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ORIGINAL ARTICLE

Differences in clinical manifestations, treatment, and concordance rates with two major sets of criteria for Behçet's syndrome for patients in the US and Japan: data from a large, three-center cohort study

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Abstract
Objective To compare Behçet's syndrome (BS) cohorts from the US and Japan in terms of rates of concordance with the International Study Group (ISG) criteria and Japanese criteria, disease manifestations, and treatment.
Methods All BS patients seen at the NYU Hospital for Joint Diseases in the US and the Kameda Medical Center and St. Luke's International Hospital in Japan between 2003 and 2010 were included. Diagnosis of BS was made on the basis of clinical manifestations and the clinical decisions of experienced specialists familiar with BS. We classified the patients into complete and incomplete types based on their symptoms; both complete or incomplete types were assumed to fulfil the Japanese criteria.
Results A total of 769 patients (US $n = 634$, Japan $n = 135$) were reviewed. 61.5 % in the US and 63.7 % in Japan fulfilled the ISG criteria. Similarly, there was no difference in the proportions of US and Japanese patients who fulfilled the Japanese criteria. Japanese patients were less likely to be female and to have genital ulcers, but were more likely to have epididymitis and pulmonary disease. Significantly more patients were treated with colchicine, sulfasalazine/mesalazine, and NSAIDs in Japan, while significantly more patients in the US received first-line immunosuppressants.
Conclusions The concordance rates for ISG and Japanese criteria fulfillment in the US and Japan were not significantly different. These findings could help to clarify regional differences in the diagnostic and clinical features of BS.

Keywords Behçet's syndrome · Behçet's disease · International Study Group (ISG) criteria · Japanese criteria · Manifestation

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Introduction

Behçet's syndrome (BS) is a systemic inflammatory disease of unknown etiology, which was originally described by Hulusi Behçet, formerly Professor of Dermatology at the University of Istanbul [1, 2]. BS is mainly characterized by recurrent oral ulcers, genital ulcers, eye and skin involvement, but can also present with additional

manifestations of arthritis, epididymitis, as well as gastrointestinal (GI), neurological, and vascular involvement. The disease is more prevalent in the region of the Silk Road linking China to Italy, but has a global distribution at lower rates. Nonetheless, the prevalence of BS varies significantly around the world. Turkey has the highest prevalence, with 20–420 cases per 100,000 [3–5], followed by Japan, Korea, China, Iran, and Saudi Arabia, which are reported to have from 13.5 to 20 cases per 100,000 [4]. In contrast, the prevalence is quite low in the US, ranging from 0.07 to 0.38 cases per 100,000 [4, 6]. Similarly, it is well known that there are regional differences in BS manifestations [7] in Turkey and Japan, as well as in Brazil, UK, Israel, and the US, among others [3, 4, 6, 8–13].

Diagnosing BS is not an easy task, as there are no diagnostic laboratory tests, specific histopathologic findings, or imaging tests. Therefore, various diagnostic criteria have been proposed around the world. Indeed, over ten sets of criteria have been used to date, including those devised in the UK in 1969 [2], in China in 1980 [14], Iran in 1993 [15, 16], Korea in 2003 [17, 18], and the latest international criteria (ICBD), proposed in 2006 [19, 20]. Among all of these sets of criteria, the sets most frequently used globally are the International Study Group criteria ("ISG criteria") [21] and the criteria of the Behçet's Disease Research Committee of Japan ("Japanese criteria") for clinical studies of BS [19, 20, 22]. The Japanese criteria were originally published in 1974 [23], and there have been several subsequent revisions, among which the 1988 version [24] has been most frequently cited in previous studies. The latest revision was published in 2004 [25], but these latter two revisions are very similar (only a few study findings that were not attributable to diagnosis were added). Many groups around the world have validated various sets of criteria [18, 22, 26–28], but the sensitivities and specificities of these sets were somewhat different in each report and each country. Thus, the purpose of the study described in this paper was to compare Behçet's syndrome cohorts from the US and Japan in terms of concordance rates with the International Study Group (ISG) criteria and the Japanese criteria.

