Epidemiology and clinical domains of Behçet's disease in the Cantabria region, Northern Spain

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Abstract

Objective

The prevalence of Behçet's disease (BD) has a considerable geographical and temporal variability. Data regarding epidemiology in Spain are limited. Our study aimed to assess the epidemiology and clinical domains of BD in a population-based cohort from Northern Spain and to compare the results with other geographical areas of other countries.

Methods

We conducted a cross-sectional study of a well-defined population in Northern Spain. Cases of suspected BD between January 1980 and December 2018 were identified. The diagnosis of BD was established according to the International Study Group (ISG) for Behçet's Disease. The incidence of BD between 1999 and 2018 was estimated by sex, age, and year of diagnosis.

Results

Of 120 patients with probable BD, 59 patients met ISG criteria and were finally included in the study, with a male/female ratio of 0.97; mean age 49.7±14.7 years. Incidence during the period of study was 0.492 per 100,000 people, observing an increase from January 1999 to December 2018. Prevalence was 10.14 per 100,000 inhabitants in 2018. Clinical manifestations were relapsing aphthous stomatitis (100%), genital ulcers (78%), skin involvement (84.7%), joint involvement (64.4%), uveitis (55.9%), central nervous system (16.9%), vascular (10.2%), and gastrointestinal manifestations (6.8%).

Conclusion

The prevalence of BD in Cantabria is higher than in other Southern European countries. This difference may reflect a combination of geographic, genetic, or methodological variations, as well as the free accessibility to the Spanish Public Health System for the entire population. Clinical phenotypes observed are similar to those described in other world regions.

Key words

Behçet's disease, vasculitis, epidemiology, prevalence, uveitis

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Introduction

Behçet's disease is included among primary vasculitis, in the group of variable vessel vasculitis, according to International Chapel Hill Consensus Conference Nomenclature of Vasculitides (1). It can affect vessels of any size (small, medium, and large) and type (arteries, veins, and capillaries). BD is characterised by recurrent oral and/or genital aphthous ulcers accompanied by cutaneous, ocular, articular, gastrointestinal, and/or central nervous system (CNS) involvement (1-3). Its aetiology remains unknown, but genetic, inflammatory, and infectious factors have been proposed. To the present, several diagnostic criteria have been proposed being the 1990 International Study Group (ISG) for BD (4) the most widely used. More recently has been proposed the 2014 International Criteria for BD (ICBD) (5).

Epidemiology of BD shows great variability among different countries worldwide (6-24). BD was detected mainly along the historical Silk Road. The highest prevalence has been observed in countries of the Middle East such as Turkey (602/100,000) (12) or Jordan (479.8/100,000) (25, 26). In Europe, the prevalence is lower. However, in recent years the prevalence is increasing probably due to the immigration of people from countries with high prevalence and to a better understanding and early diagnosis of the disease (2). By contrast, the current trend in incidence appears to be decreasing, as reported by authors from Korea (27) and Japan (28). Therefore, epidemiology is variable and must be continuously updated.

Nevertheless, some reports were published more than twenty years ago (8, 14-16), while others include small or even non-reported sample sizes (7, 8, 12, 13, 20). In addition, there are few studies from Southern European countries (21-24).

Moreover, divergences have been observed according to sex, age, and clinical domains. Some studies show higher prevalence in males (7, 9-11, 13, 18, 19, 21) while others show greater prevalence in females (6, 8, 12, 14-17, 20, 23). The same happens regarding mean age at disease onset ranging from 24 years to 38.5 years depending on the geographic area (6, 9). According to clinical domains, oral and genital ulcers are very prevalent in all regions. Skin, neurological, vascular, and gastrointestinal involvement are more prevalent in European countries while joint and ocular involvement is similar in all the regions.

Traditionally, Spain, located in Southern Europe, is not considered a high-prevalence BD region but information available is scarce and outdated.

