Rheumatology, 2026, **65(2)**, keaf613
https://doi.org/10.1093/rheumatology/keaf613
Advance access publication 19 November 2025
Original Article

British Society for Rheumatology RHEUMATOLOGY OXFORD

Clinical science

Risk of major organ involvement in Behçet's patients with mucocutaneous onset: data from the AIDA Network Registry

Antonio Vitale[1], Francesco Gavioli[1], Valeria Caggiano[1], Jessica Sbalchiero[1], Giuseppe Lopalco[2], Gaafar Ragab[3,4], Silvana Guerriero[5], Ibrahim AlMaglouth[6], Abdurrahman Tufan[7], Roberto Giacomelli[8], Haner Direskeneli[9], Piero Ruscitti[10], Gülen Hatemi[11], Francesco Carubbi[12], Ezgi Deniz Batu[13], Seza Ozen[13], Jurgen Sota[1], Henrique Ayres Mayrink Giardini[14], Micol Frassi[15], Petros P Sfikakis[16], Florenzo Iannone[2], Maria Morrone[2], Mahmoud Ghanema[3], Moustafa Ali Saad[3], Rosanna Dammacco[5], Hamit Kucuk[7], Riza Can Kardas[7], Ibrahim Yahya Cakir[7], Luca Navarini[8], Fatma Alibaz Öner[9], Gizem Sevik[9], Martina Gentile[10], Alican Karakoc[11], Alessia Alunno[12], Hulya Ercan Emreol[13], Francesca Crisafulli[15], George Fragoulis[16], Francesco Ciccia[17], Maissa Thabet[18], Serena Bugatti[19], Alessandra Milanesi[19], Maria Sole Chimenti[20], Benedetta Monosi[20], Matteo Piga[21], Alberto Floris[21], Andrea Hinojosa-Azaola[22], Guillermo Arturo Guaracha-Basañez[22], Cecilia Beatrice Chighizola[23,24], José Hernández-Rodríguez[25], Marco Cattalini[26], Marcello Govoni[27], Ombretta Viapiana[28], Adele Civino[29], Daniela Opris-Belinski[30], Carla Gaggiano[1], Rosaria Talarico[31], Annarita Giardina[32], Giacomo Emmi[33,34], Piercarlo Sarzi Puttini[35], Maria Cristina Maggio[36], Paola Parronchi[37], Piero Portincasa[38], Alejandra de-la-Torre[39], Blanca Aguilar-Barrera[39], Stefano Gentileschi[1], Angela Mauro[40], Gian Domenico Sebastiani[41], Alma Nunzia Olivieri[42], Ali Şahin[43], Donato Rigante[44,45], Emre Bilgin[46], Emanuela Del Giudice[47], Luciana Breda[48], Amato De Paulis[49,50], Alberto Lo Gullo[51], Şükran Erten[52], Samar Tharwat[53,54], Lampros Fotis[55], Armin Maier[56], Antonella Insalaco[57], Anastasios Karamanakos[58], Alessandro Conforti[59], Özgül Soysal Gündüz[60], Abdelhfeez Moshrif[61], Francesca Li Gobbi[62], Alberto Balistreri[63], Elena Bartoloni[64], Patrizia Barone[65], Serena Guiducci[66], Andrés Gonzáles-García[67], Inés Hernanz Rodriguez[68], Giovanni Conti[69], Annamaria Iagnocco[70], Fatos Önen[71], Sulaiman M. Al-Mayouf[72], Didar Ucar[73], Bruno Frediani[1], Claudia Fabiani[74], Luca Cantarini[1,*], from the International AIDA (AutoInflammatory Diseases Alliance) Network

[1]Rheumatology Unit, Department of Medical Sciences, Surgery and Neurosciences Department of Medical Sciences, Surgery and Neurosciences, University of Siena and Azienda Ospedaliero-Universitaria Senese [European Reference Network (ERN) for Rare Immunodeficiency, Autoinflammatory and Autoimmune Diseases (RITA) Center], Siena, Italy
[2]Department of Precision and Regenerative Medicine and Ionian Area (DiMePRe-J) Policlinic Hospital, University of Bari, Bari, Italy
[3]Internal Medicine Department, Rheumatology and Clinical Immunology Unit, Faculty of Medicine, Cairo University, Giza, Egypt
[4]Faculty of Medicine, Newgiza University, 6th of October City, Giza, Egypt
[5]Department of of Translational Biomedicine and Neuroscience (DiBraiN), University of Bari, Bari, Italy
[6]Rheumatology Unit, Department of Medicine, King Saud University, Riyadh, Saudi Arabia
[7]Division of Rheumatology, Department of Internal Medicine, Gazi University Hospital, Ankara, Turkey
[8]Rheumatology, Immunology and Clinical Medicine Unit, Department of Medicine, Università Campus Bio-Medico di Roma, Rome, Italy
[9]Department of Internal Medicine, Division of Rheumatology, School of Medicine, Marmara University, Istanbul, Turkey
[10]Rheumatology Unit, Department of Biotechnological and Applied Clinical Sciences, University of L'Aquila, L'Aquila, Italy

