

Behçet's Disease: A Review and a Report of 12 Cases from Sweden

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In a retrospective study of 12 patients with Behçet's disease, more than half were found to originate from the Near East, where the prevalence of the disease is known to be high. The immigrant patients were all males, whereas 3 of the 5 patients with Swedish ancestry were females. Certain differences emerged between the two groups, including different sex ratio and absence of HLA B5 association and pathergy skin reaction among the Swedish patients. Moreover, serious neurological and ocular symptoms showing no tendency to recede with age afflicted all the Swedish female patients. Urogenital symptoms were, besides ulcers, common in both groups, including prostatitis, urethritis, orchitis, chronic sterile cystitis and relapsing salpingitis. Although the material does not allow statistical inferences, the estimated prevalence was higher than expected among both Swedish and immigrant patients. Recent studies, including the diagnostic criteria proposed by the "International Study Group for Behçet's disease", are discussed in relation to previously used criteria as well as present findings. The sensitivity and specificity of the first mentioned criteria and the ones proposed by Mason & Barnes seemed equal. **Key words:** *Aphthae; Ethnic groups; Genital ulceration; Neurologic manifestations; Urogenital symptoms; Uveitis.*

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REVIEW OF RECENT STUDIES

A syndrome consisting of relapsing oral and genital ulcerations and uveitis was described in 1937 by Behçet (1). Later, characteristic skin manifestations, meningoencephalitis, arthritis and vascular occlusion have been added. Histopathologically, evidence of vasculitis is found. The etiology is not known. A recently suggested association to streptococcal antigen and dental treatment remains to be confirmed (2).

Pathergy, i.e. the production of a sterile pustule in 24-28 h upon an aseptic needle prick, is considered as characteristic of Behçet's disease (BD). The previously reported high prevalence of this phenomenon in Turkish BD patients has, however, decreased after the introduction of disposable needles, possibly due to their finer calibre (3). The long-term use of such needles in Western countries might partly explain the failure to demonstrate pathergy in patients from Europe (4). Alternatively, the lack of pathergy and also of the leukocyte antigen (HLA) B5 association in European patients could be attributable to genetic factors. Such factors could also explain why the majority of BD patients in populations from the Near East are male (5), while an equal sex ratio of BD patients has been noted in other Western countries (6).

The lack of specific diagnostic laboratory tests makes the diagnosis of BD entirely dependent on clinical findings, i.e. based upon the constellation of past or current presence of certain organ manifestations according to suggested criteria. Several sets of diagnostic criteria have been in use (7, 8). In an attempt to increase the accuracy of current criteria, the "International Study Group for Behçet's disease" (ISG) has recently presented its version (9), considered to be superior in specificity and equal in sensitivity to the former ones. In the ISG criteria (Table I) oral aphthae are made mandatory and certain characteristic but unfrequent features, e.g. thrombophlebitis and epididymitis, have been excluded. Theoretically it has been estimated that if the ISG criteria are applied, 3% of the patients previously diagnosed as BD patients would escape that classification (9).

Further use of the ISG criteria will prove their validity. Concerns have already been raised about the fact that many normal adults have aphthae and that three of the four other criteria derive from the skin (10). However, this rather underlines the importance of not overlooking or misjudging the characteristic skin changes, the detailed descriptions of which are included in the ISG criteria. The inclusion of "pseudofolliculitis" as a major criterion has previously been controversial (11) but seems reasonable due to its sensitivity as the most frequent skin manifestation of BD (12). A skin biopsy would easily disclose the vessel-based nature of "pseudo-folliculitis" in contrast to clinically resembling changes, such as the

Table I. Diagnostic criteria according to the "International Study Group for Behçet's disease" (9)

The diagnosis BD requires aphthae and two other criteria. Findings are applicable only in the absence of other clinical explanations.

Recurrent oral ulceration	Minor aphthous, major aphthous, or herpetiform ulceration observed by physician or patient, which recurred at least 3 times in one 12-month 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 ophthalmologist
Skin lesions	Erythema nodosum observed by physician or patient, pseudofolliculitis or papulopustular lesions; or Acneiform nodules observed by physician in postadolescent patients not on corticosteroid treatment
Positive pathergy test	Read by physician at 24-48 h

Table II. Analysis of cases presented in this review

EM = East Mediterranean.

