WORLD VIEW

Ocular features of Behçet's disease: An international collaborative study

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Objective: To investigate the clinical features of ocular lesions in Behçet's disease in different countries.
Methods: A descriptive questionnaire survey was performed.
Results: 25 eye centres in 14 countries returned questionnaires on prevalent cases in 2006. Clinical data were analysed on 1,465 patients with ocular lesions. Recurrent oral aphthous ulcers were reported in 94.5%, skin lesions in 69.5% and genital ulcers in 61.4%. Most of the patients had bilateral and recurrent intraocular inflammation. Poor visual acuity was seen in 18.9% in women, but 24.8% in men ($p<0.01$). Panuveitis was seen more in men than in women ($p<0.01$). 23% of the patients had visual acuity equal to or worse than 20/200 at the final visit. The patients with poor vision were more frequently in India, Iran and Japan than in other countries ($p<0.01$).
Conclusions: We report the largest contemporary international case series of patients with ocular involvement in Behçet's disease. Panuveitis was significantly more frequent in men than women, and men tended to have a worse visual prognosis. There were some differences in the clinical pattern of Behçet's disease in different countries. Despite modern treatment, the disease still carries a poor visual prognosis with one-quarter of the patients blind.

Behçet's disease is a multisystem disorder characterised by recurrent oral aphthous ulcers, skin lesions, genital ulcers and ocular lesions. The disease often leads to blindness in severely affected individuals. It is most prevalent between the second and fourth decades of life. Behçet's disease is found predominantly between East Asia and the Mediterranean basin, and is uncommon in the American continents, Oceania and sub-Saharan Africa.[1] The distribution of uveitis and intraocular inflammation may differ in different regions of the world. In Japan, Behçet's disease is one of the three most frequent diagnoses in patients with uveitis.[2] The highest prevalence rate of the disease has been reported from Turkey.[3] This disease is strongly associated with the major histocompatibility complex antigen HLA-B51, first reported in 1973.[4] Populations with a high prevalence of HLA-B51 lie predominantly north of the equator, spanning Japan and Western Europe between 30° and 45° N.[5] The frequency of ocular involvement in patients is thought to be between 50 and 70%.[6–10] The characterisitic ocular feature is a relapsing uveitis, which may involve the anterior segment, posterior segment or both. The classification of the patient's uveitis is important both therapeutically and prognostically, because those lesions affecting the posterior part of the eye tend to be persistent and blinding.[11] The disease may be more severe in men than in women.[12]

In the present study, we examined the differences in ocular features in Behçet's disease between regions and ethnic groups on a worldwide scale and retrospectively analysed the clinical features, ocular manifestations, visual outcomes and complications in more than 1400 Behçet's patients with ocular involvement.

METHODS

Descriptive questionnaires were sent to 132 ophthalmology centres by email and airmail. Responses were collected from 25 eye centres in 14 countries; Australia, Germany, Greece, India, Iran, Italy, Japan, Jordan, Morocco, Portugal, Turkey, Saudi Arabia, Tunisia, and the UK. Clinical data were analysed on 1465 prevalent cases with ocular lesions. The descriptive questionnaire surveyed details of patients' gender, age of disease onset, HLA-B51 positivity, extraocular lesions, type of intraocular inflammation and final visual acuity. We divided the visual prognosis into two groups based on the visual acuity in the better eye at their final visit as less than 0.1 (20/200, poor vision) and equal to or more than 0.1 (good vision).

We did not ask which classification criteria were used to include patients in the study. The age of disease onset was based on the estimation of the respondent doctors. The relapse of ocular inflammation was confirmed by ophthalmologists during the observation period. Data are presented as mean $\pm$ standard deviation (SD). Statistical analysis was performed using the χ^2 test. Values of $p<0.01$ were considered statistically significant.

