Behçet's syndrome in children and young people in the United Kingdom & Republic of Ireland: A prospective epidemiological study

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ORIGINAL ARTICLE: Original articles are based on clinical, laboratory, therapeutic and translational research. Systematic reviews and consensus statements are classified under original articles and should be formatted as such:

- Title page
- Abstract (250 words. Objectives, Methods, Results and Conclusion)
- Clinical trial registration number (for all RCTs)
- Keywords (up to 10)
- Key messages (up to 3, maximum 15 words each)
- References (up to 50 for original articles, 150 for systematic reviews)
- Tables/figures (up to 6)
- Word Count: Up to 3,500

Abstract

Objectives. To define the incidence and prevalence of Behçet's syndrome (BS) in children and young people (CYP) up to the age of 16 years in the United Kingdom (UK) and Republic of Ireland (ROI).

Methods. A prospective epidemiological study was undertaken with the support of the British Paediatric Surveillance Unit (BPSU) and the British Society of Paediatric Dermatologists (BSPD). Consultants reported anonymised cases of BS seen. The International Criteria for Behcet's Disease were used to define cases(1). A follow-up study at one year examined progression of disease and treatment.

Results. Over a two-year period, 56 cases met definite criteria for BS. For children under 16 years of age, the two-year period prevalence estimate was 4.2 per million (95% CI 3.2 to 5.4) and the incidence was 0.96 per million person years (95% CI 0.66 to 1.41).

Mucocutaneous disease was the most common phenotype (56/100%), with ocular (10/56; 17.9%), neurological (6/56; 10.7%) and vascular involvement (3/56; 5.4%) being less common. Median age at onset was 6.34 years and at diagnosis was 11.72 years. The majority of cases (85.7%) were white Caucasian. Apart from genital ulcers, which were more common in females, there were no significant differences in frequency of manifestations between male or females, nor between ethnicities. Over 83% of cases had three or more non-primary care healthcare professionals involved in their care.

Conclusion. BS is extremely rare in CYP in the UK and most have mucocutaneous disease. Healthcare needs are complex, and coordinated care is key.

Key words: **Behçet's syndrome, children, young people, incidence, prevalence, outcome**

Rheumatology key messages (3 statements; 15 words max)

- Behçet's syndrome in UK children is extremely rare with an incidence of 0.96 per million-person years (95% CI 0.7 to 1.4)
- Mucocutaneous disease was the commonest sub-type; eye disease was rare compared to other cohorts
- The majority of children (85.7%) were of white ethnicity

Abbreviations: anti-TNF, anti-tumour necrosis factor; BS, Behçet's syndrome; BPSU, British Paediatric Surveillance Unit; BSPD British Society of Paediatric Dermatologists; CI, confidence interval; CYP, children and young people; ICBD, International Criteria for Behçet's disease; IQR, interquartile range; ISG, International studies group criteria; PEDBD, pediatric Behçet's disease criteria; ROI, Republic of Ireland; UK, United Kingdom

INTRODUCTION

Behçet's syndrome (BS) is a rare multi-system inflammatory variable vessel vasculitis which can affect children, but is more commonly described in adults(2, 3). It is characterised by recurrent oral and genital ulceration, inflammatory eye disease, gastrointestinal, neurological, and skin involvement. Complications such as blindness, permanent neurological injury, or major blood vessel involvement can lead to marked disability in young people, particularly if there is diagnostic delay(3, 4).

Prevalence rates of BS vary, with higher rates in countries along the historic Silk Route(5). Adult studies from the United Kingdom (UK) estimate prevalence between 0.60-2.0 per 100,000 of the population(6, 7). Studies show that juvenile-onset disease before the age of 16 years occurs in 2.2-17.6% of cases(8-13). Conflicting results exist in studies comparing adult-onset to juvenile-onset BS, with possibly more joint and gastro-intestinal features in children and less skin and eye involvement than adults(11, 14, 15). A UK-wide epidemiological study and survey of management of children with BS has not been previously undertaken.

This study was undertaken in order to establish the UK and Republic of Ireland (ROI) incidence and prevalence of BS in children under 16 years of age. Other study aims were to describe the clinical manifestations, time to diagnosis, healthcare needs, and outcome. A one-year follow-up of this cohort was undertaken to address disease progression. Comparison between different sets of diagnostic criteria was also undertaken, namely: the International Criteria for

Behçet's disease (ICBD); the International Studies Group (ISG) criteria; and specific paediatric classification criteria (PEDBD)(1, 16, 17).

