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Behçet's syndrome in Italy: a detailed retrospective analysis of 396 cases seen in 3 tertiary referral clinics

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Abstract

Behçet's syndrome (BS) is a multisystemic disorder displaying a marked variability across different geographic areas. The main aim of this study was to analyze demographic and clinical features of a cohort of BS patients diagnosed in three tertiary referral centers in Italy and detect potential associations between the different manifestations. Medical records of 396 patients (218 females, 178 males) were retrospectively analyzed. Mean age at onset was 30.00 ± 18.75 years with a female-to-male ratio of 1.22:1. Mucocutaneous features were the most frequent starting manifestations of BS, followed by eye inflammation. Erythema nodosum ($p = 0.007$), arthritis/arthralgias ($p = 0.0115$), and central nervous system (CNS) signs ($p = 0.014$) were significantly over-represented in female patients, whereas male gender was associated with lower mean age at onset ($p = 0.031$), higher frequency of pseudofollicular lesions, and uveitis ($p = 0.00134$ and $p < 0.0001$ respectively), particularly for posterior segment involvement and panuveitis ($p < 0.0001$). Regarding the association between disease features, genital ulcers were negatively associated with uveitis ($p < 0.0001$) and vascular involvement ($p < 0.0001$). Other negative associations were detected between uveitis and gastrointestinal involvement ($p = 0.008$), pseudofolliculitis and CNS signs ($p = 0.031$), vascular involvement ($p = 0.002$) and erythema nodosum ($p = 0.013$). Logistic regression identified male gender and genital ulcers, respectively, with a higher (OR 2.199 [1.397–3.461], $p < 0.001$) and lower risk (OR 0.157 [0.090–0.273], $p < 0.0001$) of developing major organ involvement. Our evaluations found that the disease had started mostly in the second and third decade with most severe features in the male gender, and that patients presenting with mucocutaneous manifestations were less prone to develop major organ involvement.

Keywords Behçet's syndrome · Epidemiology · Italy · Clinical features

Part of the following topical collection: Behcet disease.

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Introduction

Behçet's syndrome (BS) is a relapsing–remitting immune-mediated systemic disorder of unclear etiology. Oral ulcerations, the lifetime sign of BS, along with the other clinical stigmata including genital ulcers, skin manifestations and intraocular inflammation characterize its main features [1]. Nevertheless, any organ may be virtually involved, with central nervous system (CNS), gastrointestinal and vascular involvement being relatively common [2–4]. BS is also associated with a poor quality of life [5]. Different authors are considering BS as a polygenic autoinflammatory condition [6, 7], and several arguments have also led to the newly developed concept of "MCH-I-opathy" [8, 9]. However, pathologic pathways of BS remain largely unknown and no single common denominator has been identified [10, 11]. In addition, a marked geographic variability from both an epidemiological and clinical standpoint further highlights the complexity of BS. In fact, despite having a worldwide distribution, BS is particularly prevalent among the ancient "Silk Route" populations. Indeed, the highest prevalence of BS has recently been reported in Jordan with an estimated prevalence of 660 per 100,000 [12], followed by Turkey (420 cases per 100,000 adults) [13], while a lower frequency has been detected in the rest of the world, especially in Western countries [14]. With regard to clinical manifestations, the highest frequency of gastrointestinal involvement has been reported in Japan [15, 16]. Similarly, pathergy reaction has been variably reported according to the ethnic origin with higher sensitivity and specificity in Middle East countries and much lower in the Western world [17, 18]. BS also differs between certain subgroups of patients. For instance, it is believed to be more severe among young male patients, who display a higher mortality, mainly due to major vessel disease and CNS involvement. Ocular disease, on the other hand, accounts for the highest morbidity, leading to one of the most debilitating outcomes, especially in young males [18, 19]. Contemporary epidemiological studies from different countries have highlighted the aforementioned geographic variability of BS in terms of incidence, prevalence, and clinical features [12, 20–23]. We herein report a retrospective overview of BS epidemiology in relationship with patients attending three referral rheumatology centers in Italy during a 24 month-period, focusing on the various associations between clinical features, gender differences, and potential predictors of disease severity.

