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Familial aggregation of juvenile idiopathic arthritis with other autoimmune diseases: Impact on clinical characteristics, disease activity status and disease damage

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Abstract

Objectives: To evaluate the impact of family history of autoimmune diseases (FHADs) on the clinical characteristics and outcome of juvenile idiopathic arthritis (JIA).

Methods: We retrospectively reviewed children with JIA seen in 7 pediatric rheumatology clinics from 6 Arab countries. All included patients met the International League of Associations for Rheumatology classification criteria for JIA and had a disease duration greater than 1 year. Data were collected at the last follow-up visit and comprised clinical findings, including FHADs. Disease activity and disease damage were assessed by Juvenile Arthritis Multidimensional Assessment Report, and juvenile arthritis damage index (JADI) respectively. Disease activity was categorized as remission off treatment, remission on treatment, or active disease.

Results: A total of 349 (224 females) JIA patients with a disease duration of 5 (interquartile range 2.9-7.5) years were included. The most frequent JIA categories were polyarticular JIA and oligoarticular JIA, followed by systemic JIA. There were 189 patients with FHADs and 160 patients without FHADs. The most frequent FHADs were diabetes mellitus (21.2%), JIA (18.5%), rheumatoid arthritis (12.7%). Among patients with FHADs, 140/189 (74.1%) achieved clinical remission, while 131/160 (81.9%) patients without FHDs had clinical remission (odds ratio [OR] = 1.2, 95% CI 0.97-1.5). Rate of consanguinity, enthesitis-related arthritis (ERA) and psoriatic arthritis were higher in patients with FHADs (OR = 0.6, 95% CI 0.4-0.9 and OR = 1.2, 95% CI 1.1-1.4). Also, articular JADI correlated significantly with presence of FHADs (OR = 1.1, 95% CI 1.0-1.1).

Conclusion: This study shows that autoimmune diseases cluster within families of patients with JIA with a high proportion of ERA and psoriatic arthritis. JIA patients with FHADs are likely to have more disease damage.

KEYWORDS

consanguinity, familial arthritis, familial autoimmune diseases, juvenile arthritis damage index, juvenile arthritis disease activity score, juvenile idiopathic arthritis

1 | INTRODUCTION

Juvenile idiopathic arthritis (JIA) is the most common chronic childhood idiopathic rheumatic disease, and to date has largely been regarded as a polygenic disorder. However, the exact etiology and pathogenesis of JIA are not well-defined.[1,2] Like other autoimmune and autoinflammatory disorders, the interactions of epigenetic and environmental factors contribute and influence the disease susceptibility and expression.[3,4] The observational studies confirm that co-occurrence of more than 1 autoimmune disease in individuals and within families because of sharing common genetic susceptibility factors support the concept of genetic influence in the pathogenesis of JIA. The consanguineous marriage in Arab countries reaches 50%-75% of all marriages, which might underscore the overall prevalence of autoimmune diseases and the influencing role of genetic factors in the disease phenotype and outcome.[5] Predicting JIA outcome is challenging; most of the studies related the long-term outcomes to various predictors, including JIA category, diagnostic delay and late initiation of the appropriate treatment.[6,7] Also, other factors such as biomarkers could add value to the clinical variables.[8] A high aggregation of autoimmunity including familial JIA is observed among first- and second-degree relatives of patients with JIA; however, the knowledge about this observation is limited.[9-12] Of note, recently, familial JIA gained more attention, and might be associated with guarded outcome.[13-15] Most studies that have looked at the familial aggregation of autoimmunity in JIA patients and their relatives, and have focused on the association and the estimated risk of autoimmune diseases among individuals and their relatives. However, the impact of clustering of autoimmunity has not been adequately studied.[9,16,17] There are scarce data published on JIA long-term outcome in JIA patients with relatives with autoimmune diseases.[18] Our study aimed to determine whether the family history of autoimmune diseases (FHADs) affects the clinical characteristics and outcome of JIA in a highly consanguineous population.

