Phenotype heterogeneity in Late-onset Behçet's syndrome: A cohort from a referral center in China

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Research

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Abstract

Objectives To evaluate the demographic, clinical and major organ involvement of patients with late-onset Behçet's syndrome (BS) in a tertiary centre in China.

Methods It was a cross-sectional study of consecutive BS patients in Huadong Hospital of Fudan University between September 2012 and January 2020, we identified 152 late-onset BS patients diagnosed after age of 40 years. We compared clinical variables between patients with disease onset age before and after 40 years. The relative risks (RRs) of clinical variables were calculated between two age groups. Moreover, a hierarchical cluster analysis was conducted according to twenty-nine variables to determine homogeneous subgroups of patients.

Results Late-onset BS patients had a higher incidence of intestinal ulcer (late-onset : early-onset, RR 1.47), but a lower incidence of ocular involvement (RR 0.54) and folliculitis (RR 0.46). Female was associated with genital ulcer, erythema nodosum, and arthritis. Four clusters (C1–C4) were formed. C1 (n = 71) the largest cluster, defined as mucocutaneous group. C2 (n = 20), the arthritis group, C3 (n = 39), the gastrointestinal type, all patients presented with intestinal lesion, and five cases with esophageal ulcer. In C4 (n = 22), showing a mixture of uveitis and vascular group, fifteen patients presented with uveitis and eight had vascular lesion, and one cases had central nervous system lesions.

Conclusion This is the first cluster analysis to be carried out in a cohort of late-onset BS patients in China. The significantly lower prevalence of folliculitis in late onset BS and the overall milder disease course suggest that testosterone status may influence disease activity.

Introduction

Behçet's syndrome (BS) is a rare heterogeneous inflammatory multisystem disorder affecting individuals of both genders with equal frequency [1]. Except for Recurrent aphthous stomatitis, the clinical manifestations of BS are variable and include genital ulcers and skin, joint, ocular, gastrointestinal, cardiovascular and central nerve system involvements. Major organ involvements are the main causes of morbidity and mortality [2]. The average age of onset peaks at the second to third decades, so it generally is regarded as a disease of young adults. The clinical features and course of the disease are closely associated with gender and age [3, 4]. Despite affecting almost all organs, major organ involvement rarely coexists with each other. Diagnosis beyond

the age of 60 years is unusual. Due to its rarity and heterogeneous characteristics, the knowledge about the onset in geriatric ages is limited. Epidemiological studies generate conflicting results [5, 6]. Even within the same geographical region, the results varied from individual cohorts [5, 7]. Late onset BS still is not well defined [8, 9]; it usually affects both genders equally.

Although it is one of the endemic regions, in China epidemiological data of late-onset adult BS are absent. Therefore, in the present study, we try to describe the clinical phenotype and the major organ

involvement in a well-defined racial characteristic cohort. An unsupervised clustering analysis was employed to identify the aggregation of clinical phenotypes.

Patients And Methods

Cohort overview

A cross-sectional study of BS patients was conducted in the Division of Rheumatology in Huadong Hospital, Fudan University from September 2012 to January 2020. The revision of International Study Group criteria (ISG) [10], Japan revised criteria (JPN) [11], Cheng and Zhang criteria (China) [12], and International Criteria for BS (ICBD) [13] were selected for inclusion. The final diagnosis was verified by at least 2 rheumatologists.

Exclusion criteria included: malignancies, infectious disease or other autoimmune diseases. Detailed clinical and laboratory data were recorded, including demographic data, laboratory assessments, imaging studies and pathological findings. This study was approved by the ethics committee of Huadong Hospital and all patients gave consent to participate in the study.

All patients were tested for complete blood count, liver and renal function, erythrocyte sedimentation rate, C reactive protein, serum IgG, IgA, IgM levels, total IgE level, complements, autoantibodies, including rheumatoid factor, and antinuclear antibodies. All patients underwent ultrasonography, computed tomography, or magnetic resonance imaging, upper and lower endoscopies, and ocular examination.

Assessment of clinical manifestation, major organ involvement and severity

Clinical manifestation was judged by senior attending rheumatologists in our Division having substantial experience of diagnosing BS patients, who were regularly supported by medical doctors with other specialties.

