Behçet's Disease in Patients of German and Turkish Origin Living in Germany: A Comparative Analysis

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ABSTRACT. ***Objective.*** To evaluate the relationship between ethnic origin and manifestations of Behçet's disease (BD) in patients of German and Turkish origin living in Germany.

Methods. Between 1995 and 2000, 32 patients of German and 33 patients of Turkish origin living in Germany were evaluated for the entire spectrum of disease manifestations, disease severity, HLA associations, sex, age at disease manifestation, and time to diagnosis.

Results. There were no statistically significant differences between German and Turkish patients. There was no association of sex or HLA-B51 with any manifestation of BD. The only significant difference between the 2 groups was the median time from the first manifestation of the disease to diagnosis, which was 0 years for the Turkish, but 3.5 years for the German patients ($p = 0.0005$). Additionally, 4 patients of German origin had been misdiagnosed as having spondyloarthropathy (SpA) before the final diagnosis of BD was made (12%). In comparison to Turkish patients living in Turkey (data from the literature), only 2 differences were found: one concerned the frequency of ocular involvement (lower in the patients in Turkey), and the other the male to female ratio, which was reported as 1.03:1 in Turkey, but 3.7:1 in Germany.

Conclusion. Our results do not favor an ethnic influence on the expression of BD. Environmental influences may be responsible for the higher frequency of ocular manifestations and the higher male to female ratio in patients living in Germany compared to those living in Turkey. (J Rheumatol 2004;31:133–9)

Key Indexing Terms:
BEHÇET'S DISEASE
HLA-B51 ASSOCIATION
DISEASE SPECTRUM
GERMAN AND TURKISH ORIGIN

Behçet's Disease (BD) is a multisystem vasculitis of unknown origin. It is characterized by recurrent aphthous stomatitis, genital ulcerations, cutaneous symptoms such as papulopustules or erythema nodosum, a positive pathergy phenomenon, and ocular inflammation with retinal vasculitis. It is classified according to the International Study Group Criteria[1-3]. Oligoarthritis, meningoencephalitis or central nervous system (CNS) vasculitis, deep vein thrombosis, and arterial aneurysms are less common. The disease is most frequent in countries along the ancient Silk Route from Japan to the Middle East and the Mediterranean Basin, but is rarely encountered in Northern Europe and North America[4]. Ethnic origin and environmental factors are believed to modulate the prevalence and expression of BD, because they have been reported to differ between various geographical areas. Thus, the pathergy reaction is considered highly sensitive and specific for BD in patients originating from Turkey, the Middle East, Japan, and Korea[5-8], but is often negative in patients from Western European countries or the USA[9-11]. Gastrointestinal (GI) involvement occurs in one-third of Japanese patients, but is rare in patients from Mediterranean countries[12]. Regional differences also have been described for disease severity. For example, patients from the UK and the USA are reported to have more widespread disease with arthritis, CNS vasculitis, and other vascular problems than patients from Middle Eastern or Mediterranean countries[13]. In Israeli Jewish patients, BD was reported to be most severe for those originating from North African countries compared to those originating from Iran/Iraq or Turkey, with a higher rate of ocular disease[14]. Eye disease was more severe in Japanese patients compared to patients from the UK[15].

We evaluated whether the ethnic origin of German or Turkish patients with BD living in Germany influenced the expression of the disease.

MATERIALS AND METHODS

The divisions of Rheumatology/Clinical Immunology and the Ophthalmology/Uveitis Outpatient Clinic at Tübingen University Hospital function as a tertiary interdisciplinary care center. Consequently, most patients had had symptoms of BD such as uveitis or mucocutaneous mani-

