

Behcet's Disease: Experience in a Tertiary Rheumatology Centre in Singapore and a Review of the Literature

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Abstract

Introduction: The only reported study on Behcet's disease (BD) in Singapore found that only 15% of 34 BD patients managed at a tertiary dermatology centre had arthritis and 6% had eye complications with no other systemic manifestations. The aim of our study was to characterise the clinical manifestations and outcome of patients with BD at a tertiary rheumatology centre in Singapore. **Materials and Methods:** The International Study Group (ISG) and the O'Duffy (OD) criteria were used. The demographics, manifestations and outcome of our patients with BD were recorded. **Results:** Thirty-seven patients were included in our study. Twenty-three (62.2%) satisfied both ISG and OD criteria. Fourteen (37.8%) did not fulfil the ISG criteria but fulfilled the OD criteria and of these 6 were the incomplete form and 8 the complete form. The male to female ratio was 1:1.1. The mean age of onset of disease was 32.7 years (range, 15 to 58 years). The commonest presentations were recurrent oral ulcers (37, 100%), genital ulcers (24, 64.9%), joint (21, 56.8%) and cutaneous manifestations (18, 48.6%). The most common systemic manifestations were arthritis (16, 43.2%), gastrointestinal manifestations (15, 40.5%) and uveitis (13, 35.1%). There were 2 cases of Neuro Behcet's and 2 cases of venous thrombosis. Visual impairment from uveitis was the commonest cause of morbidity. There were no deaths in our series of BD. **Conclusion:** BD is a relatively rare rheumatologic condition in Singapore. However, because its systemic complications are not rare, early diagnosis and prompt treatment are essential.

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Key words: Epidemiology, Singapore, Uveitis, Vasculitis

Introduction

The only published study on Behcet's disease in Singapore by Tan E et al¹ (34 patients at the National Skin Centre) found that only 15% had arthritis and 6% had eye complications with no other systemic manifestations. These findings are different from epidemiological studies from other countries published in the literature,^{2,4} probably because the patients were mainly referred for cutaneous rather than systemic manifestations as a result of referral bias. The clinical outcomes of these patients were also not studied. The aim of our study was to characterise the clinical manifestations and outcome of patients with Behcet's disease (BD) at a tertiary rheumatology centre in Singapore, as BD is a clinical diagnosis where early diagnosis and treatment reduces morbidity and mortality.

Materials and Methods

Tan Tock Seng Hospital is a 1200-bed hospital with the largest rheumatology service in Singapore. The case records of patients from the Rheumatology, Allergy and Immunology Centre, Tan Tock Seng Hospital, who were diagnosed with Behcet's disease from 1 January 1993 to 31 December 2002, were studied. The patients were identified from hospital discharges with ICD code 1361 and from consecutive outpatients diagnosed with BD during the same period. They were referred from family physicians, dermatologists, ophthalmologists, general physicians and emergency physicians. The International Study Group (ISG)⁵ and the O'Duffy (OD) criteria⁶ were applied. Patients who satisfied either the ISG and/or the OD criteria were recruited into our study. The demographics, age of onset,

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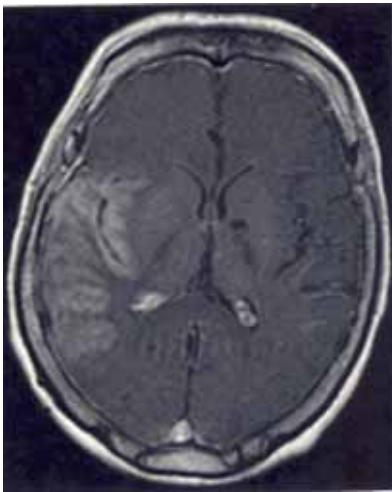


Fig. 1a. Post-gadolinium T1 weighted MRI brain before treatment of meningoencephalitis.

