Validation of the classification criteria commonly used in Korea and a modified set of preliminary criteria for Behçet's disease: A multi-center study

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ABSTRACT

Objective. *Recently we have proposed a modified set of criteria to settle the questions raised regarding the International Study Group (ISG) criteria for Behçet's disease (BD). The aim of the present study was to validate the two pre-existing criteria sets commonly used in Korea, the ISG criteria and the criteria of the Behçet's Disease Research Committee of Japan (Japanese criteria), as well as the proposed modified criteria.*

Methods. *The study population included 155 consecutive patients with BD and 170 controls with non-Behçet's rheumatic diseases. Detailed data for all of the subjects were recorded prospectively by the participating physicians on a standard form that listed the clinical features of BD. The sensitivity, specificity, and accuracy of each set of the criteria were measured.*

Results. *Of the three criteria sets employed, the modified criteria were the most accurate, with an accuracy of 96.3%. The ISG criteria often failed to classify the following patients with BD: patients with only oral and genital ulcerations, certain patients with intestinal ulcerations, patients who did not manifest oral ulcerations, and patients with acute disease but fewer than three recurrent oral ulceration relapses in a 1-year period. The Japanese criteria also failed to categorize the following patients with BD: patients with oral and genital ulcerations, and patients with oral ulcerations, skin lesions, and a positive pathergy reaction. In addition, the Japanese criteria misclassified some of the control subjects with non-Behçet's uveitis as having BD.*

Conclusions. *The results of this study suggest that there are some points that need to be reconsidered in the clinical application of the two pre-existing sets of criteria. Although the modified criteria were the most accurate, further validation studies will be required in other ethnic populations.*

Introduction

Behçet's disease (BD) is a chronic inflammatory multisystem disorder of unknown etiology. In addition to the triple symptom complex originally described by Hulusi Behçet, which encompassed oral ulcerations, genital ulcerations, and uveitis (1), the disease may also involve other organs, including the skin, joints, vessels, gastrointestinal tract, heart, lungs, and central nervous system (CNS). Some variations in the clinical features of this disease, however, have been noted in different geographic areas, of which the remarkable ones include the prevalence of HLA-B51, ileocecal ulcerations, and a positive pathergy reaction, as well as a gender-related predisposition to the disease (2-5).

Since clear pathognomonic clinical features and laboratory tests are lacking, the classification or diagnosis of BD mainly relies on the criteria that consist of the characteristic clinical manifestations. On the other hand, if the classification criteria are perfect, those might indeed designate diagnostic criteria. However, a certain portion of patients will always be misclassified. Therefore, an experienced physician, considering the clinical features of an individual patient, is the only one who can establish the diagnosis (6), but many clinicians may hesitate in diagnosing patients who do not fulfill the criteria. In general, diagnostic criteria primarily apply to individual patients, but classification criteria are usually used in epidemiological and clinical research.

Table I. Amodified set of preliminary criteria for Behcet's disease.

Clinical features	Score
1. Recurrent genital ulcerations Painful aphthous ulceraton or scarring confidently detected by physician or patient The exclusion of genital ulcerations associated with herpes genitalis, chancre, or chancroid	2
2. Recurrent oral ulcerations Painful aphthous ulceration confidently detected by physician or patient	1
3. Skin lesions a) Erythema nodosum-like lesions confidently detected by physician or patient b) Pseudofollicullitis or papulopustular lesions only detected by physician with the exception of lesions related to puberty or corticosteroid therapy	1
4. Ocular lesions Anterior uveitis, posterior uveitis or retinal vasculitis diagnosed by ophthalmologist	1
5. Pathergy reaction Papule or pustule observed by physician at 48 hour, done by intradermal prick with 20-22 gauge disposable needle	1
6. Ileocecal ulcerations The exclusion of inflammatory bowel diseases or intestinal tuberculosis	1

Behçet's disease can be classified or diagnosed when the score is 3 or greater.
*Finding helpful for classification or diagnosis: HLA-B51.

Since Mason and Barnes' initial diagnostic criteria in 1969 (7), several criteria had been widely used, which had hindered comparisons of clinical studies and collaborative research. The criteria of the International Study Group (ISG) therefore were formulated to warrant uniformity in the clinical studies, rather than the diagnosis of the individual case. The ISG criteria include recurrent oral ulcerations (ROU) that appear at least three times in a 1-year period, plus the presence of any two of the following clinical items: recurrent genital ulcerations, eye lesions, skin lesions, and a positive pathergy reaction (8).