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festations and arthritis for longer periods of time before they finally came to our hospital. In all of the Turkish and 35% of the German patients, BD had already been either suspected or correctly diagnosed by the colleagues who had referred the patients to us. We studied 32 patients of German and 33 patients of Turkish origin all living in Germany (24 of the Turkish patients were born in Germany, the others lived in Germany for at least 10 years; the first manifestations of BD in the latter occurred while they were already living in Germany), who had visited our outpatient clinic between the years 1995 and 2000. All patients except 3 (2 in the German and one in the Turkish group) fulfilled the International Study Group Criteria[1] (Table 1). The 3 patients not fulfilling the criteria had typical ocular manifestations with panuveitis and retinal vasculitis and a positive pathergy phenomenon, and consequently were diagnosed as having BD, despite absence of typical cutaneous manifestations and oral ulcerations. The latter symptoms also did not occur during the observation period. Only 2 of the patients were related to one another (mother and son in the Turkish group). Seventy percent of the Turkish and 72% of the German patients had primarily been referred to the Department of Ophthalmology, whereas the remaining patients were first seen in the Department of Rheumatology. The following variables were studied: oral aphthous ulcers, skin lesions (pseudofolliculitis, papulopustules, erythema nodosum, vasculitis), pathergy reaction, ocular disease (anterior uveitis, posterior uveitis, retinal vasculitis), arthritis, vascular, CNS or GI manifestations, epididymitis. Patients were interviewed about the occurrence of any of the symptoms and the time at which the respective manifestations had occurred by 2 rheumatologists (IK, IG), one of them also speaking Turkish (IG). Both rheumatologists interviewed and examined each patient in order to exclude any interobserver variation. Data relating to the entire spectrum of disease manifestations were also collected from the medical files. Additionally, a complete physical (IK, IG) and ophthalmological examination (NS) was performed at least at 2 different times to reveal symptoms possibly not recognized by the patients. The pathergy test was performed in each untreated patient according to the standard procedure, i.e., an intracutaneous needle prick on the forearm, considered positive if a sterile papulopustule occurs after 24 to 48 h. Pathergy testing was not performed on patients under immunosuppressive therapy, as this would have influenced the result. HLA typing was performed by oligonucleotide sequencing. With the exception of the symptoms at onset of BD, manifestations were only considered for further analysis when seen and documented by a physician. Such symptoms and manifestations had to have been documented by any physician who had seen the patient in the past, for example the patient's primary care physician, but not necessarily by one of the rheumatologists who performed this study. In cases of neurological or GI involvement, this was required to have been proven by nuclear magnetic resonance scan, analysis of cerebrospinal fluid, electrophysiological methods, or endoscopy, again also by any physician who had cared for the patient in the past. For evaluation of overall disease severity, the scoring system described by Krause, *et al* was applied[14,16]. Severity score was calculated as the sum of 1 point for each mild symptom, 2 for each moderate symptom, and 3 for each severe manifestation. In addition to the original scoring system we also regarded cutaneous leukocytoclastic vasculitis as a typical skin lesion and scored it as mild (1 point), and deep vein thrombosis in extremities other than the legs (for example in the arms) as moderate (2 points) (Table 2).

Statistical analysis. For differences between manifestations of the disease and ethnic origin, sex, and association with HLA-B51, the odds of developing a symptom (and other binary traits) were compared between groups by odds ratio (OR), for which approximate 95% confidence intervals (CI) were computed along with p values for the hypothesis that the OR is 1. For associations between HLA-B51 or sex with any of the symptoms, both patient groups (German and Turkish) had to be taken together, because otherwise the number would have been too low to be analyzed. Considering a dozen symptoms, adjustment for multiple testing was performed by the Bonferroni-Holm procedure for any significant association. Age at first manifestation, diagnosis, and time to diagnosis were compared by Wilcoxon rank test, while van der Waerden's test was applied to severity scores.

RESULTS

The median duration of BD was 6.5 years (range 2 to 23) in the German and 8.8 years (range 3 to 30) in the Turkish patient group (p = 0.0035). The median observation period in our hospital was 5 (range 2 to 12) and 5 (range 2 to 13) years (p = 0.66), the median number of visits during the observation period 8.5 (range 5 to 12, SD 4.9) and 11 (range 2 to 53, SD 11.6), respectively (p = 0.54). In the German patient group there were 20 men and 12 women, in the

Table 2. Severity of Behçet's disease[14, 16].

