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Uveitis in sibling pairs with juvenile idiopathic arthritis

H. Säilä1, K. Kotaniemi1,2, A. Savolainen1, H. Kautiainen1, M. Leirisalo-Repo2 and K. Aho3

1Rheumatism Foundation Hospital, Heinola, 2Helsinki University Hospital, Helsinki and 3National Public Health Institute, Helsinki, Finland

Abstract

Objective. To ascertain the occurrence and characteristics of uveitis in sibling pairs affected with juvenile idiopathic arthritis (JIA).

Methods. The sibling series comprised 80 JIA patients from 37 families with two or three JIA children, seen at the paediatric department of the Rheumatism Foundation Hospital in Heinola, Finland. An ophthalmologist examined the children for uveitis two to four times a year and the course of the condition was recorded during the follow-up.

Results. Uveitis was diagnosed in 21 of the 80 patients (26%). Three pairs (3.4 pairs expected) were concordant for the presence of asymptomatic uveitis. Two patients with enthesis-related arthritis had acute unilateral uveitis. Among the remaining cases, uveitis was chronic and continuously active at the end of follow-up in 13 instances, but in spite of this only one patient had impaired vision. HLA allele B27 occurred more frequently in patients with uveitis than in those without uveitis (52 vs 30%, P = 0.073) and all six subjects in the pairs concordant for chronic uveitis carried this allele.

Conclusions. The observed concordance rate for uveitis did not differ from that expected. Although the uveitis was chronic in most instances, its course was usually mild.

Key words: Uveitis, Juvenile idiopathic arthritis, Siblings.

Juvenile idiopathic arthritis (JIA) comprises a heterogeneous group of chronic arthropathies of childhood [1]. Family and twin studies have provided some evidence for a genetic component in its aetiology [2, 3] and accumulating data indicate significant associations between particular HLA alleles and certain forms of JIA [3, 4].

Uveitis is the most frequent extra-articular manifestation of childhood rheumatic diseases. It has been reported in 10–20% of patients with JIA, although lower and higher figures have been published [5–7]. One form, tending to occur in older children, especially in boys, is typically acute HLA B27-associated anterior uveitis. Another form, frequently associated with antinuclear antibody (ANA) positivity and running a chronic, asymptomatic course, occurs most commonly in persistent pauciarticular, especially in girls with early-onset disease. This form is also frequently seen in patients with rheumatoid factor-negative polyarthritis, whereas it seldom occurs in the systemic form of the disease. Uveitis develops at a variable interval from the onset of arthritis. It is usually asymptomatic and often bilateral.

Rosenberg and Ross [8] reported a sibling pair with pauciarticular JIA concordant for the presence of chronic uveitis. Subsequently, two sibling series have provided information on the presence or absence of uveitis in patients with JIA [9, 10]. At the Rheumatism Foundation Hospital we have recorded 37 families with at least two siblings with JIA. We report here the occurrence and characteristics of uveitis in these patients.

Patients and methods

The Rheumatism Foundation Hospital is a semi-private clinic, which receives JIA patients from university hospitals and other central hospitals in Finland, and directly from primary care, especially if the patient lives in a region nearby. The hospital provides in- and outpatient care. Some of the patients come to the hospital only once or twice, but severe cases are constantly monitored.

In the present study, JIA patients (when appropriate) and their parents were systematically asked about their
family history of rheumatic diseases. The study period covered about 15 yr and the total number of JIA patients among whom the familial cases were found was estimated to be 2000. Altogether, 37 families with two or three affected siblings were identified; the total number of patients with JIA was 80. All satisfied the Durban criteria for the disease [1]. Except for five patients, all the other patients had been treated at the Rheumatism Foundation Hospital.

All the patients had been examined at least once, usually two to four times a year, by an ophthalmologist at central hospitals or at the Rheumatism Foundation Hospital. The examination involved detection of best corrected visual acuity, ocular pressure (when possible), biomicroscopy and examination of the fundus of the eye. The type of uveitis was determined and complications of uveitis were sought. Patients with uveitis were checked at intervals of 1–3 months.

ANA were determined using indirect immunofluorescence. Details of the technique varied during the study period. HLA B27 typing was carried out by direct immunofluorescence on separated lymphocytes/thrombocytes, using fluorescein isothiocyanate-conjugated monoclonal mouse antibody.

Statistical comparisons were carried out using the \( \chi^2 \) test, Fisher’s exact test and Student’s \( t \)-test.

**Results**

Uveitis was a feature of JIA in 21 (26%) of the 80 patients. Six of the 37 families had three affected sibs (each triplet representing three sib pairs). Thus, the total number of sib pairs was 49. Three of the pairs were concordant for the presence of uveitis, 29 pairs were concordant for its absence and 17 were discordant. Computing from these figures, the expected number of pairs concordant for uveitis would be 3.4.

The main characteristics of the 21 patients with uveitis are shown in Table 1. There were 11 boys and 10 girls in the series. Of the three pairs concordant for the presence of chronic uveitis, one pair was concordant and two pairs were discordant for gender. In these three pairs, the asymptomatic uveitis was ongoing in one sibling and resolved in the other. One of the three pairs was concordant for the presence of ANA and two pairs were discordant. All six subjects were positive for HLA B27.

Both of the two boys with acute uveitis initially had a diagnosis of oligoarthritis, fulfilled the Durban criteria for enthesitis-related arthritis and had had an episode of acute unilateral uveitis, in both cases preceding the onset of joint symptoms by 9 months.

