New insights into Behçet's disease in Ireland: the Midwest cohorts

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ABSTRACT

Objective. *The epidemiology of Behçet's disease (BD) remains poorly understood with limited international data on disease burden, progression and treatment outcomes.*

The aims of this study were to determine the natural history of BD in the Midwest region of Ireland and compare our findings with those from other European and Mediterranean studies.

Methods. *We established a cohort of patients with BD in the Midwest Region of Ireland based on ISGBD and/or ICBD criteria. Longitudinal data were captured on demographic and clinical characteristics, disease activity and clinical outcomes.*

Results. *The cohort included 24 Caucasian patients (16 women, 8 men) and one male patient with Middle Eastern ancestry, who satisfied the diagnostic criteria for BD. Based on the ISGBD criteria, the point prevalence of BD was 6.2 per 100,000 population. The most common clinical manifestation was oral aphthosis (100%) followed by genital aphthosis (92%) and skin lesions (92%), arthralgia/arthritis (40%), ocular involvement (32%), vascular thrombosis (12%) and pathergy phenomenon (8%). Only 1 patient was HLA-B*51 positive. A long-term multidisciplinary approach that included physician specialists, nurse specialists, and general practitioners was adopted for ongoing patient care.*

Conclusion. *The prevalence of BD in Ireland is higher than previously reported with a significant proportion experiencing laryngeal destruction. There are many similarities as well as several differences in the epidemiology of BD by country and indeed within countries. We fully advocate the need for national and international collaborative efforts in order to further understand the complex aetiology and immunopathology of BD in order to improve the clinical, physical, psychological wellbeing of patients.*

Introduction

Behçet's disease (BD) was originally described along the Silk Route, which stretched from central China to the Mediterranean sea. First described by a Turkish Professor, Hulusi Behçet in 1937 (1), the incidence was noted to increase from North to South within the European continent (2). It is a unique category of vasculitis with distinctive clinical manifestations and complex immunopathogenesis. Epidemiological studies have shown that the prevalence is highest in Mediterranean countries [with Turkey reporting a prevalence of up to 602 per 100,000 population (3)] and the Far East. In contrast, studies from Northern European populations report a much lower burden of disease that varies from 0.64 to 4.9/100,000 population (4-8). Due to its chronic relapsing and remitting course, BD exerts a significant impact upon a patient's quality of life, both physically and mentally (9).

The Republic of Ireland is an island made up of 70,280 square kilometers (of which 68,890 square km of land area) that lies on the European continental shelf in the periphery of Northwest of Europe. Founded by the Celtic tribes from Scotland between 600-150 BC with the Gaelic emergence by the first century AD, it consists of 4 provinces and is further divided into 32 counties with an estimated population of 4.59 million (10). It is geographically located in the temperate zone, with mild weather all year round. Being an island nation, Ireland has remained a relatively genetically stable population with a high degree of ethnic homogeneity for many years. However, some five thousand Spanish soldiers making up the Spanish Armada were shipwrecked across the Irish Western Seaboard in

Table I. Phenotypic characteristics of patients with Behçet's disease along with their HLA-B*51 status.

ID	Sex	Age	Oral Aphthosis	Genital Aphthosis	Ocular Features	Skin Features	Pathergy Reaction	Vascular Features	Gastrointestinal Features	Otolaryngeal Features	HLA-B*51
1	F	36	+	+	-	+	-	-	-	+**	-
2	M	54	+	+	+	+	+	-	+	+**	-
3	F	39	+	+	-	+	-	-	-	+**	-
4	F	25	+	+	-	+	-	-	-	+	-
5	M	51	+	+	+	+	-	+	-	-	+
6	M	58	+	-	+	+	-	-	-	+	-
7	F	40	+	+	-	-	+	-	-	-	-
8	M	36	+	+	-	+	-	-	-	-	-
9	F	40	+	+	-	+	-	-	-	-	-
10	F	54	+	+	-	+	-	+	-	-	-
11	F	84	+	+	+	+	-	-	-	-	-
12	F	68	+	+	-	+	-	-	+	-	-
13*	M	47	+	+	-	-	-	+	-	-	-
14	F	40	+	+	-	+	-	-	-	-	-
15	F	24	+	+	-	+	-	-	-	-	-
16	F	26	+	+	-	+	-	-	-	-	-
17	M	65	+	+	-	+	-	-	-	-	-
18	F	39	+	+	-	+	-	-	+	-	-
19	F	25	+	+	+	+	-	-	-	-	-
20	F	20	+	+	+	+	-	-	-	-	-
21+	M	32	+	+	+	+	-	-	-	-	-
22	F	26	+	+	-	+	-	-	-	+**	-
23	F	40	+	+	-	+		-	-	-	-
24	M	59	+	+	-	+	-	-	-	-	-
25	M	72	+	-	+	+	-	-	-	+**	-