Methods

Participants and study design

We conducted a retrospective review of medical charts related to 396 consecutive patients with BS, admitted between January 2015 and January 2017 in 3 tertiary referral rheumatologic centers working in Central–North and Southern Italy. In this regard, all data from BS cases were retrospectively examined. Basic demographic and clinical information included gender, age, age at onset, disease duration, human leukocyte antigen (HLA)-B51, clinical manifestations at onset, and clinical manifestations throughout disease course. Therapeutic data in terms of past and current therapies were also collected. BS was diagnosed according to the international study group criteria (ISG) [24] or according to the international criteria for Behçet's disease (ICBD) [25]. All patients were referred and followed-up regularly in the three referral centers. Conditions simulating BS were ruled out. Patients whose disease manifested prior to the age of 16 years were considered to have childhood BS.

Organ involvement was investigated in a personalized manner and not by a pre-established protocol, with the following examinations: clinical history, physical examination, full blood chemistry and class I HLA haplotype evaluation. In case of strong suspicion of ocular, neurological, gastrointestinal involvement, patients were also seen by a dedicated ophthalmologist, neurologist and gastroenterologist, respectively. Patients undergoing biologic therapy were also screened for active or latent infections by performing chest X-ray film, Mantoux and/or QuantiFERON test, urine colture, liver markers for HBV and HCV infections, serology for HIV, syphilis and *Toxoplasma gondii*.

Primary aim of the study was to summarize clinical features of BS patients systematically followed-up in three tertiary rheumatologic centers in Italy with particular focus on gender differences and potential association among the different manifestations. Further area of our research consisted in trying to detect specific disease clusters as well as predictors of disease severity.

Protocol approval

The study adhered to the tenets of the Declaration of Helsinki and was approved by the local Ethic Committee. Written informed consent was obtained from all patients or their legal guardians.

Statistical analysis

Data were analyzed using IBMSPSS Statistics for Windows, version 24 (IBM Corp., Armonk, NY, US). Descriptive statistics was used to calculate mean and standard deviation (SD) or median and interquartile range (IQR) as appropriate. Categorical variable were analyzed by Pearson's chi-square test or Fisher's exact test as required, while means were compared with Mann–Whitney *U* test. The normality of continuous data was assessed with the Shapiro–Wilk test. Binary logistic regression was employed to identify potential predictors of major organ involvement define as ocular, neurologic, gastrointestinal or vascular involvement. Headache, in the absence of other neurological features and/or positive MRI findings, was not considered a specific neurological feature of BS. Similarly, only endoscopically documented lesions were classified as a sign of gastrointestinal involvement and analyzed statistically. A factor analysis was conducted to identify target organ associations. More precisely, a principal component analysis was conducted on seven items with orthogonal rotation (varimax). The seven items included oral aphthosis, genital aphthosis, erythema nodosum, pseudofolliculitis, papulopustular lesions, joint involvement (arthritis) and uveitis. For a more plausible way of grouping features and, therefore, advancing pathogenetic hypothesis, only symptoms occurring close in time (i.e. at disease onset) were considered. Symptoms presenting at onset with a frequency lower than 5% were excluded from the model to preserve robustness. Kaiser's criterion with an eigenvalue higher than 1 was employed to retain factors, whereas redundancy between variables was assessed with Bartlett's test of sphericity. To finalize data computation of non-continuous variables, the correlation matrix was constructed from tetrachoric correlation coefficients. A p value of less than 0.05 was set as the threshold for statistical significance, and all tests were two sided.

Results

In total, 396 patients fulfilling ISG or ICBD criteria were enrolled in the study and the majority of them were females, with a female/male ratio of 1.22/1. The mean ± SD age of this cohort and the median ± IQR age at onset were 44.65 ± 12.75 and 30.00 ± 18.75 years, respectively. Mean age at onset ± SD for males and females was 28.66 ± 12.53 and 31.29 ± 12.99 years, respectively, with a statistically significant difference ($p = 0.031$). Figure 1 illustrates the distribution of age at disease onset. Outbreak of BS was recorded in 81% of patients before 40 years, with the highest frequency during the second and third decade.