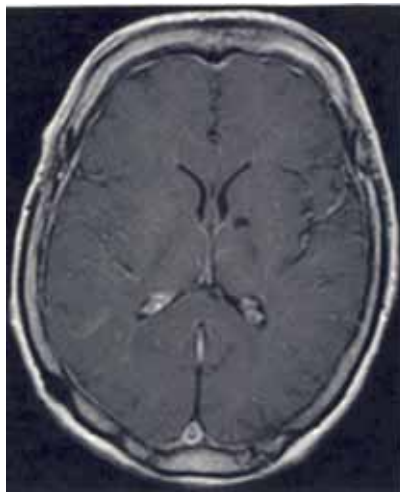


Fig. 1b. Post-gadolinium T1 weighted MRI brain after treatment of meningoencephalitis.



Fig. 2. Venogram showing right subclavian vein thrombosis.

initial and subsequent manifestations, treatment and outcome were recorded. In addition to being assessed by a rheumatologist, patients were evaluated by dermatologists, ophthalmologists, gastroenterologists or other medical specialties where indicated.

Results

Thirty-seven patients were included in our study. Twenty-three (62.2%) satisfied both ISG and OD criteria. Fourteen (37.8%) did not fulfil the ISG criteria but fulfilled the OD criteria. Of these, 6 were the incomplete form and 8 the complete form. The male to female ratio was 1:1.1 (18 males, 19 females). There were 27 Chinese (73%), 7 Malays (18.9%), 2 Indians (5.4%) and 1 Caucasian (2.7%). The mean age of onset of disease manifestation was 32.7 ± 10.6 years (range, 15 to 58 years).

The commonest presentations were recurrent oral ulcers (100%), genital ulcers (64.9%), joint (56.8%) and cutaneous manifestations (48.6%). Erythema nodosum ($n = 15$) and papulopustular lesion or acneiform eruptions ($n = 12$) were the most common cutaneous manifestations.

Systemic manifestations included arthritis (16, 43.2%), gastrointestinal manifestations (15, 40.5%) and uveitis (13, 35.1%). Oligoarthritis involving the ankles, knees and wrists occurred in 11 (73.3%) of the patients with arthritis. Four patients had monoarthritis and 1 had involvement of the sacroiliac joints. All except 1 patient had non-deforming arthritis. Five patients only had arthralgia.

Recurrent abdominal pain ($n = 10$) and diarrhoea ($n = 7$) were the commonest manifestations of gastrointestinal BD. Gastrointestinal ulcers were found in the ileocaecum ($n = 3$), sigmoid ($n = 1$) and rectum ($n = 1$), of which 2 patients developed perforations of their ileocaecal ulcers.

Of these 5 patients with gastrointestinal ulcers, 4 were females. The only male patient who had gastrointestinal ulcers involving the ileocaecum had perforation. The other patient with perforated ileocaecal ulcers was a Malay female who first presented with acute abdomen requiring emergency laparotomy.

A total of 13 patients had uveitis. More males ($n = 9$) than females ($n = 4$) had uveitis. The patterns of uveitis were anterior ($n = 5$), intermediate ($n = 2$), posterior ($n = 2$) and panuveitis ($n = 4$). Eight patients had bilateral eye involvement while 5 had unilateral eye involvement.

There were only 2 cases of Neuro Behcet. One patient presented with transient ischaemic attack while the other patient had meningoencephalitis (Fig. 1). These 2 patients were males and both recovered completely. Venous thrombosis occurred in 2 patients. They were also males with 1 patient having right subclavian vein thrombosis (Fig. 2) and the other developing right femoral and popliteal vein thrombosis. Neither patient had pulmonary embolism. No patient had cardiovascular, pulmonary or genitourinary complications.

There is no single manifestation that paralleled disease activity in all the 37 patients studied. Different patients had different manifestations and clinical course. However, most patients flared stereotypically as the manifestations that recurred during flares were usually those that the patients had at the time of presentation, with the exception of gastrointestinal ulceration, vascular thrombosis and Neuro Behcet.

