The proportional Venn diagram of Behçet's disease-related manifestations among young adult men in Turkey

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ABSTRACT

Objectives. *To determine the frequency of the features associated with Behçet's disease (BD) in a young men population and generate a proportional Venn diagram of those features.*

Methods. *Data was collected from 3714 otherwise healthy men recruited for military service at the entrance. Study was conducted in a two-step procedure. Firstly, all participants were questioned by a general practitioner via using visual Behçet's questionnaire. Those participants, in whom at least one BD-related manifestation of the disease (oral ulcer, genital ulcer, folliculitis, erythema nodosum, uveitis, venous involvement of the lower extremities) have been demonstrated, were further examined by a rheumatologist at the second-stage of the study.*

Results. *The areas of intersection among the 6 individual BD-related manifestations produced 63 mutually exclusive symptom groups. Sixteen out 63 of these groups were functionally operative in our study population. Forty-seven (1.2%) of the all participants were considered to have at least 1 of the BD-related manifestation after examined by rheumatologist. The prevalence rates of the individual manifestations among the study population were as follows; oral ulcer 29 (0.78%), folliculitis 31 (0.83%), genital ulcer 9 (0.24%), venous involvement 13 (0.35%), erythema nodosum 4 (0.10%) and uveitis 3 (0.08%). The group consisting of oral ulcer with folliculitis was the largest proportion of participants followed by the group having oral ulcer only, accounting for 0.29% and 0.18%, respectively. Four (0.1%) of the participants were fulfilled the International Study Group for BD criteria following rheumatologic and ophthalmologic examinations. After excluding the group having oral ulcer with folliculitis, additional 12 cases had features suggesting BD though they didn't fulfill the International Study Group for BD criteria.*

Conclusion. *The Venn diagram of this study demonstrates that International Study Group for BD criteria can detect almost the quarter of 16 cases suspected as having BD. We suggest that the application of information regarding the frequencies of individual BD-related manifestations and their association with each other in a general population might serve as a helpful tool for physicians while making diagnosis.*

Introduction

Behçet's disease (BD) is a multisystem inflammatory disorder of unknown etiology characterized by recurrent oral and genital ulcers, skin lesions, and uveitis. Other features include arthritis, thrombophlebitis, a positive pathergy test, central nervous system and gastrointestinal lesions (1). The disease has a quite heterogeneous presentation in which patients with the disorder may manifest all or only some of these clinical features. Due to the lack of generally accepted diagnostic test, diagnosis of BD mostly relied on recognition of several of its more distinctive clinical features. It is of importance to note that none of these features is specific for BD. Furthermore, each and every one of these features might be associated with diseases other than BD and some might also be seen as an isolated finding (2). Given the heterogeneity of organ system involvement, the International Study Group for Behçet's Disease (ISGBD) established a classification criteria in 1990 which require the presence of recurrent oral ulceration plus any 2 of the following: recurrent genital ulceration, eye lesions, skin lesions (erythema nodosum, folliculitis, pustules), or positive finding on pathergy test (3).The findings are not

valid if any other clinical explanation is present, while the criteria permit diagnosis in the absence of concomitant happening of individual findings.

Although ISGBD criteria enabled a better interpretation of different studies and collaborative research around the globe, and not proposed to serve for diagnosis, several case reports have been found in the literature and in clinical practice who had findings fitting to BD, but who lacked findings to fulfill the criteria (4, 5). Furthermore, ISGBD criteria are known to be especially useful in areas where the disease prevalence is low. However, the utility of these criteria is less practical in countries where the disease prevalence is remarkably high.

In view of the above data, we suggest that establishment of the prevalence of individual (BD-related) findings and their relation with each other by means of Venn diagram in a population, in which the disease is prevalent, may offer a better insight about the nature of BD in such populations.

In the present study, we conducted a field survey in a young healthy male population in order to estimate the frequency of the findings associated with BD, either alone or in combination and further examined those who have combination of findings for the presence of BD.

Methods

The survey was conducted among newly recruited young, healthy men in a military unit located in Ankara, Turkey. All of the enlisted personnel of the unit (n = 3714), deployed from all over the country for basic military training were included in this study. The survey was carried out in two stages. Interviews conducted at the admission period and all participants had been free of any severe medical conditions including Behçet's disease.

