Clinical manifestations of Behçet's disease in 137 Italian patients: Results of a multicenter study

N. Pipitone[1], L. Boiardi[1], I. Olivieri[2], F. Cantini[3], F. Salvi[4], R. Malatesta[5], R. La Corte[6], G. Triolo[7], A. Ferrante[7], D. Filippini[8], G. Paolazzi[9], P. Sarzi-Puttini[10], G. Restuccia[1], C. Salvarani[1]

[1]Unità di Reumatologia, Arcispedale Santa Maria Nuova, Reggio Emilia; [2]Unità di Reumatologia, Ospedale di Potenza; [3]Unità di Reumatologia, Ospedale di Prato; [4]Dipartimento Scienze Neurologiche and [5]Unità di Reumatologia, Ospedale Bellaria, Bellaria; [6]Unità di Reumatologia, Ospedale S. Anna, Ferrara; [7]Cattedra di Reumatologia, Università di Palermo; [8]Unità di Reumatologia, Ospedale Niguarda; [9]Unità di Reumatologia, Ospedale di Trento; [10]Unità di Reumatologia, Ospedale L. Sacco, Milan, Italy.

Nicolò Pipitone, MD, PhD; Luigi Boiardi, MD, PhD; Giovanna Restuccia, MD; Carlo Salvarani, MD, Chief of Rheumatology Unit; Ignazio Olivieri, MD, Chief; Fabrizio Cantini, MD, Chief of Rheumatology Unit; Fabrizio Salvi, MD; Renato Malatesta, MD; Renato La Corte, MD; Giovanni Triolo, MD, Chief of Dept. of Rheumatology; Angelo Ferrante, MD; Davide Filippini, MD; Giuseppe Paolazzi, MD; Piercarlo Sarzi-Puttini, MD.

Please address correspondence and reprint requests to: Dr. Carlo Salvarani, Unità di Reumatologia, Arcispedale Santa Maria Nuova, Reggio Emilia, 42100, Italy.
E-mail: Carlo.Salvarani@asmn.re.it

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ABSTRACT

Objective. *To determine the type and frequency of clinical features of Behçet's disease in a population of Italian patients.*

Methods. *We retrospectively studied 137 Italian patients (76 males and 61 females, age at onset 29.6 ± 12.2 [mean ± SD] years) seen consecutively in nine different referral centers. The duration of follow-up at study entry was 10.9 ± 8.2 years. Virtually all patients fulfilled the classification criteria developed by the International Study Group for Behçet's disease. The clinical manifestations of the patients were recorded by the attending physicians using specifically designed forms.*

Results. *The most frequent manifestations at disease onset were oral (78.3%) and genital aphthae (29.2%) followed by inflammatory ocular involvement (20%) and arthritis (14.2%). The commonest (>50% of cases) manifestations observed throughout the disease course were oral aphthae (99.3%), genital aphthae (62.8%), various cutaneous lesions including erythema nodosum (81.8%), and inflammatory ocular disease (60.6%). Panuveitis and posterior uveitis/retinitis occurred more frequently in males compared with females (28.9% versus 11.5% and 57.9% versus 36.1%, respectively; $p < 0.05$). 61.6% of our patients were HLA-B51 positive.*

Conclusion. *Behçet's disease in Italian patients is characterized by a variety of clinical manifestations in agreement with the medical literature. Panuveitis and posterior uveitis/retinitis occur more frequently in male patients.*

Introduction

Behçet's disease (BD) is an inflammatory vasculopathy involving blood vessels of all sizes that occurs predominantly in countries lying along the antique "Silk Road", a route of travel and commerce that connected the eastern Mediterranean with East Asia. Its distribution along this route gives credence to the hypothesis that the disease may have been carried by migrants, although it is unclear whether the transfer involved exogenous agent(s) or genes.

Epidemiological studies have shown that Turkey has the highest prevalence (0.08–0.42%), while the frequency in Korea, China and Japan is on the order of 15-20 cases per 100,000 and in the UK it is as low as 0.64 cases per 100,000 (1,2). However, the true prevalence of the disease in different countries remains difficult to establish because of the rarity of the disease, the paucity of population-based studies (2, 3), and the very limited numbers of disease registers available (4). Studies performed in hospitals have been used to estimate the prevalence of the disease in different areas, but they tend to underestimate by selecting cases with more severe disease and/or multiple organ involvement (severity bias). On the other hand, the advantage of hospital-based studies is that they provide a unique opportunity to review the full spectrum of disease manifestations.