*Patient fulfills ICBD but not ISGBD criteria; **Significant structural laryngeal changes related to BD; +Patient is from Middle Eastern ancestry.
Note: Age calculated as of August 31st, 2017.

1588, and may have influenced the Irish gene pool beyond the Celtic and Hibernian influence. More recently, political instability in the Middle East has exacerbated the migration flow, which may have further influenced the epidemiology of certain diseases in Ireland, including BD.

Methods

Study design and study population

We included all patients with BD who satisfied the International Study Group for Behçet's Disease (ISGBD) or the International Criteria for Behçet's Disease (ICBD) criteria at University Hospital Limerick (UHL) in a population-based cohort study. The rheumatology programme at UHL is the sole referral centre for patients with BD in the Midwest region of Ireland, serving one twelfth of the total Irish population (10). Demographic and clinical characteristics including symptom complex, organ involvement, inflammatory markers, treatment strategy along with response rates, and adverse effects were captured at baseline and on follow-up visits on all patients. The point prevalence was calculated on the 1st of August 2017 in reference to the national census conducted in 2016 (10). The study was approved by the local ethics committee and is in accordance with the Declaration of Helsinki.

Statistical analysis

Statistical analysis was performed using SPSS 22.0 software for Macintosh. Data are presented as median and interquartile ranges unless otherwise stated. *P* values of <0.05 was considered statistically significant.

Results

Demographic characteristics

A total of 25 patients including 24 Caucasian-Irish (16 women, 8 men; F/M ratio 2:1) and a male patient with Middle Eastern ancestry (a Syrian refugee) were identified fulfilling the diagnostic criteria for BD and were included in the study (median age 40.0 years, interquartile ranges 29.4-56.3 years) (Table I and II). 24 patients fulfilled the ISGBD criteria while all 25 patients fulfilled the ICBD criteria. Two patients were paternal half-sisters. The Middle Eastern patient left Syria in 2016 to seek asylum in Ireland, but had been diagnosed with BD in his country of origin many years prior to his referral to our service. The demographic and characteristic distributions of the patients are summarised in Table I. The point prevalence of BD on the 1st of August 2017 was 6.5 per 100,000 population. However, if based only on the ISGBD criteria, the point prevalence of BD was 6.2 per 100,000 population.

Clinical manifestations

The most common clinical manifestation occurring at any point during the course of the disease was recurrent oral aphthosis, with all 25 patients (100%) developing it at some point during the clinical course, mostly as the initial presentation (23 patients, 92%), and this was followed by genital aphthosis (23 patients; 92%) and skin lesions (23 patients; 92%). Other manifestations include arthralgia or arthritis (10 patients; 40%), ocular involvement (8 patients; 32%), vascular thrombosis (3 patients; 12%) and pathergy phenomenon (2 patients; 8%).

Table II. Demographic and clinical characteristics of BD in the Midwest Cohort Study and comparisons with other Northern European studies.