Received: 17 April 2025. **Accepted:** 21 October 2025

[11]Department of Internal Medicine, Division of Rheumatology, Cerrahpasa Medical School, Istanbul University-Cerrahpasa, Istanbul, Turkey; Behçet's Disease Research Center, Istanbul University-Cerrahpasa, Istanbul, Turkey
[12]Department of Life, Health & Environmental Sciences, Internal Medicine and Nephrology Division, University of L'Aquila, ASL1 Avezzano-Sulmona-L'Aquila, San Salvatore Hospital, L'Aquila, Italy
[13]Pediatric Rheumatology Unit, Department of Pediatrics, Hacettepe University School of Medicine, Ankara, Turkey
[14]Rheumatology Division, Faculdade de Medicina, Hospital das Clinicas (HCFMUSP), Universidade de Sao Paulo, Sao Paulo, Brazil
[15]Rheumatology and Clinical Immunology, Spedali Civili and Department of Clinical and Experimental Sciences, University of Brescia, [European Reference Network (ERN) for Rare Immunodeficiency, Autoinflammatory and Autoimmune Diseases (RITA) Center], Brescia, Italy
[16]Joint Academic Rheumatology Program, National and Kapodistrian University of Athens Medical School, [European Reference Network (ERN) for Rare Immunodeficiency, Autoinflammatory and Autoimmune Diseases (RITA) Center], Athens, Greece
[17]Department of Precision Medicine, Università Degli Studi Della Campania Luigi Vanvitelli, Naples, Italy
[18]Internal Medicine Department, Farhat Hached University Hospital, Faculty of Medicine of Sousse, University of Sousse, Sousse, Tunisia
[19]Department of Internal Medicine and Therapeutics, Università di Pavia and Division of Rheumatology, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy
[20]Rheumatology, Allergology and Clinical Immunology, Department of Systems Medicine, University of Rome Tor Vergata, Rome, Italy
[21]Rheumatology Unit, Department of Medical Sciences, University and AOU of Cagliari, Cagliari, Italy
[22]Department of Immunology and Rheumatology, Instituto Nacional de Ciencias Médicas Y Nutrición Salvador Zubirán, Mexico City, Mexico
[23]Pediatric Rheumatology Unit, Azienda Socio-Sanitaria Territoriale (ASST) Gaetano Pini Centro Specialistico Ortopedico Traumatologico (CTO), Milan, Italy
[24]Department of Clinical Sciences and Community Health, Research Center for Adult and Pediatric Rheumatic Diseases, University of Milan, Milan, Italy
[25]Autoinflammatory Diseases Clinical Unit, Department of Autoimmune Diseases, Hospital Clinic of Barcelona, August Pi I Sunyer Biomedical Research Institute (IDIBAPS), University of Barcelona, Barcelona, Spain
[26]Pediatric Clinic, University of Brescia and Spedali Civili di Brescia [European Reference Network (ERN) for Rare Immunodeficiency, Autoinflammatory, and Autoimmune Diseases (RITA) Center], Brescia, Italy
[27]Rheumatology Unit, Department of Medical Sciences, Azienda Ospedaliero-Universitaria S. Anna—Ferrara, University of Ferrara, Ferrara, Italy
[28]Rheumatology Unit, Department of Medicine, University and Azienda Ospedaliera Universitaria Integrata of Verona, Verona, Italy
[29]Pediatric Rheumatology and Immunology Unit, Vito Fazzi Hospital, Lecce, Italy
[30]Rheumatology and Internal Medicine Department, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania
[31]Rheumatology Unit, Department of Clinical and Experimental Medicine, University of Pisa, Italy
[32]UOC Medicina Interna, Ambulatorio di Reumatologia, ARNAS Civico Di Cristina Benfratelli, Palermo, Italy
[33]Department of Medical, Surgical and Health Sciences, University of Trieste, Italy, and Clinical Medicine and Rheumatology Unit, Cattinara University Hospital, Trieste, Italy
[34]Centre for Inflammatory Diseases, Department of Medicine, Monash Medical Centre, Monash University, Clayton, VIC, Australia
[35]Rheumatology Unit, Ospedale Sacco, Milan, Italy
[36]University Department of Health Promotion, Mother and Child Care, Internal Medicine and Medical Specialties (PROMISE) 'G. D'Alessandro', University of Palermo, Palermo, Italy
[37]Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy
[38]Clinica Medica 'A. Murri', Division of Internal Medicine, Department of Precision and Regenerative Medicine and Ionian Area (DiMePre-J), University of Bari Aldo Moro, Bari, Italy
[39]Neuroscience Research Group (NEUROS), Neurovitae Center for Neuroscience, Institute of Translational Medicine (IMT), School of Medicine and Health Sciences, Universidad del Rosario, Bogotá, Colombia
[40]Department of Biomedical and Clinical Sciences, Fatebenefratelli Hospital, Università di Milano, Milan, Italy; Pediatric Rheumatology Unit, Department of Childhood and Developmental Medicine, Fatebenefratelli-Sacco Hospital, Milan, Italy
[41]U.O.C. Reumatologia, Ospedale San Camillo-Forlanini, Rome, Italy
[42]Department of Woman, Child and of General and Specialized Surgery, University of Campania 'Luigi Vanvitelli', Naples, Italy
[43]Division of Rheumatology, Department of Internal Medicine, Sivas Cumhuriyet University Medical Faculty, Sivas, Turkey
[44]Department of Life Sciences and Public Health, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy
[45]Rare Diseases and Periodic Fevers Research Centre, Università Cattolica Sacro Cuore, Rome, Italy
[46]Faculty of Medicine, Division of Rheumatology, Sakarya University, Sakarya, Turkey
[47]Department of Maternal Infantile and Urological Sciences, Sapienza University of Rome, Polo Pontino, Rome, Italy
[48]Department of Paediatrics, University of Chieti-Pescara, Chieti, Italy
[49]Department of Translational Medical Sciences, Section of Clinical Immunology, University of Naples Federico II, Naples, Italy
[50]Center for Basic and Clinical Immunology Research (CISI), WAO Center of Excellence, University of Naples Federico II, Naples, Italy
[51]Unit of Rheumatology, Department of Medicine, ARNAS Garibaldi Hospital, Catania, Italy
[52]Department of Rheumatology, Faculty of Medicine Ankara City Hospital, Ankara Yildirim Beyazit Universitesi, Ankara, Turkey
[53]Rheumatology and Immunology Unit, Internal Medicine Department, Mansoura University, Mansoura, Egypt
[54]Department of Internal Medicine, Faculty of Medicine, Horus University, New Damietta, Egypt
[55]Department of Pediatrics, Attikon General Hospital, National and Kapodistrian University of Athens, Athens, Greece
[56]Rheumatology Unit, Department of Medicine, Central Hospital of Bolzano, Bolzano, Italy
[57]Division of Rheumatology, Ospedale Pediatrico Bambino Gesù, IRCCS [European Reference Network (ERN) for Rare Immunodeficiency, Autoinflammatory and Autoimmune Diseases (RITA) Center], Rome, Italy
[58]Department of Rheumatology, 'Evangelismos' General Hospital, Athens, Greece
[59]Ospedale San Paolo di Civitavecchia, U.O. Medicina Generale, ASL Roma 4, Civitavecchia, Rome, Italy
[60]Division of Rheumatology, Department of Internal Medicine, School of Medicine, Manisa Celal Bayar University, Manisa, Turkey
[61]Rheumatology Department, Faculty of Medicine, Al-Azhar University, Assiut, Egypt
[62]Rheumatology Unit, Hospital S. Giovanni di Dio, Azienda USL-Toscana Centro, Florence, Italy
[63]Bioengineering and Biomedical Data Science Lab, Department of Medical Biotechnologies, University of Siena, Siena, Italy

[64]Rheumatology Unit, Department of Medicine and Surgery, University of Perugia, Perugia, Italy
[65]Department of Clinical and Experimental Medicine, University of Catania, Catania, Italy
[66]Division of Rheumatology, Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy
[67]Systemic Autoimmune Diseases Unit, Department of Internal Medicine, Hospital Universitario Ramón y Cajal, IRYCIS, Madrid, Spain
[68]Department of Ophthalmology, Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain
[69]Pediatric Nephrology and Rheumatology Unit, Azienda Ospedaliero Universitaria (AOU) G Martino, Messina, Italy
[70]Academic Rheumatology Center, Dipartimento Scienze Cliniche e Biologiche, Università degli Studi di Torino, Turin, Italy
[71]Division of Rheumatology, Department of Internal Medicine, School of Medicine, Dokuz Eylül University, Izmir, Turkey
[72]Department of Pediatrics, College of Medicine, King Faisal Specialist Hospital and Research Center, Alfaisal University, Riyadh, Saudi Arabia
[73]Department of Ophthalmology, Cerrahpasa Medical School, Istanbul University-Cerrahpasa, Istanbul, Turkey; Behçet's Disease Research, Center Istanbul University-Cerrahpasa, Istanbul, Turkey
[74]Ophthalmology Unit, Department of Medicine, Surgery and Neurosciences, University of Siena and Azienda Ospedaliero-Universitaria Senese [European Reference Network (ERN) for Rare Immunodeficiency, Autoinflammatory, and Autoimmune Diseases (RITA) Center], Siena, Italy

*Correspondence to: Luca Cantarini, Research Center of Systemic Autoinflammatory Diseases and Behçet's Disease Clinics, Department of Medical Sciences, Surgery and Neurosciences, University of Siena. Rheumatology Unit, Policlinico 'Le Scotte', Viale Bracci 16, 53100 Siena, Italy. E-mail: cantariniluca@hotmail.com

Abstract

Objectives: The progression of Behçet's disease (BD) from a mucocutaneous-limited form to major organ involvement (MOI) represents a significant challenge. This study aims to identify patients without MOI at BD onset who are at increased risk of developing MOI in later stages.