Numerous studies have demonstrated heterogeneity of the disease pattern in different patients (5-7); furthermore, there are also significant differences between racially distinct populations even within the same geographical area (4,8, 9), suggesting a role for genetic factors. In this study we report the clinical features of BD in a large sample of Italian patients seen in 9 referral centers. To our knowledge, this is the second large hospital-based study reporting on the type and frequency of the clinical manifestations of BD in an Italian population after the study by Pivetti-Pezzi *et al*. published in 1995 (10). However,

unlike their study which focused on pediatric patients, our study encompassed patients of all age groups in order to provide a more balanced picture of BD, since some of the clinical manifestations appear to be associated with age at disease onset (6).

Patients and methods

This study was started in 1999 and the data were collected and analyzed by August 2004. 137 Italian patients (76 males and 61 females, ratio male to female: 1.3, age at onset 29.6 ± 12.2 years) seen consecutively in 9 different referral centers were included. All patients but one fulfilled the classification criteria developed by the International Study Group for BD (ISG) (11). The patient that did not meet the above criteria had no oral aphthae (a prerequisite for fulfilling the ISG criteria), but was diagnosed with BD based on a highly suggestive combination of clinical manifestations including papulopustular lesions, anterior and posterior uveitis, epididimitis, and involvement of the central nervous system (CNS).

The patients'symptoms and signs were recorded on standardized forms by physicians trained in the recognition and management of BD. Briefly, for each patient the following data were recorded: date of birth; date of disease onset; duration of follow-up; presence of HLA-B51; pathergy reactivity; and clinical manifestations with their respective dates of onset. All patients were investigated and treated as considered appropriate by their attending physicians according to best clinical practice. The duration of follow-up at study entry was 10.9 ± 8.2 years.

Ocular disease was diagnosed by ophthalmologists as "anterior eye involvement", "posterior eye involvement" or both. Retinal vasculitis was considered part of posterior eye involvement since retinal vasculitis and posterior uveitis are closely associated. Iatrogenic complications (such as cataract or glaucoma) and ocular involvement thought not to be disease-related were not reported. Arthritis was diagnosed in the presence of inflammatory joint pain and swelling. CNS involvement was investigated as deemed appropriate by the attending physicians. However, headache in the absence of other neurological features was not considered a specific neurological manifestation of BD for the purpose of this study, in accordance with other authors (12). Disease manifestations occurring with a frequency of <1% were not reported. HLA-B51 typing was performed by a standard microtoxicity assay. Disease severity was assessed using the scoring system originally proposed by Krause *et al*. (13). Briefly, disease manifestations were divided into "mild" (e.g. oral aphthosis), "moderate" (e.g., arthritis) and "severe" (e.g. uveitis). The total severity score was calculated as the sum of mild features (one point for each), moderate features (two points for each), and severe features (three points for each), respectively. This score has also been successfully used by other authors to grade disease severity in BD (14).

Statistical analysis was carried out using the chi-square test or Fisher's exact test (SPSS software), as appropriate. Correlations were investigated using the Pearson's test. Data have been expressed as the mean ± standard deviation (SD) unless stated otherwise.

Results

Frequency of clinical manifestations at disease onset

Table IA shows the frequency of the clinical manifestations at disease onset. The mean time between the first and second clinical manifestation(s) was 4.2 ± 4.8 years. As expected, the most frequent heralding manifestations of BD were oral aphthae (78.3%) and to a lesser extent genital aphthae (29.2%). However, in a sizable proportion of patients other features were also observed, including arthritis (14.2%) and ocular involvement (20%). In those patients who had no oral or genital ulcerations at disease onset, the most frequent initial clinical manifestations were arthritis (42.9%), cutaneous le-

Table I. Frequency of clinical features in patients with Behçet's disease.

Clinical features	Percentage
A. At disease onset	
Oral aphthae	78.3%
Genital aphthae	29.2%
Oral and/or genital aphthae	82.5%
Cutaneous lesions	22.5%
Papulopustular lesions	10%
Follicular lesions	8.3%
Acne	2.5%
Erythema nodosum	10%
Inflammatory ocular involvement	20%
Anterior uveitis	13.3%
Posterior uveitis & retinal vasculitis	14.2%
Panuveitis	7.5%
Arthritis	14.2%
Central nervous system involvement	5%
Superficial venous involvement	1.7%
B. In patients with Behçet's disease without aphthosis (oral and genital aphthae) at disease onset.	
Clinical features	Percentage
Cutaneous lesions	28.6%
Papulopustular lesions	9.5%
Follicular lesions	9.5%
Acne	4.8%
Erythema nodosum	9.5%
Inflammatory ocular involvement	28.6%
Anterior uveitis	9.5%
Posterior uveitis & retinal vasculitis	23.8%
Panuveitis	4.8%
Arthritis	42.9%
Central nervous system involvement	9.5%
Superficial venous involvement	4.8%

sions including erythema nodosum (28.6%), and ocular involvement in 28.6% of cases (Table IB).