RESULTS

Clinical data on 1465 subjects were collected from Germany (109 cases), UK (105), Greece (120), Turkey (239), Portugal (1), Italy (177), Morocco (15), Tunisia (62), Jordan (12), Saudi Arabia (27), Iran (337), India (104), Australia (12) and Japan (197). Men and women accounted for 979 and 454 cases, respectively. The gender of 32 subjects was not recorded. The percentages of men and women were 68.3% and 31.7%. The male-to-female ratio was calculated as 2.15:1. The mean age of disease onset was 27.5 ± 10.5 years (3–71 years old). Recurrent oral aphthous ulcers were reported in 94.5%, skin lesions in 69.5% and genital ulcers in 61.4% (fig 1).

Type of intraocular inflammation

Intraocular inflammation was bilateral in the majority of patients (85.6% in women, 85.5% in men). Recurrence of uveitis was seen in 95.6% of women and 95.7% of men (table 1). No difference was detected between sexes in laterality and incidence of relapse of uveitis.

Abbreviations: CAPSII, combined anterior and posterior segment intraocular inflammation

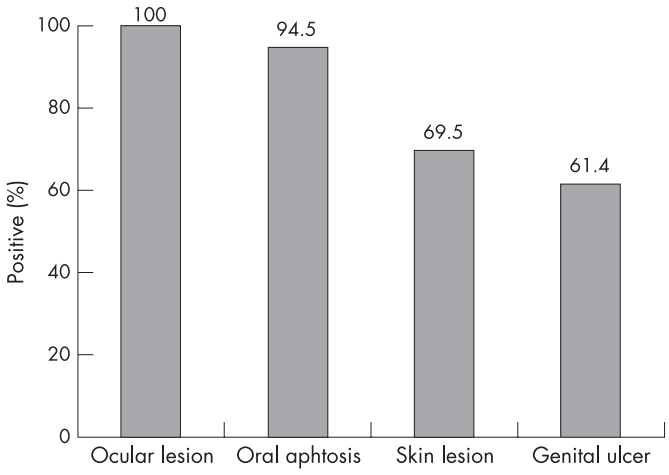

Figure 1 Percentages positive for ocular and extraocular lesions are shown. In this study, we have collected the data limited to patients with ocular inflammation (100%). Recurrent oral aphthous ulcers were reported in 94.5%, skin lesions in 69.5% and genital ulcers in 61.4%.

Anterior segment intraocular inflammation (ASII) and combined anterior and posterior segment intraocular inflammation (CAPSII, panuveitis) were seen in 10.1% and 89.9% of women (table 1), while in men only 4.6% of the patients suffered from ASII alone, and 95.4% had panuveitis/CAPSII. The percentage of CAPSII, which is thought to be more serious in terms of visual prognosis, was significantly higher in men than in women ($p<0.01$, table 1).

Visual prognosis

We divided the visual prognosis into two groups based on the visual acuity at their final visit. The percentage of poor vision, less than 0.1 (20/200) in the better eye, was 23.3% in total (table 2). By gender, poor visual acuity was seen in 18.9% in women but 24.8% in men ($p<0.01$, table 1). The frequencies of patients with reduced visual acuity by region are summarised in table 1. The patients with poor vision were reported more frequently in India, Iran and Japan compared with other countries ($p<0.01$, table 2). However, Japanese patients were followed up significantly longer (17.7 ± 10.9 years) compared with patients overall (10.3 ± 8.4 years, $p<0.01$). In contrast, patients with poor vision in Italy (8.8%) were significantly fewer than in other countries ($p<0.01$, table 2).

Analysis by country

The mean age of disease onset was calculated as 27.4 ± 10.4 (mean $\pm$ SD) years old for the whole cohort. Japanese patients were the oldest (34.3 ± 10.3 years old). In other countries, however, symptoms began younger than 30 years old. The percentage of men by country is shown in table 2. This was significantly different only in India ($p<0.01$, table 2).

