Disease Characteristics of Behcet's Disease Among Filipino Patients Seen in Rheumatology Clinics

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Abstract

Introduction: Behcet's disease (BD) sometimes called behcet's syndrome or silk road disease is an immune-mediated systemic vasculitis. This condition remains a clinical challenge for physicians. There are many reports, mostly case series and nationwide surveys, on clinical manifestations of BD from different parts of the world. In the Philippines where BD is rare and underreported, physicians might not be familiar with the clinical manifestations of this disease. The aim of this research is to describe the disease presentation of BD among Filipinos to increase awareness and avoid delay in diagnosis which might pose a threat for the development of irreversible, sometimes fatal complications.

Methods: A manual search was done for medical records with diagnosis of BD in the clinics of rheumatology staff of PGH. The diagnosis of BD was based on the 2006 International Criteria for BD. We noted the demographic data, clinical manifestations, results of ancillary procedures, treatment and outcomes. The study follows a descriptive design.

Results: There were 31 patients with the diagnosis of BD found from the manual search. Most of them were female (77%). The mean age at diagnosis was 38.6 years ± 10.4 (SD) and the mean time duration from onset of first symptom to diagnosis was 41 months (range three to 180 months). Three patients had a family member who also had BD (10%). The most common features of the disease were oral ulcers (94%), ocular manifestation (68%), and cutaneous disease (65%). The pathergy test was positive in 17%.The most common treatments prescribed were oral steroids (74%), colchicine (58%), and NSAIDs (48%). There was symptom control or improvement in a third of patients but there were still symptom recurrence in some. Thirteen patients (42%) had recurrent oral ulcerations while 23% had recurrence of skin lesions. Two of the patients (six percent) developed blindness. There was no death recorded.

Conclusion: There is an average delay of three years in the diagnosis of BD that hinders appropriate early treatment. Moreover, BD remains to be a clinical challenge for physicians. While a third of the cohort had good outcomes, half still had symptom recurrences and the occurrence of blindness in two patients underlines the potential of the disease to disable. We recommend expansion of the cohort to include the BD patients of other rheumatologists in the Philippines to have an idea on the actual prevalence and incidence of how this uncommon disease in our locality, and to have a better understanding of its clinical presentation and disease management in our country.

Keywords: bechet's disease, bechet's syndrome

Introduction

Behcet's disease (BD) sometimes called behcet's syndrome, morbus behcet, behcet-adamantiades or silk road disease is an immune-mediated systemic vasculitis that often presents with mucous membrane ulceration and ocular involvement. BD was originally seen along the Silk Road, going from East (China) to West (Spain and Portugal), but due to trade and colonization, it is now seen everywhere in the world.[3] There are many reports, mostly case series and nationwide surveys, on clinical manifestations of BD from different parts of the world. There is difficulty in comparing the case series with the nationwide surveys because of the difference in patient selection. According to a review done by Davatchi et al., clinical manifestations are much similar in nationwide surveys, while they may differ in case series. The difference is mainly due to the specialty of the centers. Ocular manifestations are more often reported from ophthalmology centers, while mucocutaneous manifestations are more reported from dermatology centers. The new International Criteria for Behcet's Disease (ICBD 2006) is as follows:

Symptoms	Points
Oral aphthosis	2
Genital aphthosis	2
Ocular lesion	2
Skin lesions	1
Vascular manifestation	1
Positive pathergy test	1
Total score ≥ 3 = classify a patient with BD 98.2% sensitivity, 95.6% specificity, 97.3% accuracy[5]	

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Behcet's disease (BD) carries an overall mortality rate as high as 16% at five years. Rupture of coronary or pulmonary arterial aneurysm carries a high mortality rate. Saadoun et al. studied mortality data from 187 patients fulfilling the international criteria for BD from a single center in France. The mortality rate at one year and five years was 1.2% and 3.3%, respectively. The main causes of death included major vessel disease (arterial aneurysm and Budd-Chiari syndrome, 43.9%), cancer and malignant hemopathy (14.6%), central nervous system involvement (12.2%), and sepsis (12.2%).

