Familial aggregation of Behçet’s disease in Turkey

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Abstract

Objective—Familial aggregation of Behçet’s disease has been reported previously. The current study aimed at investigating the sibling recurrence risk ratio ($\lambda_s$) for Behçet’s disease, which is of value in the estimation of the magnitude of genetic factors in the pathogenesis of Behçet’s disease.

Methods—170 consecutive unrelated index cases (98 male, 72 female) were interviewed with a detailed questionnaire to ascertain their family trees and the manifestations of Behçet’s disease in their relatives. Subsequently, the immediately older sibling, or if an older sibling was not available, the immediately younger sibling, was selected as the second sibling for the evaluation. These siblings were contacted by telephone, and all subjects with recurrent oral ulcers were invited for examination.

Results—31 of the 170 index cases had 51 relatives fulfilling the International Study Group criteria. Among 166 second siblings, seven had Behçet’s disease (six male, one female) and 22 siblings (eight male, 14 female) with recurrent oral ulcers were identified. Sibling recurrence rate—defined as the ratio of the risk of being affected among the siblings of patients and the risk of being affected in the general population—was found to be 4.2%, which gives a $\lambda_s$ value for Behçet’s disease of between 11.4 and 52.5 in Turkey.

Conclusions—A high $\lambda_s$ value supports a strong genetic background for Behçet’s disease which will be helpful in designing genetic linkage studies.

Behçet’s disease is a systemic vasculitic disease characterised mainly by recurrent oral and genital aphthous ulcers, uveitis, and skin findings. The cause of Behçet’s disease is not definitely known, but various immunological abnormalities induced by particular microbial agents or other environmental factors in genetically susceptible subjects have been suggested.¹

A peculiar geographical distribution, association with a class I HLA antigen, and a familial aggregation have been regarded as evidence supporting a genetic influence on the pathogenesis of Behçet’s disease. Although there are reports of patients with Behçet’s disease from all over the world, its prevalence is particularly high in a region extending from the Mediterranean basin to Japan along the Silk Route. Behçet’s disease is strongly associated with HLA-B51 and it has been confirmed in different ethnic groups.² ³

Most cases of Behçet’s disease are sporadic and the parents of patients are unaffected, but a familial aggregation of Behçet’s disease has been reported previously⁴–¹²; a positive family history for Behçet’s disease has been included in some of the previous diagnostic criteria.¹³ A higher incidence of familial aggregation was noted in juvenile patients with Behçet’s disease.¹⁴ In addition to the patients with full blown Behçet’s disease, an increased prevalence of isolated manifestations of the disease, such as recurrent oral ulcers, genital ulcers, or a positive skin pathergy test, has also been found among first degree relatives of the patients.¹⁵–¹⁷ Analysis of multicafe families did not show any particular Mendelian inheritance pattern,¹⁸ but a genetic anticipation, in the form of earlier disease onset in the children of affected parents, was found in some families.¹⁹

Sibling recurrence risk ratio ($\lambda_s$) is widely used to demonstrate familial aggregation, and is defined as the ratio of the risk of being affected among the siblings of patients and the risk of being affected in the general population. A significant deviation from unity suggests familial aggregation, and it is a good way of quantifying the genetic effects without knowing the exact mode of inheritance of the disease studied.¹⁷

This study aimed at investigating the $\lambda_s$ value for the estimation of the magnitude of genetic factors in the pathogenesis of Behçet’s disease in a tertiary referral centre in Turkey.

Methods

The study group consisted of 170 unrelated consecutive patients followed up at the Behçet’s disease outpatient clinic of the Division of Rheumatology, Department of Internal Medicine, Istanbul School of Medicine. All index patients fulfilled the criteria of the International Study Group (ISG) for the classification of Behçet’s disease.²² Initially (first step), index cases were interviewed with a detailed questionnaire including a pedigree drawing to identify (a) possible cases of Behçet’s disease among their relatives and (b) siblings with recurrent oral ulcers or other manifestations of Behçet’s disease.

Subsequently (second step), we used the method described by Sun-Wei Guo to calculate the recurrence rate in siblings.²³ To avoid an ascertainment bias we defined the immediately older sibling, or if an older sibling was not available, the immediately younger sibling to be ascertained as the second sibling of the index case for the purposes of evaluation. These siblings were interviewed by telephone about their symptoms and signs of Behçet’s disease.
A standard questionnaire was used to determine the presence of (a) recurrent oral ulcers (recurrent at least three times in one 12 month period), (b) recurrent genital ulcers, (c) eye disease causing blurred vision and a red eye, or diagnosed with uveitis by a doctor, and (d) skin lesions, such as painful red nodules in the legs or frequent spots or acne-like lesions over the arms and legs. All subjects with recurrent oral ulcers were invited for further examination.

