Original Article

Performance of Classification Criteria for Behcet's Disease in an Egyptian Cohort

Mohamed Ahmed Hussein, Mona I Ellawindi[1], Gaafar Ragab

Department of Internal Medicine, Rheumatology and Clinical Immunology Unit, Faculty of Medicine, Cairo University, [1]Department of Community Medicine, Faculty of Medicine, Cairo University, Cairo, Egypt

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Address for correspondence:
Dr. Mohamed Ahmed Hussein, Department of Internal Medicine, Rheumatology and Clinical Immunology Unit, Faculty of Medicine, Cairo University, Cairo, Egypt.
E-mail: m-ahmed79@cu.edu.eg

Abstract

Background: The revised Japanese criteria, the International study group (ISG), the International criteria for Behcet's disease (ICBD) 2006, and the revised ICBD 2010 are frequently used for the classification of Behcet's Disease (BD). In this study we evaluated the performance of these criteria sets in Egyptians.

Methods: A total of of 461 Egyptian patients over 5 years were studied. It included 256 patients classified as BD based on expert opinion and 205 patients with other autoimmune and/or autoinflammatory diseases with symptoms similar to BD. Performance of the revised Japanese criteria, ISG, ICBD 2006, and the revised ICBD 2010 was evaluated evaluated in terms of sensitivity, specificity, negative predictive value (NPV), negative likelihood ratio (NLR), positive predictive value (PPV), positive likelihood ratio (PLR), diagnostic odd ratio (DOR), and Youden's index (YI).

Results: ICBD 2010 carried the highest sensitivity (98.83%), NPV (98.48%), DOR (1645), and YI (0.94) with lowest NLR (0.01). On the other hand, ICBD 2006 and ISG were very specific (99.51%, 99.41%, respectively) with PPV (99.49%, 99.40%) and PLR (155.35, 126.33), respectively.

Conclusions: ICBD 2010 is a very good criteria set to be used in Egyptian BD patients based on its very high sensitivity, accepted specificity, and power of discrimination that enables early patients classification, management, and prognosis.

Key Words: *Behcet's disease, classification criteria, clinical diagnosis, criteria performance*

Introduction

Behcet's disease (BD) is a type of vasculitis that can affect arterial and venous sides of any organ including large- and medium-sized arteries, arterioles, veins, venules, and small vessels as well.

There is no pathognomonic test(s) for diagnosis of the disease, so different classification/diagnostic criteria were proposed to classify the disease for research purposes and to guide the diagnosis. There are about 17 criteria sets[1] among which the revised Japanese,[2] International study group (ISG),[3] International criteria for BD (ICBD) 2006,[4] and revised ICBD 2010[5] are the most commonly used and validated on the different ethnic groups of patients. Egypt is considered has high incidence of the disease being a Mediterranean country,[6] but such criteria have not yet been not validated in Egypt, so we carried out this study to assess the performance of these four criteria sets on a cohort of Egyptian patients and compare it with other previously assessed geographical regions.

Methods

This study included patients attending outpatient clinic of Internal Medicine, Rheumatology and Clinical Immunology division at Kasr Alainy medical school, Cairo University. The data were collected from available fully completed files of 600 Egyptian patients over the past 5 years. A checklist was created to chart the adherence of patients to clinical experts' opinion for diagnosis of BD.

This process was carried out and validated by two of the coauthors independently. The whole process was finally revised and validated by all authors.

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Out of these 600 patients, 461 were included in the study. Two hundred and fifty-six of them were classified as BD based on expert opinion depending on the important clinical manifestations commonly seen in the disease including:

- Mucocutaneous manifestations such as orogenital aphthosis, papulopustular rash, and erythema nodosum.
- Ocular manifestations consistent with the disease according to expert ophthalmologists like uveitis and retinal vasculitis.
- Vascular manifestations including venous thromboembolism, superficial thrombophlebitis, arterial thrombosis, and aneurysms, especially aortic and pulmonary aneurysms.
- Central nervous system (CNS) lesions consistent with the disease namely parenchymal involvement and venous sinus thrombosis.
- Musculoskeletal manifestations including arthralgia or arthritis.
- Gastrointestinal (GIT) involvement such as aphthosis and bleeding while transient, mild manifestations were not considered.
- Epididymoorchitis.
- Positive pathergy test.

The other included 205 patients were diagnosed to have other autoimmune or autoinflammatory diseases that mimicked or shared at least one major symptom of BD including patients with systemic lupus erythematosus, antiphospholipid syndrome (primary or secondary), granulomatosis with polyangiitis, Vogt–Koyanagi–Harada syndrome, multiple sclerosis, inflammatory bowel disease, recurrent idiopathic oral aphthosis, and ankylosing spondylitis.

We excluded 139 patients who had other autoimmune and autoinflammatory diseases that did not mimick or share at least one major symptom of BD.