HLA Class I was typed in 556 subjects, and HLA-B51 was detected in 62.0% (348 subjects) of the patients. The country-by-country frequencies of HLA-B51 are shown in table 2. Behçet's patients had HLA-B51 more frequently in Greece ($p<0.01$) but less frequently in the UK ($p<0.01$) than in the whole cohort (table 2).

DISCUSSION

Behçet's disease is an inflammatory disorder of unknown cause, characterised by recurrent oral aphthous ulcers, genital ulcers, ocular lesions and skin lesions. Involvement of the gastrointestinal tract, central nervous system and large vessels can be life-threatening, and their frequencies have been reported as 10–15% among patients with Behçet's disease.[1]

According to previous reports, about 25–45% of patients with ocular lesions eventually became blind despite therapeutic intervention.[13–16] In the present study, we found that 23% of Behçet's patients with ocular lesions had a poor visual acuity of less than 0.1 (20/200). This suggests that current medical therapy still is not good enough to stop patients going blind. Poor visual acuity to less than 0.1 (20/200) was more common in men than in women ($p<0.01$). Bilaterality and recurrence of uveitis were similar between sexes. However, the incidence of panuveitis was higher in men than in women ($p<0.01$), and since panuveitis usually has a worse prognosis than anterior segment inflammation alone, the men's poorer visual prognosis may have resulted primarily from the higher frequency of panuveitis. When the clinical features were compared in different countries, we appeared to find differences (table 2). For instance, the age at disease onset was significantly older in Japan than in other countries ($p<0.01$). The frequency of HLA-B51 also varied by region. Greek patients had a significantly high prevalence of HLA-B51 ($p<0.01$), but the prevalence in patients in the UK was significantly lower ($p<0.01$) than the overall cohort. However, HLA typing was performed only in 37% of the cohort. As far as visual prognosis was concerned, patients with poor vision in Italy were significantly fewer than in other countries despite the second-highest percentage of men ($p<0.01$). In contrast, patients with poor visual acuity were seen frequently in India, Iran and Japan compared with other countries ($p<0.01$). As shown in table 2, more than 90% of patients collected from India were men in this study. Thus, it is possible that the poorer visual prognosis in India might be due to this male bias. For Japan, patients had a significantly longer follow-up compared with the rest of the cohort ($p<0.01$). Since visual acuity generally decreases with time, this may explain the poor visual prognosis among Japanese patients. For Iran, we collected all our patients from the Shariati Hospital, which is the only referral centre in the country; we believe therefore that the results for poor visual prognosis in Iran accurately reflect the overall prevalence in Iranian Behçet's patients.

Inflammatory eye disease occurs in approximately 50–70% of all patients with Behçet's disease.[6–10] In this study, we have collected data only from those patients with ocular inflammation (fig 1). Previous studies have shown that, while uveitis typically occurs after the onset of oral aphthous ulcers, the delay between the two manifestations may be as long as 14 years; that oral aphthous ulcers do not occur at all in rare cases; and that 94% of the patients with uveitis eventually suffer bilateral ocular disease.[5] Since we showed that almost every patient with uveitis also had oral aphthous ulcers, and more than 85% of our patients had bilateral disease, our present results are consistent with previous studies.

Table 1 Type of intraocular inflammation among men and women

	Bilaterality of uveitis (%)	Recurrence of uveitis (%)	CAPSII/panuveitis (%)	Poor VA (<0.1, %)
Men	85.5	95.7	95.4**	24.8**
Women	85.6	95.6	89.9	18.9