	Country of study (year)				
	Midwest, Ireland (2017)	Yorkshire, UK (4) (1977)	Entire Scotland (5) (1992)	Dublin, Ireland (6) (1997)	Skåne, Sweden (7) (2013)
No. of patients	25	32	15	24	40
Fulfills ISGBD criteria	24	NR**	15	24	40
Total population	385,172	5,000,000	5,500,000	1,058,264	809,317
Prevalence/100 000	6.2	0.64	0.3	2.27	4.94
Male: female ratio	0.56	0.6	0.36	1.4	2.07
Ethnicity	Caucasian Irish and Middle Eastern ancestry	NR	Caucasian Scottish-Irish	Caucasian Irish	Multiethnic
HLA-B*51 association	NoA	Male patients	NoA	Male patients	NR
Clinical manifestations (%)					
Oral ulceration	100	100	100	100	100
Genital ulceration	92	91	73.3	NR	80
Skin involvement	92	66	86.7	NR	88
Ocular involvement	32	12.5	93.3	79.2****	53
Arthralgia/arthritis	40	63	NR	NR	40
Vascular thrombosis	12	25	NR	NR	20 (v)
ENT involvement	28*	6	NR	NR	NR
CNS involvement	0	25***	20	NR	0
GI involvement	8	9	53.3	NR	NR

NR: not reported; NoA: No association; (v): venous.
*ENT manifestation based on formal ENT assessment & flexible laryngoscopy; **NR as study was before the advent of ISGBD criteria; ***CNS included numbness & paraesthesia but 1 had significant neurological manifestation and died quadriplegic; ****study was based on ophthalmology referrals.

Table III. Prevalence estimates of BD (per 100,000) in selected countries within Europe.

Country/Area	Study (Year)	Patients (n)	Population	Prevalence (per 100,000)
Northern Europe				
UK (Yorkshire)	Chamberlain (1977) (4)	32	5,000,000	0.64
Scotland	Jankowski *et al*. (1992) (5)	15	5,500,000	0.3
Ireland (Dublin)	Kilmartin *et al*. (1997) (6)	24	1,058,264	2.27
Ireland (Midwest)	Adeeb *et al*. (2017)	24	385,172	6.2
Sweden (Skåne)	Mohammad *et al*. (2013) (7)	40	809,317	4.94
Central Europe				
Germany	Papoutsis *et al*. (2006) (13)	165	3,391,344	4.87
France (Paris)	Mahr *et al*. (2008) (19)	79	1,094,412	7.1
Southern Europe				
Italy (Rome)	Valesini *et al*. (1991) (49)	155	NA	19
Greece	Kaklamani *et al*. (2000) (50)	90	NA	11
Turkey				
Istanbul	Demirhindi *et al*. (1981) (27)	4	4,940	80
Ordu	Yurdakul *et al*. (1988) (29)	19	5,121	370
Ankara	Idil *et al*. (2002) (28)	16	17,256	110
Istanbul	Azizlerli *et al*. (2003) (31)	101	23,986	420
Havsa	Cakir *et al*. (2004) (30)	1	4,861	20
Tokat	Baş *et al*. (2016) (3)	14	2,325	602

The most frequently encountered skin lesion was pseudofolliculitis and/or papulopustular eruptions (18 patients, 72%) followed by erythema nodosum-like lesions, (2 patients; 8%), skin ulcer(s) (2 patients; 8%), superficial thrombophlebitis (1 patient; 4%) and pyoderma gangrenosum-like lesions (1 patient; 4%). The most common ocular manifestation was uveitis (a total of 7 patients: 5 males and 2 females were diagnosed with uveitis confirmed on slit-lamp examination while one patient presented with bilateral, painful red eyes and a transient loss of vision however had a negative slit-lamp examination). The majority had unilateral uveitis (5 patients; 20%) with the exception of two patients (8%) who had bilateral involvement. Two male patients (8%) lost their vision totally in one eye. Five (20%) patients (3 females, 2 males) had significant structural laryngeal changes related to BD on flexible laryngoscopy (11). Vascular thromboses were noted in 3 patients: 2 men and 1 woman (one patient with concomitant lower limb deep vein thrombosis and pulmonary embolus, another patient with two separate episodes of lower limbs deep vein thrombosis, and the third patient with an isolated episode of lower limb deep vein thrombosis). Only 1 patient was HLA- B*51 positive (12).

Discussion

To further explore the epidemiology of BD, we provide comparisons with selected studies from Northern European populations and endemic geographical areas (Tables II-IV).