Methods: Patients' data were drawn from the International AutoInflammatory Disease Alliance (AIDA) Network registry dedicated to BD.

Results: A total of 328 patients with exclusively mucocutaneous manifestations at BD onset were enrolled. Of these, 82 patients (25%) developed MOI over the entire follow-up period. Patients with minor oral aphthosis and no major oral aphthosis exhibited a reduced risk of developing MOI, with an odds ratio (OR) of 0.41 [95% confidence interval (95%CI): 0.22–0.79, $P=0.008$]. Conversely, patients with both major and minor oral aphthosis had a significantly higher risk of developing MOI, with an OR of 12.76 (95%CI: 1.44–113, $P=0.02$). Moreover, the development of MOI was associated with major oral aphthosis plus genital aphthosis (OR: 2.49, 95%CI: 1.1–5.6, $P=0.03$), major oral aphthosis plus pseudofolliculitis (OR: 2.9, 95%CI: 1.15–7.4, $P=0.02$) and major oral aphthosis plus both genital aphthosis and pseudofolliculitis (OR: 3.73, 95%CI: 1.22–11.4, $P=0.02$). A positive family history for BD was associated with MOI (OR: 2.85, 95%CI: 1.08–7.58, $P=0.03$).

Conclusion: A positive family history and the presence of major oral aphthosis combined with minor oral aphthosis, genital aphthosis or pseudofolliculitis are associated with MOI development in patients with mucocutaneous BD at onset.

Keywords: AIDA Network, Behçet's disease, international registry, prognosis, rare disease, uveitis

Rheumatology key messages

- This study identified clinical and familial predictors of major organ involvement in mucocutaneous-onset Behçet's disease.
- The coexistence of major oral aphthosis with genital aphthosis or pseudofolliculitis significantly increases MOI risk.
- A positive family history and combined mucocutaneous features are independently associated with MOI development.

Introduction

Behçet's disease (BD) is a chronic, systemic and relapsing inflammatory disorder characterized by a complex pathogenetic mechanism involving both autoimmune and autoinflammatory components [1]. Initially described as a triad of oral aphthosis, genital ulcers and uveitis, BD presents with a broad clinical heterogeneity, ranging from forms limited to mucocutaneous involvement to multisystemic manifestations affecting the eye, the gut, the vascular tree and the central nervous system (CNS) [2]. Diagnosis may thus prove particularly challenging, particularly in pediatric populations, wherein the disease may present with incomplete clinical features and is further complicated by possible overlapping syndromes [3].

In the early stages, the disease may present with mucocutaneous manifestations, including recurrent oral and genital ulcers, erythema nodosum and pseudofolliculitis, without signs of major organ involvement [4]. However, a significant proportion of patients develop more severe forms of the disease, with progressive involvement of internal organs over time [5]. Ocular involvement can lead to chronic recurrent uveitis and vision loss; intestinal involvement manifests as Crohn's disease-like gastrointestinal ulcerations; vascular manifestations include venous thrombosis and arterial aneurysms, while CNS involvement can result in neuro-Behçet syndromes with potentially disabling consequences [6].

This progression from an initially mucocutaneous-limited form to a more severe systemic involvement represents a significant clinical challenge, making early identification of patients at risk for severe evolution crucial. This is also relevant in cases of pediatric-onset BD, as over one-third of pediatric patients transitioning to adulthood with exclusively BD mucocutaneous involvement develop MOI after 18 years of age, during a mean follow-up of approximately ten years [7].

Despite advances in the understanding of BD pathophysiology, predicting which patients will progress from a limited to a systemic form remains difficult. Identifying early clinical or demographic predictors of disease evolution could improve patient monitoring and guide therapeutic strategies aimed at preventing major organ damage.

The objective of this study is to analyse the demographic and clinical characteristics of patients with BD at disease onset, within a large international cohort, in order to identify early predictors associated with the progression from a mucocutaneous-limited phenotype to a more severe systemic

involvement characterized by ocular, gastrointestinal, vascular or CNS involvement.

Methods

Study population

This is a retrospective, multicentre study, with patients' data drawn from the International AutoInflammatory Disease Alliance (AIDA) Network registry dedicated to BD [8]. All patients met the International Study Group (ISG) criteria and/or the International Criteria for Behçet's Disease (ICBD) [9, 10], as assessed by experienced clinicians at each participating site.

Patients presenting at disease onset exclusively with oral aphthosis, genital aphthosis, and BD-related cutaneous manifestations, without ocular, intestinal, vascular, or CNS involvement for at least 12 months after disease onset were selected. Disease onset was defined as the time at which the diagnostic criteria were first met, while ocular, intestinal, vascular or CNS involvement was collectively referred to as major organ involvement (MOI). Subsequently, patients who developed MOI at least one year after the onset of mucocutaneous symptoms were identified and distinguished from those who exhibited only mucocutaneous manifestations throughout the entire follow-up period. Subsequently, demographic characteristics, country of residence, the presence of human leucocyte antigen (HLA)-B51 haplotype, comorbidities, body mass index (BMI), smoking status, ethnic origin, familial history of BD and the specific characteristics of oral and genital ulcers (size and number of lesions) were assessed. The different mucocutaneous manifestations were analysed to evaluate their potential association with MOI development over the course of the disease. In particular, a binary logistic regression model was employed, considering patient features, each at a time, as independent variables. In contrast, the development or absence of MOI over time accounted for the dependent variable. All logistic regressions were adjusted for the entire duration of the observation period, the use of conventional disease-modifying antirheumatic drugs and use of tumour necrosis factor inhibitors. Additionally, the presence of specific mucocutaneous signs at onset was explored as a potential predictor of disease evolution. For variables associated with MOI development, the expected probabilities of MOI occurrence were calculated based on the presence or absence of the studied variables.

Definition of variables

Regarding the number of concurrently present oral and genital ulcers during aphthous attacks at disease onset, patients were stratified into three groups: 1–2 ulcers, 3–5 ulcers and >5 ulcers. Oral ulcers were categorized as minor if their diameter was <10 mm, major if >10 mm and herpetiform if small, numerous and clustered. Oral ulcer size was clinically assessed by each participating physician using visual estimation, based on their professional experience and in accordance with routine clinical practice for patient diagnosis and management. Documentation of ulcer size in the registry followed the standard recording procedures at each site. Measurements were performed without the use of standardized protocols across countries, reflecting real-world clinical practice and ensuring consistent application within each participating centre.

