Behçet's Disease in Southern Chinese Patients

CHI CHIU MOK, TAK CHEONG CHEUNG, CARMEN TSE KWAN HO, KA WING LEE, CHAK SING LAU, and RAYMOND WOON SING WONG

ABSTRACT. ***Objective.*** To describe the clinical characteristics of Behçet's disease (BD) in a southern Chinese population and compare them with those reported in other ethnic groups.

Methods. Patients with BD from 4 large regional hospitals in Hong Kong were identified from the hospital information retrieval system. Their records were retrospectively reviewed and the diagnosis was verified by at least 2 rheumatologists using the International Study Group (ISG) criteria. Demographic data and various clinical features of our patients were collected and analyzed.

Results. Between 1978 and 2000, 37 adult patients with definite BD according to the ISG criteria were identified. All patients were ethnic southern Chinese. There were 19 women and 18 men (F:M = 1.1:1). The mean age at diagnosis was 36.2 ± 10 (18–74) years. Presenting features at diagnosis, in decreasing order of frequency, were oral ulceration (100%), genital ulceration (81%), skin lesions (73%), arthritis/arthralgia (54%), and ocular lesions (35%). Among skin lesions, the commonest manifestations were erythema nodosum (74%), folliculitis (44%), and acneiform nodules (30%). Arthritis was usually polyarticular (75%) and symmetrical, and involved the upper limb joints. Anterior uveitis was the most common ocular complication (77%) and was often bilateral. Involvement of other systems such as the central nervous system, gastrointestinal (GI) tract, and cardiopulmonary system was uncommon. Vascular complications were rare. Only 2 (6%) patients had a positive pathergy test. Our patients were followed for a mean of 59.9 ± 52 months. Apart from recurrent attacks of orogenital ulceration and uveitis, new systemic features were unusual. One patient died of bowel perforation as a result of active GI disease. Compared with other reported series, our patients had fewer ocular and systemic manifestations, and a significantly lower incidence of the pathergy reaction.

Conclusions. BD is rare among southern Chinese in Hong Kong and tends to run a more benign course with less systemic involvement and fewer serious ocular complications. Whether the observed difference in clinical manifestations of the disease is related to a different HLA association or environmental factors warrants further studies. (J Rheumatol 2002;29:1689–93

Key Indexing Terms:
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Behçet's disease (BD) is a chronic relapsing systemic vasculitis of unknown etiology. It was initially described in 1937 by the Turkish dermatologist Hulusi Behçet as a triad of recurrent aphthous stomatitis, genital ulcerations, and uveitis with hypopyon[1]. However, the disease is multisystemic and may be associated with various dermatological, articular, vascular, pulmonary, and neurological manifestations. Although BD has a worldwide distribution, cases mainly cluster along the ancient Silk Route, which extends from Japan, eastern Asia, and the Far East to the Mediterranean basin[2]. The prevalence of BD varies greatly, with the highest figure in Turkey (30 to 370 cases per 100,000), followed by Japan, Korea, northern China, Iran, and Saudi Arabia (13.5 to 20 cases per 100,000). The disease is much rarer in Western countries such as the United Kingdom and the United States (0.12 to 0.64 cases per 100,000)[3-5].

The geographical variation in the prevalence of BD is also coupled with differences in the clinical expression of the disease. For example, the pathergy reaction is a common feature in Turkish and Japanese patients with BD but is nearly absent in British patients[6]. Gastrointestinal (GI) disease occurs in one-third of patients in Japan but is rare in the Mediterranean countries[7]. Patients with BD from Middle Eastern countries and the Mediterranean basin generally have less widespread disease compared to those in Western countries[8]. Neurological and GI complications are more common among pediatric patients in France and Saudi Arabia, whereas Turkish patients have more cutaneous manifestations[9].

In China, most cases of BD are found in the northern part

From the Department of Medicine and Geriatrics, Tuen Mun Hospital; Department of Medicine, Ruttonjee Hospital; Department of Medicine, Queen Mary Hospital; Department of Medicine, Pamela Youde Eastern Hospital, Hong Kong, SAR, China.

