Behçet's syndrome in Scotland

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Summary: We present the clinical details and HLA typing of 15 Celtic Caucasian patients (four male, 11 female) with Behçet's syndrome (International Study Group criteria). The males affected were younger than the affected females, and three of these males had severe uveal involvement. Two of the 15 patients had the A2 Bw6 Dr4 haplotype but this did not confer family penetrance. Eight had gastrointestinal involvement: two females required ileostomy, two females had chronic diarrhoea, one female had severe ileitis and oesophageal lesions, two males had peptic ulcers, and one female had a peptic ulcer and primary biliary cirrhosis. All of those who developed gastrointestinal symptoms had either the Dr4 or the Dr7 antigens. This study is the largest HLA survey of Celtic Caucasians with Behçet's syndrome. The clinical features and HLA haplotypes are markedly different from 'Arab' and 'Japanese' varieties of Behçet's syndrome. The expression of the Dr4 and Dr7 antigens in those with gastrointestinal involvement possibly implicates class II antigens (Dr) in the pathogenesis of the manifestations of Behçet's disease in the bowel.

Introduction

Behçet's syndrome is a multisystem disease characterized by a clinical triad of uveitis, recurrent aphthous and genital ulceration.¹ Since the first report by Behçet in 1937, many cases of Behçet's disease have been reported from the Middle East. The prevalence of Behçet's disease varies widely among races, 10/100,000 in Japan, 7/100,000 in Turkey, 5/100,000 in Israel, 0.6/100,000 in England and 0.3/100,000 in the USA. The disease is very uncommon in Britain and there are inadequate data regarding clinical and immunological features in Caucasians. The largest previous British studies in recent years^{2–4} reported 32, 33 and 70 Caucasian cases respectively in England. However, no mention was made of the ethnic origin of the patients. Gastrointestinal involvement is reported to be uncommon⁵ and may indicate a poor prognosis in Caucasians.⁶

The present study reports data on Behçet's disease in individuals from a Celtic origin (Scottish–Irish). Its aim was to ascertain the clinical features of Behçet's syndrome in patients with a Celtic origin and assess the correlation between these features and HLA typing, including the DR

serotypes as these have also been previously implicated in the immunogenetic basis for Behçet's syndrome.⁷

Patients, materials and methods

This study carried out a clinical and immunological assessment in all known Scottish patients with Behçet's syndrome. We contacted all consultant rheumatologists, gastroenterologists and ophthalmologists, practising in Scotland, by telephone or letter and asked them to allow us access to patients with Behçet's syndrome, providing the patients gave informed consent.

Fifteen patients (11 females and four males) who were resident in Scotland were identified and all agreed to be investigated. The median age of the 15 patients was 43 years (range 25–65). All patients fulfilled the International Study Group's Criteria for diagnosis of Behçet's disease (Table I). In brief, this required the presence of recurrent oral ulceration plus two of the following: recurrent genital ulceration, eye lesion (anterior or posterior uveitis), skin lesions (erythema nodosum, pseudofolliculitis or papulopustular lesions). For ethical and temporal reasons we were unable to perform the patch test on any patient.

The patients were examined by one clinician who elicited a full clinical history and obtained samples of blood. Blood was collected in an EDTA container and processed in the Department of Clinical Immunology, Glasgow Royal Infirmary. The sam-

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Table I Symptoms and signs

Patient	Aphthous ulcers	Eye signs	Genital ulcers	Skin signs	Arthralgia	CNS	GI
1	++	+		++	+		++
2	++		++	+	+		+
3	++	+	+		+		+
4	++	++	+		+	+	++
5	++	+	+	++	+		++
6	++	+		+	+		++
7	+	++	+	+	+	+	+
8	+	++	+	+	+	+	+
9	+	+		+	+		
10	+	+	+	+		+	
11	+	+	+	+	+		
12	+	+	+	+	+		
13	+	+	+	+	+		
14	+	++	+	+	+		
15	+	++		+	+		

+, mild involvement; ++, severe involvement; CNS, neurological involvement; GI, gastrointestinal involvement.

ples were processed according to standard techniques for HLA serotyping.^{8,9}

Statistics

The binomial test was used to calculate the probabilities of obtaining the observed frequencies given their expected frequencies. The expected frequencies for HLA types were taken from the West of Scotland HLA typing Registry (1,500 volunteer blood donors). The expected frequency of gastrointestinal disease was calculated from prevalence data for peptic ulcer disease, colitis and chronic colitis.¹⁰⁻¹²

Results

Fourteen patients were of Scottish origin and one female was of Irish origin. The clinical details and HLA types of these patients are shown in Tables I and II, respectively.

All patients presented clinically in the third and fourth decades, the four males presenting in the third decade and the females presenting in the third and fourth decades. The disease remains active in three males (Tables I and II, patient numbers 7, 8 and 14), and six females (Tables I and II, patient numbers 1, 3, 4, 6, 11 and 15).