Patients and methods

The charts of 769 patients with BS who were referred to one hospital in the US [the NYU Hospital for Joint Diseases BS Center (634 patients)] and two hospitals in Japan [Kameda Medical Center and St. Luke's International Hospital (total of 135 patients)] between 2003 and 2010 were reviewed. All three hospitals were tertiary referral medical centers. The diagnosis of BS was not based on any specific diagnostic/classification criteria, but was made based on clinical manifestations and the expertise of the experienced treating specialists, who were mainly rheumatologists, followed by neurologists, dermatologists, ophthalmologists, and gastroenterologists. The medical charts were reviewed for demographic information, age at onset of BS symptoms, family history of BS, disease manifestations (oral ulcers, genital ulcers, skin lesions, eye disease, vascular lesions, central nervous system lesions, GI lesions, arthritis, and epididymitis), HLA-B51 positivity, pathergy test positivity, and treatment history at baseline visit and during follow-up.

For the ISG criteria, the presence of recurrent oral ulceration is required, and two of the following four symptoms are needed for diagnosis: (1) genital ulceration, (2) eye lesions, (3) skin lesions, and (4) positive pathergy test. On the contrary, the Japanese criteria are slightly more complicated—they contain four main symptoms: (1) recurrent oral ulcers on oral mucosa, (2) skin lesions, (3) ocular lesions, and (4) genital ulcers; as well as five additional symptoms: (1) arthritis, (2) epididymitis, (3) GI lesions, (4) vascular lesions, and (5) central nervous system lesions. Patients with the four main symptoms during their clinical course are defined as the *complete type*, while those of the *incomplete type* are categorized as fulfilling any of the following four patterns: (1) three of the main four symptoms, (2) two of the main symptoms and two additional symptoms, (3) typical ocular lesions and another main symptom, or (4) typical ocular lesions and two additional symptoms during their clinical course. In addition, the Japanese criteria also defines a *suspected type* and a *special lesion type*. In the current study, we defined Japanese criteria fulfillment as being of the complete type or incomplete type, and we did not include the suspected type or the special lesion type, similar to previous reports [3]. We also adopted the 2004 revision for Japanese criteria. Per the Japanese criteria but not the ISG criteria, skin lesions include subcutaneous thrombophlebitis, so medical charts were accurately reviewed regarding this point in order to eliminate misclassification, as has been previously reported [29].

We primarily compared the concordance rates for criteria fulfillment in the US and Japanese cohorts during follow-up, in addition to disease manifestations and treatment. Secondarily, we analyzed associations between the time from the onset of symptoms to the first visit to a BS specialist (T), and the proportion of the patients who fulfilled each criteria in Japanese cohort at the first visit, who were stratified into three groups: (1) 3 months or less (early phase: $T \leq 3$); (2) 3–24 months (middle phase: $3 < T \leq 24$), or (3) more than 24 months (late phase: $T > 24$).

For statistical analysis, Fisher's exact test was used to compare categorical variables and Student's t test to

Table 1 Demographic and clinical characteristics of Behçet's syndrome patients in the US and Japan