In the Philippines where BD is rare and underreported, physicians might not be familiar with the clinical manifestations of this disease. Patients may be misdiagnosed to have sexually transmitted diseases unresponsive to antibiotics, refractory gout, sudden blindness of unknown cause, or aphthous ulceration due to vitamin deficiency. This inability to recognize the disease will definitely increase morbidity and, possibly, mortality. There is no publication about the disease characteristics of BD among Filipinos and it is interesting to discover any differences from other countries that also have BD. We hope that this study can contribute to the knowledge about BD among Filipinos and aid in facilitating its recognition among our countrymen.

Behcet's disease (BD) is uncommon and its prevalence in our country is not known. Its presentation mimics other common diseases and recognition is often a clinical challenge for physicians. Through this publication, the authors hope that physicians may learn of the disease, recognize it, and refer to the appropriate subspecialties. The study aims to describe the characteristics of BD among Filipinos.

Methods

The study follows a descriptive design and includes patients diagnosed with BD fulfilling the 2006 International Criteria for Behcet's Disease (ICBD) seen in clinics of rheumatology consultants of the Philippine General Hospital (PGH) - longest practice duration of 26 years; 1988 to 2014. Non-probability sampling was used in the selection of participants.

A manual search was done for medical records with diagnosis of BD in the clinics of rheumatology consultants of PGH. The diagnosis of BD was based on the 2006 International Criteria for BD. We noted the demographic data (gender, age at onset of BD; age at diagnosis, family history of BD), clinical manifestations, results of ancillary procedures (ESR, WBC count, and pathergy test), treatment, and outcomes. Statistical Analyses: Descriptive statistics including frequency tables

The conduct of this study was approved by the University of the Philippines Medical Research Ethics Board (UPMREB). All patient information were anonymized and kept confidential. There were no conflicts of interest for this study.

Results

There were 31 patients (77% are female) with the diagnosis of BD. The mean age at diagnosis was 38.6 years ± 10.4 (SD) and the mean duration from onset to diagnosis was 41 months (range three to 180 months) while mean disease duration from diagnosis to latest follow-up was 55.6 months (range one to 192 months). Three patients had a family history of BD (10%). Two patients with a relative with BD were diagnosed less than one year but one patient was diagnosed after four years.

Table I show the clinical features included in the 2006 International Criteria for BD. The most common feature of the disease is oral ulcer (94%). The ocular manifestations seen are uveitis and visual impairment. The cutaneous findings consist of folliculitis, erythema nodosum, and pustulosis. Vascular events like arterial thrombosis, DVT, and superficial phlebitis are seen. Pathergy test is positive in only 17% of patients. The average ESR is 44.22 ± 27.84 (SD) mm/hr and the peripheral white blood cell count is 8.38 ± 2.19 (SD) x 109/L.

The most common treatments prescribed were oral steroids (74%) and colchicine (58%, Table II). There was symptom control or improvement without any recurrence in a third of patients with mean follow-up of one year. There were recurrences in patients that were followed up with mean duration of five years. Thirteen patients (42%) had recurrent oral ulcerations while 23% had recurrence of skin lesions. Two of the patients (six percent) already presented with blindness on consult. There was no death recorded. (Table III)

Discussion

Behcet's disease (BD) is classically characterized as a triad of recurring aphthous oral ulcers, genital ulcers, and uveitis. It is more frequent and severe in persons of Eastern Mediterranean and Asian descent than those of European

Table I. Clinical features of 31 patients with BD included in the study

Features	Frequency (%)
Mouth ulcers	**29 (94)**
Ocular lesions/findings	**21 (68)**
Visual impairment	16
Uveitis	5
Skin lesions	**20 (65)**
Erythema nodosum (EN)	12
Pustulosis	5
Folliculitis	3
Genital ulcers	**18 (58)**
Vascular	**3 (10)**
DVT	1
Venous insufficiency	1
APAS	1

Table II. Treatment received by the 31 BD patients included in our study

Treatment received	Frequency (%)
Steroids	23 (74)
Colchicine	18 (58)
NSAIDs	15 (48)
Cyclophosphamide	10 (32)
Methotrexate	10 (32)
Azathioprine	2 (6)

Table III. Outcomes of 31 BD patients included in our study

Outcomes	Frequency (%)
Improved (w/o any recurrences)	9 (30)
Recurrent oral ulceration	13 (42)
Recurrent skin lesions	7 (23)
Blindness	2 (6)
Recurrent genital ulceration	1 (3)

descent. There are nationwide surveys of BD in five countries namely, Iran, Japan, China, Korea, and Germany (Table IV). The male to female ratios are variable-male predominance in Germany, China and Iran while female predominance in Japan and Korea. Our study likewise shows a female predominance. The mean age at onset is 32 years in our study and similar to that in the surveys mentioned.