Cutaneous involvement was assessed based on the presence of pseudofolliculitis, erythema nodosum and less common cutaneous manifestations, including pyoderma gangrenosum, suppurative panniculitis, skin ulcers, maculopapular rash, bullous erythema, hidradenitis suppurativa, urticarial rash, erythema induratum and erythema multiforme.

Statistical analysis

Statistical analysis included descriptive methods such as mean ± standard deviation (SD) or median (interquartile range, IQR), as appropriate according to the distribution of the data assessed with the Shapiro–Wilk test, and frequency counts with percentages [N (%)]. Binary logistic regression analysis was complemented by calculating odds ratios (ORs), obtained by exponentiating the regression model's β estimates, 95% confidence intervals (95% CI), expected probabilities of MOI development and corresponding *P*-values. The likelihood of developing MOI for variables with a *P*-value <0.1 in the logistic regression analysis was estimated based on the β estimates from the model. Specifically, for categorical variables, the probability was calculated by comparing the presence and absence of the given factor, illustrating its impact on MOI development. The influence of the country of residence on the variables associated with MOI development was evaluated by calculating the intraclass correlation coefficient (ICC), incorporating a random intercept in the logistic regression model. When investigating the association between MOI development and the combination of various mucocutaneous variables using binary logistic regression, only associations observed in at least 10 patients were considered. The significance level was 95% (*P*-value <0.05); *P*-values were two-tailed. All statistical analyses were performed using RStudio software (version 4.3.0).

Sample size and power considerations

This registry-based study included all consecutively eligible patients with BD presenting exclusively mucocutaneous manifestations at onset; therefore, no *a priori* sample-size calculation was performed. To provide an approximate assessment of statistical power, we performed a post-hoc analysis based on the observed overall MOI incidence in the cohort (82/328, 25%) and a two-sided $\alpha = 0.05$. Assuming the probability of MOI among non-exposed patients is 25%, the available sample provides ∼80% power to detect odds ratios ≥2.46 for exposures that increase risk by at least 20%, and ≤0.53 for exposures that reduce risk by at least 10%. Given the observational, all-cases design typical of rare-disease registries, effect sizes and 95% confidence intervals are reported as the primary indicators of precision.

Ethics approval and consent to participate

The Ethics Committee of Azienda Ospedaliero-Universitaria Senese, Siena, Italy (Ref. N. 14951; NCT05200715) approved the study, which was performed according to the Good Clinical Practice guidelines and the latest Declaration of Helsinki. Written informed consents for involved patients were collected. Clinical data are kept in accordance with the EU General Data Protection Regulations (GDPR), or other counterparts, on the processing of personal data and the protection of privacy (2016/679/EU).

Results

Demographic and clinical features of enrolled patients

A total of 328 patients with exclusively mucocutaneous manifestations at BD onset were enrolled. Of these, 82 (25%)

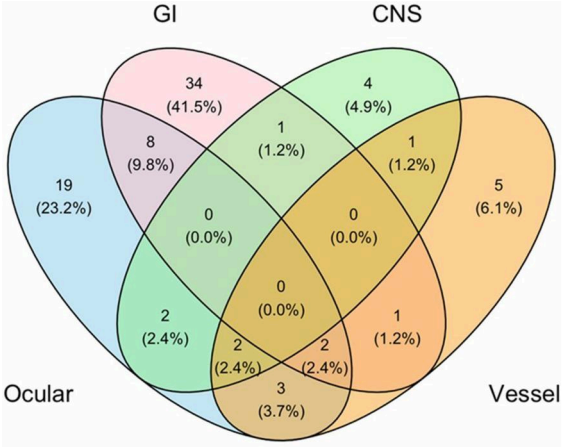

Figure 1. Euler Venn diagram illustrating the distribution and overlap of major organ involvement (MOI) in patients initially presenting with only mucocutaneous symptoms. The diagram shows the frequency and percentage of patients who developed involvement in the gastrointestinal (GI), ocular, vessel and central nervous system (CNS) systems. Each overlapping section represents patients with multiple MOI, while the non-overlapping sections indicate isolated MOI. The percentages are calculated based on the total number of patients who developed any MOI

developed MOI during a mean follow-up of 12.9 years: 36 patients (11%) developed ocular inflammatory involvement, 46 patients (14%) gastrointestinal involvement, 10 patients (3%) central nervous system (CNS) manifestations and 14 patients (4.3%) vascular involvement. The mean follow-up duration was 13.2 ± 9.44 years for patients who developed MOI and 12.7 ± 11.7 years for those without MOI development ($P = 0.73$). Fig. 1 shows the number of patients developing the different types and combinations of MOI; Table 1 summarizes the demographic and clinical features of patients enrolled and those developing MOI. The mean age at BD onset was 29.2 ± 13.7 years among patients developing MOI and 29.1 ± 15.0 years among patients not developing MOI, with no statistically significant difference ($P = 0.95$).

Regarding the initial mucocutaneous involvement, oral aphthosis was classified as minor in 159 (48.5%) cases and major in 66 (20.1%) cases; herpetiform oral lesions were described in 10 (3%) patients. The median number of aphthous attacks was 12 (IQR: 10.5) episodes per year. Complete data on the number of concomitant oral aphthosis were available for 222 (68%) cases. In these patients, the number of oral ulcers per aphthous episode was 1–2 lesions in 74 (33.3%) patients, 3–5 lesions in 101 (45.5%) patients and >5 lesions in 47 (21.2%) patients.

Genital aphthosis was observed in 220 patients (67.1%), involving the scrotum in 49 (33.6%) of the 146 males, the glans in 17 (11.6%) males, the shaft in 13 (8.9%) males, the perianal region in six (1.8%) of the 328 cases, the perineum in four (1.2%) cases, the labia minora in 26 (14.3%) of the 182 females, the labia majora in 50 (27.5%) females and the vagina in 17 (9.3%) females. Scarring of genital lesions was reported in 60 (18.3%) cases. Information on the number of concomitant genital aphthosis was available for 152 of the 220 patients with genital ulcers. In this context, 112 (73.7%) patients experienced one to two genital lesions per attack, 32 (21.1%) experienced three to five genital lesions, and eight (5.3%) had more than five lesions per attack. BD-related skin