Dr. C.C. Mok, MBBS, MRCP, FHKAM, Senior Registrar in Rheumatology, Department of Medicine and Geriatrics, Tuen Mun Hospital; T.C. Cheung, MRCP, MBBS, Senior Registrar, Rheumatology, Department of Medicine, Ruttonjee Hospital; C.T.K. Ho, MRCP, MBBS, Senior Registrar, Rheumatology and Rehabilitation, Department of Medicine, Queen Mary Hospital; K.W. Lee, MRCP, MBBS, Senior Registrar, Rheumatology, Pamela Youde Eastern Hospital; C.S. Lau, MD, FRCP, Professor in Rheumatology, Queen Mary Hospital; R.W.S. Wong, MRCP, FRCP, Consultant in Rheumatology, Queen Mary Hospital.

Address reprint requests to Dr. C.C. Mok, Department of Medicine & Geriatrics, Tuen Mun Hospital, Tsing Choon Koon Road, New Territories, Hong Kong. E-mail: ccmok@netvigator.com

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of the country[10]. The disease is very rare among southern Chinese. We examined the clinical expression and outcome of BD in a series of southern Chinese patients collected from 4 large regional hospitals in Hong Kong. Comparison was also made with other major series reported in the literature.

MATERIALS AND METHODS

The Queen Mary, Tuen Mun, Rutonjee, and Pamela Youde Eastern are 4 large regional hospitals in Hong Kong that serve around 1.5 million people in their respective catchment areas. The medical units in these hospitals are secondary referral centers for adult (age ≥ 18 yrs) rheumatology patients from family physicians. From the clinical information retrieval system provided by the hospital authority, adult patients with BD were identified by searching the patient database using the diagnostic code for BD. Case notes from hospital and outpatient clinics were retrieved and retrospectively reviewed. Cases that fulfilled the International Study Group (ISG) criteria for the diagnosis of BD were further analyzed[11].

A common datasheet was used by investigators in the various centers. Demographic features such as age of disease diagnosis, sex, duration of followup, and various clinical manifestations were recorded. The status of the patients at the time of last followup visit was also noted. A pathergy test was performed at the time of disease diagnosis in all but 3 patients. This was done by subcutaneous pricks with a 20 gauge sterile needle to the forearm skin, which was cleaned with alcohol prior to puncture. The pathergy test was considered positive if a sterile erythematous papule of more than 2 mm in diameter was observed at the puncture site after 48 h. All our patients were also referred to the ophthalmologists for assessment of ocular involvement of BD. Plain radiographs of the respective joints were taken for patients who presented with arthritis at diagnosis and during followup visits. Patients who presented with low back symptoms were evaluated for sacroiliitis by plain radiographs.

The point prevalence of BD was estimated by calculating the ratio of the total number of patients diagnosed within the study period to the total population within the catchment areas of the 4 hospitals. The age- and sex-specific rates were similarly estimated using the corresponding figures in different age groups and sexes.

Unless otherwise stated, all values were expressed as mean ± standard deviation (SD). Comparison of categorical data was made using the chi-square test. Fisher's exact test was used when the frequency was low. Continuous data were compared using Student's t test for independent samples. Statistical analysis was performed using the SPSS program (version 10.0 for Windows 98).

RESULTS

Between January 1978 and April 2000, 37 adult patients with definite BD according to the ISG criteria were identified. All patients were ethnic Chinese with their family origin in Guangdong, the largest province in southern China. As the total adult population in the catchment areas of the 4 hospitals participating in the study was 1.41 million in the year 2001[12], the estimated point prevalence of BD is 2.62/100,000 (rates for men and women are 2.61/100,000 and 2.64/100,000, respectively). The age-specific prevalence rates are shown in Table 1.

In our patients, there were 19 women and 18 men (F:M = 1.1 to 1). The mean (± SD) age at diagnosis was 36.2 ± 10 (range 18–74) years. Presenting features at diagnosis, in decreasing order of frequency, were oral ulceration (100%), genital ulceration (81%), skin lesions (73%), arthritis/arthralgia (54%), and ocular lesions (35%). Excluding recurrent oral ulceration, the mean number of ISG criteria fulfilled by our patients was 2.2 ± 0.4 (range 2–3). Only 7 (19%) patients presented with the classical triad of recurrent oral ulceration, genital ulceration, and ocular disease. No patient had a positive family history of BD.

Table 1. Age-specific prevalence rates of Behçet's disease in our study.