All patients had recurrent aphthous ulcers, some had severe involvement which incapacitated their eating habits and required hospital admission and sub-lingual lozenges while the others were managed with simple conservative therapies such as antiseptic lozenges. All patients had attended an

ophthalmologist and only patient number 2 (Table I) had no eye involvement. Five patients had severe posterior uveitis (patient numbers 4, 7, 8, 14 and 15) and required regular treatment. In addition three of these latter individuals were blind or partially blind. Eleven patients had recurrent genital ulcers. Thirteen patients had skin involvement: six had erythema nodosum (patient numbers 1, 2, 5, 6, 12 and 15), four had pseudofolliculitis or papulopustular lesions and three had a combination of these lesions (patient numbers 7, 8 and 11). Three patients had central nervous system (CNS) involvement: patient number 4 had organic confusional states and brainstem syndrome, patient number 7 had one episode of an organic confusional state and meningoencephalomyelitic syndrome, and patient number 9 had transient cerebellar dysfunction.

Five individuals with uveal involvement were assessed for expression of HLA DR7 and B5 antigens. Three of these patients expressed the DR7 antigen while only one expressed the B5 antigen.

Eight individuals had documented gastrointestinal disease. In these individuals no other precipitating cause could be found for the gastrointestinal pathology and colonic biopsies from four patients were suggestive of Behçet's syndrome.^{13,14} The nature and site of the pathology in the gastrointestinal tract in each individual is shown in Table III. The prevalence of gastrointestinal disease in the normal population is 7% (3% for peptic ulcers, 0.5% for colitis and 3.5% for chronic diarrhoea).¹⁰⁻¹² There was a significant increase of prevalence of gastrointestinal disease in our 15 patients with Behçet's syndrome ($P < 0.01$).

Table II Age, sex and HLA antigen status

Patient no.	Age	Sex	HLA haplotype status					
			A	B	C	D		
1	43	F	A2	B8 Bw26 Bw6	Cw3	DR4		
2	53	F	A24 A26	B35 B44 Bw6	Cw4	DR4 & w6		
3	41	F	A2	B12 B15 Bw4 & 6	Cw3 & 5	DR1 & 4		
4	65	F	A2 A3	B7 B14 Bw6	Cw8	DR2 & 7		
5	51	F	A11 A29	B14 B44 Bw4 & 6	—	DR7		
6	42	F	A2	B7 B27 Bw4 & 6	Cw1 & 2	DR4		
7	37	M	A2	B12 B15 Bw4 & 6	Cw3 & 5	DR4		
8	39	M	A1 A23	B17 B44 Bw6	Cw4	DR7		
9	25	F	A2	B7 B14 Bw6	Cw3	DR4		
10	38	F	A2	B7 Bw6 Bw62	—	DR1 & 4		
11	34	F	A9	B5 B7 Bw4 & 6	—	DR4 & w6		
12	52	F	A2 A11	B17 B27 Bw4	Cw2 & 6	DRw6		
13	36	M	A2 A24	B8 B40 Bw6	Cw3	DRw6		
14	49	M	A2 Aw19	B5 B7 Bw4 & 6	—	DR2		
15	42	F	A1 A9	B17 B8 Bw4 & 6	—	DR3 & 7		

Table III Site of gastrointestinal involvement

The eight individuals who had gastrointestinal involvement suffered from:
2 females had ileostomy
2 females had chronic diarrhoea
1 female had primary biliary cirrhosis and peptic ulcer
1 female had ileitis and oesophageal lesions
2 males had peptic ulcers
All individuals had positive DR4 or DR7 HLA typing.

Table IV Epidemiology and HLA status

HLA type	Number	% HLA in normal population
DR4	8/15	34%
DR7	4/15	26%
A2	10/15	44%
Bw4 & 6	7/15	60%
Bw6	13/15	85%
Cw3	5/15	42%
DR4 or 7	12/15	54%

The HLA probands which have been implicated in the genetic predisposition to Behçet's syndrome are listed in Table IV. The frequency of A2 (67%) and DR4 (54%) in the Behçet's patients was higher than expected compared with the frequencies in the normal population (44% and 34%, respectively). However, because of the small patient sample, both HLA haplotypes failed to reach significance ($P = 0.1$ and 0.2 , respectively). All eight patients with gastrointestinal involvement had either DR4 or DR7.

Discussion

The variation in prevalence of Behçet's disease in different races may be an indicator of genetic predisposition.¹⁵ The gender affected also varies from one race to another.¹⁶ More males than females are affected in Turkey and Japan,¹⁷ while in our study of Celtic patients and in a previous study of English patients² more females were affected.