2 | METHODS

2.1 | Study population

This is a multi-center retrospective, observational cohort analysis. Data were collected from 7 tertiary pediatric rheumatology clinics from 6 Arab countries between July 2010 and July 2019. We only included patients if they were younger than 14 years of age and met the International League of Association for Rheumatology criteria for classification for JIA and had a disease duration greater than 1 year with a least 2 follow-up visits.[19] It is worth mentioning that, as per our hospital policy, those who exceed 14 years of age are transferred to adult rheumatology care to provide comprehensive clinical care. Patients with chronic arthritis other than JIA were not included. The study compared JIA patients with and without familial autoimmunity which was defined based on positive family history of any autoimmune diseases, including inflammatory and non-inflammatory, among their first- or second-degree relatives. Enrolled patients were assigned to 2 groups, patients with FHADs and those without FHADs. Data were collected at the last follow-up visit including age, gender, JIA category, age at disease onset and at diagnosis, disease duration, consanguinity, FHADs. The study participants were asked whether their relatives had been diagnosed with autoimmune disease. Laboratory variables such as rheumatoid factor (RF), anticyclic citrullinated peptide (anti-CCP), anti-nuclear antibody (ANA) and human leukocyte antigen B-27 (HLA-B27) results were interpreted according to the cut-off values of the local laboratories. Also, the provided treatment focusing on conventional synthetic and biologic disease-modifying anti-rheumatic drugs (DMARDs) was reviewed.

2.2 | Outcomes

Included patients were assessed every 3-6 months with a detailed musculoskeletal examination, laboratory evaluation, and therapy was adjusted accordingly. At the last follow-up, patients were evaluated for disease activity status and disease damage. The disease activity was assessed using Juvenile Arthritis Multidimensional Assessment Report (JAMAR).[20,21] The main disease activity categories were inactive disease; either off or on treatment and active disease. Also, the damage was calculated using juvenile arthritis damage index (JADI) for both articular damage (JADI-A) and extra-articular damage (JADI-E).[22] Disease damage was only scored when it was not due to active disease and present for at least 6 months.

Completed data sheets were sent back to the principal investigator at King Faisal Specialist Hospital and Research Center (KFSH-RC), Riyadh, for analysis.

2.3 | Statistical analysis

All statistical analyses were performed using the SAS software package, version 9.4 (Statistical Analysis System, SAS Institute Inc.). Descriptive statistics for continuous variables were reported as median and interquartile range (IQR), and mean ± SD was used when deemed necessary. Categorical variables were summarized as frequencies and percentages. The strength of the correlation between FHADs and JIA characteristics and outcome was measured as odds ratio (OR) calculated from the coefficient of a binary logistic regression. The level of significance was set at P value <.05.

2.4 | Ethical considerations

These patients were previously enrolled in a cumulative damage study among Arab children with JIA under the approval of the Ethics Committee of the Research Affairs Council (RAC) at KFSH-RC (RAC#2191 110 on 19 December 2019). The study was conducted in accordance with the Declaration of Helsinki. All the collected data resulted from routine medical assessments. All data were collected

anonymously, and the confidentiality of the patients was protected. Ethical approval was also obtained by all the participating centers by their institutional research ethics committees.

