Comparison of Clinical and Laboratory Variables in Familial versus Sporadic Systemic Onset Juvenile Idiopathic Arthritis

SULAIMAN M. AL-MAYOUF, SANA M. MADI, KHALID ALMANE, and SULIMAN AL JUMMAH

ABSTRACT. ***Objective***. To compare patients with familial versus sporadic juvenile idiopathic arthritis (JIA) with respect to clinical and laboratory variables.

Methods. The familial JIA group comprised 11 affected siblings belonging to 4 families, while the comparative group comprised 22 patients selected by systematic sampling from JIA patients presenting to our pediatric rheumatology clinic; the first patient was chosen randomly and the subsequent patients chosen at intervals of 3. The 2 groups were compared with respect to demographic information, age at onset of disease, disease activity, disease damage, and laboratory variables.

Results. The 2 groups were comparable with respect to age, sex, and onset type of disease. All patients from the familial group were from a southern province of Saudi Arabia ($p = 0.001$). The familial group had an earlier age at onset of disease ($p = 0.039$), the mean number of actively inflamed joints was higher ($p = 0.009$), and functional capacity as measured by Childhood HAQ was worse ($p = 0.048$), compared with the sporadic group. Other variables showed no significant differences.

Conclusion. The comparison of patients with familial versus sporadic JIA revealed a significant difference in origin of patients and age at onset of disease. These differences may be helpful in identifying the predisposing genes in familial patients with JIA. (J Rheumatol 2006;33:597–600)

Key Indexing Terms:
JUVENILE IDIOPATHIC ARTHRITIS FAMILIAL ARTHRITIS SAUDI ARABIA

Juvenile idiopathic arthritis (JIA) is one of the most frequent childhood rheumatic diseases; it is also one of the most common chronic diseases in children and is a major cause of functional disability[1,2]. JIA represents a complex group of heterogeneous entities that includes oligoarticular, polyarticular, systemic onset, and other subtypes[3]. The etiology of JIA is poorly understood. Characteristics such as immune dysregulation and cytokine production point to an autoimmune role in the pathogenesis; on the other hand, sibling pairs and monozygotic twins affected by chronic arthritis support a genetic component in JIA susceptibility[4-7]. Several studies have examined possible genetic predisposition, and numerous associations between HLA polymorphisms and the different subtypes of JIA have been described[8,9].

Although several reports examining clinical variables in families with more than one affected member and detailed family studies of patients and first-degree relatives have been published, only a few reports compared the clinical differences between familial and sporadic JIA[6,10-13]. Our clinical observation indicates that patients with a family history of JIA have severe disease with destructive arthritis resistant to most immunosuppressive therapy (Al-Mayouf, unpublished observations). In this study we tested a hypothesis that patients with familial and sporadic JIA are different with respect to clinical and laboratory variables.

MATERIALS AND METHODS

Patients with JIA undergoing treatment in the division of Pediatric Rheumatology at King Faisal Specialist Hospital and Research Center (KFSH&RC), Riyadh, are included in this study, subject to the informed consent from their parents. KFSH&RC is the major tertiary care center in Saudi Arabia for most subspecialties, including pediatric rheumatology. All included patients fulfilled the International League of Associations for Rheumatology criteria for JIA[3]. We defined familial JIA patients as a family with more than one sibling diagnosed with JIA. Patients with familial JIA were compared with a group of patients with sporadic JIA. The total number of patients with sporadic JIA in our center is 60. The comparative sporadic group in our study was selected by systematic sampling from patients presenting to our clinic. The first patient was chosen randomly and the subsequent patients were chosen at an interval of 3. We excluded patients with spondyloarthropathies and noninflammatory familial arthropathy[14,15]. All patients (familial and sporadic groups) were compared at presentation and the last followup visit with respect to: demographic information, age of onset of JIA, disease activity, disease damage, laboratory variables, and functional class.