Organ involvement was assessed by reviewing the patient's symptoms, past medical history, physical examination, laboratory studies, imaging examinations and endoscopy findings. Ophthalmologic data recorded the type of uveitis (namely, anterior, posterior, or panuveitis), laterality, ocular findings, and ocular complications [14]. Diagnosis of intestinal BS was confirmed by extraintestinal systemic manifestations, and by the characteristic endoscopic, histopathologic, and radiological features, which helped to distinguish intestinal BS from Crohn's disease [15]. The classification of major vascular involvements in BS was adopted [16]. Vascular involvement was defined as deep venous thrombosis, major vein (vena cava, hepatic) thrombosis and arterial thrombosis or aneurysms, which were detected by doppler ultrasonography and (or) MRI (magnetic resonance imaging) and (or) computed tomography (CT) [17]. Cardiac lesions were documented as aortic valve regurgitation, intracardiac thrombi [18] and coronary artery disease [19], which were documented by echocardiography or coronary angiography and (or) CT. Atherosclerosis or other causes of cardiac lesions were carefully excluded. Myelodysplastic syndrome (MDS) was diagnosed and classified according to WHO classification [20], while patients had

typical BS manifestations. Central neurological involvement (CNS) included inflammatory parenchymal lesions, and extra-parenchymal forms causing cerebral venous sinus thrombosis [21].

Disease severity was assessed by Krause's scores [22].

Clustered variables

For clustering observations, demographic (gender, age, age at onset, duration of disease, Krause score) and clinical manifestations and major organ involvements including oral ulceration, genital ulceration, erythema nodosum, folliculitis, joint involvement, uveitis, intestinal involvements, cardiovascular involvements, epididymitis and central neurological involvement were included. In total, 29 variables were included for cluster analysis, excluding the classification criteria.

Statistical analysis

The software program SPSS (v. 20, Chicago, IL) was used for statistical analyses. Values are expressed as means $\pm$ SD or medians with 25–75% ranges, whichever was appropriate depending on whether the data were normally distributed. Student's test or the Mann Whitney U-test was used to compare numerical variables between groups. The chi-square or Fisher's exact test was used to compare categorical variables. P values <0.05 were considered statistically significant.

The TwoStep Cluster Analysis began with the selection of variables, which were classified as continuous or categorical. Continuous variables were: age, age at onset, duration of disease, and Krause Scores. Categorical variables included in the analysis were: gender, clinical manifestation (oral ulceration, genital ulcers, erythema nodosum, folliculitis, joint involvement), major organ involvement (uveitis, intestinal involvement, cardiovascular involvement, central nerve involvement and myelodysplastic syndrome). The log-likelihood method was used to determine inter-subject distance and specific classification of participants.

Results

Patient screening

We first analyzed the cohort, consisting of 1,596 individual inpatients with BS. After eliminating 334 duplicate data and 402 invalid cases (data missing, or inaccurate), 860 cases were analyzable (Fig. 1). Among them, 152 patients presented the initial manifestation of BS after age of 40.

Demographics, Manifestations, and Major organ involvements

The median age at onset of patients was 47 years (interquartile range, IQR: 43-52 years). The median disease duration was 5 years (IQR: 2-10 years). The median Krause score was 3 (IQR: 2-5). Gender ratio in our cohort, was (M:F=0.92:1). Oral ulceration was the most common manifestation; the prevalence of oral ulcers was 98.7%. The frequency of other mucocutaneous and joint manifestations were: genital ulcers

77%, erythema nodosum 36.2%, folliculitis 11.8%, arthritis or arthralgia 17.8%. The incidence of major organ involvements was: intestinal involvement 29.0%, uveitis 8.7%, vascular involvement 5.3%, esophageal ulcer 4.6%, cardiac lesion 5.6%, central nervous system involvement 4.3% and MDS 0.8% (Table 1).

Comparison between adults onset before and after 40 years

Patients with late-onset age had a higher frequency of intestinal involvement (RR 1.39), especially of intestinal ulcer (RR 1.47) and a lower frequency of ocular involvement (RR 0.54), panuveitis (RR 0.54) and folliculitis (RR 0.46) as compared with adult patients with onset before 40 years. (Table 1). There was no difference in incidence of vascular involvement and central nervous system involvement.