3 | RESULTS

The study cohort constituted 349 (224 females) JIA patients with a median age of 11.3 (IQR 8.0-15.0) years. The median age at onset was 5 (IQR 2.0-9.0) years and the median disease duration was 5 (IQR 2.9-7.5) years. The most frequent JIA categories were polyarticular JIA (31.2%) and oligoarticular JIA (30.7%), followed by systemic JIA (22.6%). Overall, there were 189 (54.2%) patients with at least 1 relative with FHADs and 160 (45.8%) patients without FHADs. There were 175 familial aggregations of autoimmune diseases. Table 1 shows the frequency of autoimmune diseases among families of JIA patients. Three main clusters of autoimmune diseases were identified. Diabetes mellitus (21.2%), JIA (18.5%), rheumatoid arthritis (12.7%) and autoimmune thyroid disease (7.4%) were the most frequent familial autoimmunities. Table 2 shows the comparison of the demographics, features and provided treatment of JIA patients with and without familial autoimmune diseases. The consanguinity rate was more noticeable in JIA patients with FHADs, while patients without FHADs had a younger age at onset. The 2 groups (patients with and without FHADs) were largely similar in clinical characteristics. However, RF negative polyarticular category, psoriatic arthritis and enthesitis-related arthritis (ERA) were more frequent in patients with FHADs. Interestingly, patients with psoriatic and ERA had a polyarticular course. The differences between ANA, RF, anti-CCP and HLA-B27 in the 2 groups were not significant. Most of the patients received methotrexate and various biologic DMARDs. Of note, anti-tumor necrosis factor blockade was the most frequent biologic DMARD prescribed, followed by tocilizumab. However, the frequency was comparable in the 2 groups.

TABLE 1 Frequency of autoimmune diseases among families of juvenile idiopathic arthritis patients

Autoimmune disease	Frequency
Diabetes mellitus	40 (21.2%)
Juvenile idiopathic arthritis	35 (18.5%)
Rheumatoid arthritis	24 (12.7%)
Autoimmune thyroid disease	14 (7.4%)
Psoriasis	12 (6.3%)
Systemic lupus erythematosus	11 (5.8%)
Vitiligo	9 (4.8%)
Celiac disease	9 (4.8%)
Inflammatory bowel disease	7 (3.7%)
Psoriatic arthritis	3 (1.6%)
Dermatomyositis	2 (1.1%)
Behçet's disease	2 (1.1%)
Gout	2 (1.1%)
Enthesitis-related arthritis	1 (0.5%)
Scleroderma	1 (0.5%)
Myasthenia gravis	1 (0.5%)
Multiple sclerosis	1 (0.5%)
Uveitis	1 (0.5%)

3.1 | Outcomes

One hundred and thirty (81.3%) patients without FHADs had inactive disease status while 140 (74.1%) patients with FHADs showed inactive disease with nearly one-third of them were in complete remission without treatment. Furthermore, 30 (18.8%) patients without FHADs and 49 (25.9%) patients with FHADs showed active disease despite intensive treatment. Overall, 107 (30.7%) patients suffered from joint damage with a mean JADI-A score of 2.1 ± 5.1, while 81 (23.2%) patients had extra-articular damage with a mean JADI-E score of 0.5 ± 1.1. The frequency of damage and the cumulative extra-articular damage were comparable between the 2 groups. However, patients with FHADs had a greater cumulative articular damage. Table 3 shows the comparison of disease status and damage between JIA patients with and without FHADs.

3.2 | Correlation and prediction

There was a significant difference between the 2 groups in favor of patients with FHADs regarding high rate of consanguinity and predisposition of clinically distinct JIA phenotypes. The probabilities of impact of FHADs on the disease characteristics and outcome are shown in Table 4. Considering only FHADs, the rate of consanguinity (OR = 0.6, 95% CI 0.4-0.9, P = .02), and certain JIA categories namely, RF negative polyarticular JIA, ERA and psoriatic arthritis (OR = 1.2, 95% CI 1.1-1.4, P = .001) were higher in patients with FHADs. Patients with familial aggregation of autoimmune diseases had more cumulative articular damage (OR = 1.1, 95% CI 1.0-1.1, P = .005). There was a correlation between FHADs and continuation of active disease. However, it was not statistically significant. In contrast, FHADs did not show significant influence on gender, age of disease onset, or cumulative extra-articular damage.