A single pediatric rheumatologist evaluated the patients, while a single pediatric physiotherapist who was blinded to the clinician assessment administered the Childhood Health Assessment Questionnaire (CHAQ)[16]. At the time of clinical evaluation all patients had relevant laboratory tests including complete blood count, renal and hepatic function, erythrocyte sedimentation rate, antinuclear antibody and rheumatoid factor levels, and radiological studies of affected joints. A single pediatric radiologist unaware of the current clinical status of the patients reviewed all radiographs.

The frequency of the various disease variables was compared between

From the Departments of Pediatrics, Physiotherapy, and Radiology, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia.

S.M. Al-Mayouf, MD, Consultant, Department of Pediatrics; S.M. Madi, PT, Department of Physiotherapy; K. AlMane, MD, Department of Radiology; S. Al Jummah, MD, Department of Pediatrics.

Address reprint requests to Dr. S.M. Al-Mayouf, Department of Pediatrics, MBC-58, King Faisal Specialist Hospital and Research Center, PO Box 3354, Riyadh 11211, Saudi Arabia. E-mail: mayouf@kfshrc.edu.sa

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familial and sporadic JIA patients using chi-squared or Fisher exact test for the binomial variables whenever appropriate, and the Student t test was used to compare continuous variables. A value of $p < 0.05$ was considered significant.

RESULTS

In total 33 patients were included. The familial JIA group comprised 11 affected siblings belonging to 4 different unrelated families (Figure 1), while the comparative group comprised 33 patients; none had a family history of JIA. Both groups were comparable with respect to age, sex, and onset type (Table 1). The familial patients had a significantly lower age at onset of disease ($p = 0.039$) and were younger at time of diagnosis ($p = 0.05$). The proportion of girls was predominant in both groups. All patients from the familial group were from the southern province of Saudi Arabia ($p = 0.001$). All patients in both groups had more than 5 actively inflamed joints at diagnosis. Systemic onset concordance was observed in 64% of the familial group versus 55% in the sporadic group. No patient in either group had oligoarticular onset disease. Disease activity variables of familial and sporadic groups are summarized in Table 2. Patients in the familial group had a higher number of actively inflamed joints than the sporadic group ($p = 0.009$). However, there was no difference with regard to the number of clinically or radiologically damaged joints, despite the functional capacity as measured by CHAQ being worse in the familial group ($p = 0.048$). With respect to extraarticular features, all patients with systemic onset had the typical quotidian fever and the classic associated rash. However, the frequency of tenosynovitis, serositis, and organomegaly was low. None had iritis. No differences were noted between the 2 groups. None of the laboratory variables were different between the 2 groups, but the hemoglobin level was found to be lower in the familial group ($p = 0.002$). No differences in treatment were noted.

Table 1. Comparison of clinical features between familial and sporadic juvenile idiopathic arthritis.

	Familial, N = 11	Sporadic, N = 22	p
Sex (% female)	9/11 (82)	16/22 (73)	0.79
Age, yrs, mean, SD	10.1 (3.74)	9.1 (4.00)	0.52
Region: percentage from the southern province of Saudi Arabia	11/11 (100)	7/22 (32)	0.001
Onset type of JIA (%)			
Sporadic	7/11 (64)	12/22 (55)	0.9
Polyarticular	4/11 (36)	10/22 (45)	0.9
Age at onset, yrs, mean (SD)	2.4 (1.9)	4.4 (3.5)	0.0398
Age at diagnosis, yrs, mean (SD)	3.5 (2.4)	5.5 (3.4)	0.05
Followup duration, yrs, mean (SD)	6.4 (3.3)	3.1 (3.4)	0.014