Gender-phenotype analysis

In regard to gender-associated clinical features (Table 2), female sex was associated with genital ulcer and erythema nodosum, $P < 0.05$. No sex difference was found in other skin-mucosal and major organ involvements.

Cluster analysis

Four distinct clusters were identified. The characteristics of each cluster are listed in Table 3.

The first cluster (C1, n=71) Skin and mucosa type, female dominance. was the largest group; it consisted of subjects with a median age at onset of 48 years (IQR: 44-52 years), mainly female (54.9%). The majority of the patients had genital ulcers (95.8%). The prevalence of erythema nodosum was 43.7% and folliculitis was 7%. This group had low proportion of major organ involvement except for cardiac lesion in 2.8%. The proportions of subjects meeting Japan revised, Cheng and Zhang, ICBD and ISG criteria were 43.7%, 97.2%, 98.6% and 47.9%, respectively. Disease severity was low; the median Krause Score was 2.

C2 (n=20) Joint involvement type, (male to female ratio: 0.53 : 1). The subjects in C2 had a median age at onset of 47.5 years (IQR: 43-51 years). All had joint involvement (arthritis or arthralgia). Folliculitis presented in 10% cases. Major organ involvement was rarely seen, except cardiac lesion in 10%. 75% subjects met ICBD and 95% met Cheng and Zhang criteria, while 25% satisfied with Japan revised criteria and 30% with ISG criteria. The median Krause Score was 4.

C3 (n=39), Gastrointestinal Behçet's syndrome (GIBS) type, sex ratio (male to female ratio: 1.05 : 1). Most subjects had intestinal involvements, including ulcers (84.6%) and perforation (15.4%), and had a median age at onset of 45 years (IQR: 42-49 years). The incidence of oral ulcers (94.9%), genital ulceration (61.5%) and folliculitis (20.5%). While the rate of erythematous nodosum (25%) was relatively lower than in the other clusters. Five cases with esophageal ulcer were in this cluster.

The proportions of subjects meeting the four classification criteria (JPN, CHN, ICBD, ISG) were 25.6%, 97.4%, 61.5% and 23.1% respectively. The median Krause Score was 5.

C4 (n=22), Mixture of uveitis and vascular, predominantly male (63.6%). Fifteen subjects had ocular lesions, including anterior uveitis (1) and panuveitis (14); the median age at onset was 47 years (IQR: 44-53.3 years). Oral aphthosis was seen in 100%, genital aphthosis 45.5%, and the frequency of folliculitis was low (13.6%). Regarding vascular involvements, there was deep vein thrombosis in 3 cases, major vein (vena cava, hepatic) thrombosis in 3 cases, major vein (vena cava, hepatic) thrombosis in 2 cases and arterial thrombosis or aneurysms in 5 cases. Central nerve involvement was seen in 3 patients. Classified by JPN, CHN, ICB, ISG criteria, the sensitivities reached 54.5%, 95.5%, 100% and 54.5% respectively. The median Krause Score was 5.5.

Discussion

In this cross-sectional study, we found a distinct clinical manifestation pattern in late-onset patients with BS. Ocular involvement was less common and intestinal lesion was more common in late-onset adults, as compared with early-onset. Female had higher incidence of genital ulcers, erythema nodosum and arthritis. Four phenotype clusters were identified, each cluster with only a small number of predominant clinical features reflecting the overall low number of organs involved in each subject. C1, skin and mucosa type; C2, arthralgia/arthritis type; C3, GIBS type, all with intestinal involvement and an aggregation of esophageal ulcers; C4, a combination of panuveitis, cardiovascular and central nervous involvement.

The lower incidence of folliculitis was reported by a Tunisian Cohort [6], which reflects age-related decline in hormone level. Testosterone might disturbed neutrophil apoptosis and cause TH1 type immune alterations in BS patients [23]. Therefore, male patients of early-onset age usually have more severe clinical phenotypes and higher mortality.

Another critical issue for patients with late-onset BS is differential diagnosis. BS is not a single disease, but a multi-systemic disorder [24]. From our cohort, we identified six patients with myelodysplastic syndrome presenting as a Behçet's like disease, three patients were at late-onset age. Previously, we compared the clinical features between BS and MDS associated with Behçet mimic [25]. MDS was related to late-onset of age, intestinal ulceration and trisomy 8.

