Occurrence of chronic inflammatory rheumatic diseases among parents of multiple offspring affected by juvenile idiopathic arthritis

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ABSTRACT

Objective. *The rarity of reports on extended multiplex families points out that the genetic component in juvenile idiopathic arthritis (JIA) might not be particularly strong. Our objective was to determine the frequency of chronic inflammatory rheumatic diseases among the parents who had two or more offspring affected by JIA.*

Methods. *During the last 17 years patients with JIA treated at the Rheumatism Foundation Hospital in Heinola and their parents have been systematically asked about the familial occurrence of rheumatic diseases. A total of 45 families with more than one sibling affected by JIA were found among about 2,300 JIA cases. In these "multicase families", 9 parents from 8 families also had a diagnosis of chronic inflammatory rheumatic disease. Their case histories were studied.*

Results. *Four of the parents had had JIA (one subsequently developed ankylosing spondylitis), and 4 had rheumatoid factor-negative chronic arthritis (one had also had chronic iritis since the age of 10, resembling that seen in JIA). Three of them had features of JIA and only one met the classification criteria for rheumatoid arthritis. One had ankylosing spondylitis.*

Conclusions. *Since the expected number of JIA cases among the 90 parents was about 0.2, there was drastic increase in JIA frequency among the parents in families with multiple offspring also affected by JIA. These results suggest that JIA susceptibility genes may likely be clustered in these families.*

Introduction

Genetic factors undoubtedly play a role in the aetiology of at least in some forms of juvenile idiopathic arthritis (JIA). Yet it is commonly believed that the risk to the sibling of a patient with JIA is not particularly strong, as shown by the rarity of reported extended multiplex families affected with JIA (1).

Chronic inflammatory rheumatic diseases do seem to cluster among the relatives of patients with JIA, however. Ansell *et al.* (2) reported a four-fold increase in the prevalence of erosive arthritis in female relatives and a three-fold increase in the prevalence of spondyloarthropathies in male relatives of JIA patients compared to a control group. Hertzberger-ten Cate and Dijkmans (3) found an increased prevalence of spondyloarthropathies among the parents of JIA patients with early-onset oligoarthritis compared to the reported population prevalence.

One reason for the occurrence in families of multiple cases of a complex disease such as JIA might be the accumulation of susceptibility genes. We collected a series of multi-case JIA families ascertained through a population-based series of JIA cases from Finland. Our earlier data provided evidence that the genetic component in JIA is higher than previously believed (4), and certainly higher than that in adult-onset rheumatoid arthritis. The aim of this report was to determine the frequency of chronic inflammatory rheumatic diseases among the parents who had two or more offspring affected with JIA.

Patients and methods

During the last 17 years patients with JIA (when possible) treated at the Rheumatism Foundation Hospital in Heinola and their parents have been systematically asked about the familial occurrence of rheumatic diseases. A total of 45 families with more than one sibling affected by JIA satisfying the Durban criteria (5) were found among about 2,300 JIA cases. These 45 "multicase JIA families" formed the basic study group.

Information on the rheumatic diseases of the parents in these multiplex JIA families was collected from the parents themselves and from the healthcare system. A total of 9 parents from 8 families were found to have a chronic rheumatic disease entitling them to specially reimbursed medication for theur condition. Eligibility for such approval in Finland requires a comprehensive medical certificate written by the attending specialist physician and approved by an expert adviser on behalf of the sickness insurance scheme. The certificates are not keyed to any specific criteria but are written to provide evidence that a subject has a specified dis-

ease and needs drug treatment for it (6). Conventional serological HLA typing used in the beginning of the study was replaced by the polymerase chain reaction with sequence specific primers (Dynal® Allset™) and sequence based typing (Visible Genetics®, GeneKit™).

Results

Individual phenotypic findings in parents with chronic arthritis

The father of family no. 1: His arthritis in both knees was diagnosed at the age of 10. During the course of the disease he has suffered symptoms of short duration in the neck and lower back. The patient was rheumatoid factor (RF)-negative. Diagnosis: juvenile RF-negative oligoarthritis.

The mother in family no. 2: Her arthritis in both knees and left ankle started at the age of 5. Later the disease progressed to chronic polyarthritis. Diagnosis: juvenile RF-negative polyarthritis.

The mother in family no. 3: Her symptoms of chronic arthritis in the knees and ankles started at the age of 9. The diagnosis of RF-negative chronic arthritis was made when the patient was 18 years old. Subsequently she developed serious asymmetric polyarthritis which led to permanent joint damage, e.g. atlanto-axial subluxation. Furthermore, at the age of 46 secondary amyloidosis was diagnosed as a complication of the rheumatic disease. Diagnosis: juvenile RF-negative polyarthritis.

In *family no. 4 both parents* suffer from rheumatic diseases. The *father* fell ill with monoarthritis of the left knee at the age of 3. Later on his right knee was also affected. In adulthood he started to have back pains, and limitations in back movements were noted. X-rays revealed bilateral sacroilitis. Diagnosis: juvenile ankylosing spondylitis. The *mother* was diagnosed as having a classical symmetric and erosive but RF-negative polyarthritis which satisfied the criteria for RA from the onset of the disease at the age of 35. Diagnosis:RF-negative RA.

