# Registry of the Spanish network of Behçet's disease: a descriptive analysis of 496 patients

M. Rodríguez-Carballeira[1], M.A. Alba[2], R. Solans-Laqué[3], M.J. Castillo[4], R. Ríos-Fernández[5], J.R. Larrañaga[6], A. Martínez-Berriotxoa[7], G. Espinosa[2], on behalf of the REGEB investigators

*[1]Department of Internal Medicine, Hospital Universitario Mutua Terrasa, Terrasa, Barcelona, Catalonia, Spain; [2]Dept. of Autoimmune Diseases, Hospital Clinic, Barcelona, Catalonia, Spain; [3]Dept. of Internal Medicine, Hospital Vall d'Hebron, Barcelona, Catalonia, Spain; [4]Unit of Connective Tissue Diseases, Department of Internal Medicine, Hospital Virgen del Rocío, Sevilla, Spain; [5]Unit of Autoimmune Systemic Diseases, Dept. of Internal Medicine, Hospital Clínico San Cecilio, Granada, Spain; [6]Dept. of Internal Medicine, Complejo Hospitalario Universitario de Vigo, Spain; [7]Dept. of Internal Medicine, Hospital de Cruces, Galdakao, Bilbao, Spain.*

*Mónica Rodríguez-Carballeira, MD*
*Marco A. Alba, MD*
*Roser Solans-Laqué, MD, PhD*
*María Jesús Castillo, MD*
*Raquel Ríos-Fernández, MD*
*José Ramón Larrañaga, MD*
*Agustín Martínez-Berriotxoa, MD, PhD*
*Gerard Espinosa, MD, PhD*

*See page 5 for a list of the members of the REGEB Project Group.*

*Please address correspondence to:*
*Gerard Espinosa, MD, PhD,*
*Department of Autoimmune Diseases,*
*Hospital Clinic,*
*Villaroel 170,*
*08036 Barcelona, Catalonia, Spain.*
*E-mail: gespino@clinic.ub.es*

*Received on July 28, 2013; accepted in revised form on November 7, 2013.*

*Clin Exp Rheumatol 2014; 32 (Suppl. 84): S33-S39.*



**Key words:** Behçet's disease, Spain, gender

*Funding: M.A. Alba was supported by Consejo Nacional de Ciencia y Tecnología (CONACyT), Mexico and by the Agencia de Gestió d'Ajuts Universitaris i de Recerca (AGAUR) (Generalitat de Catalunya).*

*Competing interests: none declared.*

**ABSTRACT**

**Objective.** *To describe the clinical features of a large cohort of 496 Spanish patients with Behçet's disease (BD) and to analyse if patient's sex influenced the initial and cumulated prevalence of disease manifestations.*

**Methods.** *Retrospective and descriptive study of 496 patients recruited in sixteen centres on the frame of the Spanish Registry of Behçet Disease Project Group. Demographic and clinical data are presented in addition to treatments and their related adverse effects. Clinical features at disease onset and during follow-up were compared according to the sex of the patients.*

**Results.** *On the whole series, female to male ratio was 1.2:1.0. Mean age at disease onset was 28.7±12.6 years (range 17–73). Oral ulcers were the most frequent initial manifestation presented in 52.0% of patients. During follow-up, eye inflammatory disease was recorded in 45.1% of patients; thrombosis in 19.7% and central nervous system involvement in 13.5%. Men had higher prevalence of ocular involvement and venous thrombosis (52.5% vs. 39.2%, p=0.004 and 26.3% vs. 9.6%, p<0.001, respectively).*

**Conclusions.** *Spanish patients with BD presented similar clinical characteristics as their counterpart in the same geographical area and other world regions. In addition, we confirmed that ocular and vascular involvements are more frequent in men than in women.*

## Introduction

Behçet's disease (BD) is a systemic inflammatory disorder of unknown cause characterised by recurrent oral and genital aphthous ulcers in combination with ocular, cutaneous, gastrointestinal and articular involvement (1). In addition, central nervous system (CNS) inflammatory lesions, venous and arterial thrombosis, and arterial aneurysms may also occur (1, 2).

Behçet's disease typically affects young individuals from 20 to 40 years but it can occur at any age (1). The ancient Silk Road, from the eastern Asia to the Mediterranean basin, is where the highest incidence rates of this inflammatory disorder are found (1). Worldwide, there is a considerable variation in the pattern of systemic involvement in BD (3). In this sense, depending on the geographic localisation male to female ratio varies (4-18). Male proportion of patients is higher in countries like Italy, Greece, France and Spain (4, 5) while women are more frequently affected in America, Israel and Korea (6-8). Ratios of 1:1 have been reported in Portugal, Italy, Iran, Japan and Turkey (9-13). Sex is not only related to differences in epidemiological distribution but also seems to influence clinical manifestations and outcome in BD patients (19-21). In fact, previous studies have reported that male gender is associated with more severe inflammatory involvement of the eye, vascular and central nervous system (19-22).

Although main features of BD have been well documented in previous studies, limited information from series derived exclusive from Southern Europe already exist. Based on the National Spanish Network for BD study, we described the largest cohort (n=496) of Caucasian patients derived exclusively from this region of Europe. In addition, we analysed if differences between male and female patients are confirmed in this specific population.