Mild	Oral aphthosis
	Genital ulcers
	Typical skin lesions (erythema nodosum, papulopustular lesions, folliculitis, *leukocytoclastic vasculitis*)
	Arthralgia
	Recurrent headaches
	Epididymitis
	Mild GI symptoms (chronic diarrhea, abdominal pain)
	Pleuritic pains
	Superficial vein thrombosis
Moderate	Arthritis
	Deep vein thrombosis (legs, *other extremities*)
	Anterior uveitis
	GI bleeding
Severe	Posterior uveitis, panuveitis, retinal vasculitis
	Arterial thrombosis or aneurysms
	Major vein thrombosis (vena cava, heptic)
	Neuro-Behçet
	Bowel perforation

Italics: added to the original scoring system.

Table 1. International Study Group criteria for the classification of Behçet's disease[1].

Recurrent oral ulceration	Minor aphthous, or herpetiform ulceration, observed by physician or patient, which recurred at least 3 times in one 12-mo period
Plus 2 of	
Recurrent genital ulceration	Aphthous ulceration or scarring, observed by physician or patient
Eye lesions	Anterior uveitis, posterior uveitis, or cells in vitreous on slit lamp examination, or retinal vasculitis observed by an ophthalmologist
Skin lesions	Erythema nodosum observed by physician or patient, pseudofolliculitis, or papulopustular lesion or acneiform nodules in postadolescent patients not on corticosteroid treatment
Positive pathergy test	Read by a physician at 24 to 48 h

Turkish group 26 men and 7 women (male to female ratio 1.7:1 and 3.7:1, respectively; 63% male in the German vs 79% male in the Turkish patient group, not significant). In both groups, the most common primary manifestation of the disease was oral aphthous ulcers (90%), mostly in association with cutaneous symptoms (60%). Table 3 depicts the disease manifestations in both groups. There was no statistically significant difference with respect to the rate of oral aphthous ulcers, genital ulcers, skin lesions, ocular disease, positive pathergy reaction, arthritis, vascular lesions, GI manifestations, or epididymitis. The frequency of CNS manifestations was too low to be statistically analyzed. The severity scores were not statistically different (p = 0.43) between the patients of German (5.5, SD 1.9) or Turkish (5.9, SD 1.8) origin (Table 3). Subdividing the cutaneous, vascular, and ocular manifestations further into folliculitis, erythema nodosum, papulopustules, cutaneous vasculitis, superficial thrombophlebitis, deep vein thrombosis, arterial vasculitis with emboli, occlusion or aneurysms, anterior, intermediate or posterior uveitis or retinal vasculitis and panuveitis, no significant differences were found between the 2 patient groups (Table 4).

There was also no difference in frequency of HLA-B51, which was positive in 75% of the Turkish and 72% of the German patients. Further, considering both ethnic groups together for statistical reasons, there was no significant association between any manifestation of BD, sex, or the presence of HLA-B51 (Tables 5 and 6).

At the time of first manifestation of the disease, the median age of the German patients was 26 years (range 14 to 48) and of the Turkish patients 25 years (range 4 to 43); at diagnosis, the Germans were aged 31.5 years (range 20 to 52), the Turkish 26 years (range 4 to 49) (difference not significant). The median time from the first manifestation to final diagnosis of BD was 0 years (range 0 to 17) in the Turkish and 3.5 years (range 0 to 21) in the German patients (p = 0.0005) (Figures 1 and 2).

In the German group, 4 patients had been diagnosed by others with seronegative spondyloarthropathy (SpA) before the diagnosis of BD was made (12%), whereas BD was correctly diagnosed in all Turkish patients.

