

## Concise report

**Registries in rheumatological and musculoskeletal conditions. Paediatric Behçet's disease: an international cohort study of 110 patients. One-year follow-up data**

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**Abstract**

**Objective.** To set-up an international cohort of patients suspected with Behçet's disease (BD). The cohort is aimed at defining an algorithm for definition of the disease in children.

**Methods.** International experts have defined the inclusion criteria as follows: recurrent oral aphthosis (ROA) plus one of following—genital ulceration, erythema nodosum, folliculitis, pustulous/acneiform lesions, positive pathergy test, uveitis, venous/arterial thrombosis and family history of BD. Onset of disease is <16 years, disease duration is ≤3 years, future follow-up duration is ≥4 years and informed consent is obtained. The expert committee has classified the included patients into: definite paediatric BD (PED-BD), probable PED-BD and no PED-BD. Statistical analysis is performed to compare the three groups of patients. Centres document their patients into a single database.

**Results.** At January 2010, 110 patients (56 males/54 females) have been included. Mean age at first symptom: 8.1 years (median 8.2 years). At inclusion, 38% had only one symptom associated with ROA, 31% had two and 31% had three or more symptoms. A total of 106 first evaluations have been done. Seventeen patients underwent the first-year evaluation, and 36 had no new symptoms, 12 had one and 9 had two. Experts have examined 48 files and classified 30 as definite and 18 as probable. Twenty-six patients classified as definite fulfilled the International Study Group criteria. Seventeen patients classified as probable did not meet the international criteria.

**Conclusion.** The expert committee has classified the majority of patients in the BD group although they presented with few symptoms independently of BD classification criteria.

**Key words:** Pediatric Behçet's disease, Epidemiology, Cohort study, Definition of disease, Early-onset Behçet's disease, Outcome.

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\*See Appendix for members of the PED-BD International Expert Committee.

## Introduction

Behçet's disease (BD) was initially reported under the association of oral genital aphthous lesions plus uveitis. Involvement of medium- and large-size vessels leads to serious complications such as neurological and ocular damage. Most BD cases cluster from Japan to the Mediterranean basin along the former Silk Route. The highest prevalence of BD is reported in Iran:  $68/10^5$ , Japan:  $10\text{--}15/10^5$  and Turkey:  $42/10^5$  [1–4]. Prevalence is markedly lower in Western countries:  $2/10^5$  in Germany and  $2.5/10^5$  in Italy [5–7]. BD is usually encountered in young adults with male predominance in Mediterranean countries. Male patients also have the worst disease course with severe ocular, neurological and vascular involvement [8]. Several attempts to define BD proposed a combination of clinical manifestations, distinguished between major and minor in accordance with their severity and frequency [9, 10]. Diagnostic criteria were defined by the International Study Group (ISG) for BD in 1990 and a convincing classification tree was proposed by an Iranian group in 1993 for adult patients only [11, 12]. BD may be observed before the age of 16 years in 4–26% of cases [5]. Data from a French epidemiological survey conducted in 1992 indicated a prevalence of 1/600 000 children under 15 years of age; however, unawareness of the disease probably caused an important underestimate [13]. In 1998, we could collect 200 paediatric BD (PED-BD) cases, but only half of them could be confirmed using the international criteria [14]. This study is aimed to set up an international cohort of patients suspected with BD and selected on homogeneous criteria. The cohort is aimed at defining an algorithm for definition of the disease in children, also reflecting the natural history. We present herein results from a 2-year study with patients' follow-up at 1 year.

## Patients and methods

### Study design

#### *First step: expert consensus formation*

In 2007, an international expert committee defined, using Nominal Group Technique, homogeneous criteria for inclusion in the PED-BD cohort study and designed an electronic patient chart that enables international collaboration. This committee included four adults and three PED-BD specialists from five countries (Turkey, Iran, Italy, Switzerland and France) (listed in Appendix), and members of either the Paediatric Rheumatology European Society (PRES) or the International BD Society (ISBD).

#### *Second step: setting-up of electronic database, international collaboration and data entry*

A web database (CleanWEB web system) was formatted in 2008, in accordance with the anonymity of patients and following the advice and recommendations of the Commission Nationale Informatique et Libertés (CNIL). Centres specializing in PED-BD (PRES, PRINTO and

ISBD members) have been called to register their patients into the database. Data entry, both retrospective and prospective, started in 2008. Records were selected if patients were not lost to follow-up and if they were first seen in the participating centre within the past 3 years. They were updated annually with the referring doctor receiving an electronic callback.