## Patients and methods

*Patients*

The Spanish Registry of Behçet's Disease (SRBD) or REGEB (*REGistro*

*de la Enfermedad de Behçet* as Spanish nomenclature) Project Group was created by the Spanish Internal Medicine Society in 2009 with the aim of compiling a large cohort of Spanish patients with this rare disorder. By July 2012, sixteen Spanish hospitals with substantial experience in the management of these cases participated in the recruitment of 529 patients that were included in the SRBD Project Group. Diagnosis of BD was performed on the basis of the International Study Group (ISG) criteria for BD (23).

Using an electronic case report, epidemiological and clinical data encompassing more than 72 variables were collected according to a standard protocol designed by the SRBD Project Group and then entered into a SPSS 19.0 statistics database. All case reports had information of at least 90% of the required variables. The Ethics Committee of each participating centre approved the study and written informed consent was obtained from all patients.

*Data collection*

Baseline clinical characteristics included demographic data and first clinical manifestation of the disease. Time of follow-up defined as the time from the fulfilment of the ISG criteria until the last follow-up examination, time in remission, treatment, adverse events and complications were collected. Day of appearance of the first manifestation of BD was considered as disease onset.

Clinical features included oral and genital ulcers, erythema nodosum, pseudofolliculitis, papulopustular lesions, acneiform nodules, and arthritis. Articular involvement was evaluated with x-rays, computed tomography (CT) scan or magnetic resonance imaging (MRI) according to sign and symptoms. Vascular involvement included thrombophlebitis, deep venous thrombosis, and arterial aneurysms, and they were documented by doppler ultrasound and/or angiography as necessary. Gastrointestinal manifestations (chronic diarrhoea, chronic recurrent abdominal pain, intestinal ulcers, bleeding or bowel perforation), urologic disease (epididymitis, orchitis) and eye involvement (anterior and posterior uveitis, panuveitis or retinal vasculitis) were collected as in other series (7, 24). Typical eye inflammation involving uvea and/or retina was confirmed by ophthalmologic evaluation. Central nervous system manifestations were classified as parenchymal or non-parenchymal (vascular) as in previous series (25, 26). Neurologic manifestations were evaluated by MRI, CT scan and/or cerebrospinal fluid examination. Comparison between male and female patients using the same described variables was performed.

Behçet's disease was considered active when patients presented typical disease manifestations at medical appointment. Patients were treated as considered appropriate by their attending physicians according to best clinical practice based on current recommendations (27). Although all medication used for treating BD was recorded, data regarding on order of administration, dosage or duration was not included in the standardised reporting format.

HLA-B51 genotyping was not available in all participating centres and therefore was not reported in the present study. Pathergy test was not recorded given the low prevalence in our area (4, 28). Case report form did not include time of the appearance or duration of each specific symptom.

*Statistical analysis*

This report is a nationwide, cross-sectional analysis of BD patients. Categorical data is summarised as percentages; significant differences or associations were analysed using the $\chi^2$ *test* or Fisher's exact tests. Continuous variables are presented as mean ± standard deviation (SD) or median (interquartile range, IQR) depending on normality demonstrated by Kolmogorov-Smirnov test. Associations of quantitative data were analysed with Student's *t*-test and with the non-parametric Mann-Whitney U-test. A two-tailed value of $p<0.05$ was taken to indicate statistical significance. When independent variables appeared to have statistical significance in the univariate analysis ($p<0.05$), they were included in a multivariate logistic regression analysis using a backward stepwise method. The odds ratios (OR) and their 95% confidence interval (CI) obtained in the adjusted regression analysis were calculated. Statistical analysis was performed using the SPSS program (IBM Corp. 2010, Armonk, NY, SPSS Statistics 19.0).

**Results**

On the entire series, 529 BD patients were included. Considering racial distribution, 496 (94.1%) were Caucasians, 23 (4.3%) Arabic, 7 (1.3%) Black, and the remaining 3 (0.6%) patients were of other origin. For the purpose of the analysis, we only included the Spanish Caucasians patients.

*Demographic characteristics*

Of 496 patients, 272 (54.8%) were women with a female to male ratio of 1.2:1.0. Mean age at disease onset was 28.7±12.6 years (range 17-73). Median follow-up was 134.9 months (IQR 180.5; range 0-758). Median delay of diagnosis was 24 months (IQR 66; range 0–410). Fifty-four patients (10.9%) had a close relative with oral aphtosis. Forty-two patients (8.5%) presented with a medical history relevant for an autoimmune disorder, being thyroid involvement the most frequent. In addition, 3 cases of an inflammatory myopathy (0.6%) were also reported.