Oral aphthosis is the most constant symptom of BD, seen in nearly every patient. Oral aphthous lesion can be seen anywhere on the oral mucosa and presents as a painful, round or oval ulceration with well-defined borders. In each attack, there may be from one to several aphthous lesions, and the number varies in different attacks. Most of the time, two or more lesions may be seen. The healing process is spontaneous and usually takes one or two weeks. This symptom was seen in 93-99% of patients in the five nationwide surveys mentioned and in 94% of patients in our cohort.

Genital ulcers are usually larger than oral ulcers, heal slower, and recur less frequently. In females, they are often wider than 10 mm and deeper than the oral aphthosis. They are seen on the vulva, vagina, and rarely on the cervix. In males, they are usually seen on the scrotum. Genital ulcers were found in 58% of our cohort and in 64-83% of the five-country surveys.

Anterior uveitis (AU) is a common ocular manifestation of BD. It produces pain, photophobia, and visual disturbance. The progress of AU follows the classical rule of attack and remission. A single attack will usually cure spontaneously without producing any sequela. Successive attacks lead to cataract formation and, less frequently, to glaucoma. Posterior uveitis (PU) and retinal vasculitis (RV), however, are the main causes of blindness in BD. Blindness was seen in 11% of the eyes in patients with pan uveitis and/or retinitis.[5] Ocular findings were present in 68% of our cohort, similar to Iran, Japan, Korea, and Germany. China had the lowest occurrence of ocular findings (35%).

The most frequent skin lesion in BD is pseudo-folliculitis, better known as behcet's pustulosis. It is a vasculitis characterized by a dome shaped (non-acuminated) sterile pustule on a round erythematous–edematous base. Erythema nodosum (EN), usually frequent and relapsing, is the second most frequent skin lesion. It is characterized by painful multiple subcutaneous nodules of varying sizes preferentially located on the lower limbs. Often, they have more erythema and edema around the lesions than the classic erythema nodosum. Skin aphthoses are painful, punched out, yellowish narcotizing ulceration usually seen peri-anal skin, buttock, the trunk, the axilla, the submammary space, and the interdigital spaces and leaves a scar after healing. Skin manifestations were seen in 65% of our cohort and in 67-87% of patients in the five-country surveys.

Pathergy phenomenon is a hypersensitivity of the skin to trauma. A papule, or a pustule, will appear at the site of trauma, surrounded by erythema. The skin is punctured perpendicular or diagonally with a 25- or 21-gauge needle with one drop of normal saline. The reaction is best seen 24 to 48 hours after the puncture. The degree of reaction, which will classify the pathergy test as positive, is not yet standardized and this phenomenon is not constant during the course of the disease. The frequency of the pathergy phenomenon has decreased during the past decades, decreasing its value as a diagnostic finding. This was seen in 34-56% of the patients surveyed, compared to only 17% of our cohort.

Vascular involvement was seen in 10% of the Philippine cohort, one case each of DVT, anti-phospholipid antibody syndrome, and venous insufficiency. This was present in eight to 13% in the surveys but quite low in Korea (1.8%). (Table III)

Laboratory findings are usually nonspecific and reflect an inflammatory state. Elevated erythrocyte sedimentation rate (ESR) seen in our cohort corroborates the presence of active disease.

Immunosuppressive drugs are used to control BD. Symptomatic therapy is directed at specific symptoms. Topical measures (i.e., local corticosteroids) should be the first line of treatment for isolated oral and genital ulcers. Acne-like lesions are usually of cosmetic concern only. Thus, topical measures as used in acne vulgaris are sufficient. Colchicine is preferred when the dominant lesion is erythema nodosum and this has also been used to prevent mucocutaneous relapse. Joint involvement may respond to prednisone, local corticosteroid injections, and nonsteroidal anti-inflammatory drugs.[7] Azathioprine is widely accepted as a steroid-sparing agent and the initial agent for ocular involvement in BD. It should be used together with systemic steroids for any patient with BD and inflammatory eye disease affecting the posterior segment.