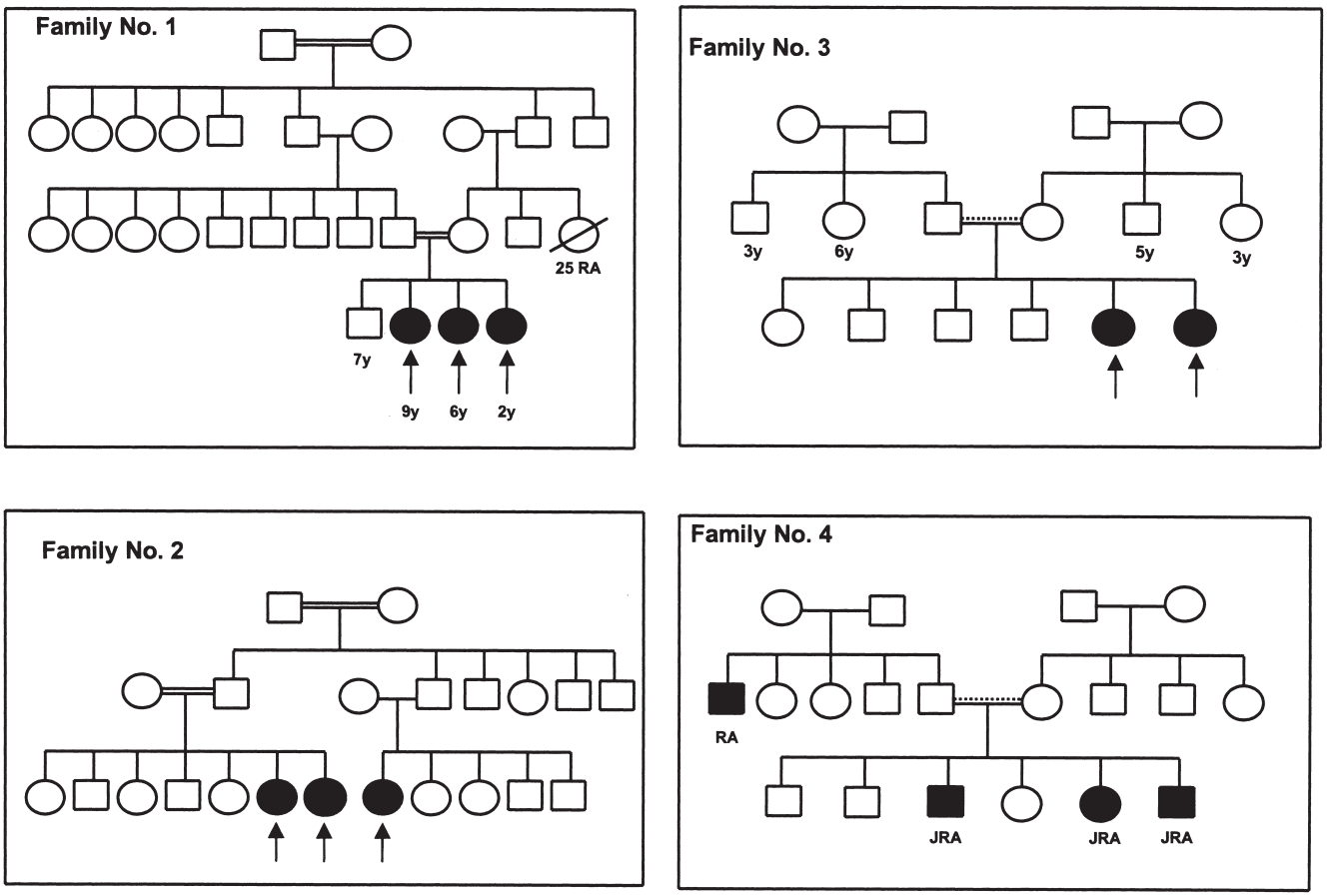

Figure 1. The familial JIA group comprised 11 siblings from 4 different unrelated families. JRA: juvenile rheumatoid arthritis.

Table 2. Comparison of disease activity between familial and sporadic juvenile idiopathic arthritis.

