Initial visit symptoms in probable Behçet's syndrome is predictive of ISG criteria fulfillment in Behçet's syndrome: data from New York and Amsterdam cohorts

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ABSTRACT

Objective. *Behçet's syndrome (BS) is a systemic vasculitis with heterogeneous clinical presentation and a relapsing disease course. The International Study Group (ISG) criteria are most often used for classification. A significant proportion of patients is classified as probable BS because they do not fulfil the criteria at initial presentation.*
The aim of this study is to explore clinical BS symptoms present at initial patient visit predictive of ISG criteria diagnosis during follow-up.

Methods. *Patients classified as probable BS at initial visit were included. Follow-up ISG status (defined as meeting criteria ISG+ vs. not meeting criteria ISG-) was abstracted from last visit. Univariable logistic regression was used to screen initial visit clinical features and symptoms with follow-up ISG status. All variables that passed screening at p<0.10 were included in the final multivariable model, which was then used to create a probability risk score.*

Results. *189 patients were included (169 from New York and 20 from Amsterdam). 71 (37.6%) patients were classified as ISG+ during follow-up. In the final model, presence of morning stiffness, genital ulcers, skin lesions, and eye disease were associated with increased odds of ISG+, adjusting for age, symptom duration and family history. This was used to create a probability risk score.*

Conclusion. *Over a third of patients with suspected or probable BS developed new manifestations over time that led to classification as ISG+ BS. The presence of morning stiffness, genital ulcers, skin lesions and eye disease at initial visit were independently associated with significantly higher odds for developing ISG+ Behçet's during follow-up.*

Introduction

Behçet's syndrome (BS) is a systemic vasculitis most commonly seen in countries along the ancient Silk Road. Clinical manifestations of BS are heterogeneous and consist of recurrent oral ulcers, genital ulcers, ocular inflammation, skin disease like erythema nodosum, pathergy positivity, arthritis, deep venous thrombosis and central nervous system vasculitis or thrombosis (1-3). The disease has a relapsing remitting course and tends to be more severe in young males of Mediterranean or Far East origin (2-5). Furthermore, clinical presentation varies with geographic area, for example gastrointestinal involvement is present in 5% of Turkish patients and up to 50% in Japanese BS patients (3, 6).

Because of the relapsing course of the disease and the variety of symptoms and organs involved, diagnoses and classification of patients can be difficult.

Various sets of classification criteria have been developed, of which the International Study Group (ISG) criteria are most often used (7). Fulfilment of the ISG criteria happens when a patient has recurrent oral ulceration (recurrent being defined as at least 3 times in one 12-month period) and any two of the following symptoms: recurrent genital ulceration, uveitis, skin lesions and pathergy positivity (read by a physician after 24–48 hours).

Differences in clinical presentation can complicate classification of the condition, especially in areas where the disease is low in prevalence and even more so when the signs and symptoms evolve gradually.

A significant proportion of patients in our outpatient clinic were initially classified as "probable BS". In some of these cases patients developed additional symptoms over time and met the ISG criteria at a later stage.

Currently in our outpatient clinic when patients are classified as a probable BS, there are no other options but to explain that at this time, they do not meet the criteria. Symptoms may evolve over time, which could or could not change the initial classification. For patients who came in hoping to get more detailed information, these general statements usually are very unsatisfactory.

In clinical practice, a tool to predict which patients would develop a "true" ISG positive BS is lacking. The goal of this retrospective study was to explore clinical manifestations and patient characteristics potentially predictive of developing ISG positive BS during follow up in our cohorts in New York and Amsterdam.

Methods

In this observational study, we included consecutive patients from our outpatient clinics in New York (NYULMC) and Amsterdam (Reade), classified as probable BS at enrolment. Patients fulfilling ISG criteria and patients with an alternative diagnosis at enrolment were excluded.

In our outpatient clinics, data on patient characteristics and clinical manifestations are recorded systematically in a database, both at enrolment as well as during follow up. Physicians (YY, FT and FK) completed questionnaires for all patients, also patients were asked to complete patient reported outcomes regarding disease manifestations and disease activity (*i.e.* RAPID3, BSAS) (8, 9).