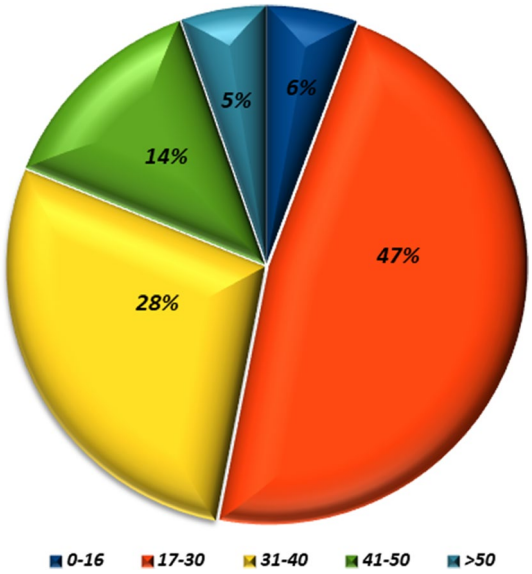

Fig. 1 Distribution of age at onset for 396 patients with Behçet's syndrome in accordance with different age groups, expressed in years

As expected, the most frequent clinical manifestations at disease onset were oral ulcers (360/396, 91%), followed by genital ulcerations (105/396, 26.5%) and uveitis (85/396, 21.5%). Table 1 details demographic characteristics alongside with the clinical features at disease onset for all patients as well as all clinical manifestations occurring during the whole course of the disease.

The most common cutaneous manifestation was pseudofolliculitis ($n = 144$), followed by pustular lesions ($n = 111$) and erythema nodosum ($n = 109$). Ocular involvement was recorded in 170 patients. Uveitis presented a bilateral involvement in 108 patients (63.53%) and unilateral in 62 cases (36.47%), for a total of 278 eyes involved. The most common eye pattern was panuveits (39%). Figure 2 shows the anatomical pattern of uveitis defined in accordance with SUN criteria [26]. A total of 21 patients (12.35%) were diagnosed with retinal vasculitis, 14 (8%) of whom as isolated finding. Additionally, one patient developed scleritis. With regard to the association between disease features, genital ulcers were negatively associated with uveitis ($\chi^2 = 29.30$, $p < 0.0001$) and vascular involvement ($\chi^2 = 16.39$, $p < 0.0001$). A trend toward a decreased prevalence of CNS involvement was observed in patients with genital ulcers, but without reaching the statistical significance ($\chi^2 = 3.73$, $p = 0.053$). Other negative associations were detected between uveitis and gastrointestinal involvement ($\chi^2 = 7.15$, $p = 0.008$), pseudofolliculitis and CNS signs ($\chi^2 = 4.67$, $p = 0.031$), pseudofolliculitis and vascular involvement ($\chi^2 = 9.90$, $p = 0.002$), pseudofolliculitis and erythema nodosum ($\chi^2 = 6.19$, $p = 0.013$). Results between HLA-B51 positive and HLA-B51 negative patients were

Table 1 Demographic characteristics and clinical features at the onset and throughout the course of Behçet's syndrome

Demographic features	Mean ± SD (median ± IQR) expressed in years
Female/male	218/178
Age	44.65 ± 12.75
Age at onset	30.00 ± 18.75
Disease duration	11.00 ± 14.00
HLA-B51, *N* (%)	235/382 (61.5%)
Clinical features at onset	*N* (%)
Oral aphthosis	360 (91%)
Genital aphthosis	105 (26,5%)
Erythema nodosum	29 (7.3%)
Psedofollicular lesions	58 (14.6%)
Papulopustular lesions	27 (6.8%)
Arthritis or arthralgia	60 (15.1%)
Uveitis	85 (21.5%)
CNS signs	18 (4.5%)
Gastrointentinal involvement	11 (2.8%)
Vascular involvement	14 (3.5%)
Clinical features throughout the course of Behçet's syndrome	*N* (%)
Recurrent oral ulcers	389 (98.2)
Genital ulcers	265 (66.9)
Pseudofollicular lesions	144 (36.4)
Papulopustular lesions	111 (28.0)
Erythema nodosum	109 (27.5)
Ocular involvement	170 (42.9)
CNS involvement	21 (5.3)
Gastrointestinal involvement	135 (34.1)
Vascular involvement	96 (24.2)