*Presenting clinical manifestations*

The main clinical features at the disease onset and during follow-up are described in Table I. Oral ulcers were the most frequent initial manifestation, recorded in 258 patients (52.0%). These ulcers were of different sizes and recurred in all patients. No patient presented only with mucocutaneous manifestations. Ocular involvement as an onset sign was present in 153 cases (30.8%). Of these, 115 presented anterior uveitis, 49 posterior uveitis and 22 retinal vasculitis. The CNS involvement was the first sign of BD in 29 patients (5.8%), 10 of them suffering from aseptic meningitis, 6 from pseudotumour cerebri, 3 from stroke, 2 from sinus thrombosis, and 8 cases suffering from miscellaneous manifestations as epilepsy, cranial nerve palsy, amnesia and CNS vasculitis. The presenting manifestation of BD was vascular involvement in sixteen (3.2%) patients;

**Table I.** Clinical characteristics at disease onset and cumulative manifestations.

| Clinical manifestations | At disease onset n. (%) | Cumulative manifestationsn (%) |
|---|---|---|
| Oral ulcers | 258 (52.0) | 496 (100) |
| Genital aphthosis | 87 (17.5) | 319 (64.3) |
| Pseudofolliculitis | 124 (25.0) | 208 (41.9) |
| Erythema nodosum | 105 (21.6) | 158 (31.9) |
| Ocular involvement | 153 (30.8) | 224 (45.1) |
| Anterior uveitis | 115 (23.1) | 161 (32.5) |
| Posterior uveitis | 49 (9.8) | 65 (13.1) |
| Retinal vasculitis | 22 (4.4) | 66 (13.3) |
| Central nervous system involvement | 29 (5.8) | 67 (13.5) |
| Aseptic meningitis | 10 (2.0) | 36 (7.3) |
| Stroke | 3 (0.6) | 12 (2.4) |
| Pseudotumour cerebri | 6 (1.2) | 12 (2.4) |
| Peripheral neuropathy | 2 (0.4) | 11 (2.2) |
| Arthritis | 87 (17.5) | 172 (34.7) |
| Fever | 36 (6.8) | 77 (15.5) |
| Aneurysms | 2 (0.4) | 5 (1.0) |
| Venous thrombosis | 14 (2.8) | 98 (19.7) |
| Gastrointestinal involvement | 2 (0.4) | 7 (1.4) |

the majority of them (n=14, 2.8%) in the form of venous thrombosis and the remaining two (0.4%) as arterial aneurysms. At the time of inclusion in the SRBD 210 (42.3%) patients presented active disease and 286 (57.7%) were in remission. Time in remission ranged from 0 to 480 months.

*Cumulative manifestations*

During follow-up, mucocutaneous manifestations were present in all patients (Table I). A benign disease evolution characterised by isolated episodes of mucocutaneous involvement was observed in 96 patients (19.3%). Of note, the initial diagnosis of these cases was faster than for others with extra-mucocutaneous manifestations (median 21.0 months [IQR 46; range 0-300] vs 24.0 months [IQR 78; range 0-420], $p$=0.002).

Eye inflammatory disease was recorded in 224 cases (45.1%) with anterior uveitis presented in 32.5% and posterior uveitis and retinal vasculitis in 13% each. Deficit in visual acuity was established in 72 of these 224 patients (32.1%). Thrombotic episodes included deep venous thrombosis of the legs (n=67), stroke (n=12), cerebral venous sinus thrombosis (n=8), inferior vena cava thrombosis (n=7), retinal thrombosis (n=2), right heart thrombosis (n=1) and Budd-Chiari syndrome (n=1). Only 5 (1.0%) patients developed arterial aneurysms.

**Table II.** Treatments used during BD evolution.

| Treatments | n. (%) |
|---|---|
| Oral corticosteroids | 385 (77.6) |
| Colchicine | 366 (73.8) |
| Cyclosporine | 148 (29.8) |
| NSAIDs | 138 (27.8) |
| Azathioprine | 123 (24.8) |
| Pentoxifylline | 89 (17.9) |
| Oral anticoagulation | 68 (13.7) |
| Topical corticosteroids | 72 (14.5) |
| Biologic agents[1] | 62 (12.5) |
| Intravenous corticosteroids | 39 (7.9) |
| Intravenous cyclophosphamide | 30 (6.0) |
| Methotrexate | 33 (6.7) |
| Thalidomide | 25 (5.0) |
| Platelet antiaggregant | 25 (5.0) |
| Chlorambucil | 13 (2.6) |
| Oral cyclophosphamide | 8 (1.6) |
| Antimalarial drugs | 5 (1.0) |

[1]Included: infliximab (n=58), adalimumab (n=3), natalizumab (n=1).
NSAIDs: non-steroidal anti-inflammatory drugs.

*Treatment*

Systemic glucocorticoids were the most frequent treatment, being used in 77.6% of patients (Table II). In 259 (52.2%) patients, the addition of at least one immunosuppressive drug was required. Of them, 113 (22.8%) subjects received more than one immunosuppressant agent. Sixty-two (12.5%) patients received a biologic agent as part of their therapy, tumour necrosis factor (TNF) inhibitors being the most frequent (infliximab n=58 and adalimumab n=3). Natalizumab was administered in one case. Indications for treatment with a biological agent included severe eye inflammatory disease (47% of cases), non-controlling arthritis (37%) and CNS or major vessel disease involvement (16%). Adverse effects were uncommon and consisted in gastrointestinal intolerance (8.1%), new onset systemic hypertension (5.6%), cataracts (3.4%), osteopenia (3.2%), renal failure (2.2%), new onset diabetes mellitus (2.2%), aseptic necrosis of the femoral head (0.8%) and bone marrow toxicity (0.6%). Infections were observed in 5.4% of cases (n=27), being bacterial infections of the urinary tract the most frequent (n=16). Of note, there were two documented cases of pulmonary tuberculosis; one of them treated previously with an anti-TNF agent.