To calculate $\lambda$ we used the data from three previous studies giving a point prevalence rate of 8–37/10,000 for Behçet's disease in Turkey. One of these studies was conducted in the total population, aged >10 years, of nine villages (n=4940) near to Istanbul (northeastern Turkey). The second study was carried out in the small town of Camas, in northeastern Anatolia; 56% of the total population aged 10 years and older (n=5131) were included in the survey. Both studies tried to ascertain subjects with recurrent oral ulcers by house visits, and then these subjects were investigated for other manifestations of Behçet's disease. The first survey identified four patients (8/10,000, 95% confidence interval (CI) 2 to 14/10,000) and the second survey identified 19 patients (37/10,000, 95% CI 20 to 54/10,000) with Behçet's disease according to the O'Duffy criteria. A recent survey of a population aged >10 years of a small town in central Turkey (n=17,256) used a similar approach and identified 16 patients with Behçet's disease meeting ISG criteria (9/10,000, 95% CI 4.5 to 13.5/10,000) and six subjects with recurrent oral ulcers and other manifestations related to Behçet's disease who did not fulfill the classification criteria.

Results

FIRST STEP

Table 1 gives the characteristics of the 170 index patients. Thirty one of the index patients (18%) had 51 family members with Behçet's disease. Four of the 12 patients with juvenile onset disease (33%) gave a positive family history compared with 27 patients with adult onset disease (17%) (odds ratio 2.4, 95% CI 0.7 to 8.7, $p=0.2$). Forty four of the 51 familial cases were already registered in our Behçet's disease clinic. Medical records were obtained from their attending doctors for the other seven patients to confirm the diagnosis; two of the seven patients had died.

The pedigrees of the index patients disclosed a total of 675 siblings (age range 7–69) with an average sibship size of 3.9. Twenty four of the 51 cases of familial Behçet's disease (19 male, five female) identified by questionnaire were siblings of the index cases. The index patients also described recurrent oral ulcers in 76 of their siblings (37 male, 39 female).

Five of the reported patients with Behçet's disease were parents, five were children, 11 were cousins, four were uncles, and two were aunts of index patients. All the four index cases with affected children (three daughters, two sons) were female. Two mother-daughter, two father-son, and one mother-son pair were found in five patients with an affected parent.

SECOND STEP

When we specified the second sibling for the evaluation as described above, we ascertained 117 older siblings, and 49 younger siblings. Four index cases (three male, one female) were eliminated from this calculation because they had no siblings. The mean (SD) age of the remaining 166 index patients was 38.8 (10.4) (range 16–66) and their mean age at the onset of Behçet's disease was 27.9 (8.6) (range 9–48). Index patients gave a positive history of recurrent oral ulcers for 26 siblings, four of whom were already diagnosed with Behçet's disease.

All 166 siblings were contacted by telephone. The mean (SD) age of the siblings was 39.6 (10.4) (range 14–68). A history of recurrent oral ulcers was confirmed in all 26 siblings reported by index cases and an additional three siblings—that is, a total of 29 siblings with recurrent oral ulcers. Eight siblings described additional manifestations related to Behçet's disease, and all of them responded to our invitation for further investigation. Four siblings were already registered in our Behçet's disease clinic and three additional cases were identified meeting the ISG criteria for the diagnosis of Behçet's disease (table 2). All but one of these seven patients were siblings of the index cases with an age at disease onset $>16$. Six of the patients were male, but the male:female ratio was not statistically different from that of index cases ($p=0.3$). The eighth patient could not be classified as having Behçet's disease. Although she had a history of arthritis, folliculitis, and thrombophlebitis, her skin pathergy test was negative.

Nine of the remaining 21 siblings (eight male, 13 female) with recurrent oral ulcers only, responded to our invitation. A skin pathergy test was found to be positive in two female siblings, and no manifestation of Behçet's disease other than recurrent oral ulcers was found in seven (two male, five female).

Sibling recurrence rate was calculated to be 4.2% for Behçet's disease (95% CI 1.2 to 7.2%), and 13.3% for recurrent oral ulcers (95% CI 8.1 to 18.5%), and the $\lambda$ value was

Table 1 Characteristics of patients with Behçet's disease

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<th>Total No (%)</th>
<th>Male No (%)</th>
<th>Female No (%)</th>
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<tr>
<td>n</td>
<td>170</td>
<td>98 (57)</td>
<td>72 (43)</td>
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<td>Age (mean (SD), range)</td>
<td>38.9 (10.4), (16–66)</td>
<td>38.7 (10.4), (16–66)</td>
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<tr>
<td>Age at onset (mean (SD), range)</td>
<td>27.8 (8.6), (9–48)</td>
<td>27.3 (8.4), (9–48)</td>
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Table 2 Patients with Behçet's disease (BD) and subjects with recurrent oral ulcers (ROU) identified among the siblings of the index cases using the method described by Guo'7 (step 2)

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<th>Total No (%)</th>
<th>Male No (%)</th>
<th>Female No (%)</th>
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<tbody>
<tr>
<td>Siblings</td>
<td>166</td>
<td>82 (49)</td>
<td>84 (51)</td>
</tr>
<tr>
<td>Patients with BD</td>
<td>7 (4)</td>
<td>6 (86)</td>
<td>1 (14)</td>
</tr>
<tr>
<td>Subjects with ROU</td>
<td>22 (13)</td>
<td>8 (36)</td>
<td>14 (64)</td>
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found to be 11.4–52.5 for Behçet’s disease in Turkey.