It is noted that 11.2% of late-onset patients had ocular lesions in our cohort, which is significantly lower than the incidence in adults with early-onset, and is consistent with what Tunali et al. reported [9]. However, our result did not suggest an increase of anterior uveitis, according to a cohort study from Turkey [26].

Observed from our previous study [27], a great proportion of GIBS patients had no obvious GI tract symptoms. Instead of recording GI symptoms [20], we order GI endoscopy for every subject at baseline to evaluate the GI involvement. We found more intestinal involvement in adult patients with onset age after 40 years than those before 40 years.

To the best of our knowledge, our study is the first time cluster analysis has been used to characterize clinical phenotypes among late-onset BS patients, which identified four distinct clusters. The skin-mucosal group comprised of the largest cluster. GIBS group represents the most common major organ involvement. However, in C4, namely a mixture of uveitis and vascular, CNS, few organs are involved for each individual patient. Only one patient concurrently presented with aneurysms and panuveitis. Another patient concurrently presented with aneurysms and CNS lesion.

Our findings could help us to identify clinical characteristics and understand the pathogenic mechanisms within specific clusters, which could contribute to better ways of managing of BS.

IGS criteria has a high specificity, but lacks sensitivity and accuracy [28]. The Japan revised criteria emphasizing ocular involvement, in the presence of ocular manifestation, only one other criterion was enough to make the diagnosis. In our cohort, we found that the proportion of subjects meeting Japan revised criteria was similar to that of ISG. Notably, the Cheng and Zhang (China) criteria had the highest sensitivity in all clusters; they retains only the original three features as major criteria (oral aphthosis, genital aphthosis, and ophthalmological manifestations), and includes extensive minor criteria representing the heterogeneous clinical features of BS, excluding for vascular lesion. ICBD was in collaboration by several countries in order to obtain better performing criteria. We found the proportion of subjects meeting ICBD was low in C2 and C3. One-fourth to two-fifths of the patients with arthropathy and GIBS did not meet ICBD. As a result, discoveries and treatment decisions would not be applicable to those patients. In consideration of the increasing sensitivity of classification criteria, a revision is required.

There are some strengths and weaknesses in this study. Among the strengths, the unsupervised statistical approach allowed searching for clinical characteristics. Besides, we distinctly included data of intestinal involvement confirmed by objective laboratory findings. Our analysis has potential limitations, in part, a single-center study could lead to selection bias. The prevalence of arterial lesions was higher than that of deep venous thrombosis. We cannot exclude a slight ascertainment bias for the prevalence of joint involvement. Finally, our study was limited by a cross-sectional study and not including medication as a clustered variable. As shown previously [29], clinical phenotypes can be highly dynamic and influenced by medication; hence, a robust longitudinal study design is required to assess the stability of these clusters.

Conclusions

To summarize, this study provided new insights into phenotype patterns in unrelated BS late-onset adult patients by a combination of comparison between early and late-onset adults and among different genders, and cluster analysis. Our findings highlight the requirement for a new revision of classification criteria to increase classification sensitivity for a subgroup of BS. Whether these findings can be translated into enhanced understanding of pathogenesis differences and guide therapy requires further clarification.

Abbreviations

BS: Behçet's syndrome; CHN: the Chinese version of Behçet's disease criteria created by Cheng and Zhang; CNS: central neurological involvement; CT: computed tomography; GIBS: gastrointestinal Behçet's syndrome; ICBT: International Criteria for BS; IQR: interquartile range; ISG: International Study Group criteria; JPN: Diagnostic criteria of the Behçet's disease research committee of Japan (1987 revision); MDS: myelodysplastic syndrome; RRs: relative risks

Declarations

Ethics approval and consent to participate

The current study was approved by the Ethic Committee of Huadong Hospital, Fudan University and was conducted under strict accordance with the Declaration of Helsinki, Good Clinical Practice guidelines, and all applicable laws and regulations in China.

Consent for publication

All subjects gave consent to participate in the study.

Availability of data and materials

Please contact author for data requests.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

J-LG designed the study, and reviewed the manuscript. D L and Y S carried out the data collection. J Z analyzed the data, wrote the manuscript. J-F L carried out the data analysis. All authors read and approved the final manuscript.

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Role of the funding source

Key Messages

- Our analysis demonstrated the phenotype discrepancy between children and adults.
- Four phenotype clusters were identified, with gastrointestinal, panuveitis and cardiovascular clusters representing commonly involved organs.