Frequency of clinical manifestations overall and according to gender

Table II shows the frequency of the clinical manifestations found in our study population stratified according to the patients' gender. As expected, oral aphthous ulcerations were the commonest clinical sign, occurring at some point in the disease course in 99.3% of our patients, while genital aphthae were recorded in 62.8% of cases.

Cutaneous lesions, taken together, were the second commonest features, being recorded in 81.8% of all patients. Of the cutaneous lesions, papulo-pustular lesions occurred with the greatest frequency (51.8%), followed by erythema nodosum (38.9%) and follicular lesions (25.5%). Acne was diagnosed in 4.4% patients only. Erythema nodosum (38.9%) was significantly over-represented in females (52.6% versus 26.3% of males; p=0.002) in keeping with numerous other studies from different countries (15-17). There was a trend for an increased prevalence of papulo-pustular lesions (51.8% globally) in males (56.6% versus 45.9% of females) which, however, did not reach statistical significance. More frequent papulo-pustular eruptions in males have previously been described in Turkish studies (15, 17).

Inflammatory ocular involvement was quite common in our population (60.6%), similar to other studies (10, 13, 14) and tended to occur prevalently in males (68.4% versus 50.8% of females, p = 0.053). In particular, posterior eye disease was diagnosed more often in males (57.9%) than in females (36.1%; p = 0.016). Similarly, panuveitis occurred more frequently in male (28.9%) than in female patients (11.5%; p = 0.020). Again, male predominance in terms of eye involvement secondary to BD is well documented in the literature (15, 16).

By contrast, arthritis was equally represented in males (42.1%) and females (44.3%) with a global frequency of 43.1%. We have been unable to confirm the association between arthritis and papulo-pustular lesions described in Turkish patients (18, 19). The reason for this discrepancy between our and the two studies quoted above (18, 19) is unclear, but may be related to differences in the genetic make-up of the populations or to the different study designs (the Turkish studies took into account only those clinical findings that occurred within a short time span, and had therefore a better chance to pick up associated clinical features). Simple arthralgia (joint pain in the absence of signs of inflammation) occurred in 28 (20.4%) patients.

Vascular involvement was another fairly frequent manifestation of BD in our sample, with an overall frequency of 30.7% (21.0% deep vein thrombosis and 10.9% superficial thrombophlebitis). Two patients were found to have thrombi in the right ventricle, one had thrombosis of the inferior vena cava, and one had Budd-Chiari syndrome. There were no significant differences between males and females. There was one case of arterial thrombosis involving the middle cerebral artery. Another patient was diagnosed as having aneurysms of the middle cerebral artery and of the anterior communicans artery, respectively. The prevalence of arterial involvement in our population is comparable to that documented by Krause in Israel (2%) (6), while other studies have shown higher frequencies in the range of 30% (7). Similarly, data from the literature shows that vascular involvement overall differs substantially between patient samples with reported frequencies ranging from 6% to 38% (5). CNS involvement was found in 17.5 of our patients, which is in agreement with previous data (5). We did not consider headache of clinical impor-

Table II. Comparison of clinical features between male and female patients occurring throughout the course of Behcet's disease in our patients' population.