METHODS

Study design

A surveillance study of the UK and ROI was undertaken with the support of the British Paediatric Surveillance Unit (BPSU) (https://www.rcpch.ac.uk/work-we-do/bpsu) and the British Society of Paediatric Dermatology (BSPD) from May 2015 to May 2017. The BPSU's methodology for the study of rare conditions is well established having been developed since 1986(18).To date, it has completed surveys in over 90 rare conditions which can affect children with a consistently high response rate from all registered paediatricians in the UK. Consultant paediatricians throughout the UK & ROI return monthly notification cards for selected conditions.

In addition to the BPSU's system, a monthly email was sent to the BSPD, so that their members could notify any cases seen during the preceding month. This dual reporting method was undertaken as some dermatologists may see children with BS without a paediatrician's involvement.

All paediatricians and dermatologists that notified a case were sent a standard questionnaire requesting demographic, clinical manifestations, investigations, management and outcome data (appendix). A one-year follow-up questionnaire was sent to all clinicians who had reported a case meeting reporting criteria.

Case definition

Reporting criteria (see figure 1) included children up to but not including the age of 16, who had 2 or more of the following features not explained by an alternative diagnosis: recurrent oral ulceration, skin involvement, genital ulceration, eye involvement, vascular involvement, neurological involvement, positive pathergy test or history or pathergy response, family history of BS in a biological parent or sibling. Reporting criteria were deliberately wide and pragmatic, to capture all potential cases.

The exclusion criteria included children over 16 years of age at time of reporting, cases reported outside of the surveillance period, those that did not meet reporting criteria, and those with alternative diagnoses to explain the clinical features (e.g. inflammatory bowel disease, monogenic auto-inflammatory diseases, systemic lupus erythematosus, primary immunodeficiency, amongst other BS mimics).

Data analysis

Cases were checked for duplicate reporting as multisource surveillance methods were used. Cases were defined as definite if they met the ICBD criteria (scoring 4 or more; Box 2) (1). Cases that did not fulfil the ICBD criteria were reviewed by an expert panel (study investigators, minimum of 4) as to whether they were incomplete BS or not BS. Where there was a lack of consensus amongst the experts, the case status was designated as inconclusive. Inconclusive cases were not included in analysis. All definite, or incomplete cases were then assessed to define whether or not ISG and PEDBD criteria were met(16, 17).

Incidence was calculated as the number of cases per total children <16 years followed up, expressed as per million-person years, using data on the total population of children <16 years in 2016 for the UK (https://www.nomisweb.co.uk/articles/924.aspx) and for the Republic of Ireland (https://statbank.cso.ie/px/pxeirestat/statire/SelectTable/Omrade0.asp?PLanguage=0). Prevalence was calculated as the two-year period prevalence per million children <16 population in the UK and ROI in 2016.

Statistical analysis

Numeric data were expressed as median and interquartile range, unless otherwise stated. The sensitivity (with exact Clopper-Pearson confidence intervals) of ISG and PEDBD criteria was calculated and compared to the sensitivity of the ICBD criteria. Chi-square test was used to compare characteristics between males and females. For observations with small counts (<5), Fisher's exact test was used. The analysis was undertaken using R (version 3.5.1).

Ethical approval

This study was approved by BPSU Executive Committee and National Research Ethics System Committee North West-Liverpool East Research Ethics Committee (Ref: 15/NW/0035; IRAS project ID: 163430); and granted Section 251 Confidentiality Advisory Group permission (Ref: 15/CAG/0103).

RESULTS

From 1st May 2015 to 31st May 2017, 149 notifications were received, 3 directly from the BSPD and the rest via the BPSU (figure 1). Of the total notifications, 69 were excluded from the study because: 39 did not meet reporting criteria (children 16 years or over, less than 2 reporting

criteria met, alternative diagnosis to BS, seen outside of surveillance dates); 22 were duplicates. In 8 cases, the questionnaire was not returned after a case was notified (response rate after notification 94.6%). Of the remaining 80 cases, 56 fulfilled the ICBD criteria and were designated as definite cases. The overall return rate for monthly BPSU surveillance cards including this study was 94.9% during the study surveillance period (unpublished data from BPSU).