The erythrocyte sedimentation rate (ESR) was elevated in 27 of 34 patients (79.4%) tested at presentation, median 32 mm/1st hour (range, 3 to 135). Among the 7 patients with normal ESR, 6 had systemic manifestations in the form of

Table 1. Characteristics of Behcet's Disease in Singapore,¹ Iran,² Korea³ and Hong Kong⁴

Characteristics	Iran ² (n = 2806)	National Skin Centre, Singapore ¹ (n = 34)	Tan Tock Seng Hospital, Singapore (n = 37)	Korea ³ (n = 1527)	Hong Kong ⁴ (n = 37)
Mean age of onset (years)	26.2 (range, 21 to 63)	37 (range, 15 to 58)	32.7 (range, 5 to 75)	33 (range, 18 to 74)	36.2
Male-to-female ratio	1:1.16	1:1.8	1:1.1	1:1.75	1:1.1
Percentage of patients					
Oral ulcers	95.5%	100%	100%	98.8%	100%
Genital ulcers	64%	97%	64.9%	83.2%	81%
Skin lesions	74%	70%	48.6%	84.3%	73%
Ocular lesions	61%	5.9%	35.1%	50.9%	35%
Articular lesions	43%	15%	43.2%	38.4%	54%
Gastrointestinal lesions	4.2%	0%	40.5%	7.3%	14%
Epididymitis	6.2%	0%	0%	0.6%	0%
Vascular lesions	8%	0%	5.4%	1.8%	11%
Neurologic lesions	3.2%	0%	5.4%	4.6%	5%

ocular, joint, gastrointestinal or combinations of these systemic manifestations.

The main treatment modality was systemic corticosteroids. More male patients (n = 12) than female (n = 8) required the use of additional immunosuppressive therapies. The most commonly used immunosuppressant was azathioprine in both groups. The other immunosuppressants that were used included sulphasalazine (n = 4), cyclosporin (n = 3), cyclophosphamide (n = 3), methotrexate (n = 3) and dapsone (n = 3). The most common reason for the use of additional immunosuppressive therapy was for control of persistent uveitis.

Visual impairment (defined as a permanent visual acuity of less than 6/60 in any eye) from uveitis was the commonest cause of morbidity. Seven of the 13 patients who had uveitis had permanent visual impairment. All these 7 patients were male. There were no deaths from BD in our series.

Discussion

The global distribution of BD suggests a geographic pattern coincident with the "silk route". BD, which is prevalent mainly in countries around the Mediterranean and Far East, is uncommon in Northern Europe and the Americas. A previous study from the National Skin Centre suggested that BD is uncommon in Singapore and this is consistent with our findings. From 1993 to 2002, only 37 cases of BD were seen at our department. Though Singapore is an immigrant society with a majority of ethnic Chinese, the prevalence of BD is low probably because most Singaporean Chinese originated from Southern China.

BD is a heterogenous relapsing, remitting, multi-systemic disease. The aetiology is unclear. There is no universally accepted diagnostic test; thus diagnosis of Behcet's disease

has relied on identification of several of its more typical clinical features. However, confusion has arisen because 5 sets of diagnostic criteria (Mason and Barnes, Behcet's Disease Research Committee of Japan, O'Duffy, Zhang, and Dilsen) were in use prior to the development of ISG criteria for diagnosis in 1990. These differences have hindered both interpretation of different trials and international multicentre collaboration. However, as there was a skew towards cutaneous features for the ISG criteria, we also chose the O'Duffy criteria which included other organ involvement. In addition, this allowed us to compare our results with the study done by Tan E et al at the National Skin Centre, Singapore who also used the ISG and O'Duffy criteria.