*Comparison between males and females*

Men were younger at disease onset (27.5±12.3 years *vs*. 29.7±12.7 years, $p$=0.042). Median interval between time of disease onset and diagnosis was 24 months for both sexes. Median follow-up was similar, 127 months (IQR 170; range 0-434) for females compared to 144 months (IQR 191; range 0–758) for males.

Presenting clinical characteristics at disease onset and cumulative manifestations during follow-up are depicted in Table III. In the univariable analysis, no statistical differences were found between men and women at initial presentation of BD. In contrast, during evolution of the disorder, isolated mucocutaneous involvement was more common in female patients than in males (23.8% *vs*. 13.9%, $p$=0.006; OR=1.93 95% CI 1.20-3.09). Interestingly, male patients presented higher prevalence of inflammatory eye involvement (52.5% *vs*. 39.2%, $p$=0.004; OR 1.71, 95% CI 1.12-2.25), thrombosis (26.3% vs 9.6%, $p$=<0.001; OR 3.41, 95% CI 2.08-5.64) and global CNS involvement (17.0% *vs*. 10.6%, $p$=0.04; OR 1.72 95% CI 1.03–2.94). In particular two severe ocular manifestations were documented more commonly in men than in wom-

**Table III.** Clinical manifestations according to the patients' sex.

| Clinical manifestations | At disease onset [1] | | Cumulative manifestations | | Univariable analysis | Multivariable analysis |
|---|---|---|---|---|---|---|
| | Male | Female | Male | Female | *p* | *p* |
| Oral ulcers | 126 (55.8) | 133 (48.8) | 224 (100) | 272 (100) | NS | NS |
| Genital ulcers | 33 (14.7) | 54 (19.8) | 140 (70.0) | 179 (75.2) | NS | NS |
| Pseudofolliculitis | 67 (29.9) | 57 (20.9) | 118 (61.1) | 90 (39.0) | NS | NS |
| Erythema nodosum | 42 (16.5) | 63 (23.1) | 61 (34.7) | 97 (43.3) | 0.008 | NS |
| Isolated mucocutaneous involvement | – | – | 31 (13.9) | 65 (23.8) | 0.006 | NS |
| Ocular involvement | 87 (38.8) | 66 (24.2) | 117 (52.5) | 107 (39.2) | 0.004 | 0.007 |
| Anterior uveitis | 56 (24.9) | 59 (21.6) | 84 (37.7) | 77 (28.2) | 0.027 | NS |
| Posterior uveitis | 32 (14.2) | 17 (6.2) | 40 (17.9) | 25 (9.2) | 0.005 | NS |
| Retinal vasculitis | 14 (6.2) | 8 (2.9) | 38 (17.0) | 28 (10.3) | 0.033 | NS |
| CNS involvement | 15 (6.6) | 14 (5.1) | 38 (17.0) | 29 (10.6) | 0.047 | NS |
| Aseptic meningitis | 5 (2.2) | 5 (1.8) | 21 (12.2) | 15 (7.1) | NS | NS |
| Arthritis | 25 (11.1) | 62 (22.7) | 71 (37.6) | 101 (43.9) | NS | NS |
| Venous thrombosis | 10 (4.4) | 4 (1.4) | 59 (26.3) | 26 (9.6) | <0.001 | <0.001 |
| Arterial aneurysms | 2 (0.8) | 0 | 3 (1.8) | 1 (0.5) | NS | NS |

NS: not significant. Data are presented as number (percentage).
[1]Without significant differences between male and female patients.