	Males	Females	All	P
Age at disease onset (years, mean ± SD)	29 ± 12	30 ± 13	30 ± 12	> 0.05
Mean disease duration (years, mean ± SD)	9.9 ± 7.9	12.1 ± 8.5	10.9 ± 8.2	> 0.05
Oral ulcers	75/76 (98.9%)	61/61 (100%)	136/137 (99.3%)	> 0.05
Genital ulcers	49/76 (64.5%)	37/61 (60.7%)	86/137 (62.8%)	> 0.05
Cutaneous lesions	61/76 (80.3%)	51/61 (83.6%)	112/137 (81.8%)	> 0.05
Papulopustular lesions	43/76 (56.6%)	28/61 (45.9%)	71/137 (51.8%)	> 0.05
Follicular lesions	19/76 (25.0%)	16/61 (26.2%)	35/137 (25.5)	> 0.05
Acne	5/76 (6.6%)	1/61 (1.6%)	6/137 (4.4%)	> 0.05
Erythema nodosum	20/76 (26.3%)	32/61 (52.6%)	52/137 (38.9%)	0.002
Epididymitis	8/76 (10.5%)	-	-	-
Inflammatory ocular involvement	52/76 (68.4%)	31/61 (50.8%)	83/137 (60.6%)	0.053
Anterior uveitis	30/76 (39.5%)	16/61 (26.2%)	46/137 (33.6%)	> 0.05
Posterior uveitis and retinal vasculitis	44/76 (57.9%)	22/61 (36.1%)	66/137 (48.2%)	0.016
Panuveitis	22/76 (28.9%)	7/61 (11.5%)	29/137 (21.2%)	0.020
Arthritis	32/76 (42.1%)	27/61 (44.3%)	59/137 (43.1%)	> 0.05
Central nervous system involvement	13/76 (17.1%)	11/61 (18.0%)	24/137 (17.5%)	> 0.05
Venous involvement	19/76 (25.0%)	23/61 (37.7%)	42/137 (30.7%)	> 0.05
Deep venous involvement	15/76 (19.7%)	15/61 (24.6%)	30/137 (21.9%)	> 0.05
Superficial venous involvement	5/76 (6.6%)	10/61 (16.4%)	15/137 (10.9%)	> 0.05
Positive pathergy test	14/31 (45.2%)	18/32 (56.3%)	32/63 (50.8%)	> 0.05
HLA-B51 positivity	38/60 (63.3%)	31/52 (59.6%)	69/112 (61.6%)	> 0.05

tance unless it was associated with other neurological features. Epididymitis affected 10.5% of male subjects. There were no documented cases of intestinal ulcerations, except for one patient who had a concomitant diagnosis of ulcerative colitis. Another patient was diagnosed as having lymphocytic colitis, while 4 patients complained of intermittent diarrhea, associated in 2 cases with abdominal pain. HLA-B51 was evaluated in 69 (50.4%) patients only, and was equally represented in females and males. No association between HLA-B51 positivity and specific clinical manifestations was found, although we previously reported a strong association between HLA-B51 and BD in Italian patients (20).

Frequency of clinical manifestations according to age of onset

Previous work has shown that some of the clinical manifestations of BD may be influenced by age at disease onset (6). Therefore, we looked at the frequencies of the clinical features recorded in our patient sample in patients older or younger than 28 years at disease onset, respectively. We chose 28 years as the cut-off point because this represented the median of the sample and thus permitted us to obtain two subgroups of similar size, and because a similar cut-off (25 years) has already been successfully used to discriminate between young and adult patients with BD (21). We found that only 2 variables discriminated between the two age groups, follicular lesions (36.9% in patients < 28 years at disease onset versus 15.3% in patients > 28 years at disease onset; p = 0.061) and papulo-pustular eruptions (43.1% in patients < 28 years at disease onset versus 59.7% in patients >28 years at disease onset; p = 0.006).

Severity of disease according to age of onset and gender

Published data has suggested that BD may be more severe in male patients and in those patients with younger age at disease onset (21). Therefore, we looked for correlations between disease severity and age at onset and gender, respectively. To grade disease severity, we used the scoring system proposed by Krause (13). Our results showed a significant correlation between disease severity and younger age at disease onset (R = 0.75, p = 0.027), whereas we found no correlation between disease severity and duration (R = 0.13, p = 0.13). We were unable to confirm the correlation between disease severity and male gender, although ocular disease appeared to occur more frequently in males, in keeping with previous studies (15,16). Finally, we found no correlation between HLA-B51 positivity and disease severity, in agreement with the results of the study by Gul *et al*. (22).

Association between disease features

Some of the features of BD have been reported as being associated with each other in a number of studies (18,19, 23, 24). In particular, in Turkish patients, the following associations have been described: arthritis and papulo-pustular skin lesions; deep vein thrombosis and superficial vein thrombosis; aphthous ulcerations and erythema nodosum; and a negative association between uveitis and erythema nodosum in female patients only (18,19,23). On the contrary, in a study carried out in Israel, Krause *et al*. identified different associations, including that of folliculitis with genital aphthae and that of papulo-pustular skin lesions with gastro-intestinal involvement (24). We report in Table III the results of the associations found in our patient population. As the table shows, we have been unable to confirm the clusters of manifestations identified in the studies quoted above, whereas we detected numerous other associations. However, the precise reason for these discrepancies is at present unclear (see also below).

