Comparing the clinical profile of adults and children with Behçet's syndrome in the UK

E.L. Makmur[1], S.H. Myers[1], L. Hanns[2], D.O. Haskard[3], P. Brogan[4], N. Ambrose[1,2,3]

[1]UCLH Department of Rheumatology, University College London Hospital, London; [2]Arthritis Research UK Centre for Adolescent Rheumatology, University College London, Rayne Institute, London; [3]Vascular Sciences Section, National Heart & Lung Institute, Imperial College London, Hammersmith Hospital, London; [4]Infection, Inflammation and Rheumatology Section, UCL Institute of Child Health and Great Ormond Street Hospital NHS Foundation Trust, London, UK.

Eric L. Makmur, MBBS*
Sam H. Myers, MBBS*
Laura Hanns, PhD
Dorian O. Haskard, DM, FRCP FMedSci, Prof.
Paul Brogan, MBChB, PhD, Prof.
Nicola Ambrose, MBBCh, PhD

*Joint first authors.

Please address correspondence to:
Dr Sam Myers,
Department of Rheumatology,
University College London Hospital,
250 Euston Road,
London NW1 2PG, UK.
E-mail: sam.myers1@nhs.net

Received on September 5, 2018; accepted in revised form on March 20, 2019.

Clin Exp Rheumatol 2019; 37 (Suppl. 121): S48-S51.

Key words: Behçet's syndrome, paediatric, juvenile onset, epidemiology

Funding: P. Brogan acknowledges support from Great Ormond Street Hospital Children's Charity. All research at Great Ormond Street Hospital NHS Foundation Trust and UCL Great Ormond Street Institute of Child Health is made possible by the NIHR Great Ormond Street Hospital Biomedical Research Centre.
The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

Competing interests: see page S-51.

ABSTRACT

Objective. *Behçet's syndrome (BS) is a rare multi-system inflammatory disorder. Clinical phenotypic variance across geographical regions is recognised but UK BS patients' variance by age groups and gender has not been studied. This study compares the clinical features of adult and juvenile onset Behçet's Syndrome (JBS) in a UK population.*

Methods. *Two clinical databases of BS patients were compared. The JBS database was collected at the Great Ormond Street Hospital for Children, London (n=46). The adult database was collected at the Hammersmith Hospital, London (n=560).*

Results. *Oro-genital aphthosis had high prevalence in both the JBS and the adult cohort (oral: 97.8% vs. 96.6%, genital: 73.9% vs. 75.7%). The JBS cohort was more likely to have gastrointestinal involvement (21.7% vs. 4.5%, p<0.001) and arthritis (21.7% vs. 9.6%, p=0.021) compared to adults. The JBS cohort was less likely to have eye involvement (4.3% vs. 37%, p<0.001), skin (21.7% vs. 55.4%, p<0.001) and vascular involvement (6.5% vs. 17.5% p=0.063). JBS females had a higher rate of genital aphthosis than JBS males (87.5% vs. 59.1%, p=0.044). Adult females had higher rates of genital (85.2% vs. 64.5%, p<0.001) and oral (99.0% vs. 93.8%, p=0.001) aphthosis than adult males. Adult males were more likely to have ophthalmological (44.9% vs. 30.3%, p<0.001) and vascular (23.0% vs. 12.8%, p=0.002) manifestations than adult females.*

Conclusion. *UK JBS patients displayed less ocular and skin manifestations compared to the adult BS patients. This information will aid clinicians in diagnosing BS in UK adult and paediatric populations.*

Introduction

Behçet's syndrome (BS) is a rare, multi-system inflammatory disorder. It may have an insidious or acute life-threatening onset and continue with a recurrent, relapsing-remitting course. The syndrome affects males and females of all ages, but is most often diagnosed in young adults of 20-40 years. Juvenile onset Behçet's syndrome (JBS) is estimated to account for 4-26% of all BS cases (1, 2) with a large international study reporting the mean age of first symptom onset in children to be 7.83 years (3). Paediatric patients generally have a longer time to diagnosis (between 3–5 years) compared with adult patients (2-6).