**Table IV.** Clinical manifestations of patients with Behçet's disease from diverse world regions.

| Clinical manifestations | Southern Europe | | | | | | America | | Asia | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Present series Spain (n=496) | Greece (45) (n=36) | Greece (32) (n=82) | France (46) (n=56) | Italy (40) (n=137) | Spain (4) (n=74) | USA (7) (n=83) | Brazil (24) (n=60) | China (47) (n=437) | Korea (6) (n=1527) | Iran (18) (n=6500) | Turkey (11) (2147) |
| Oral ulcers | 100 | 100 | 100 | 66 | 99 | 98.5 | 100 | 100 | 100 | 99 | 97 | 86.5 |
| Genital ulcers | 65 | 64 | 83 | 19 | 63 | 82 | 62 | 93 | 58 | 83 | 65 | 88 |
| Pseudofolliculitis | 42 | 26 | – | – | 25.5 | 39 | – | – | – | – | 54.5 | – |
| Ocular manifestations | 45 | 61 | 77 | 16 | 82 | 42 | 62 | 63 | 99.5 | 51 | 57 | 29 |
| Skin lesions | 75 | – | 73 | 19 | 34 | 64 | 85 | 71 | 78 | 84 | 65 | – |
| Anterior uveitis | 33 | – | – | – | 39 | 26 | 54 | – | – | – | 41 | – |
| Erythema nodosum | 32 | 56.5 | 51 | – | 43 | 29 | 46 | 26 | – | – | 22.5 | 48 |
| Articular involvement | 35 | 31 | 60 | 53 | 48 | 23 | 46 | 47 | 39 | 38 | 17 | 16 |
| Posterior uveitis | 13 | 41 | – | – | – | 29 | 54 | – | – | – | 45 | – |
| Fever | 16 | – | – | 17 | 17.5 | 39 | – | – | – | – | – | – |
| CNS involvement | 14 | 14 | 19.5 | 25 | 22 | 17 | 23 | 28 | 1 | 5 | 3.5 | 2 |
| Thrombosis | 17 | 14 | – | – | – | 27 | 15 | 5 | – | – | 2 | 11 |
| Aseptic meningitis | 7 | – | – | – | – | – | 8 | 4 | – | – | – | – |
| Stroke | 2 | – | – | – | – | – | 15 | – | – | – | – | – |
| Peripheral neuropathy | 2 | – | – | – | – | – | – | – | – | – | 0.3 | – |
| Aneurysms | 1 | – | – | – | – | – | – | – | – | – | – | 1 |
| GI involvement | 1 | – | 7 | 16 | – | – | – | 3 | 11 | 7 | 7 | 3 |
| Urologic manifestations | 1 | 17 | 18.5 | – | – | – | – | – | 6 | 0.6 | 5 | – |
| Pulmonary disease | – | 3 | 2 | – | – | – | – | – | 0 | – | 0.9 | 1 |

CNS: central nervous system; GI: gastrointestinal.
Data are presented as rounded percentages

en: posterior uveitis, 17.9% *vs*. 9.2% ($p$=0.005; OR 2.17, 95% CI 1.2–3.7) and retinal vasculitis, 17.0% *vs*. 10.3% ($p$=0.033; OR 1.79, 95% CI 1.06–2.56). The multivariable analysis performed by a logistic regression model with sex as dependent variable and clinical features statistically significant in the univariable analysis as independent variables showed that ocular involvement ($p$=0.007; OR 1.68, 95% CI 1.16–2.42) and thrombosis ($p$<0.001; OR 3.37, 95% CI 2.03-5.58) had an independent statistical significant association with male gender (Table III).

The prevalence of different treatments varied accordingly to the differences found in clinical manifestations. Therefore, colchicine (78.8% *vs*. 67.7% $p$=0.006; OR 1.76 95% CI 1.18–2.64) and non-steroidal anti-inflammatory drugs (31.5% *vs*. 23.3%, $p$=0,045; OR 1.51 95% CI 1.05–2.26) were prescribed more frequently to female subjects because of the higher frequency of mucocutaneous involvement. Anticoagulants were administered to 20.2% of men compared to 8.5% of women ($p$<0.001; OR 2.73 95% CI 1.61-4.76). This data was also similar for aspirin and other antiplatelet drugs used in 8.5% *vs*. 2.2%, respectively ($p$=0.002; OR 4.13 95% CI 1.62–10.52).

## Discussion

In the present study we described the main demographic and clinical characteristics of the largest series of BD

patients derived from Southern Europe. In addition, we confirmed that gender might influence on clinical manifestations.

Behçet's disease is characterised by recurrent oral aphtosis in combination with genital ulcers and ocular, skin, articular, neurologic, gastrointestinal or vascular involvement (1). As clinical manifestations are wide and heterogeneous, current therapy is instituted according to disease extent and severity (29), ranging from topical measures for isolated mucocutaneous involvement to TNF-inhibitors, such infliximab or adalimumab for severe involvement (3).

Prevalence of the main symptoms of BD varies widely all around the world. Heterogeneity in reported clinical manifestations are probably explained by conditions such as genetic background (HLA-B51 or other gene polymorphisms) (3, 30), environmental factors or differences in study design and referral patterns. Taking these factors into account, we found that in general, relevant symptoms in our cohort of Spanish BD patients were similar to that reported from America, Asia and importantly, from the same geographic localisation, *i.e*. Italy, Greece, Portugal and France (Table IV). Similarly to the majority of previous published series, mucocutaneous involvement was the most common pattern of disease. Since we applied the ISG criteria (23), 100% of our patients presented with oral aphthae. Genital ulcers and skin lesions in the form of pseudofolliculitis and erythema nodosum were the second most frequent manifestation. Other skin manifestations as pyoderma gangrenosum-type lesions, erythema multiforme-like lesions or palpable purpura were not observed.

Of particular interest, we found that the three variables with the greatest impact in morbidity and mortality, *i.e*. ocular complications, CNS involvement and large vessel manifestations (22, 31), were in the lower range of reported frequencies in different World series, as can be seen in Table IV.