Statistical analysis

Data were entered and analyzed using the Statistical Package for Social Sciences Software version 16 (Chicago, IL). The performance assessment for the revised Japanese, ISG, ICBD 2006, and revised ICBD 2010 was tested in included patients by measuring sensitivity, specificity, negative predictive value (NPV), negative likelihood ratio (NLR), positive predictive value (PPV), positive likelihood ratio (PLR), diagnostic odd ratio (DOR), and Youden's index (YI) measurements.[7-9]

Ethical approval

All procedures performed in the study were in accordance with the Declaration of Helsinki and was approved by The National Research Committee. Informed written consent was obtained from all included patients.

Results

This study included 256 patients with BD and 205 patients with other diagnostic entities, and Table 1 shows demographic data of included patients.

Our results showed that ICBD 2010 carried the highest sensitivity 98.83% (95% confidence interval [CI]: 96.61%–99.76%) followed by the revised Japanese criteria 86.33% (95% CI: 81.50%–90.29%) then ICBD 2006 with a sensitivity of 75.78% (95% CI: 70.06%–80.90%) and lastly, ISG 64.45% (95% CI: 58.25%–70.31%) [Table 2].

On the other hand, ICBD 2006 had the highest specificity then ISG followed by ICBD 2010 and lastly the revised Japanese criteria with a specificity of 99.51% (CI: 97.31%–99.99%), 99.49% (95% CI: 97.19%–99.99%), 95.12% (95% CI: 91.21%–97.64%), and 93.66% (95% CI: 89.40%–96.58%), respectively [Table 2].

The highest DOR among our patients was for ICBD 2010 followed by ICBD 2006 then ISG and lastly the revised Japanese criteria (1645, 638.32, 369.89, and 93.2, respectively), while YI was highest for ICBD 2010 (0.94), revised Japanese (0.800), ICBD 2006 (0.753), and ISG (0.640), respectively [Table 2].

Discussion

In this study we attempted to find the most suitable criteria set for use among Egyptian BD patients for disease classification and early diagnosis and management.

Table 1: Demographic data of included patients

	Behcet's patients (*n*=256)	BD mimics (*n*=205)
Males/females	218/38	37/168
Age (years), mean±SD	32.42±8.51	30.01±10.66

SD: Standard deviation, BD: Behcet's Disease

Table 2: Parameters of performance of different criteria sets

Validation parameter	Diagnostic criteria			
	Revised Japanese (%)	ISG (%)	ICBD 2006 (%)	ICBD 2010 (%)
Sensitivity	86.33	64.45	75.78	98.83
Specificity	93.66	99.49	99.51	95.12
PLR	13.61	126.33	155.35	20.26
NLR	0.15	0.36	0.24	0.01
PPV	94.44	99.40	99.49	96.20
NPV	84.58	68.18	76.69	98.48
DOR	93.2	369.89	638.32	1645
YI	0.800	0.640	0.753	0.94

PLR: Positive likelihood ratio, NLR: Negative likelihood ratio, PPV: Positive predictive value, NPV: Negative predictive value, DOR: Diagnostic odd ratio, YI: Youden's index, ISG: International study group, ICBD: International Criteria for Behcet's Disease

Our results showed that ICBD 2010 carried the highest sensitivity (98.83%) in line with nearly all previous studies that evaluated this set of criteria but with much higher readings. On the other hand, ISG had the least sensitivity among all criteria sets "64.45%" (95% CI: 58.25%–70.31%) in accordance with many previous studies that showed same results among their cohorts such as ICBD 2006,[4] Germany 2008,[10] China 2008,[11] Iran 2010,[12] 2013,[13] and 2016[14] as shown in Table 3 with the lowest sensitivity being among our patients which may lead to missing or delaying diagnosis of patients with poor morbidities and mortalities.

In contrast to all previous studies, our results showed a lower sensitivity of ICBD 2006 compared to revised Japanese criteria though higher than ISG Table 3.

Specificity of ISG and ICBD 2010 in our cohort were very close to previous studies shown in Table 4 but with a higher value for the former (99.49%) and a rather lesser value for the latter (95.12%). On the other hand, the specificity of ICBD 2006 and revised Japanese criteria were totally different being the first and the last, respectively, in our study versus the last and the second, respectively, in other cohorts.

The highest DOR among our patients was for ICBD 2010 then ICBD 2006, ISG, and lastly, the revised Japanese criteria. This very high discriminative power of ICBD 2010 in our work was shown also in Iran 2010,[12] 2013[13] cohorts that revealed DOR of 897 and 1050, respectively. The high DOR of ICBD 2006 in our results was also in line with Iran 2010,[12] 2013[13] and to a lesser extent in ICBD 2006,[4] Germany 2008[10] who noticed that DOR of ICBD 2006 was higher than ISG and revised Japanese criteria but in contrast to China 2008[11] who stated that DOR of ICBD 2006 was lower than that of ISG but higher than revised Japanese criteria as shown in Table 5.

