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## **Low prevalence of juvenile-onset Behcet's disease with uveitis in East/South Asian people**

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**Purpose:** There is little information on the demographic and clinical characteristics of Behcet's disease in children in different parts of the world. We sought to provide this information through a questionnaire survey of specialist eye centres.

**Methods:** Descriptive questionnaires were collected from 25 eye centers in 14 countries. The questionnaire surveyed details of juvenile-onset Behcet's disease with uveitis. Ethnic groups, clinical features, treatments, and prognosis of pediatric-age Behcet's disease were examined on a world scale.

**Results:** The clinical data of 135 juvenile-onset and 1,227 adult-onset patients with uveitis were collected. The average age of disease diagnosis in the children was 11.7 years old. Of the ethnic groups identified: 54% were from Middle East, 43% from Europe, but only 2% from East/South Asian countries. By contrast, 19.2% of adult patients were from East or South Asia. The frequency of genital ulcers in juvenile patients was 38.7%, which was significantly lower than in adult cases (53.5%;  $P < 0.01$ ).

**Conclusions:** Behcet's disease with uveitis was less common in children than in adults in East/South Asia. Although the clinical features of the systemic disease were similar between children and adults, there was a lower frequency of genital ulceration in children.

## **Introduction**

Behçet's disease is a chronic multisystem disorder characterized by oral aphthous ulcers, genital ulcers, skin lesions, ocular lesions, gastrointestinal involvement, vascular lesions and neurological manifestations. The mean age of disease onset is 25-30 years old,<sup>1</sup> and initial presentation in children is uncommon. Details of the presentation and clinical characteristics of juvenile-onset Behçet disease have been limited to case reports or small case series.<sup>2-8</sup>

One of the manifestations of Behçet's disease is uveitis. In general, uveitis in childhood is uncommon with an incidence of 4-7/100,000 children per year.<sup>9-11</sup> Unlike adults, juvenile idiopathic arthritis (JIA) is the most common identified cause of uveitis in children.<sup>12-14</sup> Even in Turkey, one of the countries of highest prevalence of Behçet's disease, JIA is the most common cause of uveitis in children, followed by idiopathic uveitis and pars planitis.<sup>15</sup> Behçet's disease is one of the three most frequent diagnoses in patients with uveitis in Japan.<sup>16-18</sup> Though the prevalence of Behçet's disease in the Japanese overall has been estimated to be 10-15/100,000,<sup>19</sup> juvenile-onset Behçet's disease is uncommon.

Accordingly, there is little information on the demography and clinical characteristics of Behçet's disease with ocular lesions in children. Against this background, we administered a descriptive questionnaire survey in a large-scale international collaborative study and compared the epidemiology, clinical phenotype and visual outcome between children and adults. A summary of the clinical features of the whole cohort has been recently reported.<sup>1</sup>

## **Methods**

Descriptive questionnaires were sent to 132 ophthalmology centers by e-mail and airmail in 2005-2006. We encouraged participants as many subjects as possible to provide their clinical data to us. Also, we gave no detail of this survey of juvenile-onset Behçet's disease to avoid a source of bias about the recruitment of patients in their institutions. Responses were collected from 25 eye centers in 14 countries; Australia, Germany, Greece, India, Iran, Italy, Japan, Jordan, Morocco, Portugal, Turkey, Saudi Arabia, Tunisia, and the United Kingdom (UK). Races of the patients were also questioned. The inclusion criteria were patients who developed the disease at less than 16 years of age. The age of disease onset was

recognized as the timing of meeting the classification criteria based on the estimation of the responding doctors. Statistical analysis was performed using the  $\chi^2$  test or F-test. Values of  $p < 0.01$  were considered statistically significant.