Age (yrs)	Number of Patients	Rates/100,000
≥ 18–24	3	1.30
≥ 25–34	13	4.64
≥ 35–44	17	5.00
≥ 45–54	3	1.25
≥ 55–64	0	0.00
≥ 65	1	0.53
Total	37	2.62

Clinical manifestations of patients. The main features of our patients at the time of diagnosis are summarized in Table 2. Recurrent oral ulceration was present in all patients and was the keystone to diagnosis. Thirty-five (95%) patients had ulcers involving the lips and the gingival and buccal mucosa. Ulceration of the tongue occurred in 20 (54%) patients. Ulcers tended to be multiple in most cases and resolved spontaneously after 1–2 weeks. Genital ulcers

Table 2. Clinical features at diagnosis of Behçet's disease in our patients. Values in parentheses are percentages.

Clinical Features	Men, N = 18	Women, N = 19	Total, N = 37	p*
Age, yrs				
Mean ± SD	39.2 ± 10.8	33.1 ± 8.3	36.1 ± 10	0.07
Range	25–74	18–48	18–74	—
Oral ulcers, n (%)	18 (100)	19 (100)	37 (100)	—
Genital ulcers	13 (72)	17 (89)	30 (81)	NS
Skin manifestations	12 (67)	15 (79)	27 (73)	NS
Erythema nodosum	8 (44)	12 (63)	20 (54)	NS
Folliculitis, pseudofolliculitis	4 (22)	8 (42)	12 (32)	NS
Acneiform nodules	5 (28)	3 (16)	8 (32)	NS
Papulopustular nodules	3 (17)	0 (0)	3 (8)	NS
Superficial thrombophlebitis	0 (0)	1 (5)	1 (3)	NS
Positive pathergy test	1/15 (7)	1/19 (5)	2/34 (6)	NS
Eye lesions	9 (50)	4 (21)	13 (35)	NS
Uveitis	7 (39)	3 (16)	10 (27)	NS
Retinal vasculitis	2 (11)	1 (5)	3 (8)	NS
Arthritis/arthralgia				
Peripheral joints	12 (67)	8 (42)	20 (54)	NS
Sacroiliitis	4 (22)	0 (0)	4 (11)	NS
Vasculitis/vascular lesions				
Central nervous system	2 (11)	0 (0)	2 (5)	NS
Gastrointestinal	0 (0)	1 (5)	1 (3)	NS
Deep vein thrombosis	0 (0)	1 (5)	1 (3)	NS
Arterial aneurysm	0 (0)	0 (0)	0 (0)	NS

* p comparison between men and women. SD: standard deviation; NS: nonsignificant.

occurred in 30 (81%) patients at diagnosis. These were localized on the scrotum (62%), penis (38%), and the perianal area (23%) in men, and on the vulva (82%), vagina (12%), and perianal area (12%) in women. Genital ulcers were usually solitary and multiple lesions were exceptional. They usually healed spontaneously in 2–4 weeks.

Skin lesions were present in 27 (73%) of our patients at diagnosis and before immunosuppressive treatment. The commonest manifestations were erythema nodosum (74%), folliculitis and pseudofolliculitis (44%), acneiform nodules (30%), and papulopustular nodules (11%). Other lesions such as phlebitis and true vasculitis were rare. The pathergy test was performed in 34 patients at disease diagnosis and was positive only in 2 (6%) cases.

Arthritis/arthralgia was described in 20 (54%) patients. This was usually polyarticular (75%) and symmetrical, and involved the upper limb joints (hands, wrists, elbows, and shoulders). Monoarticular involvement occurred in 2 patients (ankle and knee, respectively). Axial involvement (e.g., sacroiliitis) occurred in 4 (11%) patients, but their HLA-B27 status was unavailable. There was no associated spondylitis in these patients.

Eye disease was diagnosed in 13 (35%) cases. Ten patients presented with symptoms of pain, photophobia, and visual blurring, while in the others, eye lesions were picked up incidentally by slit lamp examination. Anterior uveitis was the most common ocular complication (77%) and was often bilateral (70%). Panuveitis occurred in 4 (31%) patients. Retinal vasculitis was detected in 3 (8%) patients.

Systemic involvement was uncommon in our patients. Central nervous system (CNS) disease was present in 2 (5%) patients at the time of diagnosis. Both of them had transient focal motor deficits attributable to cerebral vasculitis, which was documented by magnetic resonance imaging. Excluding ulcers in the oral cavity, involvement of other parts of the GI tract occurred only in one patient, who presented with retrosternal pain, and endoscopy revealed multiple esophageal ulcers.