Prevalence of Behçet's disease

Reported prevalence estimates of BD in Northern Europe vary between 0.64 and 4.9 per 100,000 population (4-8).

Table IV. Demographic and clinical characteristics of BD in the Midwest and comparison with selected European studies.

	Country of study (year)				
	Midwest, Ireland (2017)	Istanbul, Turkey (31) (2003)	Rome, Italy (49) (1991)	Berlin, Germany (13) (2006)	Paris, France (19) (2008)
No. of patients	25	101	155	165	79
Fulfills ISGBD criteria	24	101	NR	NR***	79
Total population	385,172	23,986**	NR	3,391,344	1,094,412
Prevalence/100 000	6.2	420	19	4.87 (1.47)****	7.1 (2.4)*****
Male: female ratio	0.56	1.06	NA	1.14	1.32
Ethnicity	Multiethnic	Multiethnic	NA	Multiethnic	Multiethnic
HLA-B51 association (%)	NoA	NR	NA	NA	20
Clinical manifestations (%)					
Oral ulceration	100	100	98	100	100
Genital ulceration	92	70.2	73	NR	80
Skin involvement	92	80.1	86	NR	90
Ocular involvement	32	27.7	92	NR	51
Arthralgia/arthritis	40	31.6	77	NR	59
Vascular thrombosis	12	4.9	18	NR	30******
ENT involvement	28*	NR	NR	NR	NR
CNS involvement	0	NR	17	NR	10
GI involvement	8	NR	34	NR	NR

NR: not reported; n: native; NoA: No association; NA: not available.
*ENT manifestation based on formal ENT assessment & flexible laryngoscopy; **23,986 questionnaires applied from a population of 7,486,000 age above 12; ***classification tree and others were used instead of ISGBD; ****4.87 prevalence for all ethnicity and 1.47 for native German; *****4.87 for all ethnicity and 2.4 in the European-origin population; ******large vessel disease rather than vascular thrombosis.

We report a point prevalence of 6.2 per 100,000 population in the Midwest region of Ireland with a population of 385,172 (10), which is substantially higher than the previous estimates from Northern European cohorts. Our findings are consistent with the current literature that suggests a trend of rising prevalence of BD globally (13-14). These observations may be related to greater physician awareness and increased detection from subspecialists, and primary care physicians.

Despite increased immigration into Ireland, particularly from the Middle Eastern and Eastern European countries within the past decade, the majority of our patients were Caucasian with Irish ancestry. One male patient of Middle Eastern ancestry emigrated from Syria at the age of 31 in 2016. The prevalence of BD within our cohort was significantly higher among women than men (M: F ratio of 0.56), contrary to studies from Middle East (15-18) and Central Europe (19) but comparable to results from Yorkshire and Scotland, our Northwest European neighbours (4-5, 20), the United States (US) (21) and the Far East (22-23). Previous and more recent epidemiological studies suggest, however, that both sexes are equally affected (24-25).

The first description of BD in the literature in Northern Europeans was by Mason and Barnes in 1969 (26). They described 33 patients of different ethnicities (21 native British, 2 West Indies, 1 Chinese, and 1 Indian) with a diagnosis of either suspected or definite BD in a London hospital. Using the criteria at the time, 25 patients were diagnosed as definite BD and 19 had symptoms of arthritis. In 1977, Chamberlain published the first and only data on prevalence of BD in the UK (4). She described 32 patients with BD (12 males, 20 females; ratio of 0.6 and a mean age of onset 24.7 years) in a Yorkshire region with a population of 5 million (prevalence of 0.64 in 100,000) (4) (Table I). Of the 32 patients, 22 satisfied the criteria for definite BD and a further 10 were classified as having probable BD. The criteria for diagnosis of BD at that time (Mason and Barnes's) were different to current classification criteria (ISGBD and ICBD) and thus may have underestimated the disease burden. Furthermore, the ethnic origins of patients were not provided.