Diagnostic criteria applied by the different authors are also varied (6-24). 1990 ISG criteria offer mild sensitivity (85%) but high specificity (96%) (4). 2014 ICBD criteria are more suitable for diagnosis due to their higher sensitivity (94.8%) despite their decreased specificity (90.5%) (5). Some reports apply Iran Classification Tree (16, 17), expert opinions (13), or O'Duffy criteria (8). However, 1990 ISG criteria are more widely used.

Taking into account all these considerations, we have evaluated the epidemiology in a well-defined population of patients from Cantabria, in Northern Spain, diagnosed according to 1990 ISG criteria for BD, and followed between 1980 and 2018.

Patients and methods

Patients and study design

We conducted an observational, retrospective, study including 120 patients diagnosed with probable BD according to expert opinion criteria in the region of Cantabria, in Northern Spain, between January 1980 and December 2018. Then, we applied 1990 ISG diagnostic criteria for BD obtaining a total of 59 patients with BD.

The three most important public hospitals of Cantabria's region were included in the study (Hospital Universitario Marqués de Valdecilla, Hospital Sierrallana and Hospital de Laredo).

Patients were identified from a database obtained from clinical data compatible with BD in reports provided by different departments of participating hospitals (Admission, Dermatology, Ophthalmology, Neurology, Gastroenterology, Internal Medicine, Emergencies, and Rheumatology). Our sample

is quite homogeneous as 57 patients are Caucasian and only 2 where from other origin (Moroccan). Follow-up was made since initial diagnostic until nowadays. Three patients died during follow-up, so they were excluded.

Diagnosis of BD was established according to ISG diagnostic criteria (Supplementary Table S1) where BD was confirmed if recurrent oral ulceration was present plus any one of the following manifestations: recurrent genital ulceration, eye or skin lesions, or positive pathergy test. CNS involvement was split into parenquimatous (cranial nerve palsy, optic neuropathy, stroke and transient ischaemic attack), and non-parenquimatous (meningitis, intracranial hypertension and cerebral venous sinus thrombosis). Gastrointestinal involvement includes Crohn's disease, irritable bowel syndrome and unspecified intestinal inflammation. Clinical characteristics of the patients belong to retrospective cumulative data.

Diagnosis and follow-up were carried out by expert rheumatologists and, in required cases, by other specialties such as Ophthalmology, Dermatology, Gastroenterology, or Neurology. This study was approved by the local Ethics Committee of the University Hospital Marqués de Valdecilla (protocol reference: 2020.083).

In 2018, the total population in Cantabria was 581,877 people, according to Cantabria Health Service's annual reports (https://www.scsalud.es/memorias) and the National Statistics Institute (https://www.ine.es/), which is the official and most important data collection centre in Spain since 1945. Cantabrian population remains steady around 550,000 inhabitants since 1980 until nowadays with little variations.

Variables and data collection

The following variables were obtained from medical records: demographic data (age at diagnosis, sex, and ethnicity), initial symptoms, and organ involvement. Clinical characteristics of the patients belong to retrospective cumulative data.

HLA-B*51 and pathergy test were performed in a small number of patients so we decided not to include these tests in this manuscript as we considered they were not representative.

To minimise entry mistakes, all data were double-checked. Finally, the information was stored in a computerised database.

Statistical and data analysis

Incidence and prevalence were reported annually (on December 31st of every year) per 100,000 person-year and per 100,000 population, respectively. The annual incidence rate was calculated as the number of new cases of BD over the population at risk for the disease in a specific year. Despite data recording starting in January 1980, the incidence was calculated from 1999 as there were no reliable data available from previous years. Regarding prevalence, the numerator was the number of living patients diagnosed with BD living in Cantabria in December 2018 and the denominator was the total population in the region. Mean age, mean age at onset, and clinical manifestations were calculated globally and stratified by sex and by age. Quantitative variables were expressed as mean and standard deviation (SD), and qualitative variables as absolute numbers and percentages (%). Statistical analysis was performed with IBM SPSS Statistics for MacOS, v. 25 (IBM Corp. Armonk, N.Y., USA).