Conflict Of Interest Statement

All authors have read and approved the final manuscript. There are no competing interests associated with this study.

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Tables

TABLE 1. Compare clinical features between late onset and adult patients with Behçet’s syndrome

Variable	Total (n=790)	Late-onset (n=152)	Early-onset (n=638)	RR (late : early) (95% CI)	P-value
Oral ulcer	786 (99.5)	150 (98.7)	636 (99.7)	0.99 (0.97, 1.01)	P=0.169
Genital ulcer	607 (76.8)	55 (77.0)	490 (76.8)	1.00 (0.91, 1.10)	P=0.964
Skin lesions	436 (55.2)	68 (44.7)	368 (57.7)	0.78 (0.64, 0.94)	P=0.004
Erythema nodosum	320 (40.5)	55 (36.2)	265 (41.5)	0.87 (0.69, 1.10)	P=0.227
Folliculitis	182 (23.0)	18 (11.8)	164 (25.7)	0.46 (0.29, 0.73)	P<0.001
Arthritis	96 (12.2)	15 (9.9)	81 (12.7)	0.78 (0.46, 1.31)	P=0.407
Arthralgia	76 (9.6)	12 (7.9)	64 (10.0)	0.79 (0.44, 1.42)	P=0.422
Ocular involvement	149 (18.9)	17 (11.2)	132 (20.7)	0.54 (0.34, 0.87)	P=0.007
Anterior uveitis	17 (2.2)	2 (1.3)	15 (2.4)	0.56 (0.13, 2.42)	P=0.550
Panuveitis	132 (16.7)	15 (9.9)	117 (18.3)	0.54 (0.32, 0.89)	P=0.012
Intestinal involvement	158 (20.0)	40 (26.3)	118 (18.5)	1.39 (1.03, 1.89)	P=0.035
Intestinal erosion	6 (0.8)	0 (0)	6 (0.9)	-	P=0.602
Intestinal ulcer	127 (16.1)	33 (21.7)	94 (14.7)	1.47 (1.03, 2.10)	P=0.035
Intestinal perforation	25 (3.2)	7 (4.6)	18 (2.8)	1.63 (0.69, 3.84)	P=0.299
Esophagal ulcer	34 (4.3)	7 (4.6)	27 (4.2)	1.09 (0.48, 2.45)	P=0.839
Vascular involvement	63 (8.0)	8 (5.3)	55 (8.6)	0.61 (0.30, 1.26)	P=0.170
Deep venous thrombosis	25 (3.2)	3 (2.0)	22 (3.4)	0.57 (0.17, 1.89)	P=0.447
Major vein (vena cava, hepatic) thrombosis	5 (0.6)	2 (1.3)	5 (0.5)	2.80 (0.47, 16.6)	P=0.247
Arterial thrombosis or aneurysms	40 (5.1)	5 (3.3)	35 (5.5)	0.60 (0.24, 1.51)	P=0.267
Cardiac lesion	44 (5.6)	5 (3.3)	39 (6.1)	0.54 (0.22, 1.34)	P=0.173
Central nervous system involvement	22 (2.8)	3 (2.0)	19 (3.0)	0.66 (0.20, 2.21)	P=0.783
MDS	6 (0.8)	3 (2.0)	3 (0.5)	0.99 (0.96, 1.01)	P=0.089

Values presented as n (%) unless otherwise stated. MDS: myelodysplastic syndrome

TABLE 2. Relative risk by gender for clinical variables among patients with Behçet’s syndrome