Estimates of disease prevalence in the UK may be derived from Behçet's Syndrome Society, which has been established in the UK for more than 30 years. The majority of members reside in the UK, although membership is not exclusively limited to the UK population and extends beyond (20). At the annual general meeting of the society in 2016, there were 855 patients (female to male ratio of 2.7) with BD among the 1050 members. Three main centres in the UK (London, Birmingham, and Liverpool) provide care for 1,221 patients with BD, with an estimated prevalence of 2.3 per 100,000 (estimated population of 53 million in England) (20).

The cause of the global variation in prevalence of BD throughout is not well understood. This in part may reflect a lack of research into the drivers of variation in incidence, prevalence and outcomes from epidemiological studies across the globe (19). Turkey has the highest recorded prevalence of BD in the world with several studies demonstrating tremendous variation in the prevalence, ranging from 20 to 602 per 100,000 population (3, 27-31). While mucocutaneous manifestations are the most common findings among

Turkish patients with BD, most studies interestingly have found a low rate of gastrointestinal involvement. Mahr *et al*. estimated the prevalence of BD in the suburbs of Paris in 2003 among patients of different ethnicities, 26% of which were of non-European ancestry (19). Quite strikingly, he discovered that the prevalence of BD among immigrants of North African or Asian ancestry was significantly higher than that in the European-origin population and comparable with rates reported from North Africa and Asia.

Parallel with a global increase in reported cases, the incidence of BD has increased over time (13, 14). Papoutsis *et al*. reported increasing incidence rates of BD using data from the German BD Registry: from 13 patients in 1984, 35 patients in 1989, to 44 patients in 1994 (13). He postulated that the rise in the incidence was likely due to increased immigration from endemic areas (*i.e*. Turkey), together with greater awareness of the disease among clinicians.

Clinical characteristics

The clinical features of BD in general follow a remitting relapsing course; however, certain manifestations such as ocular or laryngeal manifestations may eventually lead to significant morbidity, disability and impact to quality of life. Further, some patients may suffer severe life threatening disease especially if there is major vascular or neurological involvement. Furthermore, although many patients exhibit similar patterns of clinical characteristics there is wide regional variation due to differences in in disease expression. For example, intestinal Behçet's is more common in the Far East, while pathergy phenomenon or ocular inflammation is less common in patients from Northern Europe.

In our Irish cohort, the clinical manifestations of patients were largely comparable to those of other Northern European studies. The clinical features that were present at diagnosis or developed during follow-up are summarised in Table I and are compared to those of other countries. In contrast to the endemic countries, isolated anterior uveitis (rather than posterior uveitis, retinal vasculitis or panuveitis) was more common among our patients. These patients often presented with pain, redness and/or photophobia during their ocular flares instead of a reduction in visual acuity. Men were more frequently affected than women and in general required more intensive treatment. Two male patients became totally blind in one eye; the first was a patient with recurrent, conventional immunomodulator-resistant uveitis during the pre-biological therapy era. The second patient (from Syria) developed BD at a young age of 14 with uncontrolled recurrent uveitis as part of his initial presentation with eventual blindness four years later. It is noteworthy, that none of our patients developed neurological disease.

One of the most striking and important observations from our study was the frequency of significant structural laryngeal damage, a devastating feature that was observed in 20% of our cohort (2 men, 3 women) and confirmed on formal flexible laryngoscopy assessment. The findings were described in a more detailed account with photographic records in our previous study (11). Our data, along with review of the literature, suggests that laryngeal manifestations despite relatively uncommon are a part of the disease spectrum among Northern European and North American patients (4, 32-34). Chamberlain in her study described two patients in the pre anti-TNF era with laryngeal manifestations: one with trachea-esophageal fistula requiring surgery and another with arytenoid ulcer (4). We found that all 5 patients in our cohort, who were treated with anti-TNF therapy, had a stabilisation of disease and avoided the need for surgical intervention (35).

BD has predilection for both arteries and veins of all sizes, and vascular manifestations are more common and severe in men than women (36). Lower extremity venous thrombosis affecting superficial or deep veins is the most common manifestation, while arterial disease is less frequent but remains a major cause of mortality in BD (36). The reported prevalence of vascular manifestations varies from 7.7-43% depending on the geographical area. It is more common in the Middle East (14) and less common in the Far East (14, 37) and dependent upon the ethnicity of the population under study (7, 17, 38-41).