Characteristic	US	Japan	*P* value
All patients ($n = 769$), *n* (%)	634 (82.4)	135 (17.6)	
Age at onset, years (mean ± SD), years old	35.2 ± 13.7	38.1 ± 16.1	0.065
Gender (female), *n* (%)	488 (76.8)	78 (57.8)	<0.001
Oral ulcer, *n* (%)	574 (90.5)	124 (91.9)	0.744
Genital ulcer, *n* (%)	463 (73.0)	73 (54.1)	<0.001
Skin lesion[a], *n* (%)	423 (66.7)	102 (75.6)	0.052
Ocular lesion, *n* (%)	169 (26.7)	46 (34.1)	0.091
Arthritis, *n* (%)	326 (51.4)	60 (44.4)	0.155
Gastrointestinal lesion, *n* (%)	217 (34.2)	50 (37.0)	0.551
Central nervous system lesion, *n* (%)	100 (15.8)	17 (12.6)	0.428
Vascular lesion[b], *n* (%)	68 (10.7)	11 (8.1)	0.437
Pulmonary aneurysm, *n* (%)	9 (1.4)	0 (0)	0.373
Deep venous thrombosis, *n* (%)	32 (5.0)	5 (3.7)	0.659
Thrombophlebitis, *n* (%)	23 (3.6)	6 (4.4)	0.621
Epididymitis, *n* (%)	9 (1.4)	8 (5.9)	0.004
Pulmonary disease[c], *n* (%)	3 (0.5)	4 (3.0)	0.021
HLA-B51 positive, *n*, number of tested patients (%)	68/211 (32.2)	28/72 (38.9)	0.316
Pathergy test positive, *n* (%)	59 (9.3)	15 (11.1)	0.521

[a] Skin lesion does not include thrombophlebitis

[b] Vascular lesion include pulmonary aneurysm, DVT and thrombophlebitis

[c] Pulmonary disease does not include pulmonary aneurysm

Table 2 Proportions of US and Japanese patients who fulfilled the ISG and Japanese criteria for Behçet's syndrome in the US and Japan

	US ($n = 634$)	Japan ($n = 135$)	*P* value
ISG criteria, *n* (%)	390 (61.5)*,†,‡	86 (63.7)*,†,‡	0.696
Japanese criteria (total)[a], *n* (%)	439 (69.2)*	98 (72.6)*	0.471
Complete type, *n* (%)	95 (15.0)†	17 (12.6)†	0.591
Incomplete type, *n* (%)	344 (54.3)‡	81 (60.0)‡	0.253

[a] We assumed that both complete-type and incomplete-type patients fulfill the Japanese criteria.

* $P = 0.005$, $P = 0.151$: Japanese criteria (total) versus ISG criteria in the US and in Japan, respectively. †$P < 0.001$: complete type (Japanese criteria) versus ISG criteria in the US and in Japan, respectively. ‡$P = 0.01$, $P = 0.616$: incomplete type (Japanese criteria) versus ISG criteria in the US and in Japan, respectively.

ISG criteria the International Study Group criteria

compare continuous variables. A two-tailed *P* value of less than 0.05 was regarded as statistically significant. STATA version 11 (College Station, TX, USA) was used for all statistical analyses.

Results

Demographic and clinical characteristics

A total of 769 patients (US $n = 634$, Japanese $n = 135$) patients were reviewed. All patients in the Japanese cohort were ethnically Japanese. In the US cohort, patients were multiethnic: Caucasian (74.9 %), Hispanic (6.7 %), African–American (3.7 %), and Asian (5.3 %). The mean age at onset was 35.2 ± 13.7 years in the US and 38.1 ± 16.1 years in Japan. Japanese patients were less likely to be female ($P < 0.001$), have genital ulcers ($P < 0.001$), and were more likely to have epididymitis ($P = 0.004$) and pulmonary disease ($P = 0.021$). Other baseline characteristics were similar in both groups (Table 1). Additionally, we compared Asian patients in the US (34 patients) with the Japanese cohort (all 135 patients are Japanese) in order to investigate ethnic similarities. Differences in gender, genital ulcers, epididymitis, and pulmonary disease were not seen; differences were, however, seen for pulmonary aneurysm (5.9 vs. 0 %, $P = 0.04$) and age at onset (37.1 vs. 47.6 years old, $P < 0.001$).

Fulfilling ISG criteria and Japanese criteria

Proportions of the patients who fulfilled the ISG criteria were similar in both countries (61.5 % in the US; 63.7 % in Japan, $P = 0.696$) (Table 2). Likewise, there was no difference in the proportions of US and Japanese patients who fulfilled the Japanese criteria (69.2 vs. 72.6 %, $P = 0.471$).

