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A reassessment of the International Study Group criteria for the diagnosis (classification) of Behcet's syndrome

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ABSTRACT

Objective

Patients with ulcerative colitis (UC) and Crohn's disease (CD) were not represented in the diseased controls group that had been utilised in the development of the International Study Group (ISG) criteria for the diagnosis of Behçet's syndrome (BS). Having similar features, both of these conditions can pose problems in the differential diagnosis of BS. Moreover, there has been a recent awareness of coexistence of BS and familial Mediterranean fever (FMF). The aim of this study was to reassess the performance of ISG criteria among patients with BS and other rheumatological conditions, specifically including those with CD, UC, and FMF.

Methods

302 consecutive patients with BS and 438 patients with other rheumatological conditions were surveyed for the presence or absence of the features of BS by means of a standard form which had been prepared according to ISG criteria. All control patients with a history of oral ulcer had a pathergy test and an eye examination by an experienced ophthalmologist with a slit lamp. The sensitivity and specificity of the ISG criteria were calculated.

Results

Seven of 302 patients with BS (2%) did not fulfil the ISG criteria while 5 of 438 controls (1%) fulfilled the ISG criteria.

Conclusion

In this study ISG criteria performed well in correctly classifying BS. Further specificity studies might be considered in CD.

Introduction

Since Mason and Barnes' initial diagnostic criteria in 1969 (1), several criteria sets had been proposed to diagnose BS (2-4). This multiplicity was causing problems in the interpretation of studies based on different sets of patient selection criteria. Thus the ISG criteria were developed (Table I) by multicenter and international cooperation (5).

For the development of the ISG criteria 914 patients with BS had been assessed along with 308 patients with other rheumatological conditions as the control group. However patients with UC and CD were not represented among the controls. Both UC and CD can cause problems in the differential diagnosis of BS, especially through the common presence of arthritic and mucocutaneus manifestations in all three conditions. In addition there has been a recent awareness of the coexistence of BS and FMF (6).

Finally even though the ISG criteria have been around for almost a decade and have found rather wide acceptance, other sets of criteria are still being utilised by some investigators (7, 8). Therefore we thought it worthwhile to reassess the performance of the ISG criteria, including in our control group patients with UC, CD and FMF.

Materials and methods

Three hundred and two unselected and consecutive patients with diagnosed BS were studied at the Behçet's Syndrome Research Centre of Cerrahpasa Medical Faculty of University of Istanbul.

Table I. The ISG criteria for classification of patients with BS.

Recurrent oral ulceration
- Minor aphthous, major aphthous or herpetifom ulceration observed by physician or reported reliably by patient

Recurrent at least three times in one 12-month period

Plus two of followings:

Recurrent genital ulceration
- Recurrent genital aphthous ulcer or scarring, especially males, observed by physician or reported reliably by patient

Eye lesions
- Anterior uveitis
- Posterior uveitis
- Cells in vitreous on slit lamp examination
- Or retinal vasculitis observed qualified physician (ophthalmologist)

Skin lesions
- Erythema nodosum-like lesions observed by physician or reported reliably by patient
- Pseudo folliculitis
- Papulopustular lesions
- Or acneiform nodules consistent with Behçet's syndrome, observed by a physician and in post-adolescent patients not receiving corti costeroids

Positive pathergy test
- To be read by a physician at 48 h, performed with oblique insertion of a 20-22 gauge or smaller needle under sterile conditions.

Table II. Demographic characteristics, current medication, and the frequency of clinical manifestation of BS.

G	N (F)	MA ± SD	MDD ± SD	OU	GU	Skin	Eye	Path	Current therapy
BS	302(129)	34.2 ± 9.4	10.0 ± 7.2	299	257	286	180	215	C (151/302)*, AZ (109), CS (44), P (34)
CD	21(9)	32.8 ± 11.2	6.0 ± 3.7	5	1	4	0	4	5-ASA (17/19), AZ (2), M (1), P (2)
UC	34(14)	31.2 ± 14.8	5.1 ± 4.6	8	0	6	0	2	5-ASA (28/33), AZ (4), M (1), P (15)
FMF	108(50)	24.6 ± 11.4	15.0 ± 9.4	14	0	5	0	1	C (108/108)
RA	99(82)	50.9 ± 10.2	11.8 ± 7.3	17	2	7	1	2	M (49/65), S (15), AZ (1), AM (4), P (47)
SLE	72(65)	36.8 ± 11.4	8.4 ± 6.4	18	4	10	0	2	AM (47/56), AZ (8), CP (3), M (1), P (27)
AS	32(8)	41.3 ± 14.9	10.3 ± 6.3	8	0	2	0	0	S (20/29), M (5), P (1)
SSc	22(20)	40.1 ± 11.6	9.4 ± 4.9	3	0	1	0	0	M (7/19), CP (4), D-penicillamine (2), P (9)
Vasc	15(11)	40.3 ± 16.2	7.4 ± 8.5	4	0	2	0	0	M (6/13), AZ (3), CP (1), AM (1), P (11)
PsA	11(10)	41.2 ± 11.6	9.4 ± 5.8	2	0	1	0	0	M (9/9), P (3)
pSS	14(14)	56.5+10.4	8.1 ± 3.7	1	0	1	0	0	AM (14/14), M (2), P (4)
sSS	5(5)	52.6 ± 7.2	4.6 ± 3.1	1	0	1	0	0	M (4/5), AZ (3), AM (2), P (3)
DM	5(5)	52.4 ± 11.6	5.8 ± 3.1	2	0	2	0	0	M (2/4), AM (1), P (3)

G:patient groups; N: total number of patients; F: female; SD: standard deviation; OU:oral ulcers; GU: genital ulcers; Skin:skin involvement; Eye: eye involvement; Path:positive pathergy test; AS:Ankylosing spondylitis; SSc:systemic sclerosis; Vasc: vasculitis; PsA:psoriatic arthritis; pSS:primary Sjogren's syndrome; sSS:secondary Sjogren's syndrome; DM: dermatomyositis; C:colchicine; AZ:azathioprine; CS: cyclosporine; P:prednisolone; 5-ASA:5-aminosalicylic acid; M:methotrexate; S: sulfasalzine; AM: antimalarial drugs; CP: cyclophosphamide. * The number of patients on whom information was available.