Discussion

BD is a vasculitis characterized in the vast majority of cases by oral aphthous ulcerations often associated with genital aphthae and skin lesions of different types. Vascular, ocular, and internal organ involvement occurs less frequently, but contributes substantially to morbidity and mortality (17). Population-based studies have revealed that in many cases BD runs a relatively mild course, characterized mainly by recurrent bouts of aphthous ulcerations and skin lesions (2,3). By contrast, hospital-based studies tend to recruit patients with more varied and more severe disease manifestations such as inflammatory eye disease, CNS involvement, and vasculopathy.

Our study reports on the clinical features of a large sample of predominantly adult Italian patients with BD seen in 9 hospitals over a time span of 5 years. To our knowledge, this is the first large Italian study of this kind, since the only other published Italian hospital-based study on BD that we are aware of was undertaken in a pediatric setting (10). Broadly speaking, the frequency of the various manifestations that we observed appears similar to that reported in previous studies from Germany, Turkey, and Greece (14) (Table IV). We have also been able to confirm some, but not all associations previously described in the literature. In particular, we found erythema nodosum and inflammatory eye disease to occur more commonly in females and males, respec-

Table III. Associations between clinical features throughout the disease course in our study population. The strength of the associations is expressed as relative risk (RR) with confidence interval and significance (p value). Borderline associations have not been reported.

Clinical features	Relative risk (RR)	Confidence interval	p
Genital aphthae and cutaneous lesions	2.6	1.1 – 6.2	0.040
Cutaneous lesions and genital aphthae	2.6	1.1 – 0.2	0.040
Acne and folliculitis	6.5	1.1 – 36.9	0.037
Folliculitis and acne	6.5	1.1 – 36.9	0.037
Posterior uveitis and anterior uveitis	2.5	1.2 – 5.1	0.016
Anterior uveitis and posterior uveitis	2.5	1.2 – 5.1	0.018

Table IV. Frequency of aphthosis and severe clinical features in patients with BD in different studies.

Country Type of study	Italy (this study) Hospital-based	Germany (4) Registry-based	Turkey (15) Hospital-based	Greece (14) Hospital-based
Number of patients	137	89	2313	82
Oral aphthae	100%	99%	100%	100%
Genital aphthae	62.8%	74.5%	88.1%	82.9%
Inflammatory ocular involvement	59.9%	58.9%	29.1%	76.8%
Vascular involvement	30.7%	25.1%	7%	10.9%
CNS involvement	17.5%	12.8%	2.3%	19.5%

tively. These data suggest that some manifestations may be influenced by gender regardless of the different genetic make-ups and/or environments of the populations studied. We could also confirm the association, previously reported by Yazici *et al*. (21), between younger age at onset and disease severity, while we found no correlation between disease duration and severity.

Taken together, these data suggest that in BD the disease burden is not spread evenly throughout the disease course, but is mainly confined to the early years (17); this, in turn, would appear to justify an aggressive therapeutic approach early on in the presence of severe clinical manifestations. By contrast, we found no correlation between male gender and disease severity. However, ocular involvement, which is undoubtedly one of the main causes of morbidity in BD, was significantly over-represented in our male patients. We could not confirm previously reported (18,19,23,24) associations between different clinical manifestations, in particular between arthritis and papulo-pustular skin lesions. It is unclear, however, whether such discrepancies are due to the different genetic make-up of the populations considered, to environmental factors, or to differences in the study designs including patterns of referral, sample size, statistical methods, and follow-up duration. These explanations are not mutually exclusive.

In conclusion, we feel that this study contributes to highlight the clinical features of BD in hospitalized Italian patients. However, specifically designed studies are required to investigate the associations between disease features and to arrive at a realistic estimate of the prevalence of BD in Italy.

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Appendix

International Study Group Criteria for the diagnosis of Behçet's disease (11).

In the absence of other clinical explanation, patients must have:

1. Recurrent oral ulceration (aphthous or herpetiform) observed by the physician or patient recurring at least three times in one 12-month period

and two of the following:

2. Recurrent genital ulceration
3. Eye lesions: anterior uveitis, posterior uveitis, cells in the vitreous by slit lamp examination or retinal vasculitis observed by an ophthalmologist
4. Skin lesions: erythema nodosum, pseudofolliculitis, papulopustular lesions or acneiform nodules in postadolescent patients not on corticosteroids
5. Pathergy, read by a physician at 24-48 hours