#### *Third step: judgement criteria*

The expert committee performed charts review during the two international meetings in order to classify patients as definite BD, probable BD or no BD. Sharing participants in a round-robin format collected the votes. Consensus was obtained as an agreement among 80% of the experts. Patients were classified as definite or no BD if consensus was obtained. Patients without consensus were classified as probable.

#### *Fourth step: statistical analyses*

After 2 years of study, statistical analyses were conducted in order to determine the nature and sequence of signs in our patients and to analyse those classified as definite BD using the international criteria. At 4 years, these signs will then be compared between two groups of patients: (i) those who met the existing international criteria; and (ii) those who have not yet achieved these criteria and who will represent an internal control group in order to determine their sensitivity and specificity.

### Inclusion criteria

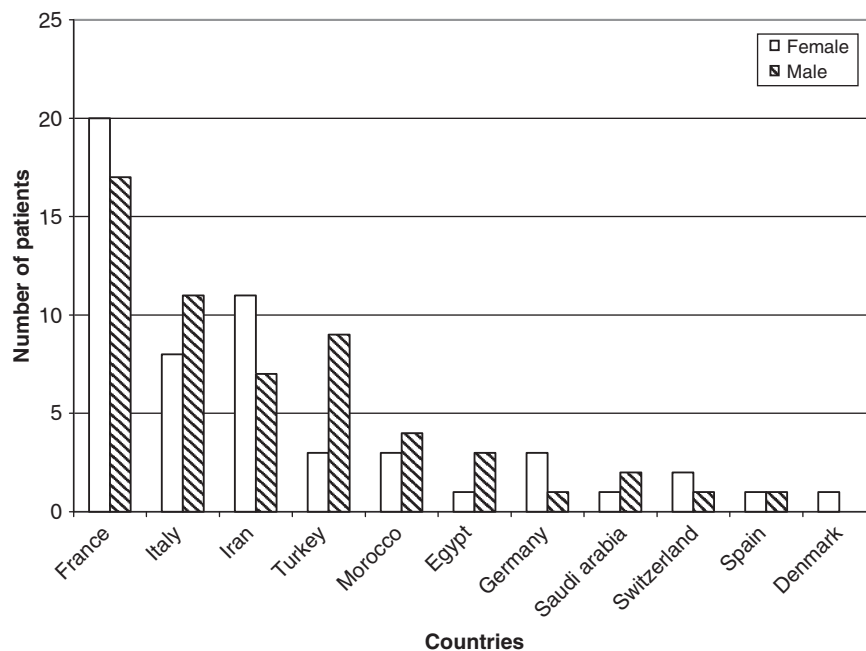
They were defined as widely as possible to avoid any prejudice by existing criteria that will serve at the end as gold standard for statistical analyses. They included: first sign related to BD before the age of 16 years; new patient or patient followed for <3 years; patient being able to be followed for 4 years; and informed consent and ethics committee approval (if applicable in the country). Experts considered recurrent oral aphthosis (ROA) (more than three attacks/year) as mandatory and being associated with at least one of following symptoms: genital ulceration (GU), erythema nodosum, folliculitis, pustulous/acneiform lesions, positive pathergy test, uveitis, retinal vasculitis, venous/arterial thrombosis and documented family history of BD.

### Information contained in the e-CRF

The electronic record (e-CRF: electronic Chart Report Form) contained demographic items, including the ethnicity and presence of consanguinity. A section has been devoted to each category of symptoms, with information on their chronology. Biological items included: inflammatory markers, predisposition to thrombosis and HLA typing.

