*Original Article*

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# The Effect of Positive Family History of Autoimmunity in Juvenile Idiopathic Arthritis Characteristics; a Case Control Study

**Mehdi Khani[1], MD; Vahid Ziaee*[2,3,4], MD; Mohamad-Hassan Moradinejad[3,4], MD; Nima Parvaneh[3,5], MD**

1. Growth and Development Research Center, Tehran University of Medical Sciences, Tehran, Iran
2. Pediatric Rheumatology Research Group, Rheumatology Research Center, Tehran University of Medical Sciences, Tehran, Iran
3. Department of Pediatrics, Tehran University of Medical Sciences, Tehran, Iran
4. Children's Medical Center, Pediatrics Center of Excellence, Tehran University of Medical Sciences, Tehran, Iran
5. Pediatric Infectious Diseases Research Centre, Tehran University of Medical Sciences, Tehran, Iran;

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## Abstract

***Objective:*** To compare Juvenile Idiopathic Arthritis (JIA) patients with and without family history of autoimmune disease with respect to clinical features and laboratory data.

***Methods:*** Sixteen JIA patients with family history of autoimmune disease were identified during study, 32 patients were chosen for comparative group from referred patients to the rheumatology clinic according to the date of referral. Two groups were compared with respect to age of onset, sex, subtype, disease activity, duration of active disease and laboratory variables.

***Findings:*** The age of onset was significantly lower in JIA patients with family history of autoimmunity (4.7 years vs. 7.0 years; *P*=0.02), polyarthicular subtype was more frequent in patients with positive family history (50% vs.25%; *P*=0.04) most of JIA patients with positive family history were in the active phase at the time of study (64% vs 25%; *P*=0.02) and had a longer duration of active disease (21.0 months vs 12.3 months; *P*=0.04). Patients with positive family history had more positive ANA (43.5%% vs 12.5%; *P*=0.01) and also more positive ADA (75% vs 20.8%; *P*=0.002). Two groups were similar according to sex, and other laboratory variables.

***Conclusion:*** JIA patients with family history of autoimmune disease seem to have a more severe disease than patients without such family history, they are younger at the onset, and have mostly poyarthicular subtype. They also have more ANA and ADA positivity. These findings are different from familial JIA case-control studies according to active disease duration, subtype, and ANA positivity.

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***Key Words:*** Juvenile Idiopathic Arthritis; Family History; Autoimmunity; Chronic Arthritis

## Introduction

Juvenile Idiopathic Arthritis (JIA) previously known as juvenile chronic arthritis is the most common rheumatic disease in children[1]. The common characteristics of different subtypes of JIA are arthritis started before the age of 16 years and duration of symptoms more than 6 weeks[2]. International League of Associations for Rheumatology (ILAR) introduced seven different subtypes of JIA based on the pattern of disease in the first 6 months including oligoarthritis, rheumatoid factor (RF) positive and RF negative polyarthritis, systemic onset, psoriatic arthritis, enthesitis-related (ERA) and other undifferentiated arthritis forms[3]. The etiology of JIA is not

*** Corresponding Author;**
**Address:** Division of Pediatric Rheumatology, Children's Medical Center, No 62, Dr Gharib St., Keshavarz Blvd, Tehran, Iran
**E-mail:** ziaee@tums.ac.ir

clearly understood but it is believed to be an autoimmune disease, in which genes and environmental factors both are responsible for its development[4].

There are several studies that reveal a strong role of genetic factors in the pathogenesis of JIA. Studies have shown increased risk of JIA in monozygotic twins, compared to the general population[5]. Many studies showed a significant increase in the risk of JIA in first-degree relatives[6]. Also Prahalad et al showed less increased risk of JIA in first-cousins of JIA patients in comparison to that of their siblings[7]. There are some similar manifestations between siblings with JIA, which may suggest familial aggregation of clinical features and genetic basis of JIA[8]. Besides these studies which provide evidences for genetic role in JIA pathogenesis, there are many studies reporting increased prevalence of autoimmune diseases in JIA patients and their families[9-12]. Autoimmune diseases like rheumatoid arthritis, spondyloarthropathy, psoriatic arthritis, JIA and type 1 diabetes are more prevalent in families of children with JIA[13]. So autoimmune diseases with various clinical features may have some shared origin of genetic susceptibility[14].

Only few case-control studies comparing clinical features and laboratory data of families with multiple JIA versus those with sporadic JIA have been performed previously[8,15,16]. In this study our subject was to compare clinical features and laboratory data in JIA patients with family history of autoimmune disease versus those without any family history of autoimmune disease and to find if there are any differences in results comparing to studies on familial JIA.