In the first stage, participants were interviewed by a general practitioner (AB) who has been trained about the manifestations of BD and the use of questionnaire. The standard questionnaire applied in the study was developed mainly for the detection of BD-related manifestations. In order to minimize the misunderstandings that can be arisen from the verbal questionnaire, pictures of the corresponding manifestations were shown to the participants concurrently. Questions in the questionnaire were as follows:

1. Have you ever had recurrent white colored, painful sores in your mouth?
2. Have you ever had sores on your genitalia?
3. Have you ever had several acnes or folliculitis over your trunk or extremities after the age of 18 ?
4. Have you ever had painful, red or violet colored, 1-5 cm in diameter lumps under your skin especially on the lower extremities ?
5. Have you ever experienced swelling of your legs with noticeable increase in width or have you ever had string-like hardenings with reddening of the overlying skin especially on the lower extremities ?
6. Have you ever experienced blurred vision with duration of a few days ?

In this stage, the participants who had at least one positive response among the 6 questions included in the questionnaire were referred to the second stage.

In the second stage, participants selected during the first stage were further questioned and examined by rheumatologists (HE and IS) for confirmation or presence of BD-related manifestations at the Rheumatology Outpatient Clinic. Patient's description of relevant lesion regarded as assenting for oral ulcer, folliculitis, superficial thrombophlebitis and erythema nodosum. However, history of genital ulcer, deep vein thrombosis, and uveitis were affirmed by direct observation of the ulcer scar, Doppler ultrasound examination, and fundoscopic examination, respectively. All participants were also investigated by laboratory screening tests, chest X-ray, fundoscopic examination and skin pathergy test. Participants fulfilling the ISGBD criteria were defined as having BD.

Results

The standard questionnaire was applied to a total of 3714 participants in the first stage of the study and 50 (1.3%) of them were found to have a history of at least 1 BD-related manifestation. In the second stage, the presence of at least 1 of the 6 manifestations questioned was confirmed in 47 (1.2%) participants following a detailed history taking and physical examination by a rheumatologist. During this stage, 3 of the participants were excluded since it was considered that their problems represented lesions other than cited in the questionnaire. The prevalence rates of the individual manifestations among the study population were as follows; oral ulcer 29 (0.78%), folliculitis 31 (0.83%), genital ulcer 9 (0.24%), venous involvement 13 (0.35%), erythema nodosum 4 (0.10%) and uveitis 3 (0.08%).Twenty-seven (0.72%) of the participants were found to have more than 1 BD-related manifestation.

Proportional Venn diagram of those manifestations was created in order to achieve a better understanding the association of manifestations with each other. The areas of intersection among

Table I. The distribution of individual manifestations and their combinations.

Groups	n	Pathergy (+)	Diagnosis
OU	7		
GU	2		
F	6	+	
V	3		
U	2		
OU + GU	1		s
OU + F	11		
GU + V	1		s
F + V	2		s
GU + F + V	2	+	s
OU + F + U	1		BD
OU + F + V	4		s
OU + GU + F	1	+	BD
OU + F + EN	2		s
OU + GU + F + EN	1		BD
OU + GU + F + EN + V	1		BD

OU: oral ulcer, GU: genital ulcer, F: folliculitis, V: venous involvement, U: uveitis, EN: erythema nodosum, BD: Behçet's disease, s: suspected as having BD.

the 6 BD-related manifestations produced 63 mutually exclusive symptom groups (Figure 1). Sixteen out 63 of these groups were operative in our study population. The clinical features of the 47 participants and the corresponding symptom groups are shown in Table I. With regard to those groups, the group consisted of oral aphthae with folliculitis was the largest proportion, accounting for 0.29% of the population.

Ocular involvement was detected in 3 of the participants by fundoscopic examination. Two of them had evidence of posterior while 1 of them had anterior uveitis. Thirteen of the participants were considered to have venous involvement and undergone Doppler ultrasound examination. The types of venous involvement in those participants were as follows: 6 had superficial thrombophlebitis, 3 had varicose veins, and 4 had deep venous thrombosis. Skin pathergy test was found to be positive in 3 out of 47 participants in the second stage. Clinical features of the participants having a positive pathergy test were as follows; 1 had oral ulcer and folliculitis, 1 had genital ulcer, folliculitis and venous involvement and the other had oral ulcer, genital ulcer and folliculitis. The diagnosis of BD was established in 4 participants according to the ISGBD criteria. The clinical features of these 4 patients are shown in Table I.

