease. Fifty-two per cent of 67 prospectively evaluated patients with recurrent oral aphthosis in Korea (an average 10 recurrences per year) developed Adamantiades Behçet's disease within 8 years after development of oral aphthous ulcers (Bang *et al.* 1995). Arthropathy, although it is also a frequent feature, is not specific and, therefore, delays diagnosis if it occurs as an onset symptom of the disease. In contrast, heart and kidneys are rarely involved in Adamantiades-Behçet's disease. Interestingly, ocular lesions, a feature which significantly influences prognosis, represented the only clinical feature whose frequency was associated with both the genetic origin of the patient and gender, confirming previous reports (Arber *et al.* 1991; de Jesus *et al.* 1997b).

The potentially severe prognosis of the disease (5% 10-year mortality; Yazici *et al.* 1996) was confirmed in our study. Retinal vasculitis leading to blindness, central nervous system and vascular involvement are the most disabling and life-threatening features. The disease led to a fatal outcome in German patients probably due to delayed diagnosis and treatment (Zouboulis *et al.* 1991).

The close association of HLA-B5, especially of the HLA-B51 split antigen, with the disease is well established. The confirmation of this association in several ethnic groups (Zouboulis *et al.* 1993a) initially led to the assumption that HLA-B51 may be directly involved in the development of Adamantiades Behçet's disease. However, current data indicate that the pathogenic gene(s) responsible for the disease is not HLA-B51 itself but other gene(s) around the HLA-B locus (Goto *et al.* 1997). Our data support the alternative suggestion that HLA-B5 (B51) is a marker of severe prognosis, being especially associated with an earlier development of the complete clinical picture, ocular lesions and vessel involvement (Takano *et al.* 1976; Lee *et al.*

1988; Oguz *et al.* 1989; de Jesus *et al.* 1997b; Makni *et al.* 1997; Messini *et al.* 1997). In addition, the poorer prognosis in male European patients compared to females is correlated with the HLA-B5 (B51) antigen (Chamberlain, 1977; Zouboulis *et al.* 1993a; de Jesus *et al.* 1997b; Messini *et al.* 1997). On the other hand, this study confirms our previous data concerning the association of moderately increased cardiolipin autoantibodies with cutaneous vasculitis (Zouboulis *et al.* 1993b) and the prognostic value of superficial thrombophlebitis for severe vascular involvement (Zouboulis, 1995).

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