Turkish Archives of Pediatrics

ORIGINAL ARTICLE
DOI: 10.5152/TurkArchPediatr.2023.22303

Non-Rheumatic Chronic Comorbidities in Children with Juvenile Idiopathic Arthritis

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What is already known on this topic?

- *Juvenile idiopathic arthritis is the most common rheumatic condition in childhood.*
- *It was previously shown that there is increased frequency of autoimmune diseases in children with juvenile idiopathic arthritis.*

What this study adds on this topic?

- *Nearly one-third of patients with juvenile idiopathic arthritis have at least 1 non-rheumatic medical condition.*
- *Atopic diseases are the most common comorbidity group in juvenile idiopathic arthritis patients.*
- *While patients with systemic juvenile idiopathic arthritis are unlikely to have autoimmune diseases, juvenile idiopathic arthritis patients with primary immune deficiencies are likely to be anti-nuclear antibody positive.*

ABSTRACT

Objective: Juvenile idiopathic arthritis is a heterogeneous group of disorders and is the most common rheumatic condition in childhood. There are scarce data regarding all comorbidities in juvenile idiopathic arthritis patients.

Materials and Methods: We aimed to identify the non-rheumatic comorbidities in our juvenile idiopathic arthritis patients. Data were obtained cross-sectionally from the medical records and the face-to-face interviews for 6 consecutive months. Those with more than 1 rheumatic disease were excluded, and conditions that were highly related to the disease, such as uveitis, were not taken into account.

Results: The study included 459 patients with female dominance (62.1%, n = 285). The median age of the patients was 12.87 (1.53-20.95) years. One hundred fifty patients (32.7%) had at least 1 comorbidity (5 patients had 3 comorbidities, and 24 patients had 2 comorbidities). The most common 3 non-rheumatic accompanying medical conditions in our patients were allergic rhinitis (n = 37, 8.1%), attention-deficit hyperactivity disorder (n = 35, 7.6%), and atopic dermatitis (n = 28, 6.1%). None of our patients with systemic JIA had any autoimmune disease. All the patients with primary immune deficiencies had anti-nuclear antibody positivity.

Conclusion: Almost one-third of our patients had at least one comorbidity. This finding might be very helpful to us in planning our multi-disciplinary approach to our patients.

Keywords: Biological products, comorbidity, juvenile idiopathic arthritis

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is a heterogeneous group of disorders, and it is the most frequently seen rheumatic disease in childhood, with a prevalence of 7-150 per 100 000.[1] It is characterized by chronic arthritis lasting longer than 6 weeks due to unknown etiology, which occurs before age 16.[2] Rather than being a single disease, JIA is an umbrella term including 7 different types of childhood chronic arthritis.[3,4] Although the discussion of reclassification of JIA is currently ongoing, oligoarticular JIA is the most common subtype according to available criteria.[5]

Medical treatment approaches in JIA were significantly improved, particularly in the last 2 decades. Increasing timely and appropriate using of intraarticular steroids, methotrexate, and several biological agents among pediatric rheumatologists ensured better disease control and outcome in this group of patients.[6]

However, arthritis is the tip of the iceberg. Despite the increased likelihood of well-control of articular inflammation with time, JIA is still responsible for many disabilities and morbidities buried in the hidden part. Considering the chronic inflammation mainly driven by

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Received: December 7, 2022
Accepted: January 5, 2023
Publication Date: March 1, 2023

Cite this article as: Haşlak F, Guliyeva V, Hotaman B, et al. Non-rheumatic chronic comorbidities in children with juvenile idiopathic arthritis. *Turk Arch Pediatr.* 2023;58(2):212-219.

autoimmunity is in the disease pathogenesis, many comorbidities would accompany JIA.[7] Comorbidity is defined as any medical condition apart from the index disease, which may be transient, active, or persistent, occurring before, during, or after the index disease.[8] Awareness of these possible comorbidities is crucial to be agile to offer the best outcomes for our patients. However, they have scantily been studied in JIA patients.

The primary aim of our study is to evaluate all the comorbidities with the exclusion of rheumatic ones in children with JIA. An additional secondary aim is to identify associated factors with the frequencies of certain comorbidities which have been considered to be highly related to JIA itself or its treatment regimens.

MATERIALS AND METHODS

The local Ethics Committee (04/04/2018-127814) of our tertiary center approved this study. We obtained written informed consent from all the patients or their parents. We followed the recommendations of the Declaration of Helsinki during the whole study process.