DISCUSSION

Regional variability in disease expression is a well known phenomenon in BD. To date, it is unclear whether this is caused by ethnic differences or mainly due to environmental influences. In the 1960s, many Turkish citizens came to Germany as foreign workers. At present more than 4 million people of Turkish origin are living in Germany. As BD is very rare in people of German origin (estimated prevalence 0.6/100,000)[12,17], but is endemic in Turkey (prevalence 80 to 370/100,000)[18,19], the Turkish patients with BD living in Germany represent a unique population for comparative studies. The non-ethnic differences are minimized in this comparison, as both patient groups share the same environment, although there may still be some differences in diet and lifestyle. Of note, the disease duration at referral was significantly longer in the Turkish than in the German patient group (Table 3), which might have caused a bias in the interpretation of disease expression between the 2 groups. Nonetheless, it is well known that most manifestations of BD in an individual patient occur within the first 2 to 5 years after the first symptoms and that all manifestations except the ocular ones tend to get better with time[20-22]. As the median disease duration in both patient groups was longer than 5 years (6.5 yrs in the German, 8.8 yrs in the Turkish group), its influence on the interpretation of disease expression probably was negligible.

Table 3. Disease expression of BD in German and Turkish patients.

Expression	German, % (n)	Turkish, % (n)	OR (95% CI)	p
Male:female, n	12:20	7:26	0.45 (0.14–1.3)	0.15
Ratio	1.7	3.7		
Age at onset, (median yrs)	26	25		0.71
Age at diagnosis, (median yrs)	31.5	26		0.06
Time to diagnosis, (median yrs)	3.5	0		0.0005*
Disease duration at referral (range)	6.5 (2 to 23) (SD 4.5)	8.8 (3 to 30) (SD 6.4)		0.0035*
HLA-B51+	75 (24)	76 (25)	1.0 (0.33–3.3)	0.94
Oral aphthae	90 (29)	93 (31)	1.6 (0.25–13)	0.62
Ocular	75 (24)	78 (26)	1.2 (0.39–4.0)	0.72
Cutaneous	66 (21)	81 (27)	2.4 (0.77–7.8)	0.14
Genital aphthae	43 (14)	63 (21)	2.2 (0.84–6.2)	0.11
Arthritis	40 (13)	42 (14)	1.1 (0.34–2.9)	0.88
Pathergy+ Absolute number	39 7 (of 18)	55 11 (of 20)	1.9 (0.53–7.3)	0.32
Vascular	15 (5)	18 (6)	1.2 (0.32–4.6)	0.78
GI	6 (2)	3 (1)	0.47 (0.02–5.1)	0.54
Epididymitis	3 (1)	9 (3)	3.1 (0.32–4.6)	0.34
CNS	6 (2)	0	NA	NA
Severity scores (range)	5.5 (2 to 10) (SD 1.9)	5.9 (3 to 10) (SD 1.8)		0.43

NA: not applicable. * Significant.

Table 4. Fine detail of disease expression in German and Turkish patients.

Manifestation	German, % (n)	Turkish, % (n)	OR (95% CI)	p
Eye	n = 24	n = 26		
Anterior uveitis	12.5 (3)	8 (2)	1.7 (0.18–22)	0.66
Intermediate uveitis	12.5 (3)	4 (1)	3.6 (0.26–190)	0.34
Posterior uveitis, retinal vasculitis	33 (8)	19 (5)	2.1 (0.49–9.7)	0.34
Panuveitis	42 (10)	69 (18)	0.32 (0.084–1.2)	0.086
Skin	n = 21	n = 27		
Folliculitis	24 (5)	32 (9)	0.36 (0.14–2.6)	0.54
Papulopustules	52 (11)	55 (15)	0.88 (0.24–3.2)	1.00
Erythema nodosum	52 (11)	48 (13)	1.2 (0.33–4.3)	1.00
Cutaneous vasculitis	5 (1)	3.7 (1)	1.3 (0.016–110)	1.00
Vascular	n = 5	n = 6		
Superficial thrombophlebitis	60 (3)	17 (1)	7.5 (0.29–470)	0.24
Deep vein thrombosis	40 (2)	50 (3)	0.67 (0.032–12)	1.00
Arterial vasculitis	0 (0)	33 (2)	0.0 (0.0–6.3)	0.45

Number in parentheses reflects the absolute number of patients with this manifestation or the exact conditional confidence interval (CI). P values are Fisher's exact test.