Even though the ISG criteria have been validated in different ethnic groups (9-12), some problems have arisen. First, since the ROU is an obligatory criterion for the classification or diagnosis of patients with BD, those cases without ROU do not meet the criteria. Indeed, 3% of 914 patients with definite BD, in whom the oral ulcerations did not develop, were excluded in the original survey for the ISG criteria (8). In addition, some patients with BD have initially manifested in the absence of ROU, with a variable frequency of 14-48% (5,13-15), and since the interval between the initial symptoms and the second manifestations may take as long as several years (13), the ISG criteria may fail to classify these patients for a long time. Moreover some investigators have pointed out that the failure of the ISG criteria to classify or diagnose acute cases that involve severe disease, but with fewer than three ROU relapses in a one-year period, may delay the prompt initiation of treatment (16, 17). Second, most of the patients with BD (86.7%) in the original survey were recruited from countries that have had a high frequency of positive pathergy reaction, such as Iran, Turkey, and Japan; thus the sensitivity of the ISG criteria could be low in ethnic areas with a low frequency of a positive pathergy reaction (18). Korea did not participate in the original survey, and the rate of the positive pathergy reaction has been reported to be low, at around 35% (19). On the other hand, the criteria of the Behçet's Disease Research Committee of Japan (Japanese criteria) (20) have still employed widely in Korea, together with the ISG criteria (21), probably for the aforementioned reasons.

Recently, we have proposed a modified set of guidelines to overcome the difficulties associated with the ISG criteria. Our modified criteria consist of the clinical items that showed improved performance in our previous study (Table I) (21). The purpose of this study therefore was to validate the ISG criteria and the Japanese criteria, both of which are commonly used in Korea, and the modified criteria. In addition, the problems associated with each set of the criteria are discussed.

Table II. Demographic findings in the patients with Behçet's disease and control subjects.

	Behçet's patients (n = 155)	Controls (n = 170)
Male : female ratio	1 : 1.98	1 : 1.74
Age (years, mean ± SD)	39.2 ± 10.2	37.8 ± 11.8
Disease duration (months, mean ± SD)	52.7 ± 48.8	52.7 ± 48.2

Materials and methods

In the period from February 2002 thru May 2002, 155 consecutive and unselected patients with BD were recruited from the 7 tertiary medical centers in different regions of Korea, in whom the diagnosis was based on the clinical decision of the experienced rheumatologists familiar with BD. In addition, 170 age- and sex-matched control subjects from the same medical centers consisted of patients with non-Behçet's rheumatic diseases, inflammatory bowel diseases (IBD), or recurrent aphthous stomatitis. Diagnoses of non-Behçet's rheumatic diseases, including systemic lupus erythematosus (SLE), Sjögren's syndrome, and spondyloarthropathy, were based on the internationally accepted criteria (22-24), and IBD was diagnosed on the basis of endoscopic and histologic findings. Informed consent was obtained from all the subjects, who were ethnically homogenous Koreans.

Detailed data for each patient with BD and each control were recorded prospectively by the participating rheuma-

Table III. Diagnoses of patients in the control group.

Diagnosis	No.	(%)
Systemic lupus erythematosus	46	(27.1)
Sjögren's syndrome	26	(15.3)
Spondyloarthropathy*	61	(35.9)
Recurrent aphthous stomatitis	27	(15.9)
Ulcerative colitis	8	(4.7)
Crohn's disease	2	(1.8)

*Spondyloarthropathy (SpA) patients consisted of 43 with ankylosing spondylitis, 8 with undifferentiated SpA, 8 with reactive arthritis, and 2 with psoriatic arthritis.

Table IV. Clinical manifestations of Behçet's disease (BD) in the patient with BD and controls.