The mean age of disease onset in our study was similar to that reported in other studies (Table 1). Unlike the earlier study by Tan et al, the male-to-female distribution was similar in our cohort. In 1984, Yazici et al⁷ showed that the males had more severe disease with worse outcome. Our small series of patients showed similar results as male patients had a higher incidence of uveitis and other systemic involvement, a greater need for additional immunosuppressive therapies, and more permanent morbidity mainly from visual impairment.

Many types of cutaneous manifestations have been reported in BD but the most frequently observed are orogenital ulcers, pseudo-folliculitis (papulo-pustular lesion), erythema nodosum and the pathergy reaction. Similar to the study by Tan et al, most of our patients presented with oral (100%) and genital ulcers (64.9%). However, being a tertiary referral centre for rheumatology, 56.8% of our patients also had joint manifestations at the time of presentation.

Arthritis in BD is usually non-deforming, non-erosive,

monoarticular or oligoarticular, with a predilection for the lower limbs and, lasting from several weeks to months.⁸ Ours were similar except for 1 patient who had deforming arthritis and another who had involvement of the sacroiliac joints. Reports of sacroiliac joint involvement in BD have been variable and this may be due to interobserver variation in the interpretation of the sacroiliac joints on a plain radiograph of the pelvis.⁹ Some authors feel that sacroiliac joint involvement is due to an association of 2 diseases, namely BD and ankylosing spondylitis rather than a causal relationship.

Chronic, relapsing, bilateral uveitis involving both anterior and posterior uveal tracts in BD is a significant cause of morbidity. Frequent anterior uveitis with hypopyon, in which the inflammatory exudates in the anterior chamber forms a layer of white cells, can result in cataracts and glaucoma. An analysis of 2806 cases of BD by Davatchi et al in 1995² revealed that ocular complications like uveitis and retinal vasculitis were seen in 61% of patients. This is in contrast to the small series by Tan et al, which showed that only 2 out of 34 patients (5.9%) had uveitis and none had permanent visual impairment. At the Singapore National Eye Centre, a retrospective review of 252 cases of uveitis seen in a Uveitis Clinic over 24 months revealed only 11 cases of BD.¹⁰ All their patients had vitritis and retinal perivascular sheathing on fundal examination. Nine (91%) had retinal infiltrates, macular oedema and iritis. Retinal venous occlusions were reported in 8 (73%) patients, retinal arterial occlusions in 4 (36%) patients and hypopyon in 2 (18%) patients. Their other systemic manifestations included recurrent mouth ulcers (100%), genital ulcers (54.5%), erythema nodosum (27.5%), arthritis (45.5%) and deep venous thrombosis (9%). In our own series, 13 (24.3%) had uveitis and 7 (19%) had permanent visual impairment. That all these 7 patients were male suggest that male sex may be associated with more severe eye lesions, a finding that has been observed by other researchers.

Up to 50% of patients may experience abdominal pain and diarrhoea.¹¹ In our series, 45.9% of the patients had either diarrhoea or recurrent abdominal pain. This has been postulated to be due to gastric and small intestinal ulcers. For reasons that remain unclear, gastrointestinal ulceration shows a distinct geographical variation. It occurs in about 1% of patients from Japan¹² but is rare among patients from the Mediterranean basin. In our series, 13.5% of our patients had gastrointestinal ulceration. Female patients appeared to be more predisposed to gastrointestinal ulceration as 4 out of 5 patients were female. Although the classical site of gastrointestinal ulceration is in the ileocaecal region, Kasahara et al¹³ found no predilection for any particular site and frequent relapses in 40%. This was similar to our findings as 3 patients had ulcers in the

ileocaecum, while 1 patient had sigmoid colon ulcer and another had rectal ulcer. However, relapses were infrequent in our patients; this occurred in the only male patient with ileocaecal ulcers.