Sw = Swedish heritage.

Urological symptoms: U = urethritis, C = cystitis, P = prostatic, O = orchitis, E = epididymitis, S = salpingitis.

Vascular symptoms: DVT = deep vein thrombosis, TF = superficial thrombophlebitis, PE = pulmonary embolism, CVT = central vein thrombosis.

Case No.	Sex	Ethnic origin	Age of onset of significant morbidity	Age at time of study	Oral ulcers	Genital ulcers	Ocular lesions	Skin lesions	Arthritis	Urological symptoms	Vascular symptoms	Neurological symptoms	HLA	Diagnosis*
1	M	EM	31	38	+	+	***	+		U, P		+	B5-pos	+
2	M	EM	25	29	+	+	+	+	+		TF		B5-pos	+
3	M	Sw	48	54	+	+	***	+	+	U, E, P	TF		B5-pos	+
4	F	Sw	19	33	+	+	***	+	+	S	DVT	+	B27-pos	+
5	F	Sw	35	46	+	+	+	+	+			+		+
6	M	Sw	42	47	+	+		+		U, O, E	DVT, TF			+
7	M	EM	35	36	+	+		+	+					+
8	F	Sw	21	30	+		+			U, C				-
9	M	EM	25	29	+	+		+		U, E, O	PE		B5-pos	+
10	M	EM	34	38	+	+			+	U, P				-
11	M	EM	26	28		+		+			TF			-
12	M	Spain	59	60	+		?	+	+		CVT			-

*Diagnosis of definite BD (+) or probable BD (-) according to the Mason & Barnes and ISG criteria.

**Blind on one eye.

pustules of acne (10). The ISG criteria also emphasize the necessity of excluding similar conditions, e.g. microbial pyoderma.

The natural course is notoriously unpredictable and protean symptoms from the neurological, ocular and vascular systems can occur at any time. Morbidity is reported to be lower in females and after a period of 3-7 years (7, 13).

The therapeutical approach is still a matter of debate. In cases with predominantly muco-cutaneous involvement, treatment with colchicine, dapsone or thalidomide is usually attempted (14-16). In ocular disease oral corticosteroids have for a long time been the mainstay of systemic treatment. In addition, recent studies have advocated the use of cyclosporine and azathioprine (17, 18). However, neither drug is effective in lower doses, and long-term studies confirming the benefits and assessing the side effects are still lacking.

In Japan and the eastern Mediterranean area the prevalence of BD is known to be high (5). In Sweden until recently very few patients have been encountered. According to official nationwide statistics, the reported morbidity of BD patients in Sweden over the last two decades has increased fivefold, indicating a rising prevalence (19). A seemingly high number of immigrants presenting with BD in the southern Stockholm area evoked our interest in the possible differences in prevalence, presenting mode and phenotypical characteristics in relation to ethnic origin, age and sex.

PATIENTS AND METHODS

During the 8-year period 1981-89, 12 patients with major features of BD were seen at the Department of Rheumatology, Huddinge Hospital, which serves a defined geographical area in the Stockholm region with 345,000 residents. Using the ISG criteria (Table I), 8 patients

were defined as definite BD. Four patients with several features characteristic of BD and considerable morbidity, not fulfilling the proposed criteria but with no other tentative diagnoses, were included as probable BD. In all patients extensive efforts were made to rule out other clinical conditions mimicking BD. The hospital charts were studied retrospectively and all the patients were reexamined at the time of the study. Routine laboratory tests, anti-neutrophil cytoplasmic antibodies (ANCA), anticardiolipin antibodies, antinuclear antibodies (ANA) and HLA typings were performed. Additional investigations such as nerve-conducting velocity studies, electromyogram and skin or muscle biopsies were undertaken when clinically indicated.