Table I. Demographic characteristics and clinical phenotypical features listed globally and according to sex distribution.

	Total (n=59)	Female (n=30)	Male (n=29)	*p*-value (female *vs*. male)
Age, mean ± SD	49.7 ± 14.7	50 ± 15.2	49.4 ± 14.4	0.918
Age at onset, mean ± SD	35.8 ± 12.7	36 ± 11.9	35.6 ± 13.7	0.231
Duration, mean ± SD	12.5 ± 10.1	12.6 ± 10.5	12.4 ± 9.7	0.527
Relapsing oral ulcers	59 (100%)	30 (100%)	29 (100%)	1
Genital ulcers	46 (78%)	22 (73.3%)	24 (82.8%)	0.532
Skin	50 (84.7%)	25 (83.3%)	25 (86.2%)	1
Pseudofolliculitis	38 (76%)	18 (72%)	20 (80%)	0.589
Erythema nodosum	20 (40%)	17 (52%)	7 (28%)	0.017
Uveitis	33 (55.9%)	15 (50%)	18 (62.1%)	0.435
Unilateral/bilateral	21 (63.6%) / 12 (36.4%)	10 (66.7) / 5 (33.3%)	11 (61.1%) / 7 (38.9%)	--
Anterior uveitis	17 (51.5%)	7 (46.7%)	10 (55.6%)	0.399
Intermediate uveitis	0 (0%)	0 (0%)	0 (0%)	1
Posterior uveitis	10 (30.3%)	5 (33.3%)	5 (27.8%)	1
Panuveitis	6 (18.2%)	3 (20%)	3 (16.7%)	1
Joint	38 (64.4%)	20 (66.7%)	18 (62.1%)	0.789
Arthralgia	36 (61%)	20 (100%)	16 (88.9%)	0.430
Arthritis	22 (37.3%)	11 (55%)	11 (61.1%)	1
Central nervous system	10 (16.9%)	7 (23.3%)	3 (10.3%)	0.299
Parenchymatous	6 (60%)	6 (85.7%)	0 (0%)	0.024
Non-parenchymatous	7 (70%)	4 (57.1%)	3 (100%)	1
Parenchymatous +non-parenchymatous	3 (30%)	3 (42.9%)	0 (0%)	0.237
Vascular	6 (10.2%)	3 (10%)	3 (10.3%)	1
Deep venous thrombosis	3 (50%)	2 (66.7%)	1 (33.3%)	1
Arterial thrombosis	0 (0%)	0 (0%)	0 (0%)	1
Aneurysms	1 (1.7%)	1 (33.3%)	0 (0%)	1
Other vascular manifestations	Myocardial Infarction 1 (1.7%), Aortitis 1 (1.7%)	None	Myocardial Infarction 1 (33.3%), Aortitis 1 (33.3%)	--
Gastrointestinal	4 (6.8%)	3 (10%)	1 (3.4%)	0.612
Unspecified intestinal inflammation	3 (75%)	2 (66.7%)	1 (100%)	1
Crohn's disease	1 (25%)	1 (33.3%)	0 (0%)	1
Irritable bowel syndrome	0 (0%)	0 (0%)	0 (0%)	1

CNS: central nervous system; CI: confidence interval; SD: standard deviation.
Values are expressed as numbers (n) and percentages (%), unless otherwise stated.