Diagnosis of BS relies primarily on clinical features due to the lack of disease-specific diagnostic tests. This process is complicated by overlap of the symptoms with other auto-inflammatory, rheumatological and gastrointestinal disorders. At least 15 different sets of clinical diagnostic criteria have been proposed by international and national groups (7). The International Study Group criteria developed in 1990 is commonly encountered in the scientific literature, but newer ICBD criteria created in 2006 is reported to have increased sensitivity (8). This appears to also be the case in the JBS cohorts (9). There have been few publications comparing adult and JBS in endemic regions (2, 6). These studies have found higher rates of gastrointestinal and neurological involvement and less urogenital involvement in the JBS cohorts, with similar levels of uveitis.

In addition, males have been reported to have higher prevalence of ocular, skin and vascular manifestations (10-11).

To our knowledge, this is the first paper examining the clinical profile of Behçet's syndrome in the UK and comparing a JBS and adult cohort.

Materials and methods

We examined two historical clinical cohorts. All patients were diagnosed clini-

cally with BS by an adult or paediatric rheumatologist with expertise in BS.
The adult cohort was derived from patients attending a tertiary rheumatology referral centre at Hammersmith Hospital, London, who were first seen between 1985 and 2013.
The JBS cohort was derived from patients at a large tertiary referral centre for paediatric rheumatology in London based at Great Ormond Street Hospital. It was created by retrospective case note review of paediatric patients diagnosed with BS between 1987 and 2012 (4).
Both centres received referrals from a similar catchment area - both from Greater London and from further afield within the UK.

Comparison of the databases
The authors had access to both databases. The databases were trimmed by identifying and retaining only the variables common to both. The lifetime prevalence of clinical features explored included oral aphthosis, genital aphthosis, uveitis, skin lesions, arthritis, and endoscopy-confirmed gastrointestinal involvement.
The adult database included patients from a wider range of years with longer follow up compared to the JBS database. The JBS database had a considerably smaller number of patients. HLA-testing and pathergy testing were routinely tested in the adult database while the JBS database had other recorded variables such as a positive family history and length of time to diagnosis. These variables were excluded from the final analysis due to inability to directly compare between the two cohorts.
The recording of clinical phenotypes also differed slightly between the two databases. Headaches were the only neurological symptom observed in the JBS database whereas in the adult database isolated headaches were disregarded as they were very common and seen as non-specific. The differing sampling criteria precluded a meaningful comparison of neurological symptoms. Arthralgia was also not included in our comparison of articular symptoms as it was very common and non-specific in both populations. Finally, only gastrointestinal involvement proven on examination or investigations were included in our comparison, with the exclusion of non-specific abdominal pain.

Table I. Prevalence of clinical manifestations in the JBS (n=46) and adult (n=560) cohorts.

Clinical manifestations	JBS (%)	Adult (%)	Chi-Square test *p*-value
Oral aphthosis	97.8	96.6	0.656
Genital aphthosis	73.9	75.7	0.785
Uveitis	4.3	37.0	**<0.001***
Skin lesions	21.7	55.4	**<0.001***
Vascular	6.5	17.5	0.055
Arthritis	21.7	9.6	**0.021***
Gastrointestinal	21.7	4.5	**<0.001***

Chi-square test was applied to test for any difference in prevalence between JBS and adult cohorts for each clinical manifestation. JBS: juvenile onset Behçet's syndrome.**p*-value was significant at <0.05.

Data analysis
Clinical manifestations were positively recorded throughout the disease course and lack of recorded clinical findings was presumed to be absence of the clinical feature. The clinical characteristics of the JBS and adult patients were cross-tabulated, and the chi-squared test or Fisher's exact test was used to test for associations between clinical manifestations and age or gender. Statistical significance was pre-determined at $p \leq 0.05$. All statistical analyses were completed with IBM SPSS Statistics version 25.