In relation to the clinical findings according to sex, we found that men had cumulative higher prevalence of ophthalmologic involvement in addition to vascular disease. Anterior uveitis, posterior uveitis and retinal vasculitis were all significantly most common in male. In addition, thrombosis was almost three times more frequently recorded in men than in women. Previous studies concluded that young male patients usually suffer more severe disease (32) in the form of ocular (33), CNS (31, 34) and vascular inflammatory manifestations (35-37). Consequently, BD in men is usually more resistant to treatment (38, 39).

Ocular manifestations were more common and generally more severe in men than in women in several cohorts (18, 20, 21, 40, 41). In one of the largest studies available (Turkey, n=2313) (20), anterior and posterior uveitis or retinal vasculitis affected 38% of males compared to 20% of females with a more severe evolution. The CNS involvement in male patients was significantly more frequent and severe in several previous studies (8, 20, 21, 31). The same data was similar for vascular involvement, with large vein thrombosis, superficial phlebitis, arterial occlusions and aneurysms being predominant in men (20, 21, 42).

In contrast to the severe features reported in men, mucocutaneous and articular involvements are more frequently observed in women (20, 21, 32). Interestingly, frequent episodes of oral ulceration during early years of BD are related to more serious course and development of major organ involvement in male patients (43). In the present study, we found a higher prevalence of erythema nodosum in female patients, in accordance with previous series (20, 40, 42). Other differences between male and female patients included a higher prevalence of pulmonary manifestations in men (32, 42).

Previous history of autoimmune involvement of the thyroid recorded in some of our patients probably reflects the high prevalence of chronic autoimmune thyroiditis observed in general population (5–20% in women and 1–2% in men) (44). In addition, as the frequency of myopathy is not increased in BD and given the low number of affected patients suffering from an inflammatory myopathy (n=3), we believe that the presence of both diseases was probably due to a random association.

The strength of the present series included the large number of patients derived from the same geographical zone. However, our study has several limitations including those inherent to all registry-based cohort series, *i.e*. its retrospective design, the accuracy of the clinical diagnosis as judged by the attending physician, limited availability of treatment modalities and the inability to collect some specific data such as the time of the appearance of each manifestation, and the HLA-B51 genotyping status. In addition, registry studies derived from reference hospitals tended to collect patients with more severe disease, such as inflammatory eye disease, CNS involvement and vasculopathy. Some of the statistical significant differences between men and women could be due to the number of patients analysed and importantly, clinical significance is less well defined in many of them. Finally, discrepancies between published studies could be secondary to genetic influences, environmental factors, and differences in study designs or variable definitions. In spite of these limitations, our study represents a real picture of Spanish patients with BD.

In conclusion, Spanish patients with BD presented similar clinical characteristics to BD patients from other world regions. In addition, we confirmed that ocular and vascular involvements are more frequent in men than in women.

## Members of the SRBD Project

The members of the SRBD Project Group or REGEB (REGistro de la Enfermedad de Behçet) who contributed to this study are as follows:

*Juan Carlos Mejía*
Dept. of Autoimmune Diseases, Hospital Clinic, Barcelona, Catalonia, Spain;

*Ferran Martínez-Valle* and *Enric Munté*
Dept. of Internal Medicine, Hospital Vall d'Hebrón, Barcelona, Catalonia, Spain;

*José Luis Callejas*
Unit of Autoimmune Systemic Diseases, Dept. of Internal Medicine, Hospital Clínico San Cecilio, Granada, Spain;

*Rocío González*
Unit of Connective Tissue Diseases, Dept.

of Internal Medicine, Hospital Virgen del Rocío, Sevilla, Spain;

*Antonio Vidaller* and *Xavier Solanich* Dept. of Internal Medicine, Hospital Universitari de Bellvitge, L'Hospitalet de Llobregat, Barcelona, Catalonia, Spain;

*Luis Trapiella* and Ricardo *Gómez de la Torre*
Dept. of Internal Medicine, Hospital Central de Asturias, Oviedo, Spain;

*María Teresa Herranz*
Dept. of Internal Medicine, Hospital General Universitario Morales Meseguer, Murcia, Spain;

*José Todolí*
Dept. of Internal Medicine, Hospital Universitari I Politècnic La Fe, Valencia, Spain;

*Guadalupe Fraile*
Dept. of Internal Medicine, Hospital Universitario Ramón y Cajal, Madrid, Spain;

*Francisco José Muñoz-Rodríguez*
Dept. of Internal Medicine, Hospital de Mollet, Barcelona, Catalonia, Spain;

*Patricia Fanlo*
Dept. of Internal Medicine, Hospital Virgen del Camino, Pamplona, Spain;

*Isabel García-Sánchez*
Dept. of Internal Medicine, Hospital Infanta Leonor, Madrid, Spain;

*Eva Fonseca*
Dept. of Internal Medicine, Hospital de Cabueñes, Gijón, Spain.