Results

Patients and demographic characteristics

We studied 120 patients with suspected BD according to expert opinion. 59 pa-

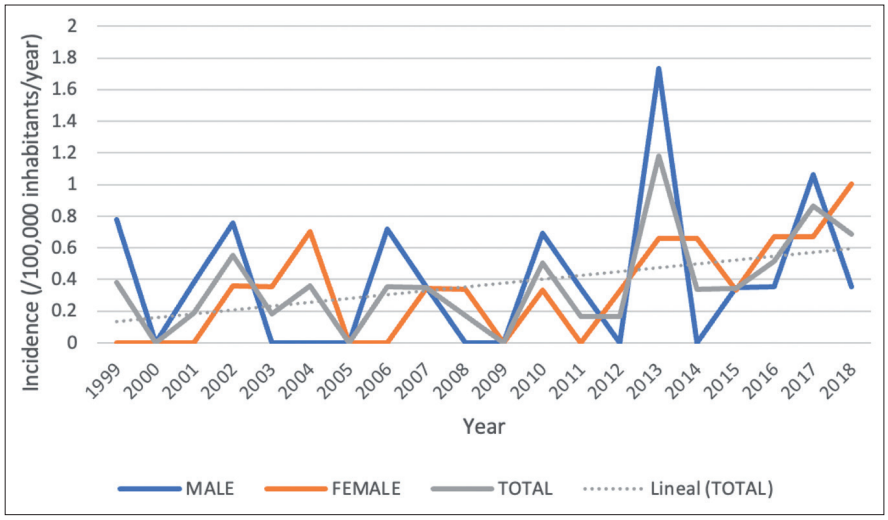

Fig. 1. Annual incidence of Behçet's disease in our series.

Table II. Distribution of clinical phenotypes according to age ranges at the time of the last evaluation in our series of patients with Behçet's disease.

	10-19 (n=5)	20-29 (n=13)	30-39 (n=22)	40-49 (n=11)	≥ 50 (n=8)
Age, mean ± SD	35.2 ± 10.7	38.3 ± 11.7	47.1 ± 8	63.1 ± 10.6	66 ± 11.7
Age at onset, mean ± SD	17.4 ± 0.548	24.2 ± 1.95	33.9 ± 3	45.5 ± 2	58.3 ± 8.5
Relapsing oral ulcers	5 (100%)	13 (100%)	22 (100%)	11 (100%)	8 (100%)
Genital ulcers	5 (100%)	10 (76.9%)	20 (90.9%)	6 (54.5%)	8 (100%)
Skin	4 (80%)	12 (92.3%)	16 (72.7%)	10 (90.9%)	8 (100%)
Uveitis	3 (60%)	6 (46.2%)	15 (68.2%)	5 (45.5%)	4 (50%)
Joint	4 (80%)	6 (46.2%)	14 (63.6%)	8 (72.7%)	6 (75%)
Central nervous system	1 (20%)	2 (15.4%)	3 (13.6%)	2 (18.2%)	2 (25%)
Vascular	0 (0%)	0 (0%)	1 (4.5%)	3 (27.3%)	2 (25%)
Gastrointestinal	0 (0%)	0 (0%)	2 (9.1%)	1 (9.1%)	2 (25%)

SD: standard deviation.
Values are expressed as numbers (n) and percentages (%), unless otherwise stated.

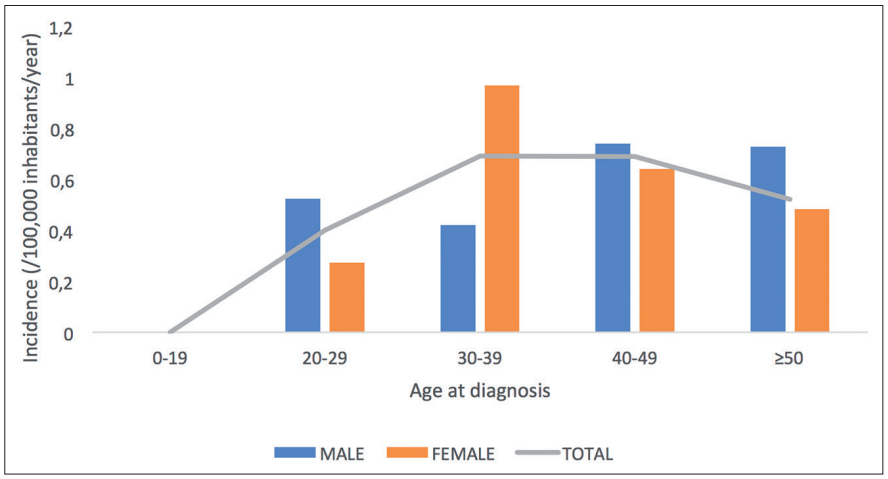

Fig. 2. Incidence of Behçet's disease stratified by age and sex.

tients met ISG diagnostic criteria (30 females and 29 males), with a male to female ratio (M/F) of 0.97. Fifty-six were Caucasian and three had Moroccan origin. Three patients died during follow-up so they were excluded from the study. The main demographic features are summarised in Table I.