Ethics
Permissions were gained from the data controllers of the databases. As the databases comprised of previously collected, non-identifiable information, ethical approval was already in place. Patients' written informed consent was obtained for research purposes.

Results

Demographics
There were 46 patients in the JBS cohort while the adult cohort consisted of 560 patients. The ratio of females to males was 1.09 and 1.19 for the JBS and adult cohort respectively. The prevalence of clinical manifestations in each cohort is described in Table I.

- Major manifestations
Oral and genital aphthosis were common for both JBS and adult cohorts with no significant difference between the groups. Eye involvement was uncommon in JBS compared with adults (4.3% *vs*. 37%, $p<0.001$). Skin involvement was also less prevalent in JBS (21.7% *vs*. 55.4%, $p<0.001$).

- Other manifestations
There was a significantly higher frequency of arthritis in JBS compared to the adults (21.7% *vs*. 9.6%, $p=0.021$). The JBS cohort also demonstrated higher rates of endoscopy proven GI involvement compared to the adult group (21.7% *vs*. 4.5%, $p<0.001$). There was a trend of more vascular events in adults compared to JBS (6.5% *vs*. 17.5%, $p=0.063$).

Gender differences in distribution of clinical manifestations
Table II summarises the gender distribution of clinical manifestations for both cohorts.
For the JBS cohort, genital aphthosis was significantly more common in females than males (87.5% *vs*. 59.1%, $p=0.044$). No other significant gender differences were seen.
In the adult cohort, a greater number of clinical manifestations showed gender differences. Females were more likely to have genital aphthosis (85.2% *vs*. 64.5%, $p<0.001$) and oral aphthosis (99.0% *vs*. 93.8%, $p=0.001$). Males were more likely to have ophthalmological (30.3% *vs*. 44.9%, $p<0.001$) and vascular (12.8% *vs*. 23.0%, $p=0.002$) manifestations. Skin, joint and gastrointestinal manifestations were not significantly different between the two genders for the adult cohort.
Comparison of the female JBS *versus* female adult cohorts found that the

Table II. Prevalence of clinical manifestations by gender in the JBS and adult groups.

Clinical manifestations	JBS			Adult		
	Female (n=24) n (%)	Male (n=22) n (%)	Fisher's exact test *p*-value	Female (n=304) n (%)	Male (n=256) n (%)	Chi-Square Test *p*-value
Oral aphthosis	24 (100%)	21 (95.5%)	0.478	301 (99.0%)	240 (93.8%)	<0.001*
Genital aphthosis	21 (87.5%)	13 (59.1%)	0.044*	259 (85.2%)	165 (64.5%)	<0.001*
Uveitis	0 (0.0%)	2 (9.1%)	0.223	92 (30.3%)	115 (44.9%)	<0.001*
Skin	3 (12.5%)	7 (31.8%)	0.159	167 (54.9%)	143 (55.9%)	0.826
Vascular	0 (0.0%)	3 (13.6%)	0.101	39 (12.8%)	59 (23.0%)	0.002*
Arthritis	6 (25.0%)	4 (18.2%)	0.725	31 (10.2%)	23 (9.0%)	0.628
Gastrointestinal	6 (25.0%)	4 (18.2%)	0.725	17 (5.6%)	8 (3.1%)	0.159

Fisher's exact test or Chi-square test was applied to test for any differences in prevalence of each clinical manifestation between male and female groups in each cohort. JBS: juvenile onset Behçet's syndrome.*p-value was significant at <0.05.

relationship for each category of clinical manifestation (as covered above) was consistent with the overall JBS and adult comparison. This also applied to the male JBS *versus* male adult cohorts with one exception: the prevalence of arthritis was more similar between male JBS (18.2%) and male adult (9.0%) groups (p=0.248) compared to the overall JBS and adult comparison (p=0.021).