This dedicated, multidisciplinary outpatient clinic currently has around 4500 registered patients. Among these already diagnosed patients the sensitivity of the ISG criteria was reassessed. All except 29 patients had been diagnosed after the publication of the ISG criteria in 1990.

Studying additional 438 consecutive patients with other rheumatological conditions reassessed the specificity of the same criteria, in turn. These patients were consecutive patients studied from the rheumatology outpatient clinic, the dedicated FMF outpatient clinic and the Department of Gastroenterology, all of Cerrahpasa Medical Faculty.

After their physical examinations we asked all patients with BS and other diseases about the history of the presence or absence of the features of BS and recorded their responses on a form that listed the ISG criteria. Furthermore all control patients with oral ulcer had a pathergy test and a slit lamp eye examination by an experienced ophthalmologist.

After coding the data we entered them onto a computer database. The Statistical Package for Social Science (SPSS) software was used in the analysis.

Table III. The true and false positives and negatives diagnoses according to the ISG criteria.

G	N	TP	TN	FP	FN
BS	302	295	0	0	7
SLE	72	0	69	3	0
CD	21	0	20	1	0
RA	99	0	98	1	0
UC	34	0	34	0	0
FMF	108	0	108	0	0
Others	104	0	104	0	0

G=patient groups; N=total number of patients; TP=true positives for ISG criteria; TN=true negatives; FP=false positives; FN=false negatives.

Results

Table II shows the demographic characteristics patients and the frequency of the clinical manifestations related to BS including disease duration and the types of medication used. Seven of 302 patients with BS (2%) did not fulfil the ISG criteria, while 5 patients among 438 controls (1%) - 3 with systemic lupus erythematosus, 1 with rheumatoid arthritis and 1 with CD - fulfilled the ISG criteria (Table III). There were no patients with FMF or UC who fulfilled the ISG criteria.

Thus the overall sensitivity of ISG criteria for BS was 98% among our already diagnosed cases while the specificity was 99% among our controls.

Discussion

In this study the ISG criteria continued to perform well. Our results demonstrate a very good specificity among patients with UC and FMF.

In a retrospective survey Schwartz *et al.* recently identified 16 complete and 23 incomplete cases of BS among a patient pool of 4000 FMF patients in Israel (6).

This gives a frequency of 1% and with the relatively small number, 108 patients, with FMF we prospectively surveyed in the current study, it is hardly surprising that we did not come across any cases of such patients with combined features of FMF and BD among our cases. Furthermore even the quoted frequency of 1% is not also strictly comparable. The ISG criteria used in the current study does not designate an 'incomplete'category. If one only considers only the 'complete' cases in the Israeli series the frequency thus obtained, 0.4 %, is identical to that found in one population survey conducted in a northern region in Turkey (9).

On the other hand perhaps further testing of the criteria are required among greater number of patients with CD in that 1/21 (5%) in this series fulfilled the ISG criteria. This is particularly important for regions, like Japan, where gastrointestinal involvement is common among the native patients with BS. In Turkey, where this study was conducted, gastrointestinal involvement in BS is rather infrequent, like in other coun-

tries around the Mediterranean basin (10). On re-evaluation, the patient with CD who fulfilled the ISG criteria turned out to have genital ulcers with scars in addition to having mouth ulcers, folliculitis and a positive pathergy test. Thus,on retrospect, he indeed probably had BS rather than CD disease. It should also be pointed out that he also had a sister who was being followed with the diagnosis of BS with gastrointestinal involvement.

We do not think the false positive results among few of our patients with SLE and RA are of much clinical importance. Both diseases have other clinical and especially serological markings that are helpful in differential diagnosis.

It is worth noting here that there remain two other disease groups, Reiter's disease and sarcoidosis, among which further specificity studies of ISG criteria are needed. These groups were represented neither in the current nor in the original study.

Finally the continued satisfactory performance of the ISG criteria should not tempt us to use these in the diagnosis of individual patients. The main aim of any disease criteria is classification, for comparing groups of patients for clinical, laboratory or drug studies. While it is true that such criteria are also indeed helpful to clinicians in reminding them of the most important diagnostic features of a disease that are different from other diseases, the criteria cannot replace the individual clinical judgment that has to be made for each patient separately. For example Rao *et al.* have shown that the American College of Rheumatology 1990 criteria for the classification of vasculitis were not satisfactory in the diagnosis of vasculitis (11). It is also worth remembering that the reason that classification criteria do poorly in diagnosing the individual case is not solely due to the issues of sensitivity and specificity. Many disease criteria, especially in rheumatology, have and are being developed for rare diseases. Bayes theorem as applied to medicine (12) tells us that even for sensitivities and specificities that are near to unity, the predictive value of disease criteria would be low if we try to utilise them in a setting with a low prevalence of the condition we are trying diagnose. Furthermore, in many instances, we do not even know what this prevalence truly is.

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