Table 1. Demographic and clinical characteristics of the enrolled patients

Patients' features	Description
Sex (F/M)	182/146
Ethnicity[a]	
Caucasian, *n* (%)	233 (71)
Arab, *n* (%)	60 (18.3)
Hispanic, *n* (%)	6 (1.8)
Other, *n* (%)	7 (2.1)
Age at disease onset, years (mean±SD)	29.1 ± 14.7
Age at disease diagnosis, years (mean±SD)	34.8 ± 13.9
HLA-B51 positivity, *n* (%)[b]	156 (47.6)
Non-HLA gene mutations, *n* (%)[c]	8 (2.4)
Positive family history, *n* (%)	35 (10.7)
Pregnancy during the disease, *n* (% on females)	22 (12.1)
Ocular involvement over time	
Age at the onset of ocular involvement, years (mean±SD)	35.8 ± 13.6
Monolateral/bilateral	18/18
Uveitis	30 (9.1)
Retinal vasculitis	6 (1.8)
Gut involvement over time	
Persistent diarrhea	27 (8.2)
Hematochezia	3 (0.9)
Gastrointestinal occlusion	1 (0.3)
Recurrent abdominal pain without peritonism	16 (4.87)
Recurrent abdominal pain with peritonism	1 (0.3)
Macroscopic inflammatory lesions at endoscopy[d]	12 (25.5)
Macroscopic vasculitic lesions at endoscopy[d]	1 (2.1)
CNS involvement over time	
Parenchymal affections	7 (2.1)
Non-parenchymal affections	5 (1.5)
Vascular involvement over time	
Deep venous thrombosis	7 (2.1)
Superficial venous thromboflebitis	4 (1.2)
Stroke	2 (0.6)
Venous thrombosis in atypical sites	1 (0.3)
Dural venous sinuses thrombosis	1 (0.3)
Arterial thrombosis	1 (0.3)
Pulmonary embolism secondary to vein thrombosis	1 (0.3)
Inferior vena cava thrombosis	1 (0.3)
Arterial pseudoaneurysms	1 (0.3)

[a] Not provided in 22 cases.
[b] In 60 cases HLA-B evaluation not performed.
[c] *NOD2* gene in two patients (heterozygous c.2857A>C); *MEFV* gene in two patients (Ala744Ser and mutation and homozygous M694V mutation associated with missing codon 692–695); trisomy of chromosome eight in 2 patients; *NLRP3* gene mutation in one patient (heterozygous Val198Met); *MVK* gene mutation in one patient (heterozygous V377I).
[d] Percentage referred to the 47 patients undergoing endoscopy.
CNS: central nervous system; F: females; HLA: human leucocyte antigen; M: males; n: number; SD: standard deviation.

manifestations were observed in 192 (58.5%) patients at disease onset, including pseudofolliculitis in 135 (41.2%) cases, erythema nodosum in 68 (20.7%) and skin ulcers in 10 (3%). Other skin lesions included erythema multiforme ($n = 4$), pyoderma gangrenosum ($n = 3$), acneiform lesions ($n = 3$), livedo reticularis ($n = 2$), bullous erythema ($n = 2$), hidradenitis suppurativa ($n = 2$), maculopapular rash ($n = 1$), urticarial rash ($n = 1$), folliculitis ($n = 1$), perianal abscess ($n = 1$), erythema induratum ($n = 1$) and suppurative panniculitis ($n = 1$).

Binary logistic regression analysis of demographic and clinical factors associated with MOI development

Table 2 presents the binary logistic regression analysis results associating individual patient characteristics, who initially

Table 2: Associations between the specific patients' features and the development of major organ involvement (MOI) among patients presenting with mucocutaneous involvement at the start of Behçet's disease.

Patients' features	Number of patients presenting the feature (%)	MOI development overall, OR (95%CI, *P*-value)
Sex (male)	—	1.08 (0.59–1.97, 0.81)
Age at disease onset, years	—	0.995 (0.975–1.015, 0.66)
Early onset (<16 years)	52 (15.9)	1.11 (0.59–2.32, 0.79)
HLA-B51 (no→ yes)[a]	156 (47.6)	1.45 (0.75–2.9, 0.26)
Positive family history for BD (no→ yes)	35 (10.7)	2.85 (1.08–7.58, 0.03)
Pregnancy history after disease onset (no→yes)[b]	22 (12.1)	0.39 (0.095–1.64, 0.2)
BMI	—	0.99 (0.92–1.07, 0.82)
Smoking status	57 (17.4)	1.53 (0.72–3.2, 0.27)
Presence of comorbidities (no→yes)	98 (29.9)	0.91 (0.47–1.79, 0.79)
Rheumatologic comorbidities (no→yes)	11 (3.4)	1.11 (0.26–4.78, 0.89)
Endocrinologic comorbidities (no→yes)	23 (7)	1.34 (0.43–4.2, 0.62)
Metabolic syndrome (no→yes)	10 (3)	0.58 (0.06–5.34)
Arterial hypertension (no→yes)	36 (11)	0.64 (0.23–1.74, 0.38)
Pneumological comorbidities (no→yes)	13 (4)	0.45 (0.09–2.2, 0.33)
Neurological comorbidities (no→yes)	12 (3.7)	1.78 (0.45–7.01, 0.41)
Malignant oncological comorbidities (no→yes)	8 (2.4)	0.6 (0.07–5.6, 0.65)
Ethnic origin[c]		
Caucasic	233 (71)	Reference
Arab	60 (18.3)	1.27 (0.6–2.7, 0.53)
Hispanic	6 (1.8)	0.61 (0.06–5.8, 0.67)
Oral aphthosis features at baseline		
Concurrent oral ulcers (1–2 lesions)[c]	74 (33.3)	Reference for concurrent oral ulcers
Concurrent oral ulcers (3–5)[c]	101 (45.5)	1.94 (0.8–4.7, 0.14)
Concurrent oral ulcers (>5)[d]	47 (21.2)	2.09 (0.7–6.3, 0.18)
Minor oral aphthous ulcerations (<10 mm), (no→yes)	159 (48.5)	0.55 (0.3–1.04, 0.066)
Major oral aphthous ulcerations (>10 mm), (no→yes)	66 (20.1)	2.51 (1.27–4.9, 0.008)
Oral herpetiform ulcerations (no→yes)	10 (3)	4.65 (0.81–26.7, 0.08)
Genital aphthosis features at baseline		
Genital aphthosis (no→ yes)	220 (67.1)	1.15 (0.58–2.26, 0.69)
Concurrent genital ulcers (1–2 lesions)[e]	112 (73.7)	Reference for concurrent genital ulcers
Concurrent genital ulcers (3–5 lesions)[e]	32 (21.1)	1.67 (0.56–5.0, 0.36)
Concurrent genital ulcers (>5 lesions)[e]	8 (5.3)	1.37 (0.22–8.5, 0.73)
Skin manifestations at baseline		
Skin involvement (no→ yes)	192 (58.5)	1.34 (0.7–2.55, 0.38)
Pseudofolliculitis (no→ yes)	135 (41.2)	1.17 (0.64–2.15, 0.62)
Erythema nodosum (no→ yes)	68 (20.7)	0.86 (0.42–1.77, 0.68)
Other skin manifestations (no→ yes)	27 (8.2)	0.99 (0.33–3.0, 0.99)

The odd ratio (OR), 95% confidence intervals (95%CI) and *P*-values derive from multiple logistic regression, with the development of MOI being the dependent variable. The patients feature the independent variable adjusted for the disease duration and treatments performed. Acronyms: BMI: body mass index; HLA: human leucocyte antigen. Note that 'no → yes' indicates that the odds ratio refers to the transition from absence to presence of the patient feature under investigation.