Moreover, when we compared only the complete type groups, no difference was seen ($P = 0.591$), and the same was noted for the incomplete type groups ($P = 0.253$). In the US patients, the Japanese criteria were fulfilled significantly more often than the ISG criteria (69.2 vs. 61.5 %, $P = 0.005$). Although it was not statistically significant for the Japan patients (72.6 vs. 63.7 %, $P = 0.151$), there was a tendency for a higher fulfillment rate of the Japanese criteria. For the Japanese cohort, we collected all of the data on the time from onset of BS symptoms [median: five months; interquartile range (IQR): 0.125–78 months] and the follow-up time (median: 2.94 years, IQR: 0–24.4 years). We stratified these data into three groups (early, middle, late phase) and analyzed them, and there was no significant difference among the three groups, even when they were further stratified into complete and incomplete types (Table 3).

Treatment

We reviewed all of the treatments for BS. About a half of the BS patients in both the US and Japan used colchicine and prednisone/predonisolone (Table 4). In Japan, more patients were treated with colchicine ($P < 0.001$), sulfasalazine/mesalazine ($P < 0.001$), and nonsteroidal anti-inflammatory drugs (NSAIDs) ($P = 0.003$). In contrast, more patients in the US received methotrexate ($P = 0.004$), mycophenolate mofetil ($P = 0.008$), and dapsone ($P = 0.005$). Hydroxychloroquine use (not marketed in Japan) was also more common in the US. As for biologics, more patients in the US were treated with anti-tumor necrosis factor (TNF) alpha inhibitors (20.8 vs. 8.1 %, $P < 0.001$). Etanercept (ETN) and adalimumab (ADA) were rarely used for BS in Japan, whereas infliximab (IFX) use (approved for refractory uveitis associated

Table 3 Proportions of patients who fulfilled the ISG and Japanese criteria for Behçet's syndrome in Japanese cohort, stratified by time from onset of BS symptoms

	Time from onset of BS symptoms (T) (months)			P value
	$T \leq 3$	$3 < T \leq 24$	$T > 24$	
All patients ($n = 135$), n (%)	64 (47.4)	20 (14.8)	51 (37.8)	
ISG criteria, n (%)	34 (53.1)	12 (60.0)	34 (66.7)	0.346[b]
Japanese criteria (total)[a], n (%)	39 (60.9)	14 (70.0)	35 (68.6)	0.665[b]
Complete type, n (%)	7 (10.9)	2 (10.0)	7 (13.7)	0.934[b]
Incomplete type, n (%)	32 (50.0)	12 (60.0)	28 (54.9)	0.710[b]

ISG criteria the International Study Group criteria

[a] We assumed that both complete-type and incomplete-type patients fulfill the Japanese criteria

[b] No significant difference among the three groups

Table 4 Summary of the treatments administered to Behçet's syndrome patients in the US and Japan

Treatment	US ($n = 634$)	Japan ($n = 135$)	P value
Colchicine, n (%)	295 (46.5)	90 (66.7)	<0.001
NSAIDs, n (%)	79 (12.5)	31 (23.0)	0.003
Prednisone/predonisolone, n (%)	408 (64.4)	78 (57.8)	0.169
Sulfasalazine/mesalazine, n (%)	18 (2.8)	31 (23.0)	<0.001
Hydroxychloroquine[a], n (%)	51 (8.0)	1 (0.7)	0.001
Thalidomide, n (%)	20 (3.2)	2 (1.5)	0.400
Dapsone, n (%)	29 (4.6)	0 (0)	0.005
Cyclophosphamide, n (%)	17 (2.7)	0 (0)	0.054
First-line immunosuppressants[b]	294 (46.4)	40 (29.6)	<0.001
Azathioprine, n (%)	126 (19.9)	17 (12.6)	0.051
Cyclosporine, n (%)	40 (6.3)	14 (10.4)	0.097
Methotrexate, n (%)	101 (15.9)	9 (6.7)	0.004
Mycophenolate mofetil, n (%)	27 (4.3)	0 (0)	0.008
All anti-tumor necrosis factor alpha inhibitors, n (%)	132 (20.8)	11 (8.1)	<0.001
Infliximab, n (%)	58 (9.1)	10 (7.4)	0.618
Etanercept, n (%)	46 (7.3)	0 (0)	<0.001
Adalimumab, n (%)	28 (4.4)	1 (0.7)	0.044

