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Juvenile idiopathic arthritis in multicase families

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ABSTRACT

Objective

To characterize juvenile idiopathic arthritis (JIA) patients from multicase families.

Methods

The study series comprised 80 affected siblings belonging to 37 families. Comparisons were made with a population-based series of JIA patients from Finland and with a sibling series from the United States.

Results

The distribution of cases according to onset type was similar in the sibling and population-based series. The age at diagnosis was significantly lower in the sibling series (4.8 years vs 7.4 years; $p < 0.001$). There was more intra-pair similarity in onset and course types in the United States series compared to the Finnish series and the proportion of girls was higher in the former.

Conclusion

The only significant difference between familial and sporadic cases with JIA is an earlier onset of disease in familial cases. There is no essential difference in clinical features of the disease between patients in the multicase and sporadic groups. Differences between the Finnish and US series may be due to selection bias in the latter.

Introduction

The occurrence of multiple cases of a disease in families can have different bases: a) chance alone, b) shared environment, c) accumulation in the multicase families of the relevant susceptibility genes, and d) different pathogenetic mechanisms for familial versus sporadic disease. According to one study (1) 40% of families with multiple cases of adult rheumatoid arthritis could be explained by chance aggregation. Findings in respect of the role of genetic determinants in familial versus sporadic cases of rheumatoid arthritis have been somewhat contradictory; there seems, however, to be no doubt that an HLA marker, the shared epitope, plays an important role in determining disease concordance in monozygotic twins (2).

Two sibling series have been published on JIA. One of them, collected from England and Germany, was focused on HLA haplotype sharing and provided very little clinical information on the patients (3). The other was collected by means of a multiple advertising campaign directed to United States physicians likely to care for patients with JIA (4).

We here have collected a sibling series among 37 families, each with 2 or 3 affected children, from among a patient clientele covering about two-thirds of Finnish JIA patients. In this study we compared features of the sibling series with a population-based series of patients with JIA previously published in Finland (5, 6). In addition, some comparisons were made with a United States sibling series (4).

Patients and methods

The Rheumatism Foundation Hospital is a semi-private clinic which receives patients from university and other central hospitals, and directly from primary care, especially if the patient lives in a region near the hospital. The hospital provides in-and out-patient care in conservative rheumatology, orthopedics and rehabilitation for children and adults. Some patients attend the hospital only once or twice, but severe cases are constantly monitored.

During the last 15 years, patients with JIA (when appropriate) and their parents have been systematically asked about their family history of rheumatic diseases. The total number of patients treated at the pediatric department was 2,312. Of these, about 10% did not have JIA and some cases might have been missed during vacations. It can thus be estimated that the population of JIA cases from which the recorded multicase families derived amounted to about 2,000.

Altogether 31 families with 2 affected siblings and 6 families with 3 affected siblings were identified; the total number of JIA patients was 80. The number of affected sib pairs was 49. The series included two sets of monozygous twins (one of them verified by blood testing). In 16 families all of the children were affected by JIA. The remaining 21 families had 1-3 healthy children (median

Table I. Comparison of patients with juvenile idiopathic arthritis in the sibling and population-based series in Finland.

	Sibling series		Population series (refs. 5, 6)		P-value
Number of patients	80		114		
Boys	31	(39%)	34	(30%)	0.20
Onset type					0.54
Pauciarticular	55	(69%)	80	(70%)	
Polyarticular	20*	(25%)	21†	(18%)	
Enthesitis-related	2	(2%)	6	(5%)	
Systemic	3	(4%)	7	(6%)	
Uveitis detected	21	(26%)	18	(16%)	0.074
Positive for ANA	45	(56%)	49‡	(43%)	0.069
ESR at diagnosis (mean, SD)	34	(28)	32	(25)	0.76
Age at diagnosis, years (mean, SD)	4.8	(3.7)	7.4	(4.6)	< 0.001

*One patient was seropositive; †3 patients were seropositive; ‡information on one patient was lacking.

Table II. Comparison of the Finnish and the United States sibling series.

	Finnish series		United States series (ref. 4)		P-value
Number of patients	80		133		
Boys	31	(39%)	21	(16%)	< 0.001
Onset type					0.32
Pauciarticular	57*	(71%)	81	(61%)	
Polyarticular	20	(25%)	45	(34%)	
Systemic	3	(4%)	7	(5%)	
Mean age at diagnosis†/onset‡ (yrs)	4.8		5.3		

*Includes patients with enthesitis-related arthritis; †Finnish series: age at diagnosis; ‡United States series: age at onset.