Study Population

Among the patients with JIA under 21, who were admitted for the routine control between September 2020 and April 2021 were included in the study. Those with additional rheumatic diseases other than JIA, those with less than 6 months of follow-up duration, and those who did not approve to attend this study were excluded. Data were obtained from face-to-face interviews and their medical records cross-sectionally during consecutive 6 months.

Study Design

For the diagnosis and the classification of JIA, "The International League of Associations for Rheumatology (ILAR)" criteria were used.[2] Age, gender, follow-up durations, and the treatments received by the patients were obtained from their medical records, retrospectively. All the comorbidities were questioned, cross-sectionally.

All the non-rheumatic comorbidities declared by the patients or their parents at their face-to-face appointments were meticulously evaluated and verified by data obtained from their medical records available in either patient files or our national online health registry system.

The comorbidity term does not encompass the disease's complications, consequences, and natural course domains. Therefore, uveitis, macrophage activation syndrome (MAS), growth failure, and psoriasis, which are well-known to be JIA-related medical conditions, were not taken into account in our study.[9-12] Since JIA patients often receive intense immunosuppressive medication, we did not evaluate the recurrent or chronic infections, either.

Autoimmune diseases, atopic diseases, primary immune deficiencies (PIDs), malignancies, and attention-deficit hyperactivity disorder (ADHD) were considered to be highly related to JIA itself or its treatment inversely or directly due to several reasons that will be discussed widely below.

Therefore, these groups of diseases were aimed to be investigated further, and the effects of possible variables such as systemic disease onset, anti-nuclear antibody (ANA) positivity, biologic treatment, and gender on their frequencies were measured. However, PIDs and malignancies could not be included in this next-step analysis due to the low number of cases that may cause type 2 errors.

Laboratory Terms

In order to differentiate the rheumatoid factor (RF) positive polyarticular JIA patients from RF negative ones, at least 2 RF positive results at least 3 months apart are required in our study, consistent with ILAR criteria.[2]

Considering that patients with larger ANA titers are significantly likely to develop certain autoimmune conditions, the cut-off titer of the ANA positivity term was defined as ≥1/80 detected by the immunofluorescence assay method regardless of the staining pattern, as in several previous studies.[13-16]

Statistical Analysis

We performed the statistical analysis using Statistical Package for Social Sciences for Windows, version 22.0 (IBM Corp.; Armonk, NY, USA). We presented the ages of the patients as median (minimum-maximum) due to their abnormal distribution, which was measured using the Kolmogorov–Smirnov test. We expressed categorical variables as numbers (percentages). We compared the ages of the patients by using the Mann–Whitney *U*-test. We compared categorical variables by using the Chi-square test or Fisher's exact test, which is appropriate. The lower *P* values than .05 were defined as the statistical significance of any analysis. We used Prism software (Prism 8, GraphPad Software, San Diego, Calif., USA) to picture data in figures.

RESULTS

Baseline Characteristics

The study included 459 patients with a female dominance (62.1%, n = 285). The median age of the patients was 12.87 (1.53-20.95) years. The most common subtype was persistent oligoarticular JIA (n = 211, 46.1%), and the others were enthesitis-related arthritis (ERA) (n = 79, 17.2%), systemic JIA (n = 57, 12.4%), RF negative polyarticular JIA (n = 56, 12.2%), psoriatic arthritis (n = 27, 5.9%), RF positive polyarticular JIA (n = 18, 3.9%), and extended oligoarticular JIA (n = 11, 2.4%). Disease subtype frequencies of the patients are given in Figure 1.

While the follow-up duration of 65 patients (14.2%) was more than 10 years, it was 5-10 years in 117 patients (25.5%), 1-5 years in 226 patients (49.2%), and 6 months-1 year in 51 patients (11.1%). Anti-nuclear antibody testing was performed in all of our patients, and 198 of them (43.1%) were considered to be ANA positive.

Two hundred thirty-three patients (50.8%) were receiving at least one of the conventional-disease modifying anti-rheumatic drugs such as methotrexate (n = 214, 46.6%), leflunomide (n = 20, 4.4%), sulfasalazine (n = 16, 3.5%), azathioprine (n = 4, 0.9%), and cyclosporine (n = 1, 0.2%). Additionally, 132 patients (28.8%) were receiving systemic steroids.