CNS central nervous system *IQR* Interquartile range, *HLA* human leukocyte antigen, *SD* standard deviation

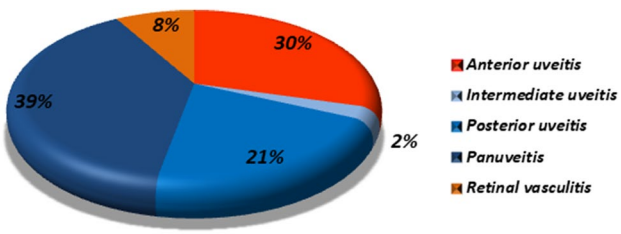

Fig. 2 Anatomical patterns of intraocular inflammation classified in respect to SUN criteria for 396 patients with Behçet's syndrome evaluated in our study

comparable. Concerning treatment strategies, biologic agents, mostly anti-tumor necrosis factor (TNF)-α, were the most frequently prescribed medications (43.43%), followed by cDMARDs administered as monotherapy (5.8%) or in association with systemic corticosteroids (12.88%) or with biologics (14.90%). Figure 3 offers an overview of the treatments employed in our cohort of BS patients, whereas Table 2 displays previous (all drugs administered in the past) and current immunosuppressive therapies. Twenty-eight patients were able to discontinue immunosuppressive treatments after a prolonged remission, and they are currently under no therapeutic regimen. The mean age of patients discontinuing treatment was approximately 45 years.

Regarding the influence of gender, the number of males was significantly higher among patients under 25 years of age ($p = 0.0075$). Indeed, the mean age at onset was significantly lower in male patients ($p = 0.031$). This subgroup also exhibited a more significant prevalence of pseudofollicular lesions and uveitis ($p = 0.00134$ and $p < 0.0001$, respectively), mostly in terms of posterior segment involvement and panuveitis ($p < 0.0001$). On the other hand, erythema nodosum ($p = 0.007$), arthritis/arthralgias ($p = 0.0115$), CNS signs ($p = 0.014$) and gastrointestinal involvement ($p < 0.0001$) were significantly over-represented in females.

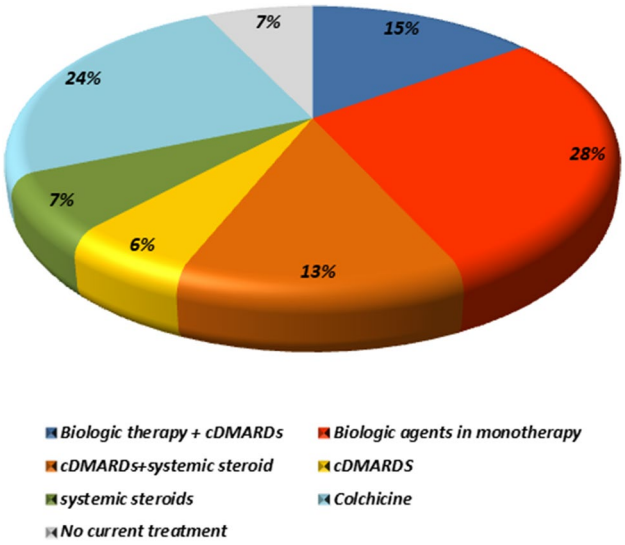

Fig. 3 Overview of treatment regimens administered in our cohort of 396 patients with Behçet's syndrome

The frequency of other clinical features was comparable between the two groups. Figure 4 shows the gender differences for each clinical manifestation with their respective statistical significance. Major organ involvement was significantly more prevalent in males ($p = 0.0016$).