Variable	Familial	Sporadic	p
No. active joints, mean (SD)	7.6 (4.9)	2.8 (3.2)	0.009
No. clinically damaged joints, mean (SD)	1.5 (1.9)	0.5 (1.2)	0.145
No. radiographic damaged joints, mean (SD)	3.3 (3.2)	1.7 (2.8)	0.116
Tenosynovitis (%)	2/11 (18)	6/22 (27)	0.88
VAS, mean (SD)	1.13 (1.27)	0.53 (0.57)	0.162
CHAQ, mean (SD)	1.25 (0.99)	0.55 (0.56)	0.048
Erythrocyte sedimentation rate, mean (SD)	41.6 (19.8)	37.9 (28.8)	0.66
Antinuclear antibody, %	43	20	0.59
Rheumatoid factor, %	38	10	0.27
Hemoglobin, mean (SD)	100.1 (11.4)	116.7 (13.6)	0.002
White cell count, mean (SD)	11.4 (3.3)	10.3 (5.4)	0.492
Platelet count, mean (SD)	509 (263.3)	389 (125.2)	0.197
Triple therapy, %	36	32	0.89

VAS: visual analog scale; CHAQ: Childhood Health Assessment Questionnaire; triple therapy: prednisone, methotrexate, cyclosporine.

DISCUSSION

We observed clinical and laboratory differences between patients with familial and sporadic JIA. Most notable is the origin of the familial patients; all of them were from the same geographical area. Interestingly, 2 families were from the same tribe, but were unrelated. Although environmental influences cannot be excluded, this striking observation may reflect differences in the immunogenetic background of the disease. Few epidemiological studies have reported data to support the existence of differences in JIA between ethnic groups[17]. In contrast, several studies have examined the clinical differences between familial and sporadic cases in selected rheumatic diseases; the findings of these studies have been somewhat contradictory[12,18,19]. In a report by Saila, *et al*[12], 80 siblings with JIA, most of whom had oligoarticular onset disease, were compared to 114 patients from a population-based series. Familial cases were characterized by a significantly earlier age at onset; otherwise the clinical features of familial and sporadic cases were similar[12]. Our study showed similar findings with respect to age at onset: patients with familial disease were significantly younger at onset of JIA and were diagnosed earlier than patients from the sporadic group. This observation has been noted in several rheumatic diseases with familial cases[12,18]. The majority of our patients with familial JIA had a systemic onset subtype (64%) and the remainder had a polyarticular onset subtype (36%); no patient in our cohort had oligoarticular onset disease. The high degree of concordance with respect to onset type seen in our cohort is inconsistent with previous reports[7,11,12]. In a population of European origin most familial JIA was oligo or polyarticular onset, familial systemic onset type was exceedingly rare, and only a few affected sib pairs were described as having systemic onset JIA[12]. The explanation for our finding is unclear. However, our hospital is the major referral center for the whole country and it may represent a cohort of JIA patients with severe disease. Another explanation could be that genetic influence plays a role in determining JIA onset type. It has been suggested that genetic factors might account for the similar onset subtype of JIA within any single family[6]. In our study, patients with familial JIA were more likely to have more actively inflamed joints versus sporadic patients, which is different from previous cohorts; again, the reasons remain unclear. This could be due to referral bias or genetic factors. However, the number of damaged joints and the treatment regimens were similar in both groups; this may suggest that patients with familial JIA either had aggressive disease or were inadequately treated. Unfortunately, our study does not support this hypothesis. The only significant laboratory difference between the 2 groups was lower hemoglobin level in the familial group; but since we did not investigate for other causes of anemia, we could not conclude whether or not this was an indicator of disease severity in the familial group.

JIA is clearly a complex group of diseases with arthritis as the main feature[3-5]. It rarely occurs as a familial disease. However, familial aggregations like those of our patients suggest the presence of genetic predisposition[20]. Although the associations are not found consistently, the increased frequency of certain HLA antigens in patients with JIA suggests the presence of disease susceptibility genes within the major histocompatibility complex[7]. Positional cloning of the predisposing genes is a recent strategy that has been successful in mapping and cloning genes involved in common diseases such as psoriasis and very rare diseases such as familial recurrent arthritis[21-23]. Our collection of patients is ideal for homozygosity mapping of the disease locus.

We conclude that comparison of patients with familial versus sporadic JIA revealed marked differences in the origin of patients and the age at onset of disease; the significance of these findings is uncertain at present. However, it may be valuable in future studies to determine the predisposing genes in familial JIA patients.

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