4 | DISCUSSION

Using standardized and validated outcome tools and measurements is inconsistent among JIA studies. Various clinical and laboratory variables have been suggested as predictors for disease damage and quality of life of patients with JIA.[6,23,24] Data about the disease activity status and disease damage of JIA are increasingly reported worldwide. However, there is scant data from Arab countries. Of note, the prevalence of JIA categories and disease course and prognosis are variable among different ethnicities.[7,15,25] High rate of consanguinity might influence the

TABLE 2 Demographics and clinical features of JIA patients with and without familial autoimmune diseases

	Total	JIA with familial autoimmune diseases	JIA without familial autoimmune diseases
Number of patients	349	189	160
Gender, M:F ratio	1:1.8	1:1.7	1:1.9
Current age, y (median)	11.3 (8.0-15)	12 (8.0-15)	12 (8.0-13)
Age at onset, y (median)	5.0 (2.0-9.0)	5.8 (3.0-9.0)	4.2 (2.0-8.5)
Disease duration, y (median)	5.0 (2.9- 7.5)	5.0 (3.0-7.6)	5.0 (2.4-7.4)
Consanguinity (%)	51.3	57.1	44.4
JIA categories			
Oligo persistent	88 (25.2%)	35 (18.5%)	53 (33.1%)
Oligo extended	19 (5.4%)	12 (6.4%)	7 (4.4%)
Poly RF+	27 (7.7%)	11 (5.8%)	16 (10%)
Ploy RF−	82 (23.5%)	51 (26.9%)	31 (19.4%)
Systemic	79 (22.6%)	39 (20.6%)	40 (25%)
Psoriatic	23 (6.6%)	18 (9.5%)	5 (3.1%)
ERA	24 (6.9%)	17 (8.9%)	7 (4.4%)
Undifferentiated	7 (2%)	6 (3.2%)	1 (0.6%)
ANA	102/337	52/181	50/156
RF	27/298	15/165	12/133
Anti-CCP	16/182	10/103	6/79
HLA-B27	8/135	6/87	2/48
Methotrexate	240	130 (54.2%)	110 (45.8%)
Adalimumab	87	47 (54%)	40 (46%)
Etanercept	82	47 (57.3%)	35 (42.7%)
Tocilizumab	74	44 (59.5%)	30 (40.5%)
Infliximab	14	9 (64.3%)	5 (35.7%)
Anakinra	13	7 (53.8%)	6 (46.2%)
Abatacept	8	6 (75%)	2 (25%)

Abbreviations: Anti-CCP, anticyclic citrullinated peptide; ERA, enthesitis-related arthritis; F, female; HLA, human leukocyte antigen; JADI-A, juvenile arthritis damage index-articular; JADI-E, juvenile arthritis damage index-extra-articular; JIA, juvenile idiopathic arthritis; M, male; RF, rheumatoid factor.

phenotype and outcome. Recently, we demonstrated a positive correlation of family history of JIA with cumulative disease damage and continuation of active disease in JIA patients, denoting that familial JIA might be a potential predictive factor for disease outcome.[26] Autoimmune diseases are a heterogenous group with a wide spectrum of clinical manifestations and predisposition to clustering of autoimmunity. The importance of FHADs was previously recognized; the co-existence of selected autoimmune diseases in relatives of JIA patients with autoimmune disease has been observed. Evidence revealed a higher prevalence of diabetes mellitus, chronic arthritis and autoimmune thyroid disease within JIA families than in control families.[9,27,28] However, it is unclear whether familial aggregation of autoimmunity represents a burden in the long-term outcome of JIA patients. Khani et al.[18] found that 16 JIA patients with FHADs were mostly of the polyarticular category and younger at onset, with likely persistent active disease. However, they did not report the cumulative disease damage. In the current study, we reported the influence of familial aggregation of autoimmunity in the phenotype and outcome of a large multi-center cohort of JIA patients in a highly consanguineous population. Our study showed variability in the frequency of JIA; patients of relatives with familial aggregation of autoimmunity had a higher frequency of RF negative polyarticular JIA, ERA and psoriatic arthritis with polyarticular course. The exact explanation for this discrepancy among JIA categories compared to other studies remains unclear. However, genetic factors might influence the phenotypic variability. There was a positive correlation between active disease and articular damage and familial aggregation of autoimmunity, showing that the presence of FHADs might be considered as a likely predictive factor for the disease status and