The mother in family no. 5: She had chronic uveitis in the left eye since the age of 10. RF-negative oligoarthritis with symptoms in both knees was diagnosed at the age of 27. Diagnosis: RF-negative oligoarthritis (commencing in childhood as uveitis).

The mother in family no. 6: She had RF-negative oligoarthritis with symptoms in the knee joints since the age of 25. Diagnosis: RF-negative oligoarthritis.

The father in family no. 7: He had arthritis in both knees since the age of 54 and was positive for anti-nuclear antibodies. Diagnosis: RF-negative oligoarthritis.

The mother in family no. 8: She had widespread pains fulfilling the diagnostic criteria for fibromyalgia. X-ray examination verified bilateral sacroilitis at the age of 35. Diagnosis: ankylosing spondylitis and fibromyalgia.

None of the parents in the eight families were consanguinous.

The children. Of the 18 affected children in the above eight families, 15 had oligoarthritis, one had RF-negative polyarthritis and 2 had systemic onset juvenile arthritis. The siblings of the patients with systemic disease both had oligoarthritis. The patient with RF-negative polyarthritis had two siblings with oligoarthritis.

All the cases (both parents and children) in which the arthritis commenced in childhood met the Durban criteria for JIA (5). The cases with ankylosing spondylitis met the criteria for this condition (7).

The HLA types of the affected parents are shown in Table I. Both of the cases with ankylosing spondylitis were positive for the HLA allele B27. Two of the 3 cases with juvenile oligoarthritis or polyarthritis were positive for HLA-A2 and one was positive for HLA-DR8 (alleles with an increased prevalence in JIA). All 4 cases with adult onset chronic peripheral arthritis were positive for HLA-A2 and two were positive for HLA-DR8. One case (the patient with uveitis commencing in childhood) possessed the allele HLA-DR4. The prevalences of HLA-A2, HLA-B8 and HLA-B27 in the Finnish population are 45%, 16% and 14%, respectively.

Discussion

Table I. HLA types of the parents with chronic arthritis.

Family	Parent	Diagnosis	Haplotype				
			A	B	C	DR	DQ
1	father	RF-negative JIA (oligoarthrits)	0101	0801	0701	0301	0201
			0201	3901	1203	1201	0301
2	mother	RF-negative JIA (polyarthritis)	0301	4001	0202	0801	0301
			0201	4002	0304	1101	0402
3	mother	RF-negative JIA (polyarthritis)	0301	0801	0304	0401	0302
			2402	4001	0701	1302	0604
4	father	RF-negative JIA/AS	0201	2705	0202	0801	0301
			2402	4402	0701	1101	0402
4	mother	RF-negative RA*	0201	0702	0304	1302	0602
			0301	4001	0702	1501	0604
5	mother	RF-negative oligoarthritis +	0201	1501	0303	0401	0302
			0301	4001	0304	0801	0402
6	mother	RF-negative oligoarthritis	0201	1302	0401	0101	0303
			0301	3501	0602	0901	0501
7	father	RF-negative oligoarthritis	0201	3901	0102	0801	0402
			2402	5601	0702	1301	0603
8	mother	RF-negative AS	0201	1801	0202	0801	0301
			2501	2705	1202	1101	0402

All cases were rheumatoid factor negative. * Rheumatoid arthritis satisfying the ACR criteria; + disease commenced in childhood as chronic uveitis.

We have previously reported a higher than expected frequency of siblings with more than one JIA case (4). Although genetic factors most likely were involved in this familial clustering of JIA, the role of a shared environment could not be excluded. To obtain more evidence on the role of genetic factors in the etiology of JIA, we studied in the work described here the occurrence of chronic inflammatory rheumatic diseases among parents who had two or more offspring affected with JIA.

The survey of the clinical history of the parents with inflammatory rheumatic diseases revealed interesting findings. Among these 9 parents there were 4 cases of JIA (one case had been diagnosed as juvenile RF-negative oligoarthritis, two as juvenile RF-negative polyarthritis and one as juvenile ankylosing spondylitis). None of the 5 parents with onset of the disease in adulthood had RF-positive RA, although one met the classification criteria for RA. Of the 3 RF-negative parents with oligoarthritis the disease in one had commenced in childhood as chronic uveitis. One female patient had ankylosing spondylitis. HLA findings in the chronic arthritis cases commencing in adulthood were compatible with the conception that most, if not all, of them had JIA with onset in adult age rather than genuine RA.

The prevalence of JIA in children of North European ancestry is about 1 per 1000 (8). Since the mean age of the patients is 7-8 years at the onset of the disease, the cumulative incidence of JIA in Finnish adults is about 2 per 1000. Thus, one would expect about 0.2 cases among the 90 parents of these children. However, four JIA cases were found, i.e. 20 times more than expected. In addition, there were four cases of RF-negative chronic peripheral arthritis, most of whom may have represented JIA cases with onset in adult age. Earlier, HLA-DPB1*0301 was found to be a risk factor for both polyarticular JIA and RF-negative adult RA (9), suggesting that adult-onset JIA might represent one subtype of RF-negative RA. This accumulation of JIA-type diseases in two generations in pedigrees ascertained through multiple affected siblings having JIA strongly argues for a role of genetic factors rather than a shared environment. The increased frequency of JIA among the parents in these families supports our earlier contention that the genetic component in JIA is higher than previously believed (4).

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