RESULTS

Clinical history. Oral lesions preceded other symptoms in all but 2 patients. Lesions of the central nervous system were the earliest manifestations in one patient and skin complaints in one patient. The male-female ratio was 3:1. The 3 females were all of Swedish ancestry. The progress of the disease showed no regular periodicity or detectable influence by external factors. The distribution of symptoms among the patients is shown in Table II.

Oral ulcerations were present in 11 of the 12 patients. They were indistinguishable from ordinary aphthae and clearly discernible from herpes by the lack of vesicles, and negative serology and immunofluorescence.

Genital ulcerations on genital organs, in perineum or adjacent skin, similar to those seen in the mouth, appeared in 10 patients.

Ocular lesions occurred in 6 patients as relapsing anterior uveitis with or without retinal vasculitis. Blindness of one or both eyes occurred in 3 patients, 2-4 years after the first ocular manifestations. Hypopyon (pus in the anterior chamber) was not seen.

Table III. Diagnostic criteria according to Mason & Barnes (8)

A minimum of three major or two major and two minor criteria is required.

Major criteria	Minor criteria
Buccal ulceration	Gastrointestinal lesions
Genital ulceration	Thrombophlebitis
Eye lesions	Cardiovascular lesions
Skin lesions	Arthritis
	Central nervous system lesions
	Family history

Skin lesions as described by the ISG criteria (9) and Nazarro (12) were seen in 10 patients. Erythema nodosum, seen in 7 patients, confirmed to previous descriptions in being recurrent and in healing without residual lesions. All 10 patients had "pseudo-folliculitis", i.e. long-standing, multiple, tender, follicular papules, evolving from pustules into ulcers ("skin aphthae") and healing with scars. Comedones were lacking, and bacterial samples were negative. "Acneiform nodules", i.e. small, transient, very painful and bright red lesions regressing within a few days without ulcerations or scars, were not noted in any of the patients. Only one patient had a history of pathergy (No. 1). Additional skin lesions were exanthema, herpes zoster and nummular and intertriginous eczema, encountered in one patient each.

Joint involvement was present in 7 patients as subacute, non-erosive mono- or oligoarticular selflimiting arthritis affecting small or large joints. Morning stiffness was lacking. Arthralgias were prevalent but not considered specific for BD. One patient with low back pain and x-ray changes compatible with sacroiliitis was HLA B27 positive.

Vascular occlusion. Deep vein thrombosis occurred in 2 patients and superficial thrombophlebitis in 4. Patient No. 12 had acute central vein thrombosis without clinical signs of retinal vasculitis. Patient No. 9 had clinically significant pulmonary embolism verified with scintigram, without any detectable signs of deep vein thrombosis in peripheral vessels.

Neurologic manifestations occurred in 3 patients. In patient No. 1 recurrent, non-infectious meningitis occurred during a 5-year period together with marked changes in personality. In patient No. 4 the disease started with relapsing sterile meningoencephalitis, followed by a 10-year long remission after which acute cerebrovascular lesion with hemiparesis developed. Patient No. 5 had an initial attack of aseptic meningitis with ataxia, hemisymptoms and diplopia. After this followed 10 years free from neurological disease. She then developed cerebral thrombosis with facial paresis and hemisymptoms.

Gastrointestinal disease. Bloody diarrhea and a perianal fistula were noted in one patient with normal coloscopy and normal biopsy from the rectal mucosa (No. 6).

Urogenital symptoms were, besides ulcers, seen in 7 patients. Five male patients had urethritis. Three of these also developed prostatitis and 2 had epididymitis and/or orchitis, where repeated bacterial cultures and urethroscopy did not reveal any microbiological cause. Patient No. 4 had five episodes with relapsing salpingitis preceding the diagnosis BD.

In patient No. 8, also female, relapsing sterile cystitis occurred over a period of years with endoscopy showing diffuse inflammatory cystitis and urethritis, demanding repeated dilatation of urethra.

Myalgias were present periodically in 7 of the 12 patients, at times severe and most prominent in the legs. Lack of muscle weakness and normal creatine kinase and electromyogram ruled out myositis.