The prevalence of BD in Cantabria in December 2018 was 10.14/100,000 inhabitants. decreasing with age as only 8 patients of the total were older than 50 years. Annual incidence of BD in Cantabria between 1999 and 2018 was 0.492 per 100,000 population (0.496/100,000 population in men and 0.488/100,000 population in women). Incidence was steady until 2013 when a peak in total incidence was observed (1.18/100,000 population/year) and then pulled back in 2014 to 0.33/100,000 population/year. Later, the incidence has progressively increased until nowadays (Fig. 1). According to age, the incidence was higher in males older than 40 years and between 30 and 39 years in females.

The mean age of patients in December 2018 was 49.7±14.7 years (95% CI: 45.9–53.5), the mean age at onset was 35.8±12.7 years (95% CI: 32.6–39), and the mean duration of the disease was 12.5±10.1 years (Table I). According to sex, mean age was 49.4±14.4 years (95% CI: 43.9–54.8) in males and 50±15.2 years (95% CI: 44.2–55.8) in females, the mean age at onset was 35.6±13.7 years (95% CI: 30.4–40.8) in males and 36±11.9 years (95% CI: 31.7–40.2) in females, and mean duration of the disease was 12.4±9.7 years in males and 12.6±10.5 years in females (Table I).

Clinical phenotypes

Clinical manifestations according to clinical phenotype domains, are reported in Table I. Relapsing aphthous stomatitis (defined as 3 or more relapses per year) was present in 100% of patients as it is mandatory for diagnosis. Genital ulcers were present in 46 patients (78%). The skin was involved 50 subjects (84.7%). Uveitis was detected in 33 (55.9%) and joint involvement raised to 38 (64.4%). Central nervous system, vascular and gastrointestinal manifestations were observed in 10 (16.9%), 6 (10.2%), and 4 (6.8%), respectively. Males suffered uveitis more frequently than females (62.1% *vs.* 50%, respectively) and anterior was the most common kind of uveitis globally (51.5%) and in both genders separately (55.6% in males and 46.7% in females) followed by posterior uveitis (30.3%).

Table III. Epidemiological phenotypes of Behçet's disease in other geographic regions.