After excluding the group having oral ulcer with folliculitis, there were 12 additional participants who had features suggesting BD and did not fulfill the ISGBD criteria Table I. Based on the number of BD patients fulfilling the ISGBD criteria (4 of 3714 participants), the prevalence rate of BD was estimated as 10/10,000 among young Turkish men.

Discussion

Diagnosis of BD entirely depends on proper history taking and typical clinical manifestations. One of the major problems in establishing an adequate diagnosis of BD, however, is the fact that no significant pathognomic finding or diagnostic laboratory testing has been defined yet (1, 2). Considering the difficulties mentioned above, ISGBD developed classification criteria which mainly ensure uniformities of patients for studies of the epidemiology, pathogenesis, follow-up, and treatment of the disease, rather than the diagnosis of the individual case (3).

Preparation of a classification criteria mainly based on determination of discriminative performance for individual manifestations. With respect to ISGBD criteria, performance of any given BD-related manifestation was measured as the performance of each manifestation to discriminate BD patients from other disorders such as systemic lupus erythematosus, ankylosing spondylitis, F + EN + Vrheumatoid arthritis, and recurrent aphthous stomatitis (6). To our knowledge, no data have been found regarding their performance to discriminate patients with BD from those healthy individuals. Although ISGBD criteria have enabled differentiation of BD from other entities associated with oral ulcers, for example patients with only orogenital ulcerations, of whom most patients can be considered to have a BD, do not meet the ISGBD criteria.

In clinical practice, an individual who does not fulfill the criteria but having BD-related manifestations accepted either as having an isolated disease or as a candidate who has a potential to develop BD in the future. Having been classified as BD does only mean that the patient has a particular set of BD-related manifestations. Thus it is not a label that serves to separate patients from healthy individuals.

Almost all previous studies investigating the prevalence of BD in population have been designed to accept participants who had either oral ulcers or had oral ulcers in combination with genital ulcers for the second stage of the survey (7-10). Thus, participants who hadn't had those index findings were not questioned and examined further Table II. Despite the oral ulcer has been accepted as being the most common and important clinical feature, a substantial proportion of patients (13.5-27%) does not initially presented with

Table II. Comparison of the present study with previous field surveys.

	Fener survey	Çamas survey	Istanbul survey	Present survey
Population	4940 inhabitants ≥ 10 years old	5131 inhabitants ≥ 10 years old	23986 inhabitants ≥ 12 years old 47 previously diagnosed BD patients	3714 healthy males, mean age : 20.6 years
First stage	OU or GU or pathergy : 317	OU : 817	OU or previous BD : 2289	6 BD-related features : 50
Second stage (suggested as BD)	18	28 / 666*	700 / 1989*	47
Third stage (diagnosed as BD)	4 (O'Duffy's)	19 (O'Duffy's)	101 (47+54) (ISGBD)	4 (ISGBD)
Prevalence	8 / 10,000	37 / 10,000	42 / 10,000	10.7 / 10,000
Suspected,but diagnosed as BD	14	9	13	not 12

OU: oral ulcer, GU: genital ulcer, BD: Behçet's disease, ISGBD: International Study Group for BD criteria; * the number of patients undergone examination at the second stage.

Table III. Association of oral ulcer with other manifestations (OU: oral ulcer).

Manifestation	Total	OU (-)	OU (+)
Genital ulcer	9	5	4
Folliculitis	31	10	21
Erythema nodosum	4	0	4
Uveitis	3	2	1
Vein manifestations	13	8	5
Pathergy positivity	3	2	1

oral ulcer (5, 11). Although the prevalence of oral ulcer was found to be lower in this study as compared to previous studies, this might be explained by the characteristics of our study population which consist of otherwise healthy young males, and also our method using visual questionnaire that may reduce the misinterpretation of oral lesions.

In this study, the presence of at least 1 BD-related manifestation was found in 47 out 3714 of the participants. When those participants having only 1 manifestation and those having oral ulcer with folliculitis excluded, there were additional 16 participants who had 2 or more BD-related manifestations. Four out 16 of them were diagnosed as BD according to ISGBD criteria while remaining 12 participants were classified as suspected BD. As it can be obviously seen on table 4, only 7 out 12 of those participants had oral ulcers.

Although this study was not designed to investigate the prevalence of BD, our results showed a prevalence of 10/10000, which is in line with the previous surveys conducted in Turkey (Table II) (7-10). Considering the fact that our study population consists of young, healthy males, demonstration of a similar rate of prevalence in this study as compared with the previous ones supports the confidence of our results and indicates that the prevalence of the disease is sizeable among the young, otherwise healthy population, as well.