## Subjects and Methods

Our study was performed in Children's Medical Center, the pediatric center of excellence and tertiary pediatric center in Iran. During 3 years (2010-2012) all JIA patients who had autoimmune disease in their first degree relatives were included in this study. For comparative group one patient before and one after the case in the registry sequences were selected. In comparative group, patients who had any family history of autoimmune disease in their relatives were excluded. All patients were diagnosed and classified according to International League of Associations for Rheumatology (ILAR) classification criteria for JIA[3]. This study was approved by ethical committee of Tehran University of Medicial Sciences.

Clinical and laboratory data was collected from patients' documents at their first presentation and follow up sessions. Comparison of two groups performed with respect to age of onset, sex, subtype (course type), active disease duration, response to trearment and laboratory parameters such as ESR, CRP, Reumatoid factor (RF), Antineuclear antibody (ANA), Anti-cyclic citrullinated peptide (AntiCCP) antibodies, and Adenosine deaminase (ADA). Active disease duration was considered as the total period of time in which patient had actively inflamed joints. An active joint was defined as one with swelling or decreased range of motion with warmness, pain, or tenderness[17]. For comparing response to treatment, patients were categorized in 3 groups: First group comprised patients with active disease at the time of study, second group included the patients who had inactive disease at the time of study but had not met the remission criteria yet and third group were in clinical remission on medication at the time of study (clinical remission on medication was defined as 6 months of inactive disease while consuming medication)[18].

The data was analysed using chi-square test and t-test by SPSS version 19. *P* value <0.05 was considered to be significant.

## Findings

During 3 years, we identified 16 JIA patients who had autoimmune disease in their first-degree relatives, and 32 patinets were selected as comparative group. Among all 48 cases included in this study, 16 patients had the following aoutoimmune diseases in their family members; Reumatoid Artritis(RA) ,Juvenile Idiopathic Arthritis(JIA), Systemic Lupus Erithematous (SLE), Graves disease, Behcet disease, Dermatomyositis, Polychondritis and Psoriasis (Table 1).

**Table 1:** Autoimmune disease in patients' families

| Variable | no (%) |
|---|---|
| **Rheumatoid Arthritis or Juvenile Idiopathic Arthritis** | 8 (50) |
| **Systemic Lupus Erythematous** | 2 (12.5) |
| **Graves disease** | 2 (12.5) |
| **Behcet disease** | 1 (6.25) |
| **Dermatomyositis** | 1 (6.25) |
| **Polychondritis** | 1 (6.25) |
| **Psoriasis** | 1 (6.25) |

Table 2 compares two series of patients with and without family history. The age at onset of disease was significantly lower in the positive family history group, 4.7±3.5 years vs 7.0±3.0 years (*P*=0.02). The proportion of girls was predominant in both groups but higher in family history group 11 (68%) vs 17 (53%) which was not statistically significant.

The subtype of disease was more frequently polyarthicular in positive family history group, 8 out of 16 (50%) while most of the patients without family history had pauciarthicular subtype, 20 out of 32 (62.5%), the percent of systemic subtype patients was equal in two groups (12.5%), so they were excluded of statistical test. In the group of positive family history patients were more likely to have polyarthicular subtype in comparison to population based group, 8 (50%) *vs.* 8 (25%) (*P*=0.04). Patients in positive family history group had more ANA positivity, 7 (43.5%) *vs.* 4 (12.5%) (*P*=0.01) and also more ADA positivity 9 (74%) *vs.* 5 (20.8%) (*P*=0.002) but the difference between blood ADA levels in two groups was not significant. Other laboratory variables (RF, AntiCCP, ESR & CRP) were not significantly different in two groups.

Most of the patients in family history group were in the active phase at the time of study 9 (64%) vs 8 (23%) (*P*=0.02), and the duration of active disease was longer in family history group 21±13.4 months vs 12.3±9.7 months (*P*=0.04) for 1 patient were lacking, ANA value for 1 patient

**Table 2:** Comparison of JIA patients with and without family history of autoimmune diseases

| Variable | with family history | without family history | *P*. Value |
|---|---|---|---|
| **Onset Age, yrs. (mean± SD)** | 4.7 (3.9) | 7.0 (3.0) | 0.02 |
| **Sex (female)** | 11 (68%) | 17 (53%) | 0.4 |
| **Subtype (course type)** | | | 0.1 |
| **Polyarthicular** | 8 (50%) | 8 (25%) | |
| **Pauciarthicular** | 5 (31.3%) | 20 (62.5%) | 0.04* |
| **Systemic** | 2 (12.5%) | 4 (12.5%) | |
| **Psoriatic** | 1 (6.3%) | 0 | |
| **Rheumatoid factor (positive %)** ‡ | 2 (14.3%) | 1 (3.2%) | 0.2 |
| **Antineuclear Antibody (positive %)** | 7 (43.5%)♦ | 4 (12.5%) | 0.01 |
| **AntiCCP (positive %)** | 0 | 2 (7.1%) | 0.3 |
| **Adenosine Deaminase (positive %)** †↗ | 9 (75%) | 5 (20.8%) | 0.002 |
| **Adenosine Deaminase level (mean, SD)** | 21.4 (19.2) | 13.4 (6.9) | 0.07 |
| **ESR (mean, SD)** | 28 (28) | 35.7 (30) | 0.4 |
| **C-reactive Protein (mean, SD)** | 26.7 (39.2) | 24.9 (18.1) | 0.8 |
| **Disease Activity** | | | |
| **Active** | 9 (64.3%) | 8 (25.8%) | 0.02 |
| **Inactive** | 0 | 8 (25.8%) | |
| **Remission on medication** | 5 (35.7%) | 15 (48.4%) | |
| **Active disease duration, months (mean± SD)** | 21 (13.4) | 12.3 (9.2) | 0.04 |