Of the 56 definite cases, 26 were incident (new to the reporting clinician in the preceding 4 weeks) and the other 30 were prevalent (cases that the clinician had seen prior to the preceding 4 weeks). Using ICBD criteria, the incidence of BS in the UK and ROI in children under 16 years was 0.96 per million person years (95% CI 0.66 to 1.41); and the 2 year period prevalence estimate was 4.2 per million children <16 years (95% CI 3.2 to 5.4), based on 2016 census data from the UK Office for National Statistics (ONS) and ROI Central Statistics Office**.** The two-year period prevalence for children fulfilling ISG (n=31) and PEDBD criteria (n=29) was 2.3 per million children <16 years (95% CI 1.6 to 3.3); and 2.2 per million children <16 years (95%CI 1.5 to 3.1) respectively.

The median age of onset of symptoms was 6.34 years [interquartile range (IQR) 3.44, 8.90]; median age of first presentation 10.61 years [IQR 6.66, 12.90]; and median age of diagnosis 11.72 years [IQR 8.85, 13.44]. Of the 52 cases where age at diagnosis was reported, 4/52 (7.7%) were under 5 years of age, with 27(51.9%) in the 5-12 year age range, and 21 (40.4%) in the 13-15 year age range.

The median delay from first symptom to diagnosis was 3.50 years [IQR 1.52, 6.75].

There were slightly more female than male children reported (32/56; 55.6%). Ethnicity was recorded via Coding for Ethnic Group (Office for National Statistics, 2001 for UK wide data collection). A high proportion of children were of white background (48/56; 85.7%); 5/56; (8.9%) were of Asian/Asian British ethnicity (of which 4 were of Pakistani ethnicity, and 1 Indian); 2/56 (3.6%) were of mixed ethnicity (1 White/Black African, 1 Other mixed); and 1 (1.8%) child was of Black African ethnicity.

A family history of BS in a first degree relative was reported in 13/56 (23.2%).

Clinical features

Recurrent oral ulceration was present in all reported cases; genital ulceration was present in 51/56 (91.1%); and skin involvement in 30/56 (53.6%) (Table 1). Eye 10/56(17.9%), neurological (excluding headache) 6/56 (10.7%); and vascular involvement 3/56 (5.4%) were

less commonly observed. There was one case of visual loss reported with severe left uveitis and enucleation.

Manifestations which do not score in ICBD, ISG or PEDBD criteria such as arthralgia, arthritis, abdominal pain and headache were common.

Genital ulceration was the only manifestation which was statistically different between males and females, with all 32 female cases suffering with genital ulcers compared with 19/24 (79.2%) of males (p=0.026; Table 1). There was no statistical difference in frequency of clinical manifestations between white and non-white cases (data not shown).

Overt vasculitic disease was reported in 3 patients: one patient had both central venous and arterial thromboses; one with leucocytoclastic vasculitis on skin biopsy; one with livedo reticularis. There were no cases of thrombophlebitis or aneurysms. Neurological involvement was reported in 2/56 cases, including the aforementioned patient with central venous thrombosis; and one with sensorineural deafness secondary to BS. There were no cases of parenchymal or aseptic meningitis reported.

Pathergy response was only assessed in 12/56 (21.4%) and was positive in three cases (3/12; 25%). HLA-B51 testing was performed in 3/56 cases (5.4%), and was positive in one case.

To reduce potential recall bias, presenting features based on incident cases only (n=26) showed that mucocutaneous features were the most common presenting features (Figure 2).

Management

Figure 3 shows who was involved in the care of the patients; the majority of cases (47/56; 83.9%) were managed by three or more sub-specialities. Only 22/56 (39.3%) were seen in a dedicated Paediatric Behçet's clinic.

Table 2 shows the treatments given. Ten (17.9%) patients were not on any current treatment at the time of completion of the questionnaire and another 10/56 (17.9%) were managed on topical treatments only. Of the 24 cases on colchicine: this was without systemic immunosuppression in 19; and in combination with systemic immunosuppression in 5. In total, 16/56 (28.6%) required one or more systemic immunosuppressant.

Outcomes

Outcome was recorded at the most recent clinic visit. Categories included: a) stable off medication (5/56; 8.9%); b) controlled on topical medication (7/56; 12.5%); c) controlled on systemic therapy (29/56; 51.8%); or d) active disease despite medication (14/56; 25%).