Discussion

The adult UK cohort

The rate of oral aphthosis (96.6%) in the adult cohort is consistent with national and international studies (90-98%) (10). The prevalence of genital aphthosis of this UK adult cohort (75.7%) is comparable to the Birmingham study (84.7%) (11) and in the middle of the range reported in international epidemiological studies (64-88%) (10, 12-15). The prevalence of uveitis (37%) is also comparable to the Birmingham study (44%) (11) and at the lower range of prevalence reported in other regions (35-92%) – with the exception of Turkey and China with lower prevalence (22%, 23%). Arthritis (excluding arthralgia) was found in 9.6% of our patients, which is comparable to the Moroccan group (6.7%) (1) and also Turkey (9%) and Egypt (10%) (8). However the overall incidence of arthritis in the ICBD data was higher (23%) from the 27 countries studied (8). The incidence of gastrointestinal manifestations (4.5%) was comparable to the overall frequency of 6.3% in the ICBD study (8) but lower than the 16.5% reported in Japan (16).

Comparison of JBS vs. adult cohort in the UK

The rate of genital aphthosis in the JBS cohort (73.9%) is comparable to the 81.9% reported in the Turkish cohort (2) and the 70% rate Kone-Paut found from her study of five countries (17). This contrasts with the lower rate of 55% in Kone-Paut's larger study of 230 patients from 12 countries in Europe, North Africa and the Middle East (3).

In our study, the most striking observation was the low prevalence of uveitis in the UK JBS cohort (4.3%) compared to the adult cohort (37.0%). Reports of lower uveitis rates in JBS compared to adults are unusual. In one Japanese study, JBS had a rate of 9.7% uveitis in the first six months of BS symptom onset, rising to 25.8% for all ocular lesions during the course of the disease (18). In comparison, a large multi-centre study from Turkey found a prevalence rate of 34.9% for ocular lesions in JBS, which is similar to the adults in that population (2). A large Iranian cohort also reported similar rates in all ages (19). The international PEDBD study found a higher rate of 45.5% for all ocular lesions (3) and other international JBS cohorts range from 35-65% (20). The broader inclusion criteria of all ocular lesions in these studies (*e.g.* including conjunctivitis and papilloedema) may contribute to the difference. A prospective UK nationwide study of JBS using British Paediatric Surveillance Unit methodology, with more specific data collection is ongoing, and will cast more light on this finding, given the contrast with other cohorts.

There was a trend towards more vascular events in our adult cohort compared to the JBS cohort. This may be secondary due to the small sample size of the JBS cohort. The individual values however, are consistent with international comparisons of JBS (5-15%) (20) and adult cohorts (6-25%) (7).

Arthritis and gastrointestinal manifestations were more common in JBS. This is in keeping with international cohorts where JBS were found to have more articular and gastrointestinal symptoms (2, 3, 6).

Gender

Our study found that oral aphthosis and genital aphthosis were more common in female adults than male adults (99% *vs.* 93.8%, 85.2% *vs.* 64.5%). This is similar to a cross-sectional survey study of BS patients in the UK, showing females had higher rates of oral and genital aphthosis (21). Uveitis and vascular complications were more common in male adults than female adults (44.9% *vs.* 30.3%, 23.0% *vs.* 12.8%). This is also reported in other international studies where a male preponderance for ophthalmological symptoms is consistently reported (7, 10, 22). In a 2017 review by Hatemi *et al.* the authors point out a Turkish study which showed a similar pattern of male *versus* female prevalence (42.2% *vs.* 29.2%, p=0.014 for ocular involvement and 44.7% *vs.* 15.3%, p<0.001 for vascular involvement) (23). Hatemi *et al.* also highlighted an Italian cohort study where ocular manifestations were milder in the 1993-2011 group with a higher female:male ratio *vs.* the 1968–

1992 group with more males (23, 24). This pattern of gender-influenced distribution of clinical features was repeated in our JBS cohort albeit with statistically weaker differences. This is consistent with other JBS cohorts such as the PEDBD international cohort of 156 patients that reported significantly higher rates of genital aphthosis in females, while males had higher rates of ocular and vascular manifestations (3).