There is also an inverse relationship between

prevalence of Behçet's syndrome in races and gastrointestinal involvement. From this survey a minimum estimate of the prevalence in Scotland is 15 cases/5.5 million population (0.3/100,000 prevalence) which is similar to the prevalence in USA. In our study we reported a 50% involvement of the gastrointestinal tract compared with 30% involvement in American cases of Behçet's syndrome^{16,17} and 14% in English cases.^{3,4,18} Japanese reports have described a variable incidence of gastrointestinal complications in Behçet's syndrome patients from 12 to 40%.^{19–22} Conversely there is a relatively low proportion of gastrointestinal involvement in Turkey 5%;²³ and little or no gastrointestinal disease in cases from Israel.²⁴

There is conflict in the literature about the distribution and prognosis of gastrointestinal disease in Behçet's syndrome. When gastrointestinal ulceration is present in Japanese patients it is usually in the ileocaecal region in 90% of cases,¹⁷ 5% in the oesophagus,²¹ stomach or duodenum,¹ and another 5% in the rectal, perianal or colonic regions.^{16,22} However, perianal and colonic involve-

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ment is reported more frequently in the Western patients.⁶

The tendency for Behçet's syndrome to involve the caecum has resulted in confusion with Crohn's disease. The Japanese reports have therefore included rigid criteria for the diagnosis of intestinal Behçet's syndrome.^{17,21} However, it has been reported that the two diseases can affect the same family, suggesting that the two diseases may be closely aetiologically related.¹⁷

We have found a coincidence with primary biliary cirrhosis (lymphocytic infiltration of intra-hepatic bile ducts on liver biopsy and smooth muscle antigen-positive serology) in one of our cases. Primary biliary cirrhosis has not been reported previously in patients with Behçet's syndrome although the Budd–Chiari syndrome has been reported as a rare hepatic association.²⁵

In Japan and Turkey the commonest gastrointestinal symptom is abdominal pain and is not usually associated with intestinal ulceration but is caused by mild serosal oedema. In the majority of Japanese cases gastrointestinal involvement is usually self-limiting.¹⁶ In previously reported Western cases gastrointestinal involvement has been reported to result in a poor prognosis.²⁶ For example, 25% of our cases required ileostomy, another 25% have severe diarrhoea (one has recently had a partial colectomy for colonic ulceration and necrosis), one had recurrent oesophageal ulceration and another has primary biliary cirrhosis. None of the patients with peptic (gastric) ulcerations has had relapse of the gastric disease, although none are taking specific ulcer-healing medication. It seems that 62.5% of our patients can be regarded as suffering from severe gastrointestinal disease. In this connection, the largest British study reported 11 out of 70 Behçet's syndrome patients with gastrointestinal involvement, of which seven (65%) had chronic intestinal or colonic lesions.⁴

Our results confirm that no one proband is an ideal marker for gastrointestinal involvement in Behçet's syndrome (Table V). The HLA haplotype B51 which is found in 70% of Israeli patients with Behçet's syndrome²⁷ was not specifically tested in our patients. However the B5 proband, a marker for B51, was present in only two of our 15 Caucasian cases. The B51 proband has been recognized to confer different relative risks according to race 8.3 Turkey, 6.7 Japan, 5.1 Israel, 5.8 Italy, 7.8 France, 2.3 USA and 1.7 in the UK. In a previous study it has been reported that Caucasians from a heterogeneous ethnic origin with Behçet's syndrome have diverse HLA haplotypes.²⁸ Our patients despite being from a homogeneous ethnic origin failed to express any probands which could be proven to be significantly different from the general

Table V Frequency of probands in Behçet's syndrome with gastrointestinal involvement

HLA type	Number
DR4	5/8
DR7	3/4
A2	5/10
Bw4 & 6	5/8
Bw6	8/13
Cw3	3/5
DR4 or 7	8/12

population. One explanation for this could be as a result of a small patient population. The A2, B15, Cw3, DR4 haplotype was present in two of our patients but did not confer family penetrance as has been reported in a Danish series.²⁹

The association of DR7 antigen with uveal involvement has been reported in other studies from the UK.^{30,31} Five patients had severe eye involvement which caused a marked loss of visual acuity. Three of those patients still have severe posterior uveitis resulting in partial blindness and they all have the DR7 antigen.

All patients of Behçet's syndrome and gastrointestinal involvement in our study had either DR4 or DR7 phenotype. It has previously been reported that DR-related antigens are important determinants of colitis and coeliac disease.^{32–34} It seems possible that expression of DR-related antigens in the bowel is involved in the pathogenesis of immunologically mediated gastrointestinal disease because these antigens, when expressed in gastrointestinal mucosa, may modulate the inflammatory response. This may, in part, explain why some of the patients with Behçet's syndrome with DR4 or DR7 antigens have gastrointestinal involvement.

In summary, it is possible that Celtic patients with Behçet's syndrome may have a greater predisposition for gastrointestinal involvement and severe uveitis compared with 'Japanese' and 'Arab' varieties. In addition Behçet's syndrome is much less prevalent in Scotland but may affect women more often.

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