In the remaining 19 patients the onset of uveitis was asymptomatic and insidious. In two of them the uveitis was of short duration (< 3 months). These two patients were positive for the presence of ANA but negative for the presence of HLA B27. In five patients out of 19 (the two enthesitis-related cases excluded), asymptomatic uveitis was found before (two cases) or at the time of diagnosis (three cases) of JIA. In 13 cases, uveitis was still active at the end of follow-up.

The median duration of arthritis before the onset of eye signs was 1.2 yr. In all patients with uveitis the

<table>
<thead>
<tr>
<th>Type of uveitis</th>
<th>Sex</th>
<th>Onset type of JIA</th>
<th>Course type of JIA</th>
<th>Age at diagnosis of JIA (yr)</th>
<th>Interval to uveitis (yr)</th>
<th>Eye affected</th>
<th>ANA</th>
<th>HLA B27</th>
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\(^{a}\)Interval between the onset of arthritis and the appearance of uveitis; a negative value indicates that the uveitis was detected before the diagnosis of arthritis.
eye disease appeared within 5 yr from the onset of arthritis. Thirteen patients (62%) had bilateral uveitis. A complicating cataract was detected in eight patients and secondary (bilateral) glaucoma in one patient; one patient had cystoid macular oedema. The final visual acuity was normal (>20/40) in all children except the patient with secondary glaucoma; the sight of the right eye was impaired to the perception of light.

The demographic and clinical data in Table 1 reveal no significant differences between HLA B27-positive and -negative uveitis cases after the exclusion of the two patients with enthesitis-related arthritis.

Table 2 compares the patients with and without uveitis. There were more boys in the group with uveitis, and the frequencies of ANA-positive and HLA B27-positive cases were also higher in this group. However, the differences were not statistically significant. After exclusion of the two enthesitis-related cases, the mean age at diagnosis of JIA was significantly lower in patients with uveitis.

Discussion

In the present study, based on 49 sibling pairs, three pairs were concordant for the presence of uveitis, the expected number being 3.4. The series reported by Clemens et al. [9] consisted of 12 sibling pairs. Four of them were concordant for the presence of uveitis, and on the basis of data given in their paper the expected number was 2.5. Moroldo et al. [10] reported on a total of 71 sibling pairs. Three pairs were concordant, and the expected number was 1.3. Taken together, the data gathered here lend little support for the concept of an appreciably heightened sibling recurrence ratio in the aetiology of uveitis. Nonetheless, the findings do not rule out a modest association with some genetic marker (genotype relative risk), provided that its frequency is fairly high. This is because the frequency of a common genetic marker is not appreciably higher among siblings of patients with uveitis than in the general population here, JIA patients without uveitis and, accordingly, a modest genotype relative risk adds little to the sibling recurrence ratio [20].

About two-thirds of Finnish patients with JIA are seen at the Rheumatism Foundation Hospital. The figure is somewhat lower for patients living in northern Finland and in the Helsinki area and somewhat higher (about 75%) for patients living in the central parts of the country. Some patients are seen only once or twice, but severe cases usually remain in the care of our hospital. Our sibling series is thus to some degree selected. Selection bias is also a possibility in the two previous studies. The series published by Clemens et al. [9] was recruited from patients admitted to Juvenile Rheumatism Units at Taplow, UK and Garmisch-Partenkirchen, Germany. Some pairs had been referred specifically because both members were affected. The series reported by Moroldo et al. [10] was recruited by means of a multiple advertising campaign directed to physicians in the USA who were likely to be caring for patients with JIA. Quite obviously, both series were selected, but perhaps according to different characteristics.

In the present series, the occurrence of uveitis (26%) was higher than in our earlier, population-based series (16%) [11] from Finland. However, the difference in occurrence between these groups was not statistically significant. In a large series recently published in the USA, uveitis was found in only 9% (74/769) of patients [12]. This lower rate of occurrence in the USA is unlikely to have been due to patient selection; it probably reflects inherent differences in the presentation of uveitis.

The uveitis in our patients was in most instances asymptomatic and chronic, but its course was usually mild. Only one patient had impaired vision at the end of follow-up. For some reason there was no excess of girls.

The prevalence of the HLA allele B27 in the Finnish population is 14.5%, which is about twice as high as in most other European populations. Somewhat elevated frequencies of HLA B27 compared with the general population have been reported from other countries in a number of series of patients with JIA (cases with enthesitis-related arthritis excluded), although the differences have seldom reached statistical significance due to the low prevalence of HLA B27 [13–15]. In unselected Finnish patients with JIA, the prevalence has been about 30% [16]. In the study described here, the HLA B27 allele occurred in 52% of patients with and in 30%
of those without uveitis. Excluding the two cases with enthesitis-related arthritis, the occurrence of HLA B27 was 47% among patients with uveitis. Yet the possibility cannot be wholly excluded that some of the B27-positive cases will later develop spondyloarthropathy. It is perhaps of note that all the siblings concordant for the presence of asymptomatic uveitis were HLA B27-positive.

Histocompatibility allele profiles have been studied in uveitis associated with early-onset oligoarthritis. In two American series, the HLA allele DRB1*1104 (a split of HLA DR 5) occurred significantly more frequently in patients with chronic uveitis than in those not suffering from the disorder [17, 18]. No corresponding difference emerged in a patient series collected in Central Europe [19]. In all three series, the frequency of the allele DRB1*01 was reduced. Data on HLA allele distributions in chronic uveitis associated with other forms of JIA have not been published, probably due to the small number of cases available.

JIA clearly comprises a heterogeneous group of disease conditions, each of which is likely to have distinct genetic risk factors. The position of chronic uveitis in the classification scheme of JIA is not clear; it may represent a separate entity, irrespective of the type of arthritis accompanying its course.

References