TABLE 3 Disease activity status and disease-related damage at the last follow-up visit of JIA patients with and without familial autoimmune diseases

	Total	JIA with familial autoimmune diseases	JIA without familial autoimmune diseases
Number of patients	349	189	160
Inactive disease			
Off treatment, n (%)	85	41	44
On treatment, n (%)	186	99	86
Active disease, n (%)	78	49	30
JADI-A, ≥1, n (%)	107 (30.7)	60 (31.7)	47 (29.3)
Mean ± SD	2.1 ± 5.1	2.6 ± 6.1	1.4 ± 3.5
JADI-E, ≥1, n (%)	81 (23.2)	45 (23.8)	36 (22.5)
Mean ± SD	0.5 ± 1.1	0.5 ± 1.2	0.5 ± 1.1

Abbreviations: ERA, enthesitis-related arthritis; JADI-A, juvenile arthritis damage index-articular; JADI-E, juvenile arthritis damage index- extra-articular; JIA, juvenile idiopathic arthritis.

TABLE 4 Models obtained by a binary logistic regression analysis to estimate the correlation between family history of autoimmune diseases and JIA characteristics and outcome

	JIA with familial autoimmune diseases	JIA without familial autoimmune diseases		
	189	160	OR (95% CI)	*P* value
Gender, M:F	70:119	55:105	0.9 (0.6-1.4)	.6
Consanguinity	108 (57.1%)	71 (44.4%)	0.6 (0.4-0.9)	.02
Disease categories				
Poly RF−	51 (26.9%)	31 (19.4%)	1.2 (1.1-1.4)	.001
ERA	17 (8.9%)	7 (4.4%)		
Psoriatic arthritis	18 (9.5%)	5 (3.1%)		
Age at onset; y, median (IQR)	5.8 (3.0-9.0)	4.2 (2.0-8.5)	1.0 (0.9-1.01)	.1
Disease status				
Inactive, n (%)	140 (74.1)	130 (81.3)	1.2 (0.97-1.5)	.08
Active, n (%)	49 (25.9)	30 (18.8)		
JADI-A, ≥1, n (%)	60 (31.7)	47 (29.3)	1.1 (1.0-1.1)	.05
JADI-E, ≥1, n (%)	45 (23.8)	36 (22.5)	1.0 (0.8-1.2)	.9

Abbreviations: CI, coefficient intervals; ERA, enthesitis-related arthritis; F, female; JADI-A, juvenile arthritis damage index-articular; JADI-E, juvenile arthritis damage index- extra-articular; JIA, juvenile idiopathic arthritis; M, male; OR, odds ratio; RF, rheumatoid factor.

outcome. Our results showed some similarity to the observations from other studies.[18] Most previous studies of familial JIA have either ignored the familial aggregation of autoimmunity in JIA or have not reported long-term disease outcome.[9,10,18]

This study has its limitations, and results should be interpreted carefully. Sample size was not calculated, given the rarity of this disease and the nature of this work (retrospective observational study), in particular the sample taken from an abnormally distributed population. We are aware of the analytical challenges that arise without power analysis. Also, data were collected retrospectively for patients diagnosed over a long period with variations in management and availability of medications. Information about the relative's autoimmune disease was obtained from the participants without confirmatory review of their records. Additionally, molecular genetic studies were not considered in this work. There was no healthy matched control group. Accordingly, the prevalence rate of familial autoimmunity was not calculated.

5 | CONCLUSION

This study shows that autoimmune diseases cluster within families of patients with JIA with a high proportion of ERA and psoriatic arthritis. JIA patients with FHADs are likely to have more disease damage. To the best of our knowledge, this is the largest study showing the impact of familial aggregation of autoimmunity on long-term prediction of a highly consanguineous population-based JIA cohort. Our findings might be useful in guiding decisions about JIA management

and family counseling. Hence, FHADs should be systematically considered in the assessment of children with JIA. However, further studies are needed to assess the impact of familial autoimmunity in patients with JIA before this is incorporated as an established risk.

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