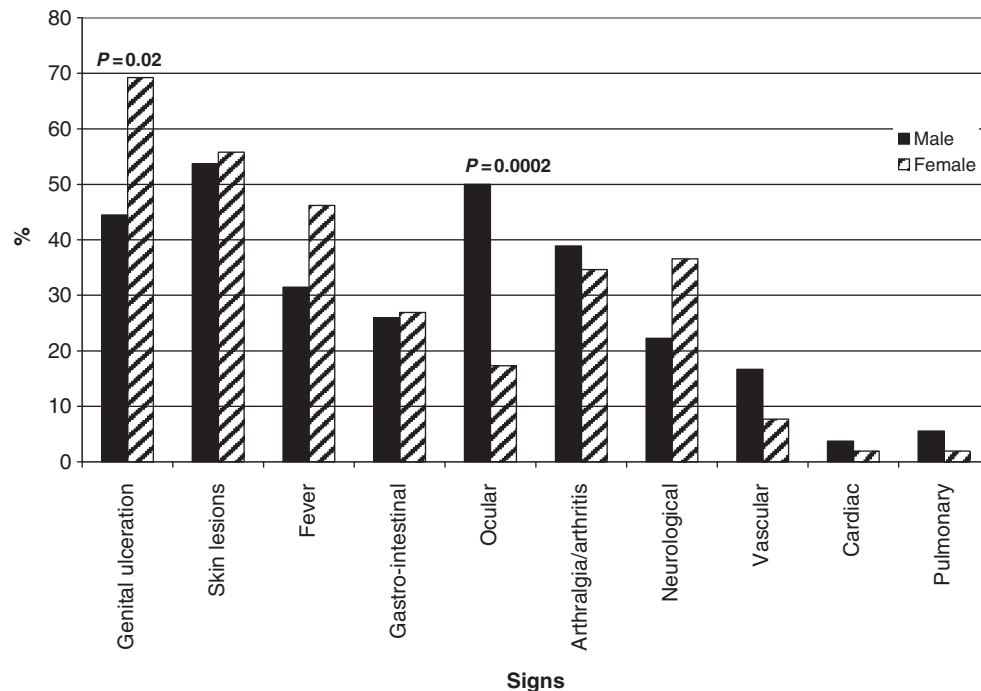
## Results

As of January 2010, 110 patients (56 males/54 females) from 16 centres of 11 countries have been included (Fig. 1). The mean age at inclusion was 13.5 years (median 14.5 years; range 3.4–21.1 years). The mean age at first

**Fig. 1** Distribution of 110 PED-BD patients by country and gender.

symptom was 8.1 years (median 8.2 years). BD was suspected at a mean age of 11.8 years (median 14.4 years). The mean delay between first symptom and BD suspicion was 3.7 years (median 2.7 years; range 0–17 years). At inclusion, 38% (42/110) of patients had only one symptom associated with ROA, 31% had two and 31% had at least three. Most frequent symptoms in addition to ROA were GU in 61% (67/110), skin lesion in 57% (63/110) and uveitis in 30% (33/110). Family history of BD was present in 21 (19%) patients with consanguinity in 4 of them. Other BD-affected relatives were as follows: mother in four cases, father in one, uncle in three, grandfather in one and cousin in one. Three relatives were affected in three families: mother and aunt in two families, father and grandfather in another. Ninety-eight per cent (106) of patients entered the study and were further analysed. Four patients with incomplete documentation were excluded. Fifty-six per cent (59/106) of them presented with one symptom: of those, ROA was present in 42% (45/106). Twenty-four per cent (26/106) had two symptoms (ROA + GU in six of them); 17 of them had three or more signs of BD. Four patients had no symptom at first evaluation, but had presented with ROA in the past and had familial history of BD. ROA was the presenting symptom in 83% of patients. GU was significantly associated with female gender ( $P=0.02$ ). Cutaneous manifestations were present in 52% (58/106) of patients (Fig. 2). They included necrotic folliculitis in 24 (29%) patients, erythema nodosum in 19 (23%), acneiform lesion in 13 (16%), skin ulceration in 7 (8%) and aphthae in 7 (8%). The pathergy test was performed in 38 patients, and was positive in 17 (45%) of them. Thirty-six (34%) patients had a history of uveitis: 7 with anterior uveitis only and 17 with

associated posterior uveitis ( $n=15$ ) and retinal vasculitis ( $n=2$ ). In patients with ocular manifestations, the male predominance (29/36) was statistically highly significant ( $P=0.0002$ ). Seven of them had visual acuity of  $<1/10$  with blindness in one case. Twelve patients had venous thrombosis and one had arterial aneurysm. Neurological signs, presented by 29/31 patients, were headaches in most cases. Other miscellaneous neurological signs were: long-tract dysfunction (one patient), brain stem dysfunction (one patient), optical nerve involvement (one patient), cranial nerve palsy (one patient), severe mental state (one patient) and seizures (three patients). Gastrointestinal symptoms in the form of abdominal pain were reported in 28 (26%) patients. Aphthae (or ulceration) were reported twice with digestive bleeding in one case. Serosal inflammation was reported in seven patients: pleuritis in three, pericarditis in three and orchitis in one. Ninety-three per cent of patients ( $n=99$ ) were receiving treatment. Fifty-nine per cent ( $n=64$ ) received colchicine, 58% steroids ( $n=63$ ) and 14% AZA ( $n=15$ ). HLA-B51 was positive in 44% of patients tested (16/36). Fifty-seven patients underwent a first-year visit. Thirty-six of them had no new symptoms, 12 had one and 9 had two. The expert committee has examined 48 files (4 of them twice) and classified 30 as definite and 18 as probable. In the definite group, the mean (s.d.) age at first symptom was 9.1 (4) years (median 9.6 years; range 1.2–15 years) and the mean (s.d.) age at diagnostic confirmation was 14.4 (4.1) years (median 15 years; range 7–22 years). They did not classify any patient as no BD. Fifteen patients had two or fewer symptoms; 11 of them were classified as probable and 4 as definite. Thirty-three patients had three or more symptoms, 26 being classified as definite and 7 as