Strengths and limitations

The methodology and format for each database resulted in differences in the types and granularity of the variables that could be compared reliably. Our study was limited to the clinical and demographic data recorded in common for the two databases. However, we believe this analysis still provides valuable information to clinicians about the UK adult BS and JBS phenotype. An in-depth analysis of the JBS cohort has been published (4).

Although we have used two single-centre databases, the high case number, the wide but similar referral catchment area and increased ethnic diversity of the Greater London area is likely to reduce selection bias.

Conclusions

BS is an uncommon multisystem syndrome, with regional variation. This study significantly adds to the body of knowledge around BS in the UK as it is the first study to profile the clinical features of BS patients in the UK by age and gender.

We showed that the UK JBS cohort have fewer eye, skin and vascular symptoms compared to the UK adult cohort. The UK JBS cohort also presents with more gastrointestinal and arthritic symptoms compared to the UK adult cohort. The adult cohort shows a phenotype consistent with the UK Birmingham study cohort (11).

Females had higher rates of genital aphthosis in both cohorts and oral aphthosis in the adult cohort. Males had higher rates of ophthalmological and vascular symptoms in the adult cohort. This information will aid clinicians in diagnosing BS in UK adult and paediatric populations.

Competing interests

L. Hanns is supported by Arthritis Research UK Grant 20164 which supports the Arthritis Research UK Centre for Adolescent Rheumatology at UCL, ULCH and GOSH. She is now employed by UCB Celltech, but at the time of this study was employed by UCL.

D.O. Haskard was the recipient of British Heart Foundation professorial support. Clinical research at Hammersmith Hospital was supported by the NIHR Comprehensive Biomedical Research Centre at Imperial College Healthcare NHS Trust. Acknowledgements also to Dr Sira Nanthapisal, who helped collate the original database for JBS.

P. Brogan declares consultancy fees from Roche, SOBI, Novartis and institutional grants from SOBI, Roche, Novartis and Novimmune. The other co-authors have declared no competing interests.