The research was in compliance with the Helsinki Declaration, and the protocol was approved by the institutional review board (IRB) at both participating centres.

Demographic data, clinical symptoms, duration of symptoms and RAPID3 score were abstracted from the initial visit to our outpatient clinics. This could either be a first rheumatology visit, but also a patient or physician initiated second opinion (for example rheumatologists, ophthalmologists). Follow-up ISG status [defined as meeting criteria (ISG+) *vs.* not meeting criteria (ISG-)] was abstracted from the last available follow up visit. Ancestry/ethnicity were aggregated by endemic (Turkey, Asia, Middle and Far Eastern countries, Arabic countries and Northern Africa) *versus* non-endemic (Italy, Greece, Spain, Portugal as well as African-American and Northern/European White).

Baseline data were evaluated retrospectively and patients were divided into two groups: those developing ISG positive BS during follow up and those who did not.

Statistical analysis was performed using SPSS, with Chi-square tests or Fisher's exact tests for categorical data and independent sample t-tests for numerical data. Univariable logistic regression was used to screen initial visit clinical features and symptoms with follow-up ISG status. All variables that passed screening at $p \leq 0.10$ were considered potentially relevant and included in the final multivariable model[2], which was then used to create a probability risk score.

This risk score was converted into a nomogram with weighed scores attributed to each variable. The total score corresponds with a probability of developing "true" ISG positive BS.

Table I. Baseline characteristics from patients who were classified as probable Behçet's syndrome at study enrolment.

Characteristics	All patients (n=189)	ISG +[a] (n=71)	ISG –[b] (n=118)
Age years (SD)	34.3 (13.7)	34.1 (13.4)	34.5 (14.0)
Male n (%)	46 (24.3)	13 (18.3)	33 (28.0)
Duration of follow up years (SD)	3.2 (2.4)	3.3 (2.5)	3.1 (2.4)
Ethnicity: endemic area n (%)[$]	43 (22.8)	14 (19.7)	29 (24.6)
Family history of BS n (%)	8 (4.2)	3 (4.2)	5 (4.2)
RAPID3 mean score (SD)	9.8 (6.8)	9.6 (6.9)	9.9 (6.7)
Morning stiffness n (%)*	88 (46.5)	40 (56.3)	48 (40.7)
Duration of symptoms years (SD)	7.3 (7.8)	7.7 (7.9)	7.0 (7.8)
Oral ulcers n (%)	174 (92.1)	66 (93.0)	108 (91.5)
Genital ulcers n (%)	108 (57.1)	47 (66.2)	61 (51.7)
- Labia	63 (33.3)	31 (43.7)	32 (27.1)
Skin disease n (%)[#]	58 (30.7)	31 (43.7)	27 (22.9)
Eye disease n (%)^	33 (17.5)	17 (23.9)	15 (12.7)
Deep venous thrombosis n (%)	4 (2.1)	2 (2.8)	2 (1.7)
Thrombophlebitis n (%)	5 (2.6)	2 (2.8)	3 (2.5)
Central nervous system n (%)	22 (11.6)	6 (8.5)	16 (13.6)
Vascular disease n (%)	7 (3.7)	1 (1.4)	6 (5.1)
Pulmonary disease n (%)	3 (1.6)	0 (0)	3 (2.5)
Arthritis n (%)	35 (18.6)	16 (22.5)	19 (16.1)
Gastrointestinal disease n (%)	40 (21.2)	14 (19.7)	26 (22.0)
Headache n (%)	12 (6.3)	5 (7.0)	7 (5.9)
Epididymitis n (% of males)	3 (6.5)	0 (0)	3 (9.1)