In support of the aforementioned findings, logistic regression identified the following two variables associated with major organ involvement: male gender and genital ulcers, respectively, with a higher (OR 2.199 [1.397–3.461], $p < 0.001$) and lower risk (OR 0.157 [0.090–0.273], $p < 0.0001$) of developing major organ involvement.

With regard to factor analysis, three components had eigenvalues over Kaiser's criterion of 1 and in combination explained 67% of the variance. Factor 1 represented the association of bipolar aphthosis with erythema nodosum as well as pseudofolliculitis. Factor 2 detected uveitis as a distinct feature and Factor 3 was represented by arthritis, which was negatively associated with papulopustular lesions with eigenvalues equal to 1.86, 1.58 and 1.21, respectively. Table 3 shows factors, their relative contribution and loadings for each variable after rotation.

Discussion

In the present study, we have reported demographic and clinical features of the largest Italian cohort of BS patients and the second of its kind after a hospital-based multicenter survey [27]. The cohort consisted of a homogeneous group of Caucasian BS patients, predominantly of Italian ancestry, seen in three university hospitals over a 2 year follow-up period.

Mean age at onset in our patients is comparable to that which is largely and already reported for BS, i.e. the third decade of life [28–32]

In line with many clinical observations in other Western countries [29, 32–34] and in contrast to some reports from Eastern countries [35, 36], our cohort of BS patients follows a slight female predilection. The highest ratio recorded comes from an Egyptian study reporting a male-to-female ratio of 30.5:1 [36], whereas in a large cohort of patients from Turkey gender distribution tended to equalize [37]. As stated by some experts, in larger samples, the sex ratio

Table 2 Past and current therapies in our cohort of patients with Behçet's syndrome

Previous cDMARDs		Current cDMARDs	
AZA	60	AZA	59
Cyc A	75	Cyc A	24
MTX	52	MTX	33
SZS	13	SZS	10
Cyclophosphamide	11	Leflunomide	1
MFM	5	MFM	3
HCQ	5	HCQ	3
Thalidomide	1	Thalidomide	1
Tacrolimus	1	Sulfasalazyn and mesalazyn	4
Previous biologic agent		Current biologic agent	
Anti-TNF-α	43	Anti-TNF-α	138
Anti-IL-1	13	Anti-IL-1	14
TCZ	6	TCZ	6
		RTX	1

AZA azathioprine, *Cyc A* cyclosporin A, *HCQ* hydroxychloroquine, *IL* interleukin, *MFM* mycophenolate mofetil, *MTX* methotrexate, *RTX* rituximab, *SZS* sulfalazine, *TCZ* tocilizumab, *TNF* tumor necrosis factor