JIA: Juvenile Idiopathic Arthritis; Anti-CCP: Anti-cyclic citrullinated peptide; ESR: Erythrocyte Sedimentation Rate

† Positive ADA defined as ADA level ≥ 15; ‡ RF value were missing for 2 patients in with family history and 1 patient without family history; ♦ ANA value for 1 patient were missing; ↗4 patients were missing data for ADA study in with family history group and in 8 patients without family history; * *P* value calculated after excluding systemic and other subtype

was lacking, 4 patients were missing data for ADA study, 8 patients were missing data for ADA study.

## Discussion

In this study JIA patients with family history of autoimmune disease were more likely to have active disease at the time of study and also they had a longer duration of active disease, despite similar treatment regimen, which may indicate that patients with family history of autoimmune disease have a more severe course. There are very few studies which compared duration of disease between familial and sporadic JIA patients.

Moroldo et al compared 164 familial JIA patients with 422 sporadic ones and they found no significant difference in duration of disease between the two groups[8]. In another study Almayouf et al compared 11 familial JIA patients with 22 sporadic JIA patients and they reported that the number of active joints were higher in familial patients than in sporadic patients, but also the number of damaged joints was not significantly different, they concluded that it may be due to more aggressive disease in familial cases or inadequate treatment[16]. In other studies on familial JIA no differences in other factors related to disease severity were reported[8,15]. An explanation for this inconsistency may be the differences between patients in our study and previous ones: we studied JIA patients with autoimmunity background and half of our patients had autoimmune disease except JIA and RA in their family, while previous studies just included familial JIA patients in their studies, and also they may have ignored family history of autoimmune disease in their comparative groups. These can implicate the idea that autoimmunity background can make JIA more severe than family history of JIA alone can make it. Testing of this hypothesis was not the subject of our study.

The patients with positive family history were younger at the onset of disease. This was also reported in both of studies on familial JIA and other familial rheumatic diseases[15,16,19-21]. Most of our patients with positive family history had polyarthicular subtype but patients in comparative group were predominantly pauciarthicular, prevalence of systemic subtype was similar in two groups, so comparison was only made between pauciarthicular and polyarthicular subtypes, and it revealed a statistically significant difference between the two groups. Saila et al compared 80 familial JIA patients with 114 population-based JIA patients, and reported that most of familial cases and population-based series were in pauciarthicular onset type[15]. Moroldo et al also found that pauciarthicular is the most prevalent subtype in their familial patients and reported no difference in the rate of conversion from pauciarthicular into polyarthicular subtype between the two groups. They believed that pauciarthicular subtype has the strongest genetic background[8]. Predominance of polyarthicular subtype in JIA patients with family history of autoimmune disease may lead to the conclusion that autoimmunity has a greater influence on polyarthicular subtype.

ANA positivity was significantly more frequent in patients with family history of autoimmune disease in our study. In Saila et al study no more ANA positivity was reported in sibling series[15]. Moroldo et al reported similar ANA positivity in pauciarthicular patients between two groups of familial and sporadic, but they also reported a familial aggregation of ANA positivity in siblings[8]. Almayouf et al did not report differences in ANA positivity between their series[22]. The explanation could be in the differences between our patients' series and the patients of previous studies; our patients had a family history of a larger group of rheumatic and autoimmune disease such as SLE, but previous studies contained patients with only JIA in their siblings. According to more ANA positivity, JIA patients with family history of autoimmune disease may have more tendency to developing other autoimmune disease, as proved in studies[9-11], and also a higher risk of uveitis, which was not tested in this study.

There is a correlation between blood ADA level and disease activity in JIA and SLE patients[23]. As we tested, positive ADA was more frequent in positive family history group, although ADA level was not different in two groups. More frequency of ADA positivity in patients with family history of autoimmune disease may indicate more severe disease in this group.

Similarity of other laboratory variables (RF, AntiCCP, ESR, CRP) in the two groups was consistent with previous findings[15,16].

## Conclusion

JIA patients with family history of autoimmune disease have some differences with population-based JIA patients according to age of onset, duration of active disease, subtype, ANA, ADA, and these findings are somehow similar to studies on familial JIA but also different from them with respect to duration of active disease, subtype and ANA.

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***Conflict of Interest:*** None

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