Author, year (ref. in text)	Region	Diagnostic criteria and study period	n cases/ population size	Prevalence (over 100,000)	Incidence /100,000 inhabitants/ year	Mean age (range) ± SD at onset and sex (% females)	Pathergy test (%)
Deligny *et al*., 2012 (6)	Caribbean Islands (Martinique)	ISG, 1997-2011	36 / 403795	7	0.72	38.5 (8-64) (61.1%)	NR
Calamia *et al*., 2009 (7)	North America (Minnesota, USA)	ISG, 1960-2005	13 / NR	5.2	0.38	31±9 (30%)	NR
Tüzün *et al*., 1996 (8)	Middle East (Çamaş, Turkey)	O'Duffy criteria, NR	19 / 5121	370	NR	NR (68%)	33.3
Al-Rawi *et al*., 2003 (9)	Middle East (Saqlawia, Irak)	ISG, 1999-2000	6 / 35125	17	NR	24.2±7 (33%)	83.3
Azizlerli *et al*.,2003 (10)	Middle East (Istambul, Turkey)	ISG, prevalence study	101 / 23986	42	NR	NR (48.5%)	69.3
Krause *et al*., 2007 (11)	Middle East (Galilee, Israel)	ISG, 15 years (not specific years have been reported)	112 / 737000	15.2	NR	30.6±10.7 (47%)	44.4
Baş *et al*., 2016 (12)	Middle East (Northern Anatolian, Turkey)	ISG, NR	14 / 2325	602	NR	NR (68%)	57
Davatchi *et al*., 2019 (13)	Middle East (Iran)	Expert opinion, 1975-2018	7641 / NR	80	NR	25.6±9.8 (44.2%)	50.4
Chamberlain, 1977 (14)	Northern Europe (Yorkshire County, UK)	Study-specific, prevalence study	32 / 500000	0.6	NR	24.7 (SD NR) (62%)	NR
Jankowski *et al*., 1992 (15)	Northern Europe (Scotland, UK)	ISG, NR	15 / 5500000	0.3	NR	NR (73%)	NR
Zouboulis *et al*., 1997 (16)	Northern Europe (Berlin, Germany)	Classification tree, 1984-1997	49 / 2170411	2.2	NR	25 (5-66) (53%)	52
Altenburg *et al*., 2006 (17)	Northern Europe (Berlin, Germany)	ISG and Classification tree, 1961-2005	590 / 3391344	4.9	1 (estimated)	26 (SD NR) (58%)	33.7
Mohammad *et al*., 2019 (18)	Northern Europe (Skane County, Sweden)	ISG, 1997-2010	40 / 809317	4.9	0.2	30.5 (11-53) (33%)	NR
Ambresin *et al*., 2002 (19)	Central Europe (Lausanne, Switzerland)	Japanese diagnostic criteria, 1990-1998	35 / 600000	0.00005	0.65	29.4±12.1 (20%)	NR
Kanecki *et al*., 2017 (20)	Central Europe (Poland, Nationwide)	NR, 2008-2014	130 / NR	3.4	0.5	NR (58.5%)	NR
Mahr *et al*., 2014 (21)	Southern Europe (Seine-Saint-Denis County, France)	ISG, 2003	79 / 1094412	7.1	NR	27.6±10.6 (43%)	20
Salvarani *et al*., 2007 (22)	Southern Europe (Reggio Emilia, Italy)	ISG, 1988-2005	18 / 486961	3.7	0.24	33±7 (50%)	NR
Peñafiel *et al*.,2007 (23)	Southern Europe (Granada, Spain)	ISG, 1990-2002	44 / 880000	5	NR	NR (80%)	13.6
González-Gay *et al*.,2000 (24)	Southern Europe (Lugo-Galicia, Northwestern Spain)	ISG, 1988-1997	16/ 240000	NR	0.66	28.7±8.9 (44%)	18.8
Suárez-Amorín *et al*., present study, 2023	Southern Europe (Cantabria, Northern Spain)	ISG, 1980-2018	59 / 581877	10.1	0.49 (1999-2018)	35.8±12.7 (50.8%)	NR

ISG: International Study Group; ICBD: International Criteria for Behçet's Disease; NR: not reported; SD: standard deviation.

Otherwise, joint and gastrointestinal tract involvement was higher in females (66.7% *vs*. 62.1% in males and 10% *vs*. 3.4% in males, respectively). CNS affection was globally higher in females than males (23.3% *vs*. 10.3%). However, males showed non-parenchymatous involvement exclusively (100%) while parenchymatous was more common in females (85.7%) and absent in males. Clinical manifestations according to groups of age at the time of the last evaluation are reported in Table II. Relapsing aphthous stomatitis was observed in all patients. Genital ulcers show high prevalence (>70%) in all ranges of age except in the groups of 40–49 and 60-69 years. The prevalence of skin involvement was higher than 70% in all groups. Regarding uveitis, there was a steady involvement (from 40% to 68%) in all age ranges. Joint involvement ranged from 46% (20–29 years) to 80% (10–19 years). Central Nervous System was affected in low rates (from 0% to 25%) in all age groups. Vascular system and gastrointestinal tract involvement

was present only in patients older than 30 years of age.