Table III. Comparison of clinical features of behcet's disease in the Philippine cohort and in five nationwide surverys

Clinical Features (%)	Philippines n=31	Iran[9] n=5059	Japan[10] n= 3316	China[11] n=1996	Korea[12] n=1527	Germany[13] n=590
Male to female ratio	0.36	1.19	0.976	1.34	0.63	1.40
Oral ulcer	94	97	98	93	99	98
Genital	58	65	73	76	83	64
Skin	65	67	87	69	84	81
Ocular	68	56	69	35	51	53
Vascular	10	9	9	8	2	13
Pathergy	17	54	44	nm	56	34

Legend: nm-not mentioned

Conclusion

Behcet's disease remains a clinical challenge for physicians. There is an average of three years' delay in diagnosis that hinders institution of early treatment. While a third of the cohort had good outcomes, half still had symptom recurrences and the occurrence of blindness in two patients underlines the potential of the disease to disable. We recommend expansion of the cohort to include the BD patients of other rheumatologists in the Philippines to have an idea on the actual prevalence and incidence of how this uncommon disease in our locality, and to have a better understanding of its clinical presentation and disease management in our country.

Acknowledgement

The authors would like to thank the following for their valuable contribution to our study: Dr. Tom Edward N. Lo, Dr. Jose Paolo P. Lorenzo, Dr. Therese Lladoc-Natividad, Dr. Geraldine Zamora-Racaza, Dr. Bernadette Heizel Manapat-Reyes and Dr. Michael L. Tee

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APPENDIX A

Disease Characteristics of Behcet's Disease among Filipino Patients seen in Rheumatology Clinics
Data Collection Form

ID No.	Case #
Initials:	Age:
Sex 0 = Male 1 = Female	
Smoking: 0=never; 1=present; 2=past Alcohol: 0=never; 1=present; 2=past Family hx of BD: 0=none; 1= positive Specify which family member:	Age at onset of symptoms: _____ Age at diagnosis: _____ Date of diagnosis: _____ Duration of disease (in years): _____

Clinical Manifestations:

	Yes	No
Criteria Features: Oral aphthosis/mouth ulcers		
Genital aphthosis /ulcers		
Skin lesions/Cutaneous (follicultis, erythema nodosum, pustulosis, ulceration)		
Ocular lesions/Ophtha findings (uveitis, retinal vasculitis, visual impairment)		
Vascular (arterial thrombosis, DVT, superficial phlebitis)		
Non-criteria features: Musculoskeletal (arthralgia, arthritis, back pain)		
Neurologic (behavioral problems, seizures, headache, aphasia, hemiplegia, cerebellar syndromes, myelopathy)		

Investigations done:

ESR : 0-yes,1- no Result _____
CRP: 0-yes, 1-no Result _____
WBC: 0-yes, 1-no Result _____

Pathergy: 0-done, 1-not done
0-positive, 1-negative

Medications:

	Yes	No
Colchicine NSAIDs Steroids DMARDs Cytotoxic MTX AZA		

Outcomes: check if any of the following occurred during the course of treatment

	Yes	No
Improvement		
Death		
Blindness		
Visual impairment		
Recurrent oral ulceration		
Recurrent genital ulcer		
Recurrent skin lesion		

APPENDIX B

WRITTEN INFORMED CONSENT FORM

I _____, give my full consent to allow Dr. Juneth Ria Limgenco-Hipe, Rheumatology fellow-in-training, to get necessary data from my patient's chart for her research entitled DISEASE CHARACTERISTICS OF BEHCET'S DISEASE AMONG FILIPINO PATIENTS SEEN IN RHEUMATOLOGY CLINICS under the direct supervision of Dr. Evelyn O. Salido and Dr. Ester G. Penserga.

I hereby declare:

That I fully understood the purpose of this study.

That my participation in this study is purely voluntary and without compensation in any form.

That all the information about the patients' data will remain confidential except for the researchers conducting and the authorized member of the research team.

That I am aware that the overall result of the study may be published in local or international journals.

_____ _____

Signature over printed name of PGH Rheumatology staff | Date