Table III. Concordance for onset type, course type and ANA positivity in Finnish and United States series.

	Finnish series 49 pairs obs/exp 95% CI*		United States series (refer 4) 71 pairs obs/exp 95% CI*	
Onset type	1.00	(0.67-1.45)	1.55	(1.17-2.02)
Course type	1.26	(1.85-1.80)	1.61	(1.22-2.10)
ANA-positivity	1.36	(0.84-2.08)	1.35†	(0.85-2.10)

*CI = confidence interval; †8 patients were missing data for the ANA studies.

1) in addition to those affected, except for one large family with 16 healthy children.

The relevant clinical and laboratory data on the patients were recorded during the first 6 months of the disease (onset type) and during later follow-up (course type). During the follow-up, all 80 patients met the Durban criteria for JIA (7). Except for five patients all had been treated at the Rheumatism Foundation Hospital.

Statistical comparisons were made using the chi-squared test, Fisher's exact test (Freeman-Halton), and the Mann-Whitney test.

Results

Table I compares the sibling and the population-based series. Distributions of cases according to onset type and erythrocyte sedimentation rate at diagnosis were similar in both. More specifically, 30% of the patients in both series had only one joint involved at diagnosis. The proportion of boys was slightly higher and uveitis and ANA-positivity tended to be somewhat more frequent in the sibling series.The age at diagnosis was significantly lower in the sibling series ($p < 0.001$).

In the American study (4) enthesitis-related arthritis had not been separated into a group of its own (the new classification of JIA was not yet in use). For comparative purposes (Table II), enthesitis-related arthritis cases were included in our series in the oligoarthritis group. The onset type in our study was somewhat more frequently pauciarticular and less frequently polyarticular; these differences were not, however, statistically significant. The same proportion of all patients in both series (16% versus 18%) had extended oligoarthritis.

The mean age at onset in the United States series was 5.3 years; that at diagnosis in our series was 4.8 years. The proportion of girls in the United States series was significantly higher than in ours.

In our sibling series 49% of the pairs were concordant for sex; most of them (71%) were pairs of females; 57% were concordant for onset type and 89% of these were pauciarticular pairs. Onset type differed from course type in 20% of individual patients. Course concordance was 61%, 53% of these being pauciarticular and 47% polyarticular pairs. Among the 6 families with 3 affected sibs, 2 of the triplets were concordant for onset type and 3 triplets were concordant for course type. Two sets of twins were concordant for course type but the onset type was unexpectedly different in a monozygous twin pair, as described previously by us (8).

The United States sibling pairs were markedly more often concordant for both onset type and course type than

would be expected on the basis of the distribution of the types [computed from figures given in the paper by Moroldo *et al.* (4)]. In our series there was no difference with regard to onset type and a small difference with regard to course type (Table III). In both series concordance for ANA-positivity was somewhat higher than expected.

Discussion

The prevalence of JIA (active and inactive disease) in the pediatric population in Finland is estimated to be 80 per 100,000 (9). As discussed elsewhere, the finding of 37 families with 80 affected siblings in a patient population of 2,000 points out that there is a fairly substantial genetic component in the etiology of JIA (10) although the role of shared environment cannot wholly be excluded.

We first compared our sibling series with a population-based series of patients with JIA previously published in Finland (5, 6). Distributions of cases according to onset type and erythrocyte sedimentation rate at diagnosis were similar in both series. The only significant difference was the lower age at diagnosis in the sibling series. This is in agreement with the tendency noted in many diseases for familial cases to have an earlier age of onset than sporadic cases. In adult rheumatoid arthritis some, but not all, studies have shown this (1,11).

The second comparison was between our sibling series and series recently published in the United States (4). Some differences emerged. First, the frequency of oligoarthritis tended to be higher and that of polyarthritis lower in our series. The reason for this is either that the U.S. series was biased toward clinical cases with more severe disease, or that the patient clientele in Finland differs to some degree from that in the U.S. Second, there was more intra-pair similarity in the onset and course types among the U.S. patients than here. A possible explanation is a selection bias toward cases resembling each other in the United States series.

Third, the proportion of girls was higher in the United States series. This may be a matter of chance and selection bias. Nevertheless, the possibility cannot be wholly excluded of some underlying difference in the genetic basis between Finnish and American patients. We conclude that siblings with JIA have an earlier age of onset than population-based cases; otherwise, the clinical expressions of familial and sporadic cases of JIA are very much alike.

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