[a] Information not provided in 60 (18.3%) cases.
[b] Performed on the subgroup of female patients.
[c] Considered the ethnic groups with at least six included patients.
[d] Information provided in 222 (68%) cases.
[e] Information provided in 152 out of 220 cases with genital ulcers.

exhibited only mucocutaneous manifestations of BD, with the risk of developing MOI over time. The OR, 95%CI and *P*-values are also reported. When considering the random effect related to the country of residence on the variables significantly associated with the MOI onset over time, the ICC explained by the country of patients' residence was 15.1% for the positive family history, 14% for the presence of major oral ulcers, 17% for minor ulcers and 12.9% for herpetiform oral lesions.

Patients with minor oral aphthosis and no major oral aphthosis exhibited a risk of developing MOI with an OR of 0.41 (95% CI: 0.22–0.79, $P = 0.008$, ICC related to patients' residence: 16.6%). Patients with major oral aphthosis but without minor aphthosis had a risk of developing MOI corresponding to an OR of 1.83 (95% CI: 0.89–3.75), without reaching statistical significance ($P = 0.1$). Patients who presented a combination of major and minor oral aphthosis exhibited a risk of developing MOI with an OR of 12.76 (95% CI: 1.44–113, $P = 0.02$, ICC related to patients' residence: 10.6%).

Combined mucocutaneous manifestations associated with the risk of MOI development

Supplementary Table S1 provides the data about the association of two different mucocutaneous manifestations and MOI development. The MOI development was associated with the combination of major oral aphthosis and genital aphthosis (OR: 2.49, 95% CI: 1.1–5.6, $P = 0.03$, ICC related to patients' residence: 13.7%) and with the combination of major oral aphthosis and pseudofolliculitis (OR: 2.9, 95% CI: 1.15–7.4, $P = 0.02$, ICC related to patients' residence: 14%).

Supplementary Table S2 highlights the risk of developing MOI based on the combinations of three mucocutaneous manifestations. The association between major oral aphthosis, genital aphthosis and pseudofolliculitis was significantly linked to the development of MOI (OR: 3.73, 95% CI: 1.22–11.4, $P = 0.02$, ICC related to patients' residence: 14.4%).

Supplementary Fig. S1 provides the number of patients characterized by the association of four mucocutaneous clinical manifestations at disease onset. The association between minor oral aphthosis, genital aphthosis, pseudofolliculitis and erythema nodosum was the only one reaching a frequency of at least 10 patients. Still, no statistically significant association with the development of MOI was found (OR: 0.68, 95% CI: 0.13–3.4, $P = 0.64$).

Fig. 2 summarizes the regression analysis results examining the association between MOI development in patients with mucocutaneous manifestations as the sole symptoms at the onset of BD and the combination of various BD-related mucocutaneous manifestations at disease onset.

Table 3 provides the probability of developing MOI based on the variables significantly associated with MOI as determined by beta estimates from binary logistic regression.

Discussion

Mucocutaneous lesions represent the hallmark of BD across all disease stages, particularly in its early phase. Notably, the high prevalence of oral aphthosis, genital aphthosis and cutaneous involvement at disease onset underscores their pivotal diagnostic significance. This is especially relevant considering many patients initially present exclusively with mucocutaneous symptoms [11, 12]. However, the absence of MOI during

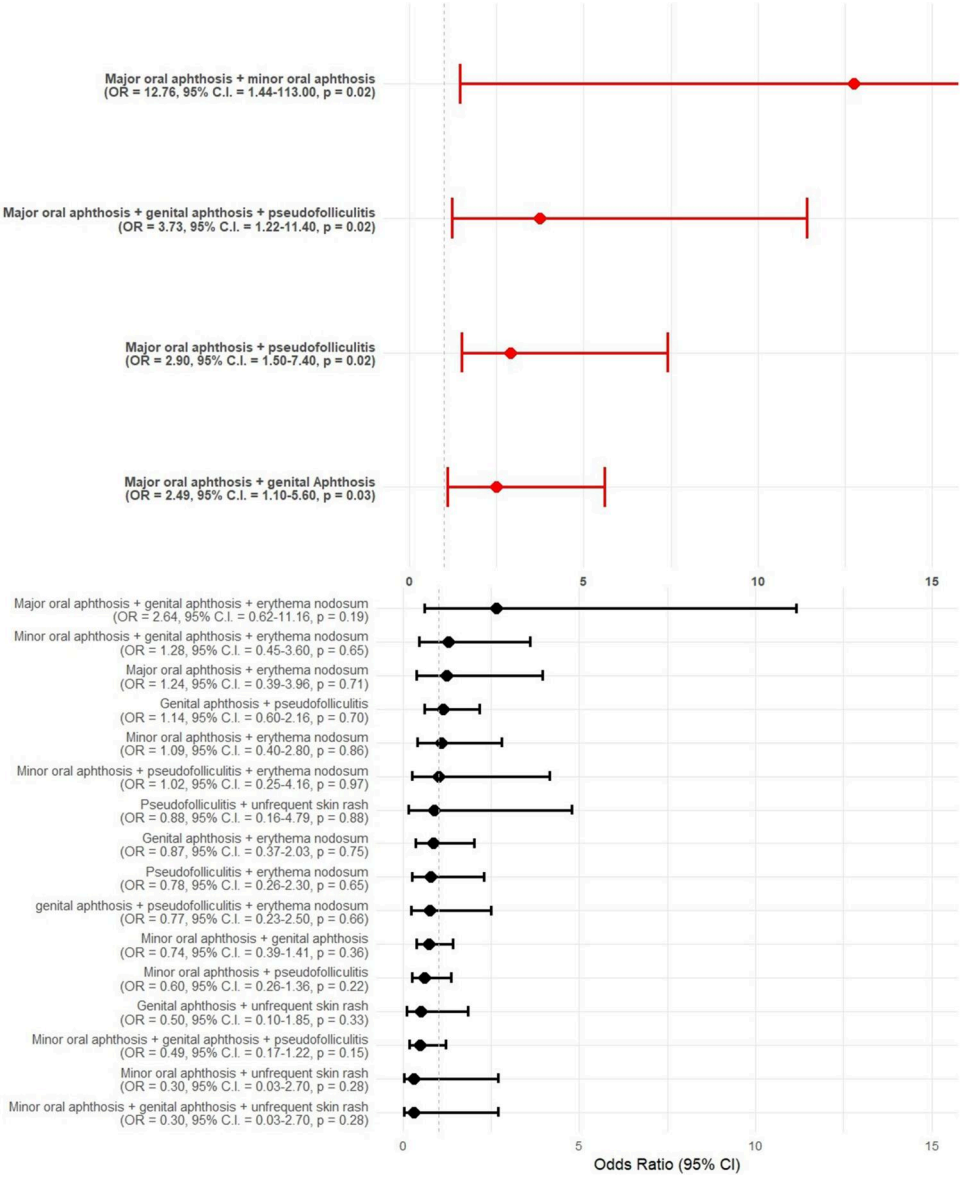

Figure 2. Forest plot summarizing the results of binary logistic regression analyses investigating the association between combinations of mucocutaneous manifestations at disease onset in patients without initial major organ involvement (MOI) and the subsequent development of MOI. Each point represents the odds ratio (OR) for developing MOI for a specific combination of clinical features, with horizontal lines indicating 95% confidence intervals. Red points and lines indicate statistically significant associations ($P < 0.05$), whereas black points and lines indicate non-significant associations. Combinations including major oral aphthosis, genital aphthosis and pseudofolliculitis were most strongly associated with subsequent MOI. MOI: major organ involvement; OR: odds ratio; 95%CI: 95% confidence interval

Table 3: Probability of developing major organ involvement (MOI) based on β estimates derived from multiple logistic regression.