All patients: all patients included in the study.
[a]ISG +: patients who did fulfill ISG criteria after follow-up.
[b]ISG -: patients who did not fulfill ISG criteria after follow-up.
SD: standard deviation; ns: not significant.
[$]Endemic area: patients from Turkey, Asia, Middle and Far Eastern countries, Arabic countries and Northern Africa. Non endemic: patients from Italy, Greece, Spain, Portugal as well as African-American and Northern/European White patients.
*Morning stiffness: morning stiffness scored as present or absent as reported by the patient.
[#]skin disease as defined by ISG criteria (erythema nodosum, papulopustular lesions, pseudofolliculitis, acneiform lesions (in post-adolescent patients not on corticosteroid treatment) observed by physician or patient).
^Eye disease as defined by ISG criteria (anterior or posterior uveitis, hypopyon or retinal vasculitis observed by ophthalmologist).

Results

189 patients were included: 169 from New York and 20 from Amsterdam. Median age was 43.4 years, 24.3% of patients was male. Average duration of follow-up was 3.2 years.

During follow up, 71 (37.6%) patients were reclassified as ISG+ after an average of 9.4 years (± 8.3 years) after onset of symptoms. The mean duration of follow-up until reclassification as ISG+ was 1.7 years (ranging from 0.0–10.3 years).

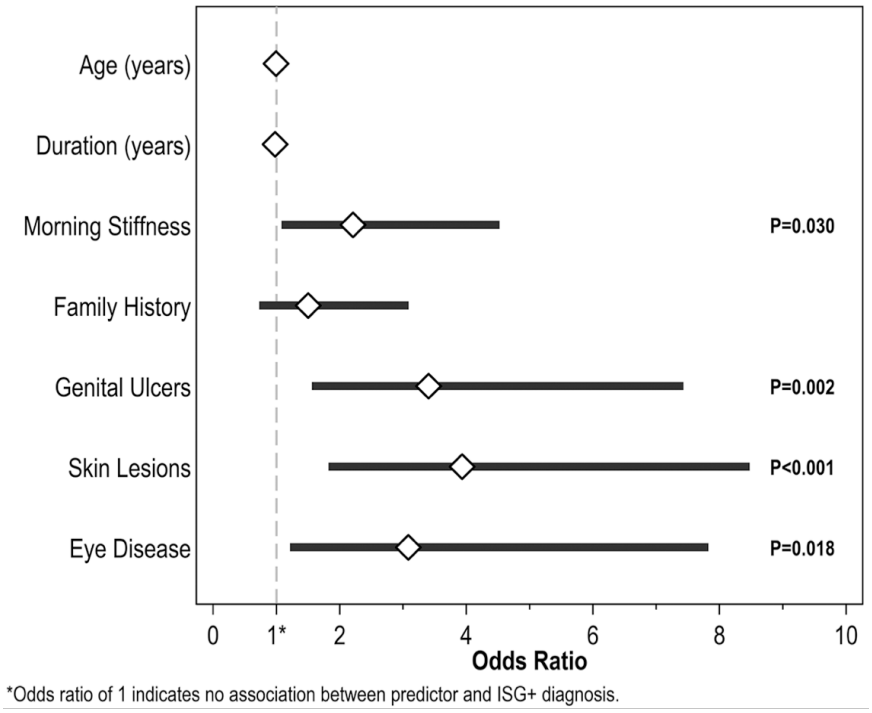

Fig. 1. Odds ratios and 95%-confidence intervals from variables identified by the logistic regression model as predicting ISG positive status.
Factors possibly associated with prevalence of ISG+ are listed, with their respective odds ratios (±SD) and *p*-values on the X-axis. Odds ratio of 1 indicates no association between predictor and ISG+ status.

Patient characteristics, clinical manifestation and RAPID3 score are reported in Table I.

Demographics as well as RAPID3 score and almost all clinical manifestations did not differ significantly between patients who were reclassified as ISG positive BS during follow up and those who did not.

In our cohorts, about a third of patients classified as probable BS at enrolment develop new manifestations over time and can be reclassified as ISG positive BS. Genital ulcerations as a new manifestation occurred 21 times in 21 patients after enrolment; new skin manifestations 54 times in 49 patients and new eye involvement 4 times in 4 patients.