Superficial thrombophlebitis was described in one patient. Another patient had thrombosis of the right internal jugular vein at diagnosis and was given anticoagulation therapy. She was negative for the antiphospholipid antibodies. Other features such as lung lesions, epididymitis, orchitis, glomerulonephritis, lymphadenopathy were not described.

Although men tend to be older at diagnosis and have more acneiform/papulopustular skin nodules, peripheral arthritis, sacroiliitis, and eye disease than women, significant gender differences in clinical manifestations of the disease could not be demonstrated in our series of patients.

Treatment history. Colchicine was given to most patients (28/37, 76%) with mucocutaneous disease. A few patients received topical corticosteroid alone for recurrent oral and genital ulcerations. Nonsteroidal antiinflammatory drugs (NSAID) were employed to relieve arthritic symptoms in 17 patients. Systemic corticosteroid and immunosuppressive agents were mainly given to patients with ocular complications and with GI or refractory mucosal disease. Besides corticosteroids, the commonest immunosuppressive agent employed was azathioprine (13 patients). Cyclosporin A was administered in 4 patients with severe and recurrent uveitis. Mesalazine was used in 2 patients with large bowel ulcers and recurrent bloody diarrhea. Other agents that had been tried for patients with refractory mucosal disease were levamisole (2 patients), dapsone (1 patient), and thalidomide (1 patient).

Treatment was generally well tolerated; only one patient developed agranulocytosis after azathioprine, while another patient developed pneumonia after immunosuppression. Very few patients developed colchicine related diarrhea with a daily dose of less than 1.5 mg. No patient developed NSAID related gastropathy and its complications.

Disease course. The mean duration of followup of our patients since diagnosis was 59.9 ± 52 (range 6–263) months. Apart from recurrent attacks of orogenital ulceration and uveitis, new systemic features were unusual. No patient developed deforming or erosive arthropathy. Four patients developed GI disease. All had evidence of overt or occult GI bleeding, and 2 manifested as recurrent abdominal pain. Colonoscopy revealed ileocecal ulcers in 3 patients and multiple rectal ulcers in the fourth. One patient had perforation of the large bowel because of active GI lesions and died of peritonitis and septicemia. Two patients were diagnosed to have aortitis and aortic incompetence on followup, and one required valvular replacement. No patient developed arterial occlusion or aneurysms during the course of disease.

New CNS symptoms, psychiatric manifestations, meningoencephalitis, and sinus thrombosis were not reported. One patient developed demyelinating peripheral neuropathy, which was thought to be unrelated to BD.

No patient developed significant ocular complications such as iris synechiae and secondary glaucoma during followup. No patient had significant loss of visual acuity at the time of data analysis.

DISCUSSION

BD is a multisystemic vasculitis of unknown etiology. Apart from the classical triad of oral ulceration, genital ulceration, and uveitis, the disease may affect various organs such as the joints, nervous system, vessels, skin, cardiopulmonary systems, and the GI tract. There is also considerable geographical variation in the prevalence and clinical expression of the disease. Although the exact prevalence is unclear, the results from our study suggest that BD is very rare among southern Chinese, with only 37 cases identified in the past 20 years in 4 large regional hospitals in Hong Kong that serve a population of almost 1.5 million people.

Although underestimation of the true prevalence of the disease is possible because some patients followed by family physicians may not be referred, BD is still a rare disease entity among southern Chinese people in Hong Kong, taking into account that all hospital patients and clinic outpatients were surveyed in the present study.

Table 3 shows the prevalence of major clinical features of BD in the literature in comparison with our southern Chinese patients. Orogenital ulcerations and dermatological and musculoskeletal manifestations occur at similar frequency compared to the Japanese, European, and Middle East series. Ocular complications, on the other hand, tend to be less common and severe. Eye disease occurs in around one-third of our patients and is much less frequent than in Japanese, European, and Turkish series[3,5,13-16]. Moreover, none of our patients had significant loss of visual acuity, indicating that eye manifestations are milder. Apart from GI disease, which occurred at a frequency similar to that in the Japanese group, other systemic features such as CNS disease and vascular lesions, thrombophlebitis, arterial/venous thrombosis, and aneurysms are less common than those reported in the European and Middle East series[3,14-16]. These suggest that BD in southern Chinese is relatively mild and the disease course is more benign.