Clinical manifestations	Behçet's patients n = 155 (%)	Controls n = 170 (%)
Oral ulcerations	153 (98.7)	83 (48.4)
Genital ulcerations	129 (83.2)	5 (2.9)
EN-like lesions	82 (52.9)	14 (8.2)
Pseudofolliculitis/PPL	80 (51.6)	26 (15.2)
Ocular lesions	45 (29.0)	13 (7.6)
Pathergy reaction	48 (31.0)	0
Intestinal ulcerations	31 (20.0)	8 (4.7)
Peripheral arthritis	61 (39.4)	57 (33.5)
Vascular lesions	17 (11.0)	7 (4.1)
Epididymitis	4 (2.6)	1 (0.6)
CNS lesions	9 (5.8)	5 (2.9)

EN: erythema nodosum; PPL: papulopuspular lesions; CNS: central nervous system.

tologists on a standard form for the presence or absence of all the features of BD that were listed in the 3 sets of the criteria (ISG criteria, Japanese criteria, and modified criteria) investigated in this study. The pathergy reaction was performed in all of the BD patients and controls, as described in our previous study (19). After coding the data, they were entered into a computer database and analyzed using the SPSS software package version 10.0 (SPSS Inc., Chicago, IL, USA). The sensitivity, specificity, and accuracy were determined in the same way as our previous study (21).

Results

Any differences in the demographic findings were not seen between patients with BD and controls (Table II). The diagnoses in the control subjects are listed in Table III. Table IV shows the frequencies of the clinical features of BD listed in the criteria, for the patients with BD and controls.

The validation results of each set of the criteria in the 7 tertiary medical centers are presented in Table V. Of the 3 sets of the criteria, the modified criteria were the most accurate (96.3%).

Table VI lists the clinical characteristics of patients with BD not meeting the individual criteria for BD. The ISG criteria failed to classify correctly 32 of 155 (20.6%) patients with BD, and the common clinical settings of these patients were as follows: patients with only ROU and genital ulcerations; patients with ROU, intestinal ulcerations, and other features of BD, such as genital ulcerations or skin lesions; patients who did not manifest ROU; acute disease patients with fewer than three ROU relapses in a 1-year period. The Japanese criteria failed to classify correctly 30 of 155 (19.4%) patients with BD, including patients with only ROU and genital ulcerations, and patients with ROU, skin lesions, and a positive pathergy reaction. In contrast, the modified criteria could classify most of the cases with BD, except for patients with unusual combinations of Behçet's features.

Table VII shows the clinical characteristics of control subjects fulfilling each of the BD criteria. One patient with Sjögren's syndrome had clinical features of ROU, genital ulcerations, and papulopuspular lesions (PPL), which satisfied all the 3 sets of the BD criteria investigated. Otherwise, there were no more control subjects meeting the ISG criteria, which appeared to be the most specific. In the case of the modified criteria, there were another two control subjects with SLE meeting these criteria. With respect to the Japanese criteria, another 7 control patients fulfilled the criteria, including 4 with ankylosing spondylitis, 1 with reactive arthritis, 1 with psoriatic arthritis, and 1 with SLE.

Table V. The validation results of each set of the criteria in the 7 tertiary medical centers.

Criteria	Sensitivity (%)	Specificity (%)	Accuracy (%)
ISG	79.4	99.4	89.8
Jap	80.6	95.3	88.3
Mod	94.2	98.1	96.3

ISG: The criteria of the International Study Group for Behçet's Disease; Jap: the criteria of the Behcet's Disease Research Committee of Japan; Mod: a modified set of preliminary criteria.

Discussion

Although the modified criteria have been established using the same method that was used to derive the ISG criteria, some differences exist between these two sets of the criteria. First, since the diagnostic value of genital ulcerations was much higher than those of the other clinical items in our previous study, the importance of the genital ulcerations is stressed in the modified criteria. Consequently, classification or diagnosis can be made based on the presence of genital ulcerations plus one more other clinical items. Second, since ROU is not an obligatory criterion, the classification or diagnosis of BD can be made even in cases that lack ROU. Third, as the frequency (over 3 times in a 1-year) of ROU is abandoned, the modified criteria may classify or diagnose acute cases with BD that have fewer than 3 ROU relapses in a 1-

Table VI. The clinical characteristics of patients with Behçet's disease who did not meet the individual criteria for Behçet's disease.