**$p<0.01$.

Table 2 Summary of clinical features of Behçet's disease on a regional basis

Countries (no. of subjects)	Age of onset (mean ± SD)	Gender (men/total, %)	HLA-B51 (%)	Poor VA (<0.1, %)
Whole cohort (1465)	27.4±10.4	68.3	62.0	23.3
India (104)	27.1±6.8	92.0**	54.5	39.0**
Iran (337)	25.3±9.2	65.6	50.1	30.0**
Japan (197)	34.3±10.3**	63.3	53.8	30.0**
UK (105)	27.9±9.4	56.9	42.9**	21.4
Tunisia (62)	29.1±8.7	67.7	61.9	21.0
Germany (109)	23.1±14.0	59.5	67.8	19.4
Greece (120)	23.3±8.2	69.2	81.9**	17.8
Turkey (239)	27.0±9.7	71.5	55.0	16.5
Italy (177)	29.5±10.5	76.3	62.0	8.8**

**p<0.01 vs total.

Inevitably, in this type of study, there will be sources of bias that may distort the results. In this study, we have identified the following:

(1) Classification bias: We did not ask which classification criteria were used to include patients in the study. It is probable that the criteria for Behçet's disease accepted for selection included Japanese Committee on Behçet disease criteria,[17] the 1990 International Study Group (ISG) Criteria,[18] and O'Duffy's criteria.[19] The use of different standardised criteria may lead to misclassification when comparing the frequencies of systemic features.

(2) Gender bias: We already alluded to this kind of bias, as the patients in India were largely male, and this may have explained the poorer visual prognosis. However, there was a higher proportion of men in Italy where the visual prognosis was best. Since the sex ratio was not significantly different among the surveyed countries except for India, this bias might apply to India only.

(3) Ascertainment bias: We had only a limited response rate to the questionnaire from 25/132 eye centres. The response was not representative of all countries and ethnic groups. For instance, we had no data from China, Korea, South East Asia and Central Asia. Accordingly, the results of the present study may not be applicable to patients from those countries. Furthermore, our findings with respect to the results of HLA typing must be taken with caution, since this was only performed in 37% of the cohort.

(4) Follow-up bias: Patients with worse disease tend to be followed for longer, and those with mild disease tend to be lost to follow-up. As we mentioned above, the longer follow-up in Japan may have contributed to the poorer visual outcome, particularly as the Japanese patients were older to start with.

(5) Referral bias: Patients with worse disease tend to be sent to tertiary referral centres where our figures came from. Therefore, our findings may only be representative of the worse end of the spectrum of disease. We have partially addressed this in Iran but not in the other countries.

(6) Treatment bias: Certain countries cannot afford new expensive drugs (eg, anti-TNF-α antibody, Interferon-α, mycophenolate mofetil, etc) and may have to rely on steroids and azathioprine. Accordingly, their results may not be as good as others. Reported recently, those new drugs could improve visual outcomes.[20–22] This issue is now under consideration as another study in the near future.

(7) Access to healthcare bias: It may be that some of the results derive from the fact that access to secondary or tertiary healthcare is different in different countries, leading to a delay in both diagnosis and treatment. This could explain the worse results from India.

(8) Immigration bias: In this study, 90% of adult patients with Behçet's disease were Turkish immigrants in Germany (data not shown). Immigration influx could be a bias in Germany, UK or Australia.

In conclusion, we have reported the largest contemporary epidemiological investigation of Behçet's patients with ocular involvement. The study emphasises that Behçet's disease is still a blinding disorder despite modern treatment, with one-quarter of the patients blind. Panuveitis was significantly more frequent in men than in women, and men had a worse visual prognosis than women. There appear to be some differences in the clinical picture of Behçet's disease in different countries, but these differences may be due to reporting. Further population-based prospective surveys are required to ascertain if these findings are real or due to ascertainment bias.

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EDUCATION

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Ciliary body metastasis masquerading as scleritis

Clinical presentation

A 54-year-old Caucasian male presented to the Cole Eye Institute for a second opinion regarding a diagnosis of iritis. He described 4 months of ongoing redness, pain and photophobia in the right eye. Initially, he was treated with topical prednisolone acetate 1% without improvement. Subsequently, homatropine 5% and combined neomycin, polymixin B and dexamethasone drops were prescribed without any relief. For a month prior to presentation, he had been off all medications and his symptoms had gradually worsened.