Still, the majority of patients did not fulfil ISG criteria at the last follow-up visit and were still considered "probable" BS.

Presence of morning stiffness, family history of BS, genital ulceration, labial ulceration, skin lesions, eye disease and retinitis were each identified in the

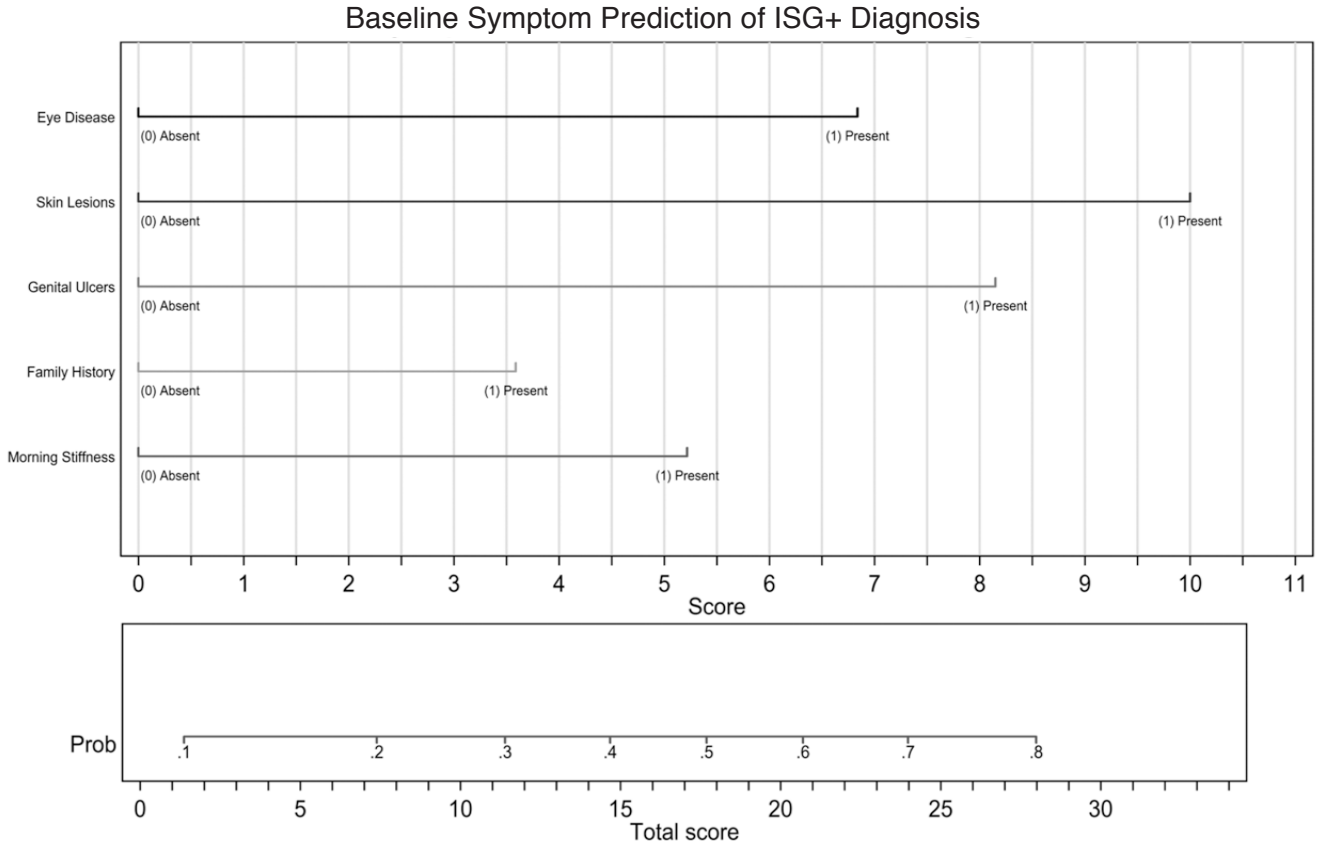

Fig. 2. Nomogram from the logistic regression model predicting ISG+ status.
Points are scored for each manifestation present at baseline (upper part of figure. Eye disease 6.8 points; skin lesions 10 points; genital ulcers 8.2 points; family history 3.6 points; morning stiffness 5.2 points). The total score corresponds with a probability of developing ISG+ BS (lower part of figure).

univariable model as being possibly associated with prevalence of ISG+. All other variables did not pass the screening for inclusion in the multivariate model, because differences between groups were not statistically significant (p-values were ≥0.10).