Table 3: Sensitivity of criteria sets in different studies (in percentage)

Criteria sets	Study									
	ISG[3]	ICBD 2006[4]	Germany 2008[10]	China 2008[11]	ICBD 2010[5]		Iran 2010[12]	Iran 2013[13]	Iran 2016[14]	Present Egyptian cohort
					Training arm	Validation arm				
Number of patients	886	2556	86	1 322	1278	1278	6128	7011	6075	461
Revised Japanese	93	87.9	-	66	88	91	85.8	85.9	88.91	86.33
ISG	92	82.4	83.7	65.4	81	85	78.1	77.5	77.9	64.45
ICBD 2006	-	96.1	96.5	87	94	95	98.2	98.3	-	75.78
ICBD 2010	-	-	-	-	93.9	94.8	96.4	96.8	96.9	98.83

ISG: International study group, ICBD: International Criteria for Behcet's Disease

Table 4: Specificity of criteria sets in different studies (in percentage)

Criteria sets	Study									
	ISG[3]	ICBD 2006[4]	Germany 2008[10]	China 2008[11]	ICBD 2010[5]		Iran 2010[12]	Iran 2013[13]	Iran 2016[14]	Present Egyptian cohort
					Training arm	Validation arm				
Number of patients	886	2556	86	322	1278	1278	6128	7011	6075	461
Revised Japanese	89	92	-	98.3	92	91	97.6	97.7	92.91	93.66
ISG	96	96	89.5	99.2	96	96	98.8	99.2	99.2	99.49
ICBD 2006	-	88.7	73.7	94.1	92	91	95.6	96.2	-	99.51
ICBD 2010	-	-	-	-	92.1	90.5	97.1	97.2	97.2	95.12

ISG: International study group, ICBD: International Criteria for Behcet's Disease

Table 5: Diagnostic odd ratio and Youden's index in different sets of patients

	ISG[3] (*n*=886)		ICBD 2006[4] (*n*=2556)		Germany 2008[10] (*n*=86)		China 2008[11] (*n*=322)		Iran 2010[12] (*n*=6128)		Iran 2013[13] (*n*=7011)		Present Egyptian cohort (*n*=461)	
	DOR	YI	DOR	YI	DOR	YI	DOR	YI	DOR	YI	DOR	YI	DOR	YI
Revised Japanese	107	0.82	84	0.80	-	-	112	0.64	246	0.83	259	0.84	93.2	0.8
ISG	243	0.87	112	0.78	44	0.73	234	0.65	294	0.77	427	0.77	369.89	0.64
ICBD 2006	-	-	193	0.85	77	0.70	107	0.81	1185	0.94	1464	0.94	638.32	0.753
ICBD 2010	-	-	-	-	-	-	-	-	897	0.94	1050	0.94	1645	0.94

ISG: International study group, ICBD: International Criteria for Behcet's Disease, DOR: Diagnostic odd ratio, YI: Youden's index

Youden's index was higher in ICBD 2010, revised Japanese criteria, ICBD 2006, and ISG close to Iran 2010,[12] 2013[13] in which the highest YI was for ICBD 2010 and lowest for ISG but with higher YI for ICBD 2006 and revised Japanese criteria (0.87 and 0.88, respectively) compared to our results. The noticed differences between our results and other studied cohorts may be explained by different clinical presentations according to the differences in ethnicity and environmental factors.

Collectively, our results were not very far from other previous studies concerned with the validation of different criteria sets in other nations and ethnicities. ISG criteria has been repeatedly found to have a lower sensitivity compared to other proposed criteria for the diagnosis of BD.[5,15] On the other hand, the revised ICBD 2010 criteria showed good discriminatory properties with improved sensitivity compared to others that reduces the lag time to diagnosis, with fewer missed patients and earlier treatment capabilities.[16]

There were two other important observations in the present study; first was the high male to female ratio in the BD arm in our study that was not far from two previous Egyptian studies that showed male to female ratio of "75%:25%" and "96.8%:3.2%," respectively[17,18] and another outdoor study with a ratio of 78%:22% in North African patients.[19] This along with the known female predominance of other autoimmune diseases (BD mimics) resulted in the totally different male/female ratio found in our study between BD and those with BD mimics.

Major limitations of our study are retrospective nature, case notes based study and referral bias. In addition lack of information on the disease duration of BD among included patients remains a major limitation of this study as the disease duration would have an impact on the various clinical features used in the classification criteria. However, it can be argued that patients and physicians found it difficult to date the disease onset with precision.

In conclusion, ICBD 2010 is very suitable for classification of BD in Egyptians and is recommended as a guide for disease diagnosis in this population owing to its very high sensitivity and acceptable specificity. Prospective validation studies with long follow-up would perhaps strengthen the findings of the present study.

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Conflicts of interest

There are no conflicts of interest.

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