Outcome was stated as “not known” in one case. Visual loss in 1 eye occurred. There were no deaths.

Performance of ISG and PEDBD criteria

Only 31/56 of the reported cases met ISG criteria and 29/56 PEDBD criteria. The sensitivity of ISG was 55.4% (95% confidence interval (CI) 41.5-68.7%); and 51.8% (95% CI 38.0-65.3%) for PEDBD.

One-year follow-up

One-year follow-up data was obtained in all 56 definite cases. At this time-point the diagnosis was still deemed by the reporting clinician to be BS in 54/56 (96.4%). Of the 2 cases that were no longer deemed to fit with a diagnosis of BS, one patient had a diagnosis of presumed monogenic autoinflammatory disease related to a variant in *TNFRSF1A* of uncertain clinical significance; the other had a final diagnosis of Stevens Johnson Syndrome.

New clinical manifestations accrued in 12/56 (21.4%), which included increase in ICBD score in three patients. Two developed skin manifestations (erythema nodosum, and pseudofolliculitis); one developed anterior and intermediate uveitis. Other new emergent features included headaches (4), fatigue (4), arthritis (2), nausea (1), generalised seizure (1; reporting clinician did not specify whether this was related to neuro-BS or not), and sclerosing cholangitis (1).

Children were seen in a secondary or tertiary care setting frequently during the 1-year follow-up, with 32/56 (57.1%) being seen four times or more, 12/56 seen three times, 11/56 twice, and 6/56 seen once. Only one patient was not seen during the 1-year follow-up period; and follow up data was not documented in 4 cases. Treatment was escalated in some patients, with the commencement of azathioprine (n=3) or anti-TNF (n=10); (Table 2).

Compared to baseline data, there was little progression in outcome at one year as defined by the proportion of patients who were stable off medication (5/56; 8.9%); controlled on only topical medication (7/56; 12.5%); or controlled on systemic therapy (dropped to 24/56 (42.9%) compared to 29/56; 51.8% at baseline). Fourteen/56 (25%) continued to have active disease despite medication. There were no deaths reported during this 1-year follow up and no additional cases of visual loss.

Cases not fulfilling ICBD criteria at baseline: Cases which were reported initially as BS by the reporting clinician but which did not meet ICBD criteria were also followed up. At one year

only 4/24 (16.7%) of these cases had accrued new features (arthritis (1), erythema nodosum & mild sensorineural deafness (1), abdominal pain and diarrhoea (1); of which only one then fulfilled ICBD criteria with development of genital ulceration and skin involvement.

Discussion

To our knowledge this is the first prospective epidemiological study of BS in children in a UK-wide population. This study highlights that this is an extremely rare disease in the UK. Prevalence is higher in certain countries, particularly those along the Silk Route: a meta-analysis of epidemiological studies of adults with BS demonstrated estimates of prevalence of 10.3 per 100,000 (95% CI 6.1,17.7), with higher rates in Turkey (119.8 per 100,000; 95% CI 59.8, 239.9), than the Middle East (31.8 per 100,000; 95% CI 12.9, 78.4), and Europe (3.3 per 100,000; 95% CI 2.1, 5.2)(5). A recent adult study in the Midwest region of Ireland estimated the point prevalence of BS based on ISG criteria as 6.2 per 100,000 population(19). The majority of children (85.7%) in our study were Caucasian, and there was a high prevalence of mucocutaneous disease, gastro-intestinal and joint involvement with little eye, vascular or neurological disease. Different phenotypes of BS possibly related to ethnicity (or genetic differences) have been shown in adult cohorts, including a high level of gastro-intestinal involvement in Japanese cohorts(20). Compared to other non-UK paediatric cohorts where mucocutaneous disease was also common, this UK cohort had more genital ulceration (51/56; 91% versus 33.6-82.7%) and less ocular involvement (10/56; 17.9% versus 27.5-66.2%). Vascular and neurological involvement was rare in nearly all paediatric cohorts. However comparisons with other studies are limited by heterogenous definitions of BS, patient populations, and organ involvement, and other methodological variations(9, 11, 12, 16, 21-23). It is therefore difficult to examine whether true differences between cohorts exist.