## References

1. SAKANE T, TAKENO M, SUZUKI N, INABA G: Behçet's disease. *N Engl J Med* 1999; 341: 1284-91.
2. JENNETTE JC, FALK RJ, BACON PA *et al*.: 2012 revised international Chapel Hill consensus conference nomenclature of vasculitides. *Arthritis Rheum* 2013; 65: 1-11.
3. HATEMI G, SEYAHI E, FRESKO I, HAMURYUDAN V: Behçet's syndrome: a critical digest of the recent literature. *Clin Exp Rheumatol* 2012; 30: S80-9.
4. RICART JM, TODOLI J, VILATA JJ *et al*.: [Behçet disease: study of 74 patients]. *Med Clin* (Barc) 2006; 127: 496-9.
5. ROUX H, RICHARD P, ARRIGHI A, BERGAOUI N: [Autochthonous Behçet's disease. Apropos of 73 cases]. *Rev Rhum Mal Osteoartic* 1989; 56: 383-8.
6. BANG D, LEE JH, LEE ES *et al*.: Epidemiologic and clinical survey of Behçet's disease in Korea: the first multicenter study. *J Korean Med Sci* 2001; 16: 615-8.
7. CALAMIA KT, WILSON FC, ICEN M, CROWSON CS, GABRIEL SE, KREMERS HM: Epidemiology and clinical characteristics of Behçet's disease in the US: a population-based study. *Arthritis Rheum* 2009; 61: 600-4.
8. CHAJEK T, FAINARU M: Behçet's disease. Report of 41 cases and a review of the literature. *Medicine* (Baltimore) 1975; 54: 179-96.
9. OLIVIERI I, LECCESE P, PADULA A *et al*.: High prevalence of Behçet's disease in southern Italy. *Clin Exp Rheumatol* 2013; 31 (Suppl. 77) : S28-31
10. SALVARANI C, PIPITONE N, CATANOSO MG *et al*.: Epidemiology and clinical course of Behçet's disease in the Reggio Emilia area of Northern Italy: a seventeen-year population-based study. *Arthritis Rheum* 2007; 57: 171-8.
11. GURLER A, BOYVAT A, TURSEN U: Clinical manifestations of Behçet's disease: an analysis of 2147 patients. *Yonsei Med J* 1997; 38: 423-7.
12. DE SOUZA-RAMALHO P, D'ALMEIDA MF, FREITAS JP, PINTO J: Behçet's disease in Portugal. *Acta Med Port* 1991; 4: 79-82.
13. KRAUSE I, YANKEVICH A, FRASER A *et al*.: Prevalence and clinical aspects of Behçet's disease in the north of Israel. *Clin Rheumatol* 2007; 26: 555-60.
14. ALTENBURG A, PAPOUTSIS N, ORAWA H, MARTUS P, KRAUSE L, ZOUBOULIS CC: [Epidemiology and clinical manifestations of Adamantiades-Behçet disease in Germany -- current pathogenetic concepts and therapeutic possibilities]. *J Dtsch Dermatol Ges* 2006; 4: 49-64; quiz 5-6.
15. MIZUSHIMA Y: Recent research into Behçet's disease in Japan. *Int J Tissue React* 1988; 10: 59-65.
16. ZOUBOULIS CC, KOTTER I, DJAWARI D *et al*.: Epidemiological features of Adamantiades-Behçet's disease in Germany and in Europe. *Yonsei Med J* 1997; 38: 411-22.
17. ZOUBOULIS CH C, KOTTER I, DJAWARI D *et al*.: Current epidemiological data from the German Registry of Adamantiades-Behçet's disease. *Adv Exp Med Biol* 2003; 528: 43-8.
18. DAVATCHI F, SHAHRAM F, CHAMS-DAVATCHI C *et al*.: Behçet's disease in Iran: analysis of 6500 cases. *Int J Rheum Dis* 2010; 13: 367-73.
19. DAVATCHI F, SHAHRAM F, SHAMS H *et al*.: Gender influence on ocular manifestations and their outcome in Behçet's Disease. A long-term follow-up of up to 20 years. *Clin Rheumatol* 2011; 30: 541-7.
20. TURSEN U, GURLER A, BOYVAT A: Evaluation of clinical findings according to sex in 2313 Turkish patients with Behçet's disease. *Int J Dermatol* 2003; 42: 346-51.
21. DAVATCHI F, SHAHRAM F, CHAMS-DAVATCHI C *et al*.: Behçet's disease: is there a gender influence on clinical manifestations? *Int J Rheum Dis* 2012; 15: 306-14.
22. KURAL-SEYAHI E, FRESKO I, SEYAHI N *et al*.: The long-term mortality and morbidity of Behçet syndrome: a 2-decade outcome survey of 387 patients followed at a dedicated center. *Medicine* (Baltimore) 2003; 82: 60-76.
23. CRITERIA FOR DIAGNOSIS OF BEHÇET'S DISEASE: International Study Group for Behçet's Disease. *Lancet* 1990; 335: 1078-80.
24. OLIVEIRA AC, BUOSI AL, DUTRA LA, DE SOUZA AW: Behçet disease: clinical features and management in a Brazilian tertiary hospital. *J Clin Rheumatol* 2011; 17: 416-20.
25. AKMAN-DEMIR G, SERDAROGLU P, TASCI B: Clinical patterns of neurological involvement in Behçet's disease: evaluation of 200 patients. The Neuro-Behçet Study Group. *Brain* 1999; 122: 2171-82.
26. SBAI A, WECHSLER B, DUHAUT P *et al*.: Neuro-Behçet's disease (isolated cerebral thrombophlebitis excluded). Clinical pattern, prognostic factors, treatment and long term follow-up. *Adv Exp Med Biol* 2003; 528: 371-6.
27. HATEMI G, SILMAN A, BANG D *et al*.: EULAR recommendations for the management of Behçet disease. *Ann Rheum Dis* 2008; 67: 1656-62.
28. BAIXAULI A, CALVO J, TAMARIT JJ, CAMPOS C, GARCIA S, HERRERA A: [Behçet's disease: retrospective study]. *An Med Interna* 2001; 18: 405-10.
29. PERRA D, ALBA MA, CALLEJAS JL *et al*.: Adalimumab for the treatment of Behçet's disease: experience in 19 patients. *Rheumatology* (Oxford) 2012; 51: 1825-31.
30. ZHANG YJ, XU WD, DUAN ZH, LIU SS, PAN HF, YE DQ: Lack of association between CTLA-4 +49A/G and -318C/T polymorphisms and Behçet's disease risk: a meta-analysis. *Clin Exp Rheumatol* 2012; 30: S46-50.
31. TALARICO R, D'ASCANIO A, FIGUS M *et al*.: Behçet's disease: features of neurological involvement in a dedicated centre in Italy. *Clin Exp Rheumatol* 2012; 30: S69-72.
32. ZOUBOULIS CC, VAIOPOULOS G, MARCO-MICHELAKIS N *et al*.: Onset signs, clinical course, prognosis, treatment and outcome of adult patients with Adamantiades-Behçet's disease in Greece. *Clin Exp Rheumatol* 2003; 21: S19-26.
33. DAVATCHI F, SHAHRAM F, CHAMS H *et al*.: The influence of gender on the severity and the outcome of ocular lesions in Behçet's disease. *Adv Exp Med Biol* 2003; 528: 67-71.
34. BENAMOUR S, NAJI T, ALAOUI FZ, EL-KABLI H, EL-AIDOUNI S: [Neurological involvement in Behçet's disease. 154 cases from a cohort of 925 patients and review of the literature]. *Rev Neurol* (Paris) 2006; 162: 1084-90.
35. AMES PR, STEUER A, PAP A, DENMAN AM: Thrombosis in Behçet's disease: a retrospective survey from a single UK centre. *Rheumatology* (Oxford) 2001; 40: 652-5.
36. DUZGUN N, ATES A, AYDINTUG OT, DEMIR O, OLMEZ U: Characteristics of vascular involvement in Behçet's disease. *Scand J Rheumatol* 2006; 35: 65-8.
37. KWON TW, PARK SJ, KIM HK, YOON HK, KIM GE, YU B: Surgical treatment result of abdominal aortic aneurysm in Behçet's disease. *Eur J Vasc Endovasc Surg* 2008; 35: 173-80.
38. YAZICI H, BASARAN G, HAMURYUDAN V *et al*.: The ten-year mortality in Behçet's syndrome. *Br J Rheumatol* 1996; 35: 139-41.
39. YAZICI H, TUZUN Y, TANMAN AB *et al*.: Male patients with Behçet's syndrome have stronger pathergy reactions. *Clin Exp Rheumatol* 1985; 3: 137-41.
40. PIPITONE N, BOIARDI L, OLIVIERI I *et al*.: Clinical manifestations of Behçet's disease in 137 Italian patients: results of a multicenter study. *Clin Exp Rheumatol* 2004; 22:

S46-51.
41. DEMIROGLU H, BARISTA I, DUNDAR S: Risk factor assessment and prognosis of eye involvement in Behçet's disease in Turkey. *Ophthalmology* 1997; 104: 701-5.
42. YAZICI H, TUZUN Y, PAZARLI H *et al*.: Influence of age of onset and patient's sex on the prevalence and severity of manifestations of Behçet's syndrome. *Ann Rheum Dis* 1984; 43: 783-9.
43. HAMURYUDAN V, HATEMI G, SUT N, UGURLU S, YURDAKUL S, YAZICI H: Frequent oral ulceration during early disease may predict a severe disease course in males with Behcçet's syndrome. *Clin Exp Rheumatol* 2012; 30: S32-4.
44. VANDERPUMP MP, TUNBRIDGE WM, FRENCH JM *et al*.: The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham Survey. *Clin Endocrinol* (Oxford) 1995; 43: 55-68.
45. BOURA P, TSELIOS K, SKENDROS P, KAMALI S, SARANTOPOULOS A, RAPTOPOULOUGIGI M: Adamantiades-Behçet disease (ABD) in northern Greece patients: experience from a single center. *Hippokratia* 2007; 11: 210-5.
46. DIANATI B, SALIBA S, ETIENNE G *et al*.: Clinical presentation of Behçet's disease in internal medicine. *Adv Exp Med Biol* 2003; 528: 81-2.
47. YANG P, FANG W, MENG Q, REN Y, XING L, KIJLSTRA A: Clinical features of chinese patients with Behçet's disease. *Ophthalmology* 2008; 115: 312-8 e4.