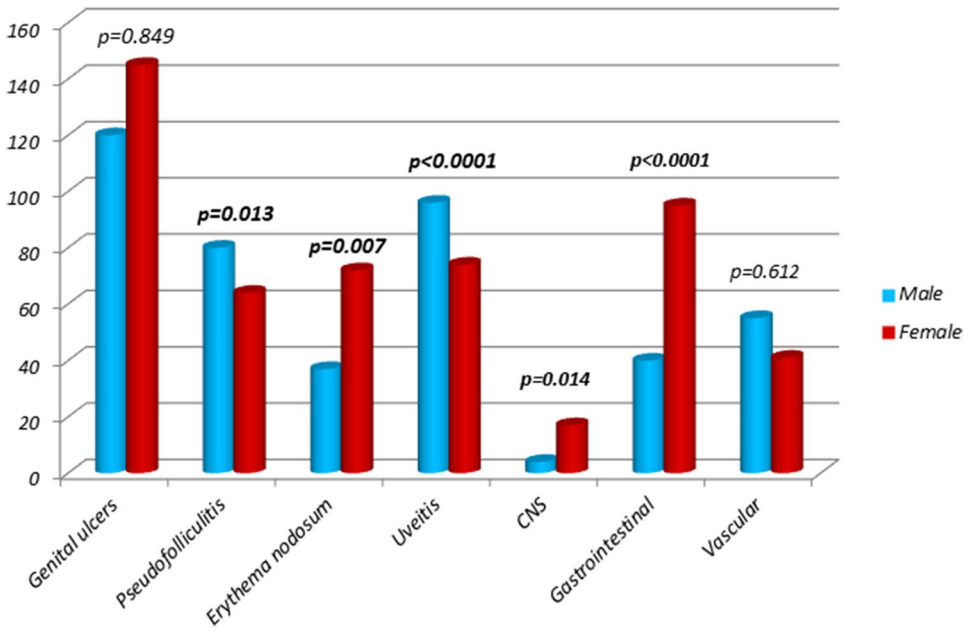

Fig. 4 Comparison of gender differences in terms of clinical features (excluding oral ulcers) for 396 patients with Behçet's syndrome evaluated in our study

Table 3 Factors extracted from the rotated loading matrix (loadings with absolute values lower them 0.300 were omitted)

Factor's eigenvalues	1.86	1.58	1.21
Percentage of variance explained	26.5	22.5	17.3
Loadings	Factor 1	Factor 2	Factor 3
Oral aphthosis	0.313	−0.892	–
Genital aphthosis	0.899	–	–
Erythema nodosum	0.504	–	–
Pseudofolliculitis	0.641	–	–
Papulopustular lesions	–	–	−0.828
Uveitis	–	0.865	–
Arthritis	–	–	0.744

decreases and catches up with the rate of nationwide surveys [16].

Our data revealed several gender differences. Male patients presented a significantly lower mean age at onset and were over-represented in terms of ophthalmologic involvement and pseudofollicular lesions, whereas females were more frequently affected by erythema nodosum, CNS and gastrointestinal involvement (when also headache and abdominal pain and not only endoscopic documentation were taken into consideration). As shown by another Italian experience [27] and also from other territorial realities [30, 31, 38, 39], some of the aforementioned differences such as uveitis and erythema nodosum suggest that certain disease manifestations appear to be gender-related and independent from environmental factors. We were unable, however, to confirm previous data reporting a higher frequency of vascular involvement in males [31, 40]. Male patients have also been associated with a more severe disease course and higher disease activity [18, 30, 31, 38, 41], which is consistent with the association found in this study between male gender and major organ involvement, further corroborated by the regression analysis. Altogether, in accordance with these results, male gender seems to be a predisposing factor for a worse overall prognosis, highlighting the need for a more aggressive and early treatment with the aim to prevent detrimental outcomes.

Broadly speaking, our results match the other studies previously published [13, 18, 27, 35, 39] by showing roughly a similar overall clinical picture, with mucocutaneous lesions as the most common manifestations and the most frequent signs at BS onset. On this relatively homogeneous cohort, the frequency of eye involvement was approximately 43%, which more or less follows the prevalence reported in other studies [27, 33, 36, 41]. In agreement with the previous Italian epidemiologic study on BS [27], we found that the posterior segment was significantly more frequently involved in male patients. Conversely, it was not possible to confirm the association between posterior uveitis and neurological involvement, found by other authors [42].

Interestingly, genital ulcers, the most pathognomonic lesion in BS, were negatively associated with uveitis and vascular involvement, thereby confirming the results from previous studies [43, 44]. Suwa et al., based on a binomial multivariate regression analysis, disclosed that genital ulcer was a preventive factor for ocular lesions, whereas Suzuki et al. found that patients with a prominent vascular disease were featured with lower risk of genital ulcerations. Based on our findings, on regression analysis, genital ulcers were found to be a protective factor of major organ involvement.