NSAIDs nonsteroidal anti-inflammatory drugs

[a] It is not marketed in Japan

[b] Included azathioprine, methotrexate, cyclosporine, and mycophenolate mofetil

with BS in Japan) did not differ significantly between the countries.

Discussion

This is the first large study that compares concordance rates for ISG and Japanese criteria fulfillment in US and Japanese BS patients. No differences were seen in the rates of ISG and Japanese criteria fulfillment.

Many sets of criteria have been proposed by various groups, but it is not clear which set of criteria should be adopted worldwide or in individual countries. We hypothesized that Japanese BS patients who are clinically diagnosed with BS tend be biased towards fulfilling the Japanese criteria, and the same is true in the US for ISG criteria fulfillment, so differences in concordance rates should emerge in each country. Both the ISG and the Japanese criteria have been validated in many countries, though primarily within a single country in each study (cf. Turkey, Iran, Korea, Brazil) [18, 22, 26, 30]. Indeed, only one study has validated various criteria in different countries, but this study was limited due to the small number of subjects investigated (8 patients in Japan, 15 in the US) [27]. We could not find any reports on a simultaneous comparison of rates of concordance with the ISG and Japanese criteria in the US and Japan that included a large number of subjects. In this study, we assessed the proportion of patients who fulfilled these two sets of criteria, as well as the clinical manifestations and treatment histories for a three-center cohort of 769 US and Japanese patients with clinically diagnosed BS. There was no significant difference in the rates of concordance with the respective criteria in the patients in either country. Even when the patients were classified by type of Japanese criteria (complete or incomplete), no significant difference was seen between US and Japanese patients. Furthermore, when the complete and incomplete types in both countries were compared individually to the ISG criteria, fewer patients in both subgroups fulfilled the criteria compared to those who fulfilled the ISG criteria. These results suggest that there is only a slight bias due to the criteria used to diagnose BS, even in these two countries with their differences in prevalence. Table 2 shows that the patients in both countries had a higher concordance rate with the Japanese criteria. This is in accord with previous articles in which the ISG criteria were found to be less sensitive than other sets of criteria [18, 30]. This is presumably due to the fact that recurrent oral ulcers are a mandatory component of the ISG criteria. It is well known that not all BS patients manifest oral ulcers [9]; in our cohort, the prevalence of oral ulcers was around 90 %, and some patients fulfilled the Japanese criteria without having oral ulcers (ten in the US and three in Japan).

We also investigated associations between time from onset and criteria fulfillment in the Japanese cohort because of the suspicion that a patient with a long history of BS is more likely to have more cumulative symptoms and therefore to fulfill the criteria. Previous validations of various criteria have not described this [17, 18, 22, 26–28, 30]. We found no statistical difference in criteria fulfillment between the two sets of criteria. This result corroborates a previous report in which the cumulative rate of appearance of symptoms increased until diagnosis, after which it plateaued during the follow-up period of 20–30 years (although it should be noted that the number of subjects included in that study was limited, and it focused on patients in a single country) [3]. Based on these results, we suggest that criteria fulfillment is not significantly influenced by the time elapsed since the diagnosis of BS was made.