Discussion

We have investigated epidemiological features and clinical domains of BD in a defined population from Southern Europe. It was noteworthy that the prevalence of BD in Cantabria (Northern Spain) was higher than in other European regions. From the analysis of the most recent reports, we observe a progressive increase in the prevalence of BD in Southern Europe. In this sense, Salvarani *et al*. reported a prevalence of 3.7/100,000 inhabitants (21) and Peñafiel *et al*. 5/100,000 (22) both in 2007, while Mahr *et al*. reported a prevalence of 7.1/100,000 (23) in 2014. One of the possible reasons for this is the upward trend of the eastern-born immigrant population in Europe. However, our cohort was very homogeneous since immigrants in Cantabria represent only 6.2% of the population.

The influence of environmental factors in genetically predisposed individuals can be another possible reason to explain this increasing prevalence. In addition, the universal accessibility of more than 95% of the population to the Public Health System, which allows the recruitment of the majority of patients suffering from this disease, may explain an increase in the prevalence of this condition in Southern Europe. Remarkably, the clinical phenotypes in Cantabria were globally comparable to those reported in other world countries. Data from our series are shown and compared with other studies in Table III and Supplementary Table S2. The prevalence of BD in Cantabria (10.14/100,000 inhabitants) is very close to the global average prevalence (10.3/100,000) reported in a recent meta-analysis by Maldini *et al*. (26), although it is the highest prevalence reported in Europe to date, followed by the prevalence reported by Mahr *et al*. in France (7.1/100,000) (21). However, the prevalence in Cantabria was lower than in regions with high prevalence such as Iraq (17/100,000) (9) or Israel (15.2/100,000) (11).

Global incidence (0.492 per 100,000 inhabitants/year) is somewhat lower than that published in Lugo region (Galicia, Northwest Spain) by González-Gay *et al*. several decades ago, who reported 0.66/100,000 (24) and lower than in other European countries (17, 19, 20) as shown in Supplementary Table S3. Incidence remains globally low while prevalence is high probably due to the long-life expectancy of patients suffering BD.

Gender distribution shows a similar distribution as the male/female ratio was 0.97. In most studies, this ratio was higher than 1.1 (2). Regarding the data from southern Europe, one study showed a higher prevalence in men (21), another in women (23), while another reported a similar distribution (22). The mean age of onset (35.8±12.7) observed in Cantabria was one of the highest ever reported. Interestingly, it applied similarly to both men and women.

In general, the frequency of clinical domains of BD in Cantabria was similar to that reported in other studies. Oral and genital aphthosis, joint and skin involvement showed similar prevalence in all studies. Eye manifestations in our sample (55.9%) are similar to other studies, although some of them show a lower prevalence (25%) (6,14). The same happens regarding neurological manifestations. We found that 16.9% of our patients experienced neuro-Behçet while Davatchi *et al*. reported a frequency of 3.9% (13). Vascular manifestations (10.2%) were one of the less frequent complications of this review, followed only by Davatchi's casuistry (8.9%) (13) and Salvarani's population-based study (6%) (22). We observed a very low frequency of gastrointestinal manifestations (6.8%) in our cohort compared to that described by Jankowski *et al*. (53.3%) (15). However, information on the frequency of gastrointestinal manifestations was not reported in most epidemiological studies of BD.

The main limitations of our study are the long study period included that might have distorted some data in the collection of patients due to technical and computer changes included throughout almost four decades, the discrepancies in data collection between the different participating centres and the low sample size finally achieved in a region of moderate population size. Likewise, this population is not representative of our entire country, since as is well known there are some genetic differences between the North and the South of Spain, as in other countries in the Mediterranean environment. Another limitation is that we did not adjust population by age, comorbidity or other cofounders as the main objective of this study was to compare our results to other similar epidemiological studies.

Conclusions

The prevalence of BD in Cantabria, Northern Spain, is somewhat higher than in other Southern European countries. This difference likely may reflect a combination of environmental, genetics, and methodological variations, as well as the universality and free accessibility to the Public Health System by the general population in our setting. However, the clinical phenotypes observed in our country are similar to those described in other world regions.

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