**Fig. 2** Clinical signs (percentages) at first visit, according to gender, in 106 PED-BD patients.**TABLE 1** List of the main symptoms in addition to oral aphthosis in patients classified as definite and probable by the committee of experts

	Confirmed (n = 30)	Probable (n = 18)
GU*	21	7
Skin lesions**	22	3
Uveitis	16	6
Arthralgia/arthritis	11	7
Gastrointestinal	12	6
Neurological***	12	3
Vascular	7	1
Fever	13	6

Significant values: \* $P=0.03$ ; \*\* $P=0.0001$ ; \*\*\* $P=0.09$ .

probable. Therefore, having three or more symptoms was significantly associated with classification as definite BD ( $P=0.0005$ ). Among our patients classified as definite, 26/30 (87%) fulfilled the ISG criteria, while 17/18 (94%) classified as probable did not meet the international criteria. The list of main signs present in each group of patients in addition to ROA is represented in Table 1.

## Discussion

This study is a first attempt to define BD in patients before the age of 16 years. Patients registered to the database were expected to have a clinical suspicion of BD, but they were not required to meet any international classification or diagnostic criteria. An international effort

has been made to obtain consensus on homogeneous inclusion criteria and to collect information prospectively. Inclusion criteria were deliberately chosen large enough so as to miss the fewest possible patients who may have BD. The group of experts considered ROA as mandatory, since this sign is present in >95% of patients with BD. Moreover, ROA is the most frequently presenting symptom of BD in patients starting their disease before the age of 16 years [14–17]. As ROA is not very specific for BD, the expert group decided to add at least one symptom from a list to consider the patient as eligible to enter the PED-BD study. The list contained similar signs to those of the ISG criteria, but also included vascular involvement and a family history of BD. At mid-term of the study, we were able to assemble a cohort of 110 patients most of them having only a few symptoms at inclusion. Almost 20% of them had familial history of BD, in accordance with the strong genetic component demonstrated in PED-BD [18, 19]. The presenting symptom was isolated ROA in 83% of the cases. In the evolution, ROA was always present in patients presenting at least three symptoms (data not shown). A few patients entered into their disease with fever, uveitis or neurological symptoms, but never with cutaneous signs and only once with venous thrombosis. Skin lesions and uveitis were reported less frequently than in adult BD (52 and 34%, respectively). Uveitis was significantly more frequent in males and GU in females. Uveitis had a severe course in 20% of the cases with reduced visual acuity of <1/10. The male predominance of uveitis has been reported in many paediatric series, also emphasizing its severity [15, 19–21]. In addition, disease

was active in most cases, while 60% of patients were receiving immunosuppressive treatment. Furthermore, during a 1-year follow-up, one-third of patients had at least one new symptom including three cases of uveitis. These data are in accordance with the study of Yazici *et al.* [8], which showed a more severe BD course in patients with younger onset (before 25 years) of their disease as compared with later-onset ones.

BD was confirmed in 30/48 (62%) patients. The number of symptoms associated with BD confirmation was three or more (including ROA),  $P=0.0005$ . Clinical signs significantly associated with BD confirmation were GU ( $P=0.03$ ) and skin lesions ( $P=0.0001$ ), and were very concordant with the ISG criteria. However, there was no clear association of BD confirmation with uveitis ( $P=0.18$ ), neurological signs ( $P=0.09$ ) and vascular involvement ( $P=0.23$ ).

In conclusion, at this initial step of the study, the expert committee has classified the majority of patients in the BD group although they did not all meet the BD classification criteria at inclusion.

#### Rheumatology key messages

- All paediatric patients with suspected BD do not meet the international criteria.
- Having at least three symptoms was significantly associated with classification as definite BD by the expert committee.
- Skin lesions and GU were significantly associated with classification as definite BD.

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## Appendix 1

PED-BD international expert committee: S. Ozen, H. Ozdogan, A. Gul, F. Shahram, M. Hofer, M. Gattorno and I. Koné-Paut.