A multivariable model and probability risk score were created. In the final model, presence of morning stiffness, genital ulcers, skin lesions, and eye disease were associated with increased odds of ISG positivity, adjusting for age, symptom duration and family history (Fig. 1). This model did not include correlated symptoms (*i.e.* genital and labial ulceration as well as eye disease and retinitis). Area under the curve was 0.718, indicating acceptable predictive capability of the final model.[2] This resulted in a probability risk score as shown in Figure 2. Using this model, a patient with skin lesions (10 points) and morning stiffness (5.2 points) has a total score of 15.2 points, corresponding with an approximate 40% probability of ISG+ BS. Adding eye disease (6.8 points) increases the total score to 22 and the probability increases to approximately 64%.

Discussion

We developed a prediction model estimating the risk of developing a "true" ISG positive Behçet using data from our outpatient clinics that have been recorded for over a decade. This provided us with a wide variety of possible predictors.

In our first analysis, however, only a few of them turned out to be significantly different between patients developing a "true" ISG positive Behçet in those who did not. This might partly be due to the low incidence of certain variables in our cohort, reflecting the heterogeneous presentation of BS. Furthermore, the disease course might be less severe in part of the patients in western countries.

Genital ulceration, labial ulceration, skin lesions, eye disease and retinitis were possibly associated with developing a "true" ISG positive Behçet. These variables all are incorporated in the ISG criteria, reflecting the clinical relevance of these criteria.

We did not include correlated symptoms (*i.e.* eye disease and retinitis, genital ulceration and labial ulceration) in the multivariable model, to avoid overrepresentation of certain organ manifestations. Given the retrospective nature of our study, it remains possible that a proportion of patients with eye disease actually had retinitis and likewise, genital ulcers were in fact, labial ulcers in a proportion of patients. Although we checked all data as far as possible.

HLA-B51 and pathergy testing are not routinely performed in our clinics. Due to a large number of missing data on these variables, we were unable to draw any significant conclusions. Pathergy testing is part of the ISG criteria. However, the majority of patients did not have a pathergy test done or the results were not available. This is explained by the retrospective analysis of the data from our outpatient clinics. Patients from the entire country came in for a second opinion, and were not always able to stay long enough in order to perform a pathergy test and evaluate the results. Incorporating these variables in our model may lead to a more robust prediction tool. Therefore, it might be interesting to perform routine HLA-B51 and pathergy testing in a selection of patients and add them to our model.

RAPID3 scores were not significantly different between both groups. This might have been an easy applicable questionnaire to use in clinical practice. The lack of difference might be due to a large burden of disease experienced by both groups, regardless of their diagnosis.

Recently, Esatoglu *et al*. presented data on patients presenting with an incomplete BS (10). During follow-up 42% fulfilled ISG criteria after a median follow-up of 1.5 years. These numbers are similar to our data. However, they focused on patients presenting with major organ involvement suggestive of BS, whereas our population consists of all patients classified as probable BS regardless of the type of organ involvement. Major organ involvement is rare in our population.

The retrospective design is the foremost limitation of our study. Although data were collected prospectively, and patients included consecutively, the questionnaires used in clinical practice were not specifically designed to address the goal of this study. Sometimes additional description of symptoms or missing data could not be retrieved by reviewing records either. However, this design allowed us to review data from a large number of patients and create a prediction model.

Future research is needed to address the usefulness of this model in a European/American cohort as well as in other cohorts.

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