Genital ulcers were the only manifestation which were statistically different between males and females in our study. Gender differences have been noted in other cohorts, although results are conflicting. Most studies confirm significantly higher rates of genital ulceration in girls (12, 16, 24). Two studies suggested greater ocular involvement in boys (including significantly more severe eye disease including posterior uveitis, retinal vasculitis and bilateral disease) compared to girls(12, 16), whereas another two studies did not see a difference(22, 24).

The median age at diagnosis in our cohort was 11.72 years [IQR 8.85, 13.44]. This compared to 13.87 +/- 3.82 years(16), 11.29 +/- 3.95(22) and 14.16 +/- 2.13(9) in other cohorts.

During study set-up, the PEDBD criteria had not yet been published. ICBD criteria were therefore used because of increased sensitivity in adult studies over ISG criteria(1), and because a UK retrospective paediatric study suggested better performance of the ICBD over the ISG criteria(24). Subsequent comparison of the criteria in this study revealed that the ISG and PEDBD criteria performed equally well, but with substantially lower sensitivity (50%) than the ICBD criteria.

Studies that have examined the performance of the various criteria in paediatric BS are difficult to compare because of differences in cohorts and definitions of BS, with no obvious gold-standard(12, 16, 22, 24, 25). Overall, ICBD appears to have better sensitivity (range 70.9-97.1%; (12, 22, 24) than ISG (range 17.4-73.7%; (12, 16, 22, 24, 25) or PEDBD (range 45.5-91.7%; (12, 16, 22, 25). Because of the weighting given to criteria in ICBD, individuals can meet the score for BS (4 or more) by only meeting 2 criteria, for example oral and genital ulceration or oral and ocular lesions(1). Both ISG and PEDBD require three criteria to be present(16, 17), therefore are possibly more specific albeit at the cost of sensitivity as suggested by our study.

Specificity has only been studied by two groups(16, 25). One used a control group (n=410) from the EUROFEVER cohort. Specificity of ISG criteria was 100% (Kappa coefficient 0.62) but only 42.9% (Kappa coefficient 0.39) for PEDBD(16). A further paediatric study using control groups with systemic lupus erythematosus, polyarteritis nodosa and Crohn's disease showed the specificity of ISG was 100%, and of PEDBD 97.7%(25).

All 80 cases which fulfilled reporting criteria (i.e. definite and incomplete BS cases) were included in a one year follow up study, which allowed us to establish if reported definite cases remained so; and to study the possible accrual of new clinical features to secure a definite case diagnosis in those with incomplete BS at study entry. This follow up study also enabled us to examine early disease progression, and complications. We observed that 21.4% accrued further clinical features within a year, although only in 3/56 (5.4%) did this lead to an increase in ICBD score sufficient to fulfil a definite BS diagnosis.

Whilst mucocutaneous disease was most common there was significant burden of disease, with nearly half of all cases requiring systemic immunosuppression; and with over 80% of cases being managed by 3 or more specialists. In one year, over half of CYP had been seen four times or more in a tertiary setting; and a quarter still had active disease. This highlights the complexity of BS; overall high burden of disease; and the need to consider multi-speciality

clinics with those with expertise in this disease when designing healthcare services to meet the needs of CYP with BS. Only 40% were seen in a dedicated Paediatric Behçet's clinic (although we do not have details of specialists within these clinics), demonstrating a clear unmet need for the majority of UK CYP with BS.

Fever was only reported in 2/56 (3.6%) in our cohort, although this may be underreported in our study. Other paediatric cohorts have had higher frequency of fever reported (30.4-47.4%)(16, 22, 24). Fever is less common in adult patients (22%), unless articular, vascular or neurological involvement occurs(26). Recent monogenic mimics of BS such as haploinsufficiency A20 have been reported(27, 28). Just under half of those with haploinsufficiency A20 had previously been diagnosed with BS(29). The difficulties with a purely clinical diagnosis of BS in epidemiological studies means that some cases of may be due to monogenic mimics. An important limitation of our study (and indeed all current published studies on paediatric BS) is that genetic screening for monogenic mimics was not undertaken systematically in all cases. Future studies of BS in children should aim to address this important concern, since this could have important diagnostic and therapeutic consequences.

In summary, BS is extremely rare in UK CYP, with mucocutaneous disease being the most common clinical manifestation. However, healthcare needs are complex and need to be considered in the future design of specialist services for this rare inflammatory syndrome.

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