Table 5. Association of HLA-B51 with disease manifestations (both patient groups taken together).

Manifestation	OR (95% CI)	p
Oral aphthae	0.75 (0.037–5.57)	0.8
Ocular	2.66 (0.75–9.31)	0.12
Cutaneous	0.92 (0.23–3.21)	0.9
Genital aphthae	1.23 (0.39–3.86)	0.72
Arthritis	0.45 (0.14–1.41)	0.17
Pathergy phenomenon	1.11 (0.27–4.73)	0.88
Vascular	0.50 (0.13–2.17)	0.33
GI	0.15 (0.006–1.63)	0.13
Epididymitis	NA	NA
CNS	NA	NA

NA: not applicable.

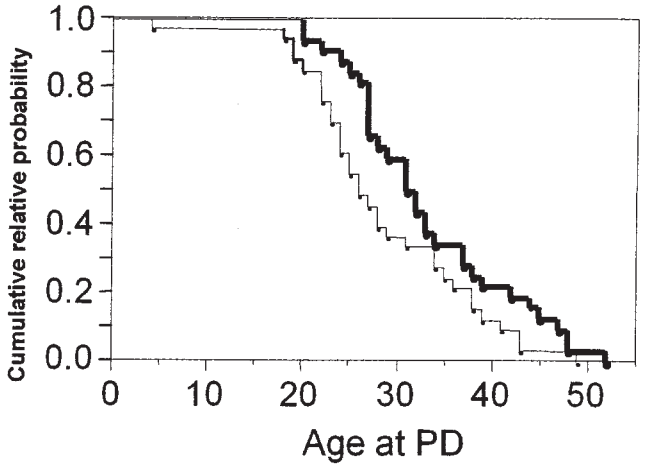

Figure 1. Age at diagnosis of BD (Kaplan-Meier plot). Bold line: German patients, fine line: Turkish. PD: primary diagnosis.

Table 6. Association of sex with disease manifestations (both patient groups taken together).

Manifestation	OR (95% CI)	p
HLA-B51	1.32 (0.39–5.34)	0.67
Oral aphthae	0.59 (0.09–4.799)	0.58
Ocular	1.18 (0.34–4.79)	0.80
Cutaneous	0.99 (0.30–3.57)	0.98
Genital aphthae	2.36 (0.79–7.74)	0.13
Arthritis	2.58 (0.87–7.95)	0.09
Pathergy phenomenon	0.47 (0.09–2.13)	0.34
Vascular	0.48 (0.07–2.14)	0.38
GI	NA	NA
Epididymitis	NA	NA
CNS	2.49 (0.095–65.5)	0.53

NA: not applicable.

Our study revealed no difference in the male to female ratio in the 2 patient groups or in other variables such as age at first manifestation, age at final diagnosis, association with HLA-B51, positivity of the pathergy phenomenon, or frequency of the various disease manifestations (mucocutaneous, articular, ocular). The disease severity was also similar in both ethnic groups.

The male to female ratio in Turkish patients living in Turkey has been reported to be 1.03:1[23], but in Turkish patients living in Germany and entered in the Berlin registry for BD, it was reported to be 2.1:1[12,17]. In the Berlin registry, the male to female ratio for the German patients was 1:1. Thus, there are more males among the Turkish patients living in Germany than among those living in Turkey. The difference in the male to female ratio of the Turks living in Germany between the data in the Berlin registry and our