Laboratory findings. During relapses moderately elevated sedimentation rate (<100 mm/h) and immunoglobulin levels were detected and also mild anaemia (hemoglobin levels >100 g/l) and mild leukocytosis. ANA, anticardiolipin antibodies and ANCA were absent. Four out of 8 tested patients were HLA B5 positive. Three of these were immigrants.

COMMENTS

In the present study the predominance of immigrants was striking. Seven of the 12 patients were from southern Europe or the Near East, whereas the percentage of immigrants from the eastern Mediterranean area in this part of Stockholm amounts to only 5%. The figures could indicate a remarkable high prevalence of the disease in this group, but the material is too small to allow statistical inferences.

The prevalence of BD as calculated on the patients with Swedish ancestry and definite diagnosis was 1/85000. The figure is higher but still compatible with the formerly reported prevalence figures from the UK and the USA, dating from the 1970s, and might reflect demographic changes occurring since the undertaking of these investigations (6, 20).

A considerable time lapse between the first symptoms or signs compatible with BD and the diagnosis of the disease was noted in several patients; e.g. in 2 cases (Nos. 6 and 8) oral ulcers had been present since childhood and were followed by other symptoms after decades. The history of BD with its extended time course makes the determination of the mean age of onset difficult. A more fruitful approach could be comparison of the mean age of onset of significant morbidity. No clearcut difference emerged, however, in this respect, between the Swedish group and the immigrants from the eastern Mediterranean area.

Regarding other manifestations included in previous sets of criteria, the arthritis seen in 7 patients in the present study conformed to the description given in other series (8) but was never a major complaint. A more infrequent manifestation in this study was pulmonary embolism (seen in one patient). Until recently, pulmonary disease was not known to occur but is now reported in about 10% of BD patients (21). The finding of a perianal fistula in one patient is considered a rare manifestation of gastrointestinal BD, previously described in only 4 patients (22).

All of the immigrant patients were males, whereas 3 of the 5 patients with Swedish ancestry were females. As BD in the Near East afflicts mainly males, further accentuation of the noted sex difference between the Swedish and the immigrant patients could be due to the predominance of young males in this Swedish immigrant population. A difference in pathergy reactivity was noted. None of the Swedish patients displayed

a pathergy reaction. It was, however, also low among the immigrants. Three out of the 4 B5 positive patients were immigrants.

Our initial conception of an increased morbidity of the immigrant patients could not be verified. Further, no changes in the morbidity of the immigrant patients were detected with respect to the course before or after their arrival in Sweden. Rather is it noteworthy that 4 of the 6 patients with ocular or neurological involvement were seen among the patients with Swedish ancestry. Of these, the 3 female patients suffered from serious symptoms showing no tendency to recede with age, in contrast to findings in reports from Turkey and Japan (7, 13). Thus most of the serious complications occurred in this minority of female patients with Swedish ancestry. The incidence and character of neurological (10%) and ocular symptoms (50%), including the proportion of blindness, are well in accordance with other series (23, 24). The patients received an individualized treatment in accordance with recommended principles. In general, the outcome of the treatment did not differ significantly from what is described in the literature (25).

Epididymitis and orchitis are recognized as distinct features appearing in about 5% of patients with BD. Reports of other non-mucocutaneous urological or genital symptoms are scarce (26–28). In the present study a variety of urological manifestations were seen in 7 patients (Table II).

In Table II the patients have been classified as definite or probable BD according to the ISG and Mason & Barnes criteria respectively (Tables I and III). In none of the patients did the choice of diagnostic criteria change the diagnosis from probable BD to definite BD or vice versa. Thus the sensitivity and specificity of the two sets of criteria seemed equal.

Whether the observed differences between patients with Swedish ancestry and those with oriental origin, as put forward in the present study, also apply to patients from other Western countries deserves further attention. As the increase in prevalence seems to be a ubiquitous Western phenomenon, such studies would favour a better understanding of this condition.

As the diagnosis and treatment of BD patients demand the cooperation of several medical specialities, an increased awareness of this condition, facilitating diagnosis and subsequent management, is desirable. This would also reduce the number of clinical investigations and laboratory tests, decreasing the total health care cost of these patients.

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