A study by Ames *et al*. found that 31.5% (23 out of 73 Caucasians) of BD patients developed a vascular thrombosis and that the risk was 6-fold higher for men than women (37). Four patients received dual-immunosuppressive therapy and 11 were treated with single therapy of either azathioprine, thalidomide or cyclosporine A, upon presentation with vascular thrombosis (37). Only 12% of our cohort developed vascular complications, and this is much lower even when compared to our Northern European counterparts (Table II).

A large variability in the prevalence of pathergy is seen throughout the globe, with the greatest reported frequency among Turkish patients (60-70%), Mediterranean and the Far East however its overall incidence has been in the decline over time (42). Only two (1 man, 1 woman) patients from our study demonstrated a positive pathergy reaction and this is in keeping with its less common and infrequent occurrences in the Northern European cohorts (8, 43-44). A comparative study of BD between Turkey and Britain revealed an absence of pathergy among British patients with BD; Davies *et al*. in a UK study found that only 1 out of 19 patients who actually originated from Cyprus (Eastern Europe) had a positive pathergy test (43, 45). Similarly, Ek *et al*. in a study from Sweden reported one of 12 patients with a positive pathergy test and was from Eastern European origin (8), while Gyldenløve *et al*. reported 2 patients from a total of 26 patients, both of Middle Eastern descent with a positive test (44).

Despite HLA-B*51 being well recognised as the strongest genetic susceptibility gene so far in BD, our analysis found no association between HLA-B*51 and BD when compared to control population. Only one patient was found to have HLA-B*51, comparable to the general population (12) (Table I). In 1997, Kilmartin *et al*. in Dublin reported a highly significant HLA-B*51 association among Irish men with BD

(6) and supported the observations of Chamberlain (4). These findings were in contrast to other reports from the same Northern European region which did not support an HLA-B*51 immunogenetic predisposition (5, 12).

Familial aggregation in BD has been reported (46-48). Concordance studies of twins have been reported in the literature, the first involving a pair of HLA-B*51 positive monozygotic (MZ) twins with concordance of BD, another involving two pairs of HLA-B*51 negative MZ twins that followed a discordant disease course further supporting the role of HLAB*51 in the genetic predisposition of BD however these are only isolated case reports or small case series (47-48). In our cohort, we identified two paternal half-sisters with BD, who presented with similar phenotypic features of orogenital ulcerations, skin pustulosis but without evidence of uveitis. One of the two proband also has a sister who subsequently was diagnosed with neuromyelitis optica (NMO).

We acknowledge the relatively small sample size of our BD cohort. We also recognise that some of the clinical manifestations may be not fully captured at clinical visits by primary physicians or subspecialists as language and cultural barriers, especially among refugees or immigrants, may limit communication and the extent of medical history. Despite these limitations, we believe that this study captures the natural history of BD in a well-defined geographic region in Ireland. Our centre is the sole primary referral unit for all patients with BD in the Midwest region. Our work to-date has defined the prevalence of disease, described novel complex phenotypic presentations, and uncovered novel genetic associations in a Northern European cohort. From comparisons with international cohorts, we recognise the many similarities as well as several differences in the epidemiology of BD by country and indeed within countries. We fully advocate the need for national and international collaborative efforts in order to further understand the complex aetiology and immunopathology of BD in order to improve the clinical, physical, psychological wellbeing of patients.

Key messages

- The prevalence of BD is higher than previously reported in the Northern European studies, and supports the general consensus that the prevalence is increasing globally.
- The prevalence is higher in women than men which supports the findings from other Northwestern European studies, United States and the Far East.
- Destructive structural laryngeal changes is a novel feature that we report and is seen in one fifth of the patients.
- Knowledge remains limited with regard to the aetiology and pathogenesis of BD, serological biomarkers, genetic factors, racial predilection and phenotypic characteristics. These areas require to be addressed in future studies. HLA-B*51 was not associated with BD among our cohort.

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