## Results

The clinical data of 1,465 Behcet's patients were successfully collected. Of which 1,362 patients were reported the age of disease onset: 1,227 patients were considered adult-onset and 135 were juvenile-onset Behcet's disease. Boys accounted for 65.2% of the cohort of juvenile-onset patients (Table 1). HLA-B51 was detected in 68.6% of children and 61.6% of adult patients. The mean age of disease diagnosis in children was 11.7 years old, and the mean follow-up period was 13.5 years (Table 1). We were able to identify the ethnic groups of 127 children: 53.5% (68 cases) of them were from Middle Eastern countries, 43.3% (55 cases) of them from Europe, and only 2.4% (3 cases) from East/South Asia (Fig. 1). One case was reported as Cuban of mixed race. Among adults, 19.2% of patients were from East/South Asia (Fig. 1). This difference in ethnicity was significantly different between adult-onset and juvenile-onset ( $p < 0.004$ , F-test).

Among children, recurrent oral aphthous ulcers in 94.8%, skin lesions in 67.4%, and genital ulcers in 38.5% (Fig. 2). In adults, recurrent oral aphthous ulcers in 94.5%, skin lesions in 70.0%, and genital ulcers in 53.5% (Fig. 2). The frequency of genital ulcers in juvenile patients was significantly lower than that of adult cases ( $P < 10^{-8}$ ,  $\chi^2$  test). More than 90% (93.9%) of juvenile patients had combined anterior and posterior segment intraocular inflammation (CAPSII/panuveitis) as adults. Most of the children suffered from bilateral recurrent CAPSII/panuveitis (Table 1). The percentage of eyes achieving a final visual acuity of 0.1 (20/200) or better in the better eye was 92.6% of children (Table 1) and 86.3% among adults. Thus, 7.4% of children but 13.7% of adult patients were legally blind. A good visual prognosis ( $\geq 20/200$ ) was more frequent in children than in adult cases ( $P < 0.033$ ,  $\chi^2$  test).

The most frequently prescribed systemic therapy was corticosteroids (57 cases, 42.2%), followed by cyclophosphamide (27 cases, 20.0%), methotrexate (25 cases, 18.5%), colchicine (18 cases, 13.3%), azathioprine (12 cases, 8.9%), cyclosporin (11 cases, 8.1%), and interferon- $\alpha$  (2 cases, 1.5%) (Table 2).

Three quarters (73.6%) of the patients received more than one drug.

## **Discussion**

In the present study, we successfully performed an international collaborative survey of the phenotypes of children with Behçet's disease and uveitis. Although several diagnostic criteria are used to make the diagnosis of Behçet's disease in adults<sup>20,21</sup>, there are none in children.<sup>22</sup> This means that the epidemiology of pediatric Behçet's disease is difficult to evaluate because there is no general agreement about either the age of onset or the age of full diagnosis. Previous studies have shown that the proportion of patients in whom the onset of symptoms occurred under the age of 16 years varies.<sup>3,23,24</sup> A study of juvenile-onset Behçet's disease from France reported that the mean age of disease onset was 7.5 years old, but the mean age at which patients met the criteria for Behçet's disease was 11.6 years old.<sup>4</sup> Since the mean age of disease diagnosis in our study was 11.7 years old (Table 1), our present results from an international study confirm these previous findings.

We showed that the visual prognosis was better in juvenile-onset patients than in adult-onset subjects. More than 20% of eyes of Behçet's patients of all ages become legally blind as reported recently.<sup>1</sup> <sup>25</sup> In the present study, 93% of the juvenile patients had final visual acuity of 0.1 (20/200) or better in their better eyes (Table 1), and visual prognosis was significantly better among children than adults. However, this statistical result may not always mean that the ocular involvement in children is milder than adults. The visual prognosis of patients from East/South Asia was poor compared with other countries in all age groups, as we reported.<sup>1</sup> Also, the prevalence of East/South Asia was significantly lower than that of Middle East and European countries (Fig 1). Thus, only a few East/South Asian children, an unfavorable group, were included in the population of the present study. Furthermore, we did not have information on ocular co-morbidity (eg cataract, glaucoma, and/or macular degeneration) as a confounding factor, which might be expected to be more common in adults. We should take up one more point that cyclophosphamide was one of the most commonly used immunosuppressive agents shown in this study. Though it is true that this old drug is cheap and experienced well in many countries, it may not be recommended for children from its toxicity.