	ISG (n = 32)	Jap (n = 30)	Mod (n = 9)
ROU + GU	14	14	
ROU + GU + GI	3	3	
ROU + GU + GI + arthritis	1		
ROU + skin lesions + PPR		4	
ROU + skin lesions + VL	1	1	1
ROU + skin lesions + CNS	1	1	1
ROU + skin lesions + GI	1	1	
ROU + skin lesions + GI + VL	1		
ROU + skin lesions + arthritis	2	2	2
ROU + GI	2	2	2
ROU + VL+ CNS	1	1	1
ROU + ocular lesions + arthritis	1		1
Patients without ROU	2		
Skin lesions + PPR + arthritis*	1*	1	1
Acute cases	2	–	–

ISG: the criteria of the International Study Group for Behçet's Disease; Jap: the criteria of the Behçet's Disease Research Committee of Japan; Mod: a modified set of preliminary criteria; ROU: recurrent oral ulcerations; GU: genital ulcerations; GI: gastrointestinal ulcerations; PPR: positive pathergy reaction; VL: vascular lesions; CNS: central nervous system lesions.
*Counted as patients without ROU; acute cases: acute disease patients with fewer than 3 ROU relapses in a 1-year period.

year period. Fourth, ileocecal ulcerations, which are absent from the ISG criteria, are included in the modified criteria (21). In the current study, the modified criteria appeared to be the most accurate.

As mentioned previously, the ISG criteria failed to classify or diagnose acute cases that lacked ROU relapsing over 3 times in a 1-year period, and patients who did not have oral ulcerations. The Japanese criteria could not classify patients with ROU, skin lesions, and positive pathergy reaction, because these patients were categorized into the suspected type by these criteria. In addition, the ISG criteria and the Japanese criteria failed to classify those patients with intestinal ulcerations plus two of the other clinical items, e.g. ROU plus genital ulcerations or ROU plus skin lesions. Moreover, the major group of patients not classified by these two criteria included those patients with only ROU and genital ulcerations: these patients were considered to have BD by most of the physicians who participated in the current study.

Table VII. The characteristics of control subjects who fulfilled all of the criteria for Behçet's disease.

Patient	Diagnosis	Clinical features	ISG	Jap	Mod
1	Sjögren syndrome	ROU + GU + PPL	+	+	+
2	SLE	ROU + GU	-	-	+
3	SLE	ROU + GU + arthritis	-	-	+
4	AS	Uveitis + PPL	-	+	-
5	AS	Uveitis + PPL	-	+	-
6	AS	ROU + uveitis	-	+	-
7	AS	ROU + uveitis	-	+	-
8	Reactive arthritis	ROU + uveitis + arthritis	-	+	-
9	Psoriatic arthritis	Uveitis + PPL+ arthritis	-	+	-
10	SLE	ROU + PPL+ arthritis + CNS	-	+	-

ISG: the criteria of the International Study Group for Behçet's Disease; Jap: the criteria of the Behçet's Disease Research Committee of Japan; Mod: a modified set of preliminary criteria; ROU: recurrent oral ulcerations; GU: genital ulcerations; PPL: papulopustular lesions; CNS: central nervous system lesions; (+) or (-): meet or do not meet the criteria; SLE: systemic lupus erythematosus; AS: ankylosing spondylitis.

It is debatable whether all of the patients who had only ROU and genital ulcerations actually had BD. Jorizzo *et al*. designated these conditions as a type of complex aphthosis, which could be a forme fruste of BD (25, 26). It is particularly noteworthy that those patients in ethnic areas where positive pathergy reactions are less prevalent, such as North America and European countries, as well as Korea (19, 27, 28), do not fulfill the ISG criteria. Furthermore, after introduction of a disposable needle, the prevalence of positive pathergy reaction decreased, as compared with the pre-AIDS era, during which non-disposable needles were used (29). Thus, patients with only orogenital ulcerations are less likely to meet the ISG criteria. Therefore, to discern BD patients with only oral and genital ulcerations, it is necessary to exclude other uncommon causes for these lesions. First, it is very important to rule out sexually transmitted diseases, such as herpes genitalis, chancre, or chancroid (21). Second, it is necessary to distinguish the orogenital lesions that appear in reactive arthritis (Reiter's syndrome), in which the mucocutaneous lesions are usually painless, shiny patches, from painful and characteristic ulcerations of BD (30).

In order to avoid overclassification (overdiagnosis) when using the modified criteria, emphasis should be put on recognizing the characteristics of genital ulcerations in BD. These lesions are quite typical and can be detectable by an experienced clinician through a careful history-taking and thorough physical examination. They resemble oral ulcerations but are often larger and deeper, more painful and longer lasting. Genital ulcerations often leave scars and recurrences occur less frequently compared with oral ulcerations (2, 3). In the current study, in retrospect one control patient with Sjögren's syndrome also had features of BD, including ROU, genital ulcerations, and PPL.