He denied any past ocular history of trauma, surgery or inflammatory disease. His past medical history was significant for a left testicular teratocarcinoma in 1987. At that time, he underwent orchiectomy and chemotherapy for suspicion of pulmonary metastases. However, subsequent wedge resection of the lung confirmed the lesions to be hamartomas. His social history was significant for smoking (1.5 pack per day for the past 30 years) and the review of systems was negative.

On examination, visual acuity was 20/20 in the right eye and 20/25 in the left eye. Intraocular pressures were 32 mm Hg in the right eye and 16 mm Hg in the left eye. Deep episcleral injection was observed inferotemporally in the right eye and a few cells were present in the anterior chamber. The iris and lens were normal. Dilated fundus examination of both eyes was normal. In addition, an ultrasound B scan was normal. Previously performed investigations were negative and included chest *x* ray, PPD, ACE level, RPR, FTA-ABS, Lyme antibody, ANA and HLA-B27.

A diagnosis of idiopathic anterior scleritis of the right eye was made. Fluorometholone 0.25% topical drops hourly in the right eye and oral indomethacin 25 mg three times a day were prescribed. Additional workup including antineutrophilic cytoplasmic antibodies, complete blood count, complete metabolic panel and chest CT with contrast were ordered.

Two weeks later, the patient returned for follow-up stating that his symptoms had improved. However, on examination, the deep episcleral injection was still present. In addition, the iris was displaced anteriorly at the 7–8 o'clock position. Yellow gelatinous deposits were observed in the corresponding quadrant in the anterior chamber angle (fig 1A). Ultrasound biomicroscopy was performed to evaluate the angle and ciliary body region (fig 1B). Transcorneal fine needle aspiration biopsy was confirmatory (fig 2).

Questions

(1) Describe the ultrasound biomicroscopic findings (fig 1B)
(2) What is the diagnosis based on fine needle aspiration biopsy (fig 2)?
(3) How would you manage this patient?

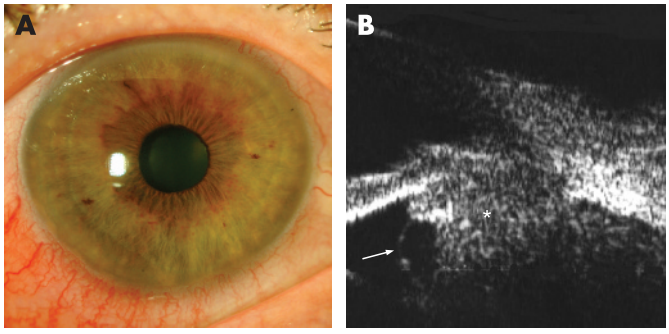

Figure 1 (A) Anterior segment photograph showing scleral injection in the inferotemporal quadrant. Note yellow gelatinous deposits in the corresponding anterior chamber angle region. (B) Ultrasound biomicroscopy was performed to evaluate the angle and ciliary body region.

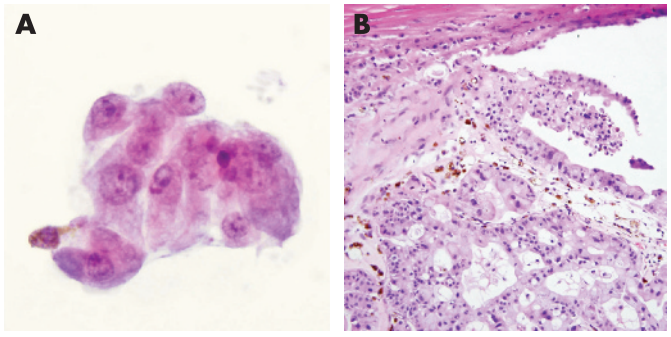

Figure 2 (A) Fine needle aspiration biopsy. (B) Histopathology of the enucleated globe.

See page 1649 for answer

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