	Probability to develop MOI
Family history	
Negative *vs* positive family history	25.86% *vs* 49.83%
Type of oral aphthosis	
No minor oral aphthous ulcerations (<10 mm) *vs* patients with minor ulcers	24.3% *vs* 34.4%
No major oral aphthous ulcerations (>10 mm) *vs* patients with major ulcers	24.1% *vs* 44.4%
No oral herpetiform ulcers *vs* patients with herpetiform ulcers	26.5% *vs* 82.3%
Minor oral aphthosis without major oral aphthosis or herpetiform ulcers	6.8%
Major oral aphthosis without minor oral aphthosis or herpetiform ulcers	34.8%
Both major and minor oral aphthosis	79.6%
Major oral aphthosis plus genital aphthosis	41.9%
Major oral aphthosis plus pseudofolliculitis	45.5%
Major oral aphthosis plus genital aphthosis plus pseudofolliculitis	52.1%

The probability was calculated for variables showing a P-value ≤ 0.1, also including patients' features approaching statistical significance, to provide a broader view of the expected probabilities.

the early years of BD does not imply a mild prognosis, as mucocutaneous lesions often precede the development of more severe organ involvement [12]. Therefore, delineating the mucocutaneous features predictive of progression to MOI is paramount to enhance risk stratification and enable rigorous monitoring of patients predisposed to ocular, gastrointestinal, CNS or vascular involvement. To date, male sex and younger age at disease onset have been identified as significant risk factors for disease severity [4, 5, 11, 13, 14]. However, existing studies have not been specifically designed to investigate patients presenting exclusively with mucocutaneous manifestations at the onset of Behçet's disease (BD) [4, 13]. Other studies are monocentric, making their findings susceptible to regional variability and centre-specific biases [11], or are constrained by small sample sizes, thereby limiting the generalizability of their results [14].

Regarding mucocutaneous manifestations predictive of MOI development, Sota *et al.* observed that genital ulcers appeared protective against MOI progression. However, this analysis was conducted on the entire BD cohort rather than specifically on patients presenting with an exclusively mucocutaneous phenotype at disease onset [4]. In more dedicated studies, younger age at disease onset was found to influence long-term prognosis, with early-onset BD being significantly associated with a higher risk of severe disease outcomes [12, 14]. This observation did not emerge in the present study, likely due to the inclusion of an international cohort. However, it should be considered in the context of disease severity stratification.

Based on the analysis conducted in the present study, specifically on patients presenting with mucocutaneous involvement at disease onset, the impact of male sex and age at onset appears to be considerably less relevant in mucocutaneous patients who progress to MOI. Indeed, the ORs for these variables, besides being non-significant, remain close to 1.0, suggesting a negligible clinical impact. Conversely, a positive family history of BD was significantly associated with an increased risk of MOI development, conferring an ~50% risk compared with 25% in patients without a familial history of BD.

From a clinical perspective, assessing the presence of minor and major oral aphthosis allows identification of patients with different likelihoods of developing MOI. Specifically, only minor aphthae, without major aphthae, appear protective, with a risk of developing MOI as low as 6.8%. According to the OR value, the presence of only major aphthae was a risk factor for MOI, but it did not reach statistical significance. In contrast, the coexistence of major and minor aphthae in the same patient significantly increased the likelihood of developing MOI. Indeed, assessing which combinations of mucocutaneous manifestations should prompt clinicians to consider a higher probability of MOI development was of interest. In this regard, the presence of major aphthosis was significantly associated with MOI, even when related with genital aphthosis or folliculitis, and to an even greater extent when combined with both genital aphthosis and pseudofolliculitis, with a progressively increasing risk highlighted in Table 3.

Noteworthy, based on ICC values, which ensure relatively low variability related to the country of residence, all statistically significant results appear to be applicable regardless of the patients' country of residence. Also, in this cohort no difference was observed in the age at BD onset between patients with or without MOI development during follow-up. This finding suggests the importance of maintaining careful long-term follow-up in patients presenting with isolated mucocutaneous manifestations, regardless of their age at disease onset, given the potential for subsequent development of MOI.

These data may assist clinicians in daily practice; however, several study limitations must be considered. A key limitation of this study concerns the measurement of oral ulcer size. In the international AIDA Network registry for BD, ulcer dimensions were estimated visually rather than measured using a standardized instrument such as a ruler. While this approach reflects real-world clinical practice and facilitates data collection in routine settings, it introduces the potential for measurement bias and misclassification, particularly around the 10 mm threshold used in our analyses. Ulcers close to this cutoff could have been inconsistently categorized across different investigators or study sites, potentially influencing the observed associations. Furthermore, the absence of a uniform measurement protocol may limit the comparability of data between centres and reduce the generalizability of our findings to clinical settings where more rigorous or calibrated measurement techniques are applied. Although this pragmatic method captures authentic clinical behavior, it does so at the expense of methodological precision. Recognizing this limitation is essential to avoid overinterpretation of the results related to ulcer size and to appropriately contextualize the conclusions drawn from this dataset. Among other limitations, the potential positivity of the pathergy test was not considered for statistical analysis, as this test is performed in a highly variable manner across different countries and centres, which affects its sensitivity and specificity [15–17]. Furthermore, the pathergy test is optional for diagnostic purposes, and thus is not routinely conducted by all centres, which may introduce selection biases [10]. Of note, the observed rate of gastrointestinal involvement may appear relatively high in this study; however, this reflects the

international nature of the study cohort. Indeed, gastrointestinal manifestations are known to be less frequent in Middle Eastern populations and more prevalent in Southern European countries, which are well represented in the present cohort [18]. Additionally, despite the large sample size, the frequency of combinations of different types of mucocutaneous manifestations was often <10, meaning that statistical analysis could not be performed for many combinations, as for the statistical methods previously described. This limitation suggests that other clinical factors may precede the development of MOI, and these aspects should be further investigated in future studies with larger patient cohorts. Finally, the small number of patients with herpetiform aphthosis rendered the findings in this article non-significant. While the data presented here suggest that herpetiform lesions may have considerable predictive value for developing MOI, this finding requires confirmation in a much larger cohort of affected patients.

Diagnostic limitations should also be highlighted, as this study has several inherent constraints. First, the classification of BD relied on retrospective chart reviews, which may be influenced by incomplete documentation or variability in diagnostic assessment across centres. Second, although all patients fulfilled internationally accepted classification criteria, differences in the availability and use of diagnostic tests between countries may have led to under- or overestimation of specific manifestations. Third, the absence of centralized review of clinical data may have introduced heterogeneity in lesion classification, particularly for mucocutaneous findings. Finally, the possibility of referral bias in tertiary centres, where patients with more severe or atypical phenotypes are overrepresented, cannot be excluded.