We also compared clinical manifestations and treatment histories. Most manifestations in the current study were largely comparable to those seen in previous reports [3, 4, 6, 9]. In particular, our study showed a predominance of females in the US compared to Japan (76.8 % female in the US, 57.8 % in Japan), which was also seen in a previous report (69.0–72.5 vs. 50.6–55.3 %) [3, 6, 9]. However, GI lesions were much more frequent than in previous reports from both countries (10–25 % in Japan, 8 % in the US in previous reports covering the period 1972–2000) [3, 4, 9]. Though our study observed a higher frequency of GI lesions than was reported by Ideguchi et al. [3] in Japan or in a prior Turkish study [11], this is likely due to the recent technical advances made in diagnostic modalities such as double-balloon enteroscopy and capsule endoscopy, and an increase in the overall diagnostic awareness of the disease and its treatment. The disease manifestations were largely similar in the US and Japan patients, except for genital ulcers, epididymitis, and pulmonary disease. This is a novel finding because of the paucity of studies directly comparing these two countries [9]. We also note that pathergy test positivity was low in both countries. Many studies have reported that pathergy test positivity is more frequent in endemic areas such as Japan and Turkey (around 50 %), and is rare in North America and Northern Europe (around 20 %), and they have also showed that this positivity is influenced by many factors, such as needle sharpness and skin sterilization [31, 32]. Pathergy test positivity has decreased over the past decade probably due to improvements in needle sharpness and sterilization. Barnes et al. also questioned the need to include the results of the pathergy test in the International Study Group criteria. However, Davatchi et al. [33] reported that although the pathergy phenomenon has declined, the increase in

specificity was useful for diagnosis, so it had not lost its value as a diagnostic test.

Additional analysis of Asian patients in the US versus the Japanese cohort showed that differences of manifestations were less prominent than those between US and Japanese patients, although differences in pulmonary aneurysm and age at onset were seen. This may suggest that ethnic similarities extend across continents.

Interestingly, more differences were seen in the treatment histories. Current treatments for BS in both the US and Japan vary widely, and include the on-label and off-label use of a variety of agents such as colchicine, steroids, immunosuppressants, and biologics. As shown in Table 4, colchicine, NSAIDs, and sulfasalazine/mesalazine were used more often in Japan, and conversely, methotrexate, ETN, and ADA were used more often in the US. Similarly, other first-line immunosuppressants were used more often in the US. As for biologics, the use of an anti-TNF alpha inhibitor is recommended by expert opinion in cases of refractory BS [34]. In our study, anti-TNF alpha inhibitors were used more often in the US. Since IFX is approved for refractory uveitis associated with BS in Japan, it is worth mentioning that Japanese regulations compensate patients for adverse reactions to medications if they are used for their approved indications, which may be a disincentive to use biologics for nonindicated conditions in Japan. However, among the 11 Japanese cases who used IFX and ADA, seven used them for GI lesions and four used them for severe uveitis. Moreover, differences were also seen in relation to non-TNF immunosuppressive treatments. We are not sure of the reason for this; further studies looking into treatment approaches in the two countries are needed to provide an explanation for it.

Our study has several potential limitations that are often seen in retrospective studies. First, there is the possibility of selection bias. However, we thoroughly reviewed all BS charts in each department potentially associated with BS, including ophthalmology, dermatology, gastroenterology, neurology, and rheumatology. Second, the three hospitals in this study are tertiary care centers. The characteristics of our population may be different from those seen in primary care clinics, though we consider BS to be rare enough that it is seen mainly in large referral centers. Nevertheless, the strength of our study is that it provides a unique opportunity to investigate concordance rates with two sets of criteria of patients in both the US (with a low prevalence of BS) and Japan (with a high prevalence), as well as to compare manifestations and treatment histories between the patients in the two countries.

In conclusion, the concordance rates of patients in the US and Japan with the ISG and Japanese criteria were not significantly different. In addition, we found that there were differences in the manifestations and treatment of BS between both countries. These findings will help to clarify regional differences in the diagnostic and clinical features of BS, and may facilitate further international research as well as comparisons of clinical practice.

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Conflict of interest None.

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