The reasons for the inter-ethnic differences in clinical manifestations of BD are not fully understood, but the HLA class I antigens may play a role. The prevalence of the HLA-B51 allele is high among patients who live in areas along the Silk Route (up to 81% of Asians), but low in white patients who live in Western countries (around 13%)[5]. In areas where the prevalence of BD is high, the HLA-B51 allele is a risk factor for development of the disease. For example, in Japan, the relative risk of BD among individuals who are HLA-B51 positive is 6.7 as compared to non-carriers of this allele, whereas it is only 1.3 in the United States[5,17]. HLA-B51 has also been linked to disease severity, although this is still a subject of debate. A study of Greek patients described that the HLA-B*5101 allele predisposed to BD at a younger age in both sexes[18]. Another study of Irish patients with BD also reported that the HLA-B51 allele was significantly associated with the male sex[19]. As a younger disease onset and the male sex have been linked to more serious disease with vascular thrombotic, ocular, and CNS manifestations[20], the HLA-B51 allele might be indirectly associated with disease severity. A recent review also described that uveitis and progressive CNS disease were more common in patients with positive HLA-B51[5]. However, no significant association between HLA-B51 and clinical severity could be found in a comparative study from Turkey and the United Kingdom[21].

Besides HLA-B51, other genes have been implicated in the susceptibility to BD. A recent study demonstrated that BD is linked to the HLA-B locus using the transmission disequilibrium test[22]. The MHC class I chain related (MIC) genes have also been found to be associated with BD. In a study of Italian patients, an association between the MIC-A6 allele with BD was reported[23]. Another study in Japan also described a strong association between disease susceptibility and the MIC-A009 allele[24]. Stratification analysis of the confounding effect of the MICA genes on HLA-B51 association, and vice versa, in these studies confirmed that the major susceptibility gene for BD was HLA-B51 itself, and the significant increase in the MICA alleles in the patient group resulted secondarily from a strong linkage disequilibrium with HLA-B51. Thus, the observed less serious manifestations of BD in our southern Chinese patients could be related to a different prevalence of HLA-B5 allele and linkage to the MIC alleles. Further studies of these alleles in our patients are of great interest.

Table 3. Prevalence of various clinical manifestations in patients with Behçet's disease of different ethnic groups.

	Sakane[5], N = 3316	Zouboulis[13], N = 130	Dilsen[14], N = 496	Kaklamani[3] N = 64	Mousa[15] N = 29	Gonzalez-Gay[16] N = 16	Current Study, N = 37
Year of study	1991	1996	1993	1997	1986	2000	2000
Ethnicity	Japanese	German	Turkish	Greek	Arabian	Spanish	Southern Chinese
Clinical features							
Oral ulcers	98	98	100	100	100	100	100
Genital ulcers	73	79	77	78	93	88	81
Eye lesions	69	48	47	75	69	44	35
Skin lesions	87	73	78	94	76	88	73
Positive pathergy test	44	53	NA	30	34	19	6
Arthritis/arthralgia	57	59	47	48	69	63	54
GI lesions	16	NA	5	3	21	19	14
CNS symptoms	11	NA	8	20	14	31	5
Vascular lesions/vasculitis	9	NA	38	8	34	44	11
Serositis	NA	NA	NA	NA	NA	NA	0
Epididymitis	6	32	NA	17	NA	NA	0

GI: gastrointestinal; CNS: central nervous system; NA: (data) not available.

Another important difference of our BD patients from other ethnic groups is the low frequency of a positive pathergy test. The positivity of the pathergy reaction varies widely in different populations (8–77%)[3]. While pathergy is considered to be highly sensitive and specific in patients with BD from Japan and Turkey, it is frequently negative in patients from the Western countries[3,6,25,26]. Although the positivity of the pathergy reaction depends on a number of factors such as disease activity, sex, HLA-B51 status, the size and type of the needle used, number of pricks, and whether an antiseptic is used to clean the skin[27-29], we believe that the low prevalence of this reaction in our Chinese patients is genuine because a standard procedure of the test was being followed by our investigators[25]. Our results support the observation that the pathergy reaction is not sensitive for the diagnosis of BD in areas where the prevalence of the disease is low. Whether the low prevalence of the pathergy reaction in our series is related to a different HLA association of the disease remains elusive.

BD is rare among southern Chinese residing in Hong Kong. Compared with other ethnic groups, southern Chinese patients tend to run a more benign course with less serious ocular complications and systemic involvement. The pathergy reaction is uncommon and insensitive for diagnosis of the disease in our locality. Whether the observed difference in disease manifestations of our patients is related to a different HLA association or linkage to the MIC alleles warrants further evaluation.

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