Neurological manifestations, also termed Neuro Behcet, are rare. However, in view of the severe morbidity and occasional mortality, it is important to recognise this entity and institute prompt treatment. Many forms of neurologic manifestations have been reported. These include benign intracranial hypertension, cranial nerve, pyramidal, cerebellar, spinal cord or peripheral nerve involvement, and acute confusional state, but the most classical manifestation is meningoencephalitis. Neuro Behcet is extremely rare, especially during the initial manifestation of BD and it usually appears several months or years after the onset of disease. A prospective study done by Serdaroglu et al¹⁴ in Turkey on 323 patients followed up over a year found that only 5.3% had involvement of the nervous system, with mean onset of neurologic symptoms 2.6 ± 5.0 years after the patients historically fulfilled OD criteria for diagnosis. Though the most common reported site of neurologic involvement in BD is the brainstem,¹⁵ Serdaroglu et al found that hemispheric lesions were as common as brainstem involvement. Headaches were of no clinical importance unless accompanied by other neurologic findings. They also found that CT scan of the brain was of little diagnostic help. In our series, 2 patients developed Neuro Behcet. Both patients had Neuro Behcet many years after onset of recurrent oral-genital ulcers. One of them had classical meningoencephalitis with involvement of the right cerebral hemisphere which recovered after treatment.

Although thrombosis and vascular lesions are not included in the major diagnostic criteria of BD, 25% to 50% of patients are likely to develop this complication.^{16,17} Venous thrombosis appears to be the major vascular lesion, reported in 7% to 33% of patients with BD and representing 85% to 93% of vasculo-Behcet. It is significantly more frequent in Arab and European populations (19% to 34%)¹⁸ than in Asian non-Arab populations (7% to 12.5%).¹⁹ In our series only 2 out of 37 patients (5%) had vascular involvement and both had venous thrombosis. Houman et al²⁰ reported that male gender and a positive pathergy test was associated with higher risk of deep venous thrombosis. Our small series was in concordance with these findings. The mechanism of venous thrombosis in BD remains unknown. Studies have failed to associate specific coagulation abnormalities such as deficiencies in protein C, protein S and anti-thrombin III, or resistance to activated protein C, with this disease,²¹ or the presence of anticardiolipin/anti β 2 glycoprotein1 antibodies.²⁰ Some authors have suggested that thrombosis in BD seems to be related more to vasculitis than to clotting disorders. Therefore, in addition

to anticoagulation, Houman et al²⁰ suggested administering corticosteroids in all cases of DVT. In cases involving the vena cava or cerebral venous sinuses, an additional immunosuppressive agent should be given. The use of antiplatelet agents remains controversial, as some investigators have shown reduced biosynthesis of prostacyclin in BD.¹⁶

Treatment of BD is directed at the suppression of inflammation and the prevention of long-term damage to the organs involved. The choice of treatment is dependent on the severity and the persistence of active disease. Patients with major organ involvement require systemic corticosteroids and possibly additional immunosuppressive therapies, including colchicine, azathioprine, cyclosporin, methotrexate, cyclophosphamide, sulphasalazine, dapsone, thalidomide, levamisole and chlorambucil. Recently, the use of anti-tumour necrosis factor monoclonal antibody for gastrointestinal Behcet's disease has also been reported.²² In addition, autologous haematopoietic stem-cell transplantation has been used by Hensel et al²³ for treatment of BD with pulmonary involvement. In our series, the most common indication for the use of high dose corticosteroids and immunosuppressive agents was for the control of uveitis.

Conclusion

BD is a rare rheumatologic condition in Singapore. However, systemic complications in BD are not rare and selection bias is the most likely reason for the different findings reported in the earlier study done in Singapore. Our study has shown that its presentation and manifestations are similar to other epidemiological studies published in the literature except for gastrointestinal ulceration which appears to be higher in our series. As systemic major organ involvement may result in life-threatening outcomes, a high index of suspicion and early diagnosis with appropriate treatment is the key to preventing morbidity and mortality in BD.

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