When the association of an oral ulcer with the other BD-related manifestations was interpreted, it was found that only erythema nodosum shows a high rate of concurrence with oral ulcer, while the rate of concurrence was found to be variable with other manifestations (Table III). In this respect, approval of an oral ulcer as a *sine qua non* of the ISG criteria eliminates a great number of individuals in the population who had BD-related manifestations, which is also true for the previously conducted field surveys in Turkey (7-10). As stated above this accounts for almost half (5 out 12) of the participants who had been classified as suspicious.

The number of different criteria/classification systems that have been proposed over the past 25 years reflects the failure of any single one to meet clinical demands (3, 5, 6). Although originators of ISGBD criteria strictly recommend that symptoms list be known as "classification" criteria rather than "diagnostic" criteria, an ongoing debate and attempts to define better criteria mostly lies in the fact that many physicians, who especially have limited clinical experience in treating BD patients, lean heavily on the ISGBD criteria to help with a diagnosis. Indeed, diagnosis of BD does not generate a great difficulty for a physician who is very familiar with the diagnosis and treatment of BD, and understands the relative importance of other serious, unlisted symptoms that the patient may be experiencing.

As it has been emphasized in several reports (5), our study also indicates that ISGBD criteria have several limitations for diagnosis, but not for classification, which makes them improper tool for the diagnosis of individual patient. Thus physicians, again, should be warned not to use these criteria as a way to diagnose individual cases of BD. Furthermore, though rare, it should be stressed that diagnosis of BD can be established even in the absence of recurrent oral ulcers.

In view of the above results, we suggest that the application of information regarding the frequencies of individual BD-related manifestations and their relation with each other in a general population by means of Venn diagram might serve as a helpful tool for physicians while making diagnosis until a novel diagnostic test or widely accepted diagnostic criteria are devised. On the other hand, while interpreting the results of this study, one should always consider that this study was conducted in a population where the disease prevalence is exceptionally high.

Since our study was conducted in a young, otherwise healthy male population, those individuals who have a potential to develop BD or BD-related manifestations in the future might have been underestimated. Furthermore, the fact that our study group composed men only may lead to a bias regarding

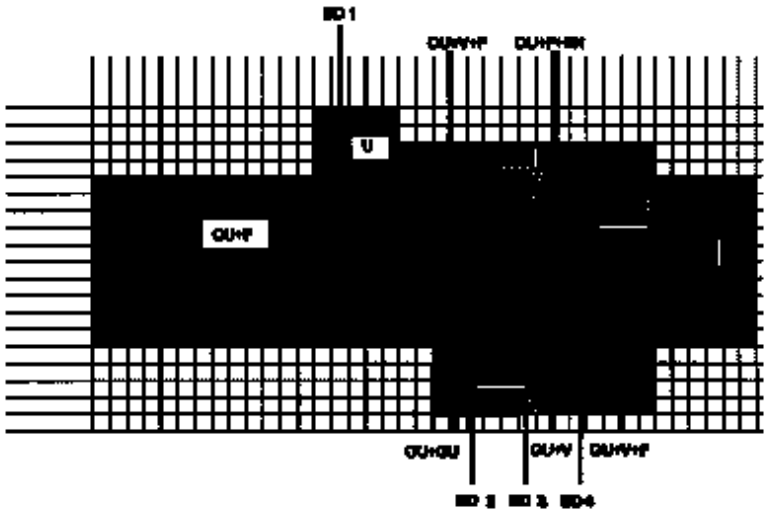

Fig. 1. Venn diagram showing all BD-related manifestations.
Abbreviations: OU: oral ulcer, GU: genital ulcer, F: folliculitis, V: venous involvement, U: uveitis, EN: erythema nodosum, BD1: OU + F + U, BD2: OU + GU + F, BD3: OU + GU + F + EN + V, BD4: OU + GU + F + EN. Each 10 squares represents 1 patient.

the conclusion about the general prevalence. However, we think that this is only a minor bias since all the previous field surveys found no difference in the disease prevalence between the both sexes. We, therefore, recommend that in order to diagnose BD during earlier phases of the disease and to differentiate it from the other diseases or isolated benign conditions, a similar survey should be conducted in a population which consists of middle aged individuals and heterogeneous by means of sex. We believe that our study is an initial step toward such an evaluation.

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