Conclusion

In conclusion, BD patients with a positive family history and those who have a combination of both major and minor oral aphthosis, or with major aphthosis in combination with genital aphthosis or pseudofolliculitis, especially when all three are present, carry an increased risk of developing MOI over time. In contrast, the presence of minor oral aphthosis alone, without major oral lesions, appears to confer a substantially lower risk. These findings highlight the importance of detailed phenotypic assessment at disease onset to guide long-term monitoring and timely intervention.

Supplementary material

Supplementary material is available at *Rheumatology* online.

Data availability

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation. Requests to access these datasets should be directed to the corresponding author.

Contribution statement

All the authors substantially contributed to the conception or design of the work, the acquisition and interpretation of data and critically revised the paper. All the authors approved the final version and agreed to be responsible for all the aspects of the work. In addition, A.V. wrote the first draft of the manuscript and performed the preliminary data analysis and interpretation. F.G., V.C., J.S., G.L., G.R., S.G., I.A., A.T., R.G., H.D., P.R., G.H., F.C., E.D.B., S.O., J.S.O., H.A.Y.G., M.F., P.P.S., F.I., M.M., M.G., M.A.S., R.D., H.K., R.C.K., I.Y.C., L.N., F.A.O., G.S., M.G., A.A., H.E.E., C.F., G.F., F. C., M.T., A.K., D.U., S.B., A.M., M.S.C., B.M., M.P., A.F., A.H.A., G.A.G.B., C.B.C., J.H.R., M.C., M.G., O.V., A.C., D.O., C.G., R.T., A.G., G.E., P.S.P., M.C.M., P.P., P.P., A.D. L.T., B.A.B., S.G., A.M., G.D.S., A.N.O., A.S., D.R., E.B., E. D.G., L.B., A.D.P., A.L.G., S.E., S.T., L.F., A.M., A.I., A.K., A.C., O.S.G., A.M., F.L.G., E.B., P.B., S.G., A.G.G., I.H.R., G.C., A.I., F.O., S.M.A., A.B., B.F., C.F. and L.C. were involved in the study according to their active role in enrolling patients in the AIDA Network Registries; A.B. is also the bioengineer involved in the technical management of the platform and registries; L.C. took care of the final revision of the manuscript and accounted for AIDA Registries Coordinator.

Funding

The authors declare no financial support was received for the research, authorship and/or publication of this article.

Disclosure statement: Emre Bilgin is an Associate Editor of Rheumatology. The other authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Acknowledgements

This research is supported (not financially) by the European Reference Network (ERN) for Rare Immunodeficiency, Autoinflammatory and Autoimmune Diseases (RITA) of the authors of this publication [A.V., V.C., J.Sb., J.So., S.Ge., A. B., B.F., C.F. and L.C.; J.H.-R.] belong to institutes that are members of the ERN RITA [Azienda Ospedaliero-Universitaria Senese of Siena; Hospital Clínic of Barcelona].

References

1. Perazzio SF, Andrade LEC, de Souza AWS. Understanding Behçet's disease in the context of innate immunity activation. Front Immunol 2020;11:586558.
2. Onder M, Gürer MA. The multiple faces of Behçet's disease and its aetiological factors. J Eur Acad Dermatol Venereol 2001; 15:126–36.
3. Yildiz M, Koker O, Kasapcopur O. Juvenile Behçet syndrome: a contemporary view and differential diagnosis in pediatric practice. Curr Opin Rheumatol 2025;37:3–14.
4. Sota J, Rigante D, Emmi G *et al.* Behçet's syndrome in Italy: a detailed retrospective analysis of 396 cases seen in 3 tertiary referral clinics. Intern Emerg Med 2020;15:1031–9.
5. Alpsoy E. Behçet's disease: a comprehensive review with a focus on epidemiology, etiology and clinical features, and management of mucocutaneous lesions. J Dermatol 2016;43:620–32.
6. Yazici Y, Hatemi G, Bodaghi B *et al.* Behçet syndrome. Nat Rev Dis Primers 2021;7:67.
7. Bozkurt T, Yildiz M, Deniz R *et al.* Clinical course of paediatric-onset Behçet's disease in young adulthood. Rheumatology (Oxford) 2025;64:2876–81.
8. Vitale A, Della Casa F, Ragab G *et al.*; Autoinflammatory Diseases Alliance (AIDA) Network. Development and implementation of

the AIDA International Registry for patients with Behçet's disease. Intern Emerg Med 2022;17:1977–86.
9. Criteria for Diagnosis of Behçet's Disease. International Study Group for Behçet's Disease. Lancet 1990;335:1078–80.
10. International Team for the Revision of the International Criteria for Behçet's Disease (ITR-ICBD). The International Criteria for Behçet's Disease (ICBD): a collaborative study of 27 countries on the sensitivity and specificity of the new criteria. J Eur Acad Dermatol Venereol 2014;28:338–47.
11. Ugurlu N, Bozkurt S, Bacanli A *et al.* The natural course and factors affecting severity of Behçet's disease: a single-center cohort of 368 patients. Rheumatol Int 2015;35:2103–7.
12. Hamuryudan V, Hatemi G, Tascilar K *et al.* Prognosis of Behcet's syndrome among men with mucocutaneous involvement at disease onset: long-term outcome of patients enrolled in a controlled trial. Rheumatology (Oxford) 2010; 49:173–7.
13. Sota J, Rigante D, Lopalco G *et al.* Clinical profile and evolution of patients with juvenile-onset Behçet's syndrome over a 25-year period: insights from the AIDA network. Intern Emerg Med 2021; 16:2163–71.
14. Talarico R, Cantarini L, d'Ascanio A *et al.* Development of de novo major involvement during follow-up in Behçet's syndrome. Clin Rheumatol 2016;35:247–50.
15. Shenavandeh S, Sadeghi SMK, Aflaki E. Pathergy test with a 23G needle with and without self-saliva in patients with Behçet's disease, recurrent aphthous stomatitis and control group compared to the 20G test. Reumatologia 2021;59:302–8.
16. Dilşen N, Koniçe M, Aral O *et al.* Comparative study of the skin pathergy test with blunt and sharp needles in Behçet's disease: confirmed specificity but decreased sensitivity with sharp needles. Ann Rheum Dis 1993;52:823–5.
17. Vitale A, Berlengiero V, Caggiano V *et al.* The diagnostic role of pathergy test in patients with Behçet's disease from the Western Europe. Intern Emerg Med 2023;18:77–83.
18. Nguyen A, Upadhyay S, Javaid MA *et al.* Behcet's disease: an in-depth review about pathogenesis, gastrointestinal manifestations, and management. Inflamm Intest Dis 2021;6:175–85.

Rheumatology, 2026, 65, 1–10
https://doi.org/10.1093/rheumatology/keaf613
Original Article