Her genital lesions were so consistent with those of BD that this patient was considered to have concurrent Sjögren's syndrome and BD. There were two SLE patients fulfilling the modified criteria: one patient had painful genital ulcerations similar to those of BD patients and the other manifested painless genital lesions, which might be regarded as the mucous lesions of SLE or causes other than BD.

The Japanese criteria, which were revised in 1987, emphasized ocular involvement and include 3 subtypes: complete, incomplete and suspected, of which complete and incomplete types are usually considered as indicative of BD in the clinical studies. According to these criteria, typical ocular lesions plus one major or two minor features can be classified into the incomplete type (20). In view of the fact that recurrent aphthous stomatitis and PPL/pseudofolliculitis are relatively common in the general population (31,32), it would not be infrequent for patients with non-Behçet's ocular diseases, such as spondyloarthritides, to meet the Japanese criteria. This might explain why several of the control patients with spondyloarthritides fulfilled the Japanese criteria in our study.

Although the entire alimentary tract may be involved in BD, the most common site of intestinal ulcerations is the ileocecal region, which is termed "intestinal BD" (2,33). The frequency of this form of BD varies in different countries, with a very low frequency in Turkey and a relatively high frequency in East Asian countries, such as Japan and Korea (3, 5, 34, 35). In the current study, the intestinal ulcerations were found in 20% of patients with BD. Since deep ulcerations in intestinal BD can extend through the bowel wall, they are prone to perforate, resulting in a poor prognosis (2,3,33,35,36). On the other hand, as patients with intestinal BD who did not meet the ISG criteria have been frequently reported in a previous Korean investigation (36) as well as in this study, we believe that the modified criteria may improve the classification or diagnosis of the patients with intestinal ulcerations. In the modified criteria, it is very important to rule out other causes of intestinal ulcerations, such as IBD and intestinal tuberculosis.

Since IBD may have similar extra-intestinal features to BD, including ROU, uveitis, erythema nodosum, and arthritis, it is often difficult to distinguish between these two disease entities (2). Whereas Crohn's disease may show many features of intestinal BD, the following findings favor intestinal involvement in BD: absence of granuloma, lymphocyte aggregations or reactive lymphoid hyperplasia in the intra-mucosal lymphoid tissues, deep ulcers occasionally associated with vasculitis (usually venulitis), and a tendency to fistula formation or intestinal perforation during the earlier stage of the disease (2,33,37). In addition, Lee *et al*. described the typical colonoscopic findings in intestinal BD as single or a few deep ulcers with discrete margins in the ileocecal area or anastomotic site, in a pattern that is distinct from those seen in Crohn's disease (36). Intestinal BD also has different distribution patterns from ulcerative colitis, in terms of right colonic predominance, discontinuous involvement, and infrequent involvement of the rectum (38). Furthermore, BD has unique clinical features, including genital ulcerations, a positive pathergy reaction, CNS involvement, and an association with HLA-B51, which are not features associated with IBD (2, 3,35). In addition, intestinal tuberculosis should be ruled out, since it shows similar clinical, pathological, and endoscopic findings to Crohn's disease and intestinal BD. A definitive diagnosis of intestinal tuberculosis relies on the identification of the organism in tissues, either by direct visualization with an acid-fast stain, by culture of the excised tissue, or using a PCR assay (39, 40). On the other hand, because only a small number of patients with IBD, especially Crohn's disease, and no patients with intestinal tuberculosis were included in the current study, validation studies including a considerable number of such mimicking cases will be required.

Sarcoidosis is a chronic inflammatory disorder that sometimes mimics BD, since it may present similar clinical features to BD, including arthritis, erythema nodosum, and uveitis (41). However, in most validation studies for the BD criteria (8-12, 21) as well as in our study, patients with sarcoidosis were not included in the control group, and a further survey is also needed to assess the validity of using this parameter. On the other hand, the variations in the clinical manifestations of BD that have been noted between different countries make it difficult to generate a unified set of the criteria that ensures the accurate diagnosis of patients all over the world. Therefore, it is worth noting that experienced physicians, who consider all of the clinical features of an individual patient, are ideally placed to establish the diagnosis of BD.

In summary, the modified criteria, which to a certain extent are derived from the ISG criteria, are the most accurate among the criteria investigated. Further validation studies in different ethnic populations will be required to confirm these results.

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