Therefore, patients that do not exhibit genital lesions seem to demand a closer follow-up. Likewise, pseudofollicular lesions have been negatively associated with vascular and CNS involvement, implying a milder overall disease course in patients displaying this cutaneous lesion. The reasons underlying these associations remain obscure. The exclusive relationship between these manifestations may reflect distinct phenotypes and suggest that patients with mucocutaneous signs are less likely to develop any major organ involvement. Nevertheless, it still remains a matter of debate which manifestations tend to cluster together and define specific phenotype expressions. Phenotyping analysis in complex heterogeneous disorders is fundamental in increasing knowledge regarding pathogenetic pathways thus providing a better and targeted treatment approach [45]. In this regard, we performed a factor analysis that identified three independent factors explaining 67% of the variance. Mucocutaneous manifestations such as bipolar aphthosis, erythema nodosum and pseudofolliculitis (Factor 1) tended to cluster together, while the second factor suggests that uveitis has the propensity to represent a distinct subset of BS. These findings are similar to what has been previously reported by Tunc et al. The authors identified the association between oral ulcers, genital ulcers and erythema nodosum, while uveitis represented a distinct feature negatively associated with erythema nodosum [46]. However, we were not able to confirm the association of vascular manifestations due to the lack of detailed data on vascular involvement. The association between joint involvement and papulopustular skin lesions was not confirmed either. Interestingly, they were inversely correlated. The latter discrepancy may be explained by the fact that we included in the analysis only arthritis and excluded arthralgias. Additionally, the inclusion of manifestations occurring only at onset could have underestimated several clinical features potentially composing other disease clusters that might have explained part of the remaining variance of the total information of the matrix. On the other hand, patients at onset were not exposed to biologic drugs that are known to mask important biologic information due to their immunosuppressive effects. These disease clusters are interesting from a pathogenetic point of view, and other studies conducting the same analysis should be warranted to shed light in this topic. In fact, the existence of clusters suggest that different pathogenetic mechanisms operate in BS and none of them leads to a unifying explanation.

No fatal events were recorded during the whole study period. This may be partially explained by the positive results obtained with the newly introduced biologic drugs that have allowed a frank improvement in terms of prognosis for BS. A total of 159 patients received biologic agents and treatment modalities conformed with the EULAR recommendations [47]. Indeed, the advent of biologic drugs, especially of monoclonal antibodies against TNF-α has revolutionized treatment of BS. They are increasingly used for the treatment of various refractory manifestations despite the lack of controlled studies [48]. The proportion of patients discontinuing treatment due to prolonged remission displayed a relatively high mean age (45 years). Indeed, it has been suggested that BS abate over time [41, 49]. In a study investigating long-term mortality on a large cohort, mortality rate tended to equalize with healthy controls in patients older than 35 years [18]. Additionally, BS runs a less severe course in non-endemic areas with milder disease expression [50].

We need to recognize the limitations of our study; first of all, the ethnic homogeneity of our cohort of patients, which limits the possibility of generalizing our results. Additionally, the retrospective nature of our study has been also responsible for some missing data, such as a detailed description of the vascular involvement that could have been necessary to confirm disease clusters. Furthermore, the multicenter nature of the study may be responsible for a slightly different way between centers of characterizing the clinical interpretation of some findings, especially concerning major organ involvement. Differences between studies may also be attributed to referral bias, depending on the center specialty and territorial level, as tertiary specialized centers are more likely to encounter complicated cases, while probably under-reporting milder forms. On this basis, an important piece of the Italian epidemiologic puzzle might be missing.

In conclusion, this study offers a detailed picture of BS in Italy and represents a further effort in the struggle of understanding BS heterogeneity. Our cohort was characterized by a wide variety of clinical manifestations and several multiple system involvement, demanding a multidisciplinary approach. Critical and more complicated cases presenting with major organ involvement require a specific teamwork with a dedicated ophthalmologist, neurologist and gastroenterologist for a better and optimized treatment approach. BS has shown to outbreak mostly in the second and third decade, with the tendency to be more severe in male patients. Different findings, some in line and others in contrast with the available medical literature, reinforce the notion of an extreme clinical variability of this syndrome. A better understanding of BS epidemiology will probably allow a fair resource administration and possibly stimulate a specifically oriented research to decipher the "scrolls" of BS pathophysiology.

Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Statement of human and animal rights The article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent Our study is retrospective and a formal consent was given by all participating patients.

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