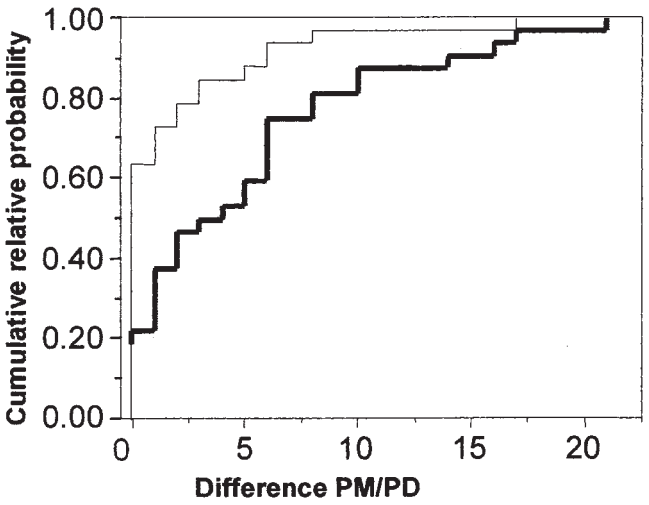

Figure 2. Time from onset to diagnosis in German patients (bold line) and Turkish patients (fine line) (Kaplan-Meier plot). PM: primary manifestation, PD: primary diagnosis.

study (3.7:1) might originate from our relatively small patient number or regionally different environmental influences. At present, we cannot explain the obvious difference in the male to female ratio between Turks living in Germany and Turks living in Turkey. We cannot exclude that there is a bias in the evaluation in so far as the Turks living in Germany often are very conservative and the women might well hesitate to report symptoms of BD such as oral or genital ulcerations or skin disease for religious reasons and thus are not diagnosed correctly.

The expression of the various manifestations of BD for Turks living in Turkey was reported as follows (Table 7): oral aphthae 100%, genital ulcers 73 to 88%, papulopustules 54 to 94%, erythema nodosum 42 to 54%, ocular involvement 28.9%, arthritis 16 to 47.4%, neurological 2 to 8%, phlebitis 10 to 38%, pulmonary 1 to 18%, and GI 3 to 5%[24]. The distribution of symptoms is the same as in the Turkish patients living in Germany analyzed in this study, except for the frequency of ocular involvement, which was considerably higher in the Turks living in Germany (our study 75%) than that reported for Turks living in Turkey (28 to 47%) (Table 7).

In contrast to our results, in the Berlin registry ocular manifestations were significantly more frequent in Turks than in Germans (66.3 vs 47.6%). This difference may be due to the lower number of patients in our study, or to the fact that we performed ophthalmological examinations in all patients, irrespective of whether they reported ocular symptoms, which might have revealed cases of hitherto undetected ocular involvement. Although the majority of the patients in both ethnic groups were primarily referred to the Department of Ophthalmology, we do not believe this influenced the overall estimate of frequency of ocular symptoms as calculated here. Because Tübingen University Hospital is a tertiary referral center, this implies that in the majority of the patients an autoimmune disease or even BD had already been suspected by the referring physicians. The patients thus had a longer disease duration or more than one manifestation of the disease at the time of referral, and the referral pattern directly reflects the prevalence and severity of the ocular manifestations in each patient population. Further, the analysis was in part retrospective, which means that we also considered symptoms (when documented by any physician in the past) that had occurred before the referral of the patients. The higher frequency of epididymitis and neuro-

Table 7. Comparison with demographic features of Turkish patients living in Turkey. The manifestations of disease, pathergy, and HLA-B51 are given in percentages.

Feature	Turkey[23]	Turkey[19]	Turkey[25]	Turkish Patients in Germany (TÜ)	Turkish Patients in Germany[12, 17] (B)
No. of patients	2147	496	92	33	86
M/F	1.03:1	6:13		3.7:1	2.07:1
Mean age at onset, median yrs	38.5	NR		26	25
Diagnostic criteria	ISG	O'Duffy		ISG	Classification Tree
HLA B51+	62.8–77[45, 48]	26.3		76	75
Pathergy+	56.8	33.3	65	55	51.8**
Oral aphthous ulcers	100	100		93	99**
Ocular	28.9	0		78	66.3
Cutaneous	47.6/54.2*	94.7/42.1*		81	75.5**
Genital ulcers	88.2	73.7		63	68.6
Arthritis	15.9	47.4		42	59**
Vascular	10.6†	NR		18	25.1**
GI	2.8	4.9		3	15.8**
Epididymitis	—	—		9	15.9**
CNS	2.2	NR		0	12.8**

* Papulopustular/erythema nodosum; † Only phlebitis reported. ** Only reported together with all the patients registered in Germany, stated that there was no significant difference between the ethnic groups. ISG: International Study Group. NR: not reported.

logical and GI involvement in the Berlin registry compared to our evaluation can only be explained by a low specificity of the questionnaire, which is used for registration of patients and does not require objective signs and examinations.