References

1. ZOUBOULIS CC, KOTTER I, DJAWARI D, KIRCH W: Epidemiological Features of Admantiades-Behçet's Disease in Germany and in Europe. *Yonsei Med J* 1997; 38: 411-22.
2. KARINCAOGLU Y, BORLU M, TOKER SC *et al*.: Demographic and clinical properties of juvenile-onset Behçet's disease: A controlled multicenter study. *J Am Acad Dermatol* 2008; 58: 579-84.
3. KONÉ-PAUT I, SHAHRAM F, DARCE-BELLO M *et al*.: Consensus classification criteria for paediatric Behçet's disease from a prospective observational cohort: PEDBD. *Ann Rheum Dis* 2016; 75: 958-64.
4. NANTHAPISAL S, KLEIN NJ, AMBROSE N, ELEFTHERIOU D, BROGAN PA: Paediatric Behçet's disease: a UK tertiary centre experience. *Clin Rheumatol* 2016; 35: 2509-16.
5. KONÉ-PAUT I, DARCE-BELLO M, SHAHRAM F *et al*.: Registries in rheumatological and musculoskeletal conditions. Paediatric Behçet's disease: an international cohort study of 110 patients. One-year follow-up data. *Rheumatology* (Oxford) 2011; 50: 184-8.
6. KRAUSE I, UZIEL Y, GUEDJ D *et al*.: Childhood Behçet's disease: clinical features and comparison with adult-onset disease. *Rheumatology* (Oxford) 1999; 38: 457-62.
7. DAVATCHI F, SHAHRAM F, CHAMS-DAVATCHI C *et al*.: Behçet's disease: from east to west. *Clin Rheumatol* 2010; 29: 823-33.
8. DAVATCHI F, ASSAAD-KHALIL S, CALAMIA KT *et al*.: 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.
9. NANTHAPISAL S, ELEFTHERIOU D, HONG Y, KLEIN N, BROGAN PA: Behçet's disease in children : The Great Ormond Street Hospital experience Refractory cutaneous vasculitis associated with MAGIC syndrome: Case report. 2013; 2013.
10. DAVATCHI F, CHAMS-DAVATCHI C, SHAMS H *et al*.: Adult Behçet's disease in Iran: Analysis of 6075 patients. *Int J Rheum Dis* 2016; 19: 95-103.
11. BLAKE T, PICKUP L, CARRUTHERS D *et al*.: Birmingham Behçet's service: classification of disease and application of the 2014 International Criteria for Behçet's Disease (ICBD) to a UK cohort. *BMC Musculoskelet Disord* 2017; 18: 101.
12. B'CHIR-HAMZAOUI S, LARBI T, ABDALLAH M *et al*.: La maladie de Behçet au Maghreb. Étude Behçet Maghreb à propos de 1460 patients. *Rev Med Interne* 2009; 30: S229-31.
13. GURLER A, BOYVAT A, UMIT T: Clinical manifestations of Behçet's disease: an analysis of 2147 patients. *Yonsei Med J* 1997; 38: 423-7.
14. ALTENBURG A, PAPOUTSIS N, ORAWA H, MARTUS P, KRAUSE L, ZOUBOULIS CC: Epidemiology and clinical manifestations of Adamantiades-Behçet disease in Germany -- current pathogenetic concepts and therapeutic possibilities. *J Dtsch Dermatol Ges* 2006; 4: 49-64; quiz 65-66.
15. DAVATCHI F: Behçet's disease: global perspective. *Indian J Rheumatol* 2007; 2: 65-71.
16. NAKAE K, MASAKI F, HASHIMOT T, MOCHIZUKI M, SAKANE T: Recent epidemiological features of Behçet's disease in Japan. *In*: WESCHLER B, GODEAU P (Ed.) Behçet's Dis Proc 6th Int Conf Behçet's Dis Excerpta Medica, Amsterdam 1993; 145-51.
17. KONÉ-PAUT I, YURDAKUL S, BAHABRI S *et al*.: Clinical features of Behçet's disease in children: an international collaborative study of 86 cases. *J Pediatr* 1998; 132: 721-5.
18. FUJIKAWA S, SUEMITSU T: Behçet disease in children: a nationwide retrospective survey in Japan. *Acta Paediatr Jpn* 1997; 39: 285-9.
19. DAVATCHI F, SHAHRAM F, CHAMS-DAVATCHI C *et al*.: Behçet's disease in Iran: analysis of 6500 cases. *Int J Rheum Dis* 2010; 13: 367-73.
20. KONÉ-PAUT I: Behçet's disease in children, an overview. *Pediatr Rheumatol* 2016; 14: 10.
21. SENUSI AA, OLA D, MATHER J, MATHER J, FORTUNE F: Behçet's syndrome and health-related quality of life: Influence of symptoms, lifestyle and employment status. *Clin Exp Rheumatol* 2017; 35 (Suppl. 108): S43-50.
22. ALLI N, GUR G, YALCIN B, HAYRAN M: Patient Characteristics in Behçet Disease. *Am J Clin Dermatol* 2009; 10: 411-8.
23. HATEMI G, SEYAHI E, FRESKO I, TALARICO R, HAMURYUDAN V: One year in review 2017: Behçet's syndrome. *Clin Exp Rheumatol* 2017; 35 (Suppl. 108): S3-15.
24. ACCORINTI M, PESCI FR, PIRRAGLIA MP, ABICCA I, PIVETTI-PEZZI P: Ocular Behçet's disease: changing patterns over time, complications and long-term visual prognosis. *Ocul Immunol Inflamm* 2017; 25: 29-36.