Variable	Total (n=152)	Male (n=73)	Female (n=79)	RR (male: female) (95% CI)	P-value
Oral ulcer	150 (98.7)	72 (98.6)	78 (98.7)	1.00 (0.96, 1.04)	P=1.000
Genital ulcer	117 (77.0)	51 (69.9)	66 (83.5)	0.84 (0.70, 1.00)	P=0.045
Skin lesions	68 (44.7)	27 (37.0)	41 (51.9)	0.71 (0.49, 1.03)	P=0.065
Erythema nodosum	55 (36.2)	20 (27.4)	35 (44.3)	0.62 (0.40, 0.97)	P=0.030
Folliculitis	18 (11.8)	10 (13.7)	8 (10.1)	1.35 (0.57, 3.24)	P=0.496
Arthritis	15 (9.9)	3 (4.1)	12 (15.2)	0.27 (0.08, 0.92)	P=0.022
Arthralgia	12 (7.9)	6 (8.2)	6 (7.6)	1.08 (0.37, 3.21)	P=0.887
Ocular involvement	6 (8.7)	2 (6.5)	4 (10.5)	0.61 (0.12, 3.13)	P=0.684
Anterior uveitis	1 (1.4)	0 (0)	1 (2.6)	-	P=1.000
Panuveitis	5 (7.2)	2 (6.5)	3 (7.9)	0.82 (0.15, 4.59)	P=1.000
Intestinal involvement	20 (29.0)	10 (32.3)	10 (26.3)	1.23 (0.59, 2.56)	P=0.541
Intestinal erosion	0 (0)	0 (0)	0 (0)	-	-
Intestinal ulcer	33 (21.7)	15 (20.5)	18 (22.8)	0.90 (0.49, 1.66)	P=0.738
Intestinal perforation	7 (4.6)	5 (6.8)	2 (2.5)	2.71 (0.54, 13.52)	P=0.262
Esophagal ulcer	7 (4.6)	5 (6.8)	2 (2.5)	2.71 (0.54, 13.52)	P=0.262
Vascular involvement	8 (5.3)	6 (8.2)	2 (2.5)	3.25 (0.68, 15.58)	P=0.108
Deep venous thrombosis	3 (2.0)	3 (4.1)	0 (0)	-	P=0.108
Major vein (vena cava, hepatic) thrombosis	2 (1.3)	2 (2.7)	0 (0)	-	P=0.229
Arterial thrombosis or aneurysms	5 (3.3)	3 (4.1)	2 (2.5)	1.62 (0.28, 9.44)	P=0.672
Cardiac lesion	5 (3.3)	4 (5.5)	1 (1.3)	4.33 (0.50, 37.84)	P=0.195
Central nervous system involvement	3 (2.0)	3 (4.1)	0 (0)	-	P=0.108
MDS	3 (2.0)	1 (1.4)	2 (2.5)	1.01 (0.97, 1.06)	P=1.000

Values presented as n (%) unless otherwise stated. MDS: myelodysplastic syndrome

TABLE 3 Characteristics of patients with Behçet's syndrome after clustering on clinical manifestations

Characteristics	C1 (n=71)	C2 (n=20)	C3 (n=39)	C4 (n=22)
Demographics				
Age at onset (IQR), years	48 (44-52)	47.5 (43-51)	45 (42-49)	47 (44-53.3)
Disease duration (IQR), years	4 (2-10)	8 (4-10)	5 (2-10)	5.5 (3.8-10)
Krause score	2 (2-3)	4 (3-4.8)	4 (4-5)	5.5 (4-6.3)
Sex Ratio (M/F)	0.82 : 1	0.53 : 1	1.05 : 1	1.75 : 1
Classification criteria				
JPN (%)	43.7	25	25.6	54.5
CHN (%)	97.2	95	97.4	95.5
ICBD (%)	98.6	75	61.5	100
ISG (%)	47.9	30	23.1	54.5
Clinical manifestation				
Oral ulceration (%)	100	100	94.9	100
Genital ulceration (%)	95.8	75	61.5	45.5
Erythema nodosum (%)	43.7	35	20.5	40.9
Folliculitis (%)	7	10	20.5	13.6
Arthritis/Arthralgia (%)	0	100	12.8	9.1
Major organ involvement				
Uveitis (%)	0	5	2.6	68.2
Intestinal involvement (%)	0	5	100	0
Esophageal ulcer (%)	1.4	5	12.8	0
Vascular involvement (%)	0	0	0	36.4
Cardiac lesion	2.8	10	0	4.5
Myelodysplastic Syndrome (%)	0	0	7.7	0
Central nervous system involvement (%)	2.8	0	0	4.5

Values presented as n (%) unless otherwise stated. JPN: Diagnostic criteria of the Behçet's disease research committee of Japan (1987 revision); CHN: the Chinese version of Behçet's disease criteria created by Cheng and Zhang; ICBD: International Criteria for Behçet's disease; ISG: International Study Group for Behçet's disease.

Figures

Figure 1

Flow chart of patients