The prevalence of oral and skin lesions were almost the same between children and adults, but quite different for genital ulcers. This is consistent with a previous study surveyed in Israel<sup>6</sup>. There is one possibility that the frequency of genital ulcer might be lower in patients before puberty. Genital ulcers were reported from 30.9% of the patients whose disease had started before 10 years old. Though the frequency was lower than that of older children (42.7%), there was no statistical significance. The reason why genital ulcers were less frequently seen in children than in adults is still unclear. It may be one of the features of younger patients with Behcet's disease.

Our study may contain some sources of bias as given previously<sup>1</sup>. (1) We did not ask which criteria were used to include patients in the study. The criteria for Behcet's disease accepted for selection included Japanese Committee's<sup>21</sup>, International Study Group's<sup>20</sup>, and O'Duffy's criteria. The use of different standardized criteria may lead to misclassification when comparing the frequencies of systemic features. However, since most of the colleagues were members of International Committee of Behcet's disease as well as uveitis-specialists, we hope that the false positive rate of diagnosis may be quite low. Also, they had used the same one for inclusion of both juvenile and adult patients absolutely. (2) We also had only a limited response rate to the questionnaire from 25/132 eye centers. Therefore the response may not have been representative of all countries and ethnic groups, it is the second possible source of bias. (3) There may have been reporting bias as the population was taken from tertiary referral centres and the cases may have been more severe, as the third source of bias. (4) Access to uveitis clinic may be another source of bias. Healthcare system is different in different countries. There may be some regional problems relevant to pediatric age group. However, when it comes to Japan, children can seek immediate medical attention as adults. It may be not enough reason of low prevalence of juvenile-onset Behcet's disease in East Asia. Japanese pediatricians previously surveyed Behcet's disease among children, however they were able to collect the medical data of only 31 cases from 1,290 hospitals throughout the country<sup>26</sup>. It may be true that the prevalence of the patients without ocular symptoms is also low in Japan.

Although there were some sources of bias that may distort the results, the authors consider that a sufficient number of patients with a relatively uncommon type of disease were analyzed. The present results would provide an indication that the clinical features of juvenile-onset Behcet's disease with ocular

lesions do differ from adult-onset disease in some respects.

In conclusion, the frequency of Behçet's disease showed racial differences in children. Only a few children suffered from Behçet's disease in contrast to the high prevalence in adults among East and South Asian people. The clinical features of Behçet's disease with uveitis were different between adult-onset and juvenile-onset patients: the prevalence of genital ulcers was less in children than in adults.

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## Figure legends

Figure 1. Ethnic groups of patients with Behcet's disease

Middle Eastern, Caucasian, and East/South Asian people were 3 major ethnic groups of Behcet's disease among adults, however, only a few East/South Asian patients suffered from the disease in childhood ( $p < 0.01$ ).

Figure 2. Major symptoms of Behcet disease

Frequency of genital ulcers was significantly lower in children than in adults ( $p < 0.01$ ).

Table 1. Summary of juvenile-onset Behcet's disease in eye centers (N=135)

Boys	65.5 %
HLA-B51	68.6 %
Age of disease onset	11.7 years old
Mean follow-up period	13.5 years
<hr/>	
CAPSII*/panuveitis	93.9 %
Bilaterality	83.6 %
Recurrence of ocular inflammation	96.3 %
Poor visual prognosis (<20/200, better eyes)	7.4 %

\*CAPSII: combined anterior and posterior segment intraocular inflammation

Table 2. Initial systemic therapies for children\*

Corticosteroids	42.2 %
Cyclophosphamide	20.0 %
Methotrexate	18.5 %
Colchicine	13.3 %
Azathioprine	8.9 %
Cyclosporin	8.1 %
Interferon-alpha	1.5 %

\*Three quarters of patients received two or more drugs as their initial therapies

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