**Discussion**

Although an increased risk of Behçet’s disease among the relatives of patients with Behçet’s disease has long been known, these data mainly rely on case reports or the frequency of familial patients in different series. A positive family history was noted among 2–3% of Japanese patients and 8–34% of the Turkish and Middle Eastern patients with Behçet’s disease.2 11 13 14 15 The varying prevalence of familial aggregation in Behçet’s disease might be explained, in part, by different methods of data collection. An increase in the frequency of cases of familial Behçet’s disease, from 3.6% in a retrospective registry analysis to 8% in a prospective analysis of 62 families, was reported from a Behçet’s disease centre in Turkey.10 11 However, description of familial aggregation with the prevalence of familial cases in a group of patients open to many biases, and recurrence risk in relatives, especially in siblings ($\lambda_s$), is a preferable way of recording and quantifying familial aggregation.

We found only two studies giving data about the recurrence risks of Behçet’s disease in relatives of patients. MacGregor et al reported the sibling recurrence rate of Behçet’s disease as 2.1% in a nationwide questionnaire based survey conducted in the UK.21 Their study group comprised mainly white subjects (94%), but no other data were given about the ethnic background of the patients. When the low prevalence rate of Behçet’s disease in the UK is taken into account, a much higher $\lambda_s$ value would be expected than in our study. A recent study by Koné-Paut et al reported that a positive family history was greater in juvenile patients with Behçet’s disease (12.3%) than in adult patients (2.2%).12 The study group consisted of patients with Behçet’s disease from France, Turkey, Israel, and other Middle Eastern countries with at least three different ethnic origins. Authors investigated the risk of Behçet’s disease among the relatives of 45 out of 106 paediatric cases and sibling recurrence risk for Behçet’s disease was found to be 8%. However, neither the ascertainment method of these families from all paediatric cases nor the ethnic origin of the study group was described in this study, which makes drawing a conclusion difficult.

We used the data from three previous studies on the point prevalence of Behçet’s disease in Turkey for the estimation of $\lambda_s$. We think that because the same investigation method and the same classification criteria were used in the first two studies that the variation of the prevalence rates (8–37/10 000) may reflect regional differences of the risk of Behçet’s disease in Turkey. The last survey which was conducted in a larger population using the ISG criteria found a prevalence rate within this range. As our study was conducted in a specialised Behçet’s disease clinic and the study group included patients with Behçet’s disease from all regions of Turkey (data not given), we preferred to use both prevalence rates for the estimation of $\lambda_s$ within a range.

An excess of male patients among siblings may partially be explained by a less severe disease course in female patients. Three female siblings with recurrent oral ulcers and additional findings (one with arthritis, folliculitis, and thrombophlebitis, and two with a positive skin pathergy test) could not be classified as Behçet’s disease during the study. However, it was possible to diagnose these subjects with Behçet’s disease using some of the previous criteria.13 The prevalence of recurrent oral ulcers in the siblings did not differ from the prevalence in a healthy Turkish population.18 However, it was previously suggested that oral and genital ulcers in first degree relatives of patients might indicate the presence of Behçet’s disease.16 Inclusion of such cases as Behçet’s disease did not increase the disease heterogeneity significantly, and an autosomal recessive model of inheritance could not be excluded either.16 Follow up data will be helpful to clarify the course of the family members with recurrent oral ulcers or other manifestations related to Behçet’s disease who do not fulfil the ISG criteria.

This study showed a high $\lambda_s$ value compared with those of other genetically complex diseases—for example, $\lambda_s$ of 6 for rheumatoid arthritis, 15 for type I diabetes mellitus, and 46 for ankylosing spondylitis.22 23 Shared environmental factors within families can contribute to familial clustering. However, environmental factors alone are unlikely to account for such a high $\lambda_s$ value.16 These findings provide strong evidence for a hereditary background in Behçet’s disease, and warrant molecular genetic studies, such as whole genome screening for the identification of susceptibility loci. Age of onset and ethnic background of patients will be helpful in designing such studies. Increased prevalence of familial aggregation in juvenile patients with Behçet’s disease may define a subgroup of patients with stronger genetic effects,12 and the frequencies of the putative susceptibility gene(s) within a population and sibling sizes may explain the varying prevalence of familial Behçet’s disease in different populations.

In conclusion, familial aggregation and a high $\lambda_s$ value up to 52.5 support a strong genetic background for Behçet’s disease. Siblings and other relatives of patients with Behçet’s disease with isolated recurrent oral ulcers need to be investigated further to determine whether these subjects are low-penetrant carriers of the disease susceptibility genes, or not.

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