Although the rate of occurrence of a positive pathergy reaction was reported to be significantly higher in Turkish patients compared to patients from the UK or the USA[9,10], this is not the case in comparison to German patients (Berlin registry: Turks and Germans 51.8%; our findings Turks 55%, Germans 39%). The pathergy reaction is reported to be positive in 57 to 65% of the Turkish patients living in Turkey[5,23,25], which is similar to the rate for Turkish patients living in Germany.

The association of BD with HLA-B5 or its split antigen HLA-B51 is well known, and has been described for most of the populations where it was examined[26-43], varying from 54% in Lebanon[44] to 77% in Turkey[45], with the possible exception of Great Britain, where it is reported to be only 15%[46]. For German patients it is 75–76% (Table 4), with the suballeles HLA-B*5101 and B*5108 being most common[37]. We could not find significant differences in the association of BD with HLA-B51 between Turkish and German patients. As well, our study did not reveal an association of HLA-B51 with any of the manifestations of BD or sex, which supports the data of Müftüoglu, *et al*[45] and Gül, *et al*[47], but contrasts with those of the Berlin registry, where ocular manifestations, vascular involvement, and skin lesions appeared to be associated with HLA-B5, as well as with findings from Azizleri, *et al*, who reported that HLA-B5 was associated with a higher frequency of genital ulcerations[17,48]. It is possible that we would have found differences in the association of individual disease manifestations with HLA-B51 if we had analyzed both patient groups separately, which for statistical reasons would require a much larger number of patients. On the other hand data from the Berlin registry may be difficult to interpret, because the HLA typing data reported to the registry were obtained by different methods performed by many different laboratories, and a distinction of the split antigens HLA-B51 and HLA-B52 was not made.

The main difference between the 2 patient groups was found when the time from the first manifestation of BD to final diagnosis was analyzed, resulting in a median of 0 years for the Turks and 3.5 years for the Germans ($p = 0.0005$). The reason for this in our opinion is that for all Turkish patients, irrespective of whether they had already presented with several manifestations of BD or not, the referring physicians had already suspected this diagnosis simply on the basis of the patients' ethnic origin. In contrast, in the German patients, this clearly was not the case, although they presented with similar disease durations and manifestations (Table 3), as had been retrospectively evaluated from the medical history. Further, in 4 German patients (12%) the symptoms of BD were misdiagnosed as SpA, whereas no misdiagnoses occurred in the Turkish patients. We propose that this is due to the rarity of BD in Germans, such that physicians in Germany are not familiar with its features. As well, even if they do consider BD in the differential diagnosis, they believe that it is less probable in people of German origin than other diseases, such as SpA, thus notably misdiagnosing it in German patients.

In summary, ethnic differences seem to play a minor role in the expression of BD, as the frequency of the various manifestations of the disease, HLA-B51 association, and age of onset were the same in Turks living in Germany, Turks living in Turkey reported in the literature, and Germans. There may be environmental influences affecting the frequency of ocular manifestations, which were more common in the Turkish patients in Germany, and the male to female ratio, which was considerably higher in the Turkish patients in Germany compared to those in Turkey. The striking difference in the time from the first manifestation to final diagnosis of BD in the German patients compared to Turkish patients also living in Germany and the considerable rate of misdiagnoses (exclusively SpA) in the German patients suggest that BD may be underestimated in patients of German origin. Further studies are required to evaluate the true frequency of BD in the German population, for example by performing field studies with experts on BD, following an example from Turkey[18] or "zero-patient-design" studies, as proposed by Yazici, *et al*[49], taking advantage of the structures of the Cooperative Regional Rheumatology Centres in Germany.

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