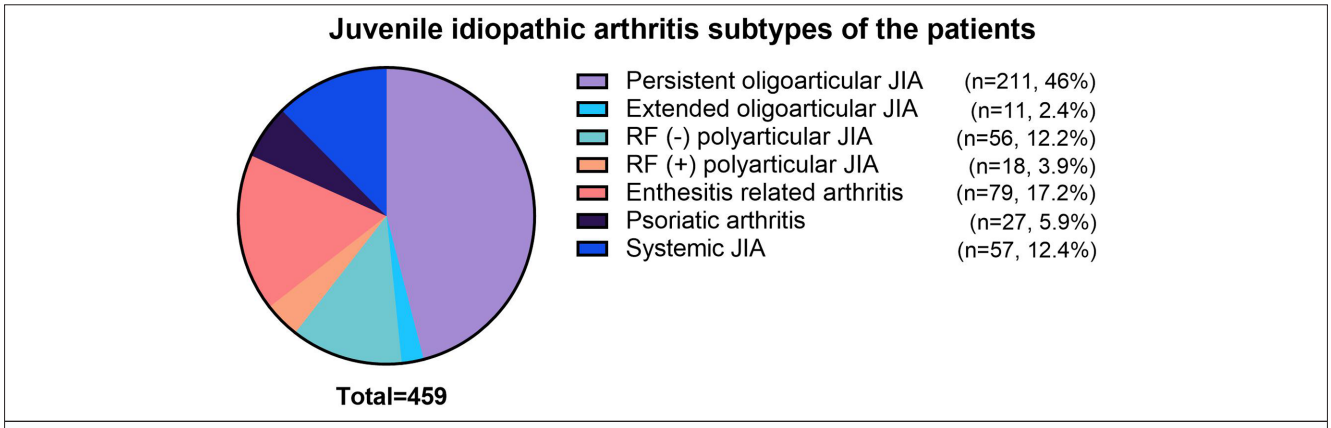

Figure 1. The subtype distribution of our patients with juvenile idiopathic arthritis.

Besides, 169 patients (36.8%) were under biological-disease modifying anti-rheumatic drugs treatment such as etanercept (n = 94, 20.5%), adalimumab (n = 46, 10%), tocilizumab (n = 12, 2.6%), canakinumab (n = 10, 2.2%), infliximab (n = 6, 1.3%), and anakinra (n = 1, 0.2%). Baseline characteristics of the patients by their disease subtypes are given in Table 1.

Comorbidities

One hundred fifty patients (32.7%) had at least one comorbidity (5 patients had three comorbidities, and 24 patients had 2 comorbidities). The most common non-rheumatic accompanying medical condition in our patients was allergic rhinitis (n = 37, 8.1%). The others were as follows: ADHD (n = 35, 7.6%), atopic

Table 1. Baseline Characteristics of the Patients by Their Disease Subtypes

	Extended Oligoarticular JA (n = 11)	Persistent Oligoarticular JA (n = 211)	RF Positive Polyarticular JIA (n = 18)	RF Negative Polyarticular JIA (n = 56)	Enthesitis-Related Arthritis (n = 79)	Psoriatic Arthritis (n = 27)	Systemic JIA (n = 57)
Age (median [min-max])	12.19 (3.97-18.83)	10.67 (1.63-20.87)	11.60 (1.53-20.95)	12.57 (5.00-20.17)	16.78 (6.86-20.94)	15.36 (4.39-20.12)	13.54 (2.49-20.38)
Gender							
Female (n, %)	9 (81.8%)	142 (67.3%)	17 (94.4%)	43 (76.8%)	23 (29.1%)	18 (66.7%)	33 (57.9%)
Male (n, %)	2 (18.2%)	69 (32.7%)	1 (5.6%)	13 (23.2%)	56 (70.9%)	9 (33.3%)	24 (42.1%)
Follow-up duration							
6 months–1 year (n, %)	2 (18.2%)	31 (14.7%)	2 (11.1%)	3 (5.4%)	7 (8.9%)	1 (3.7%)	5 (8.8%)
1-5 years (n, %)	1 (9.1%)	94 (44.5%)	9 (50%)	29 (51.8%)	46 (58.2%)	12 (44.4%)	35 (61.4%)
5-10 years (n, %)	4 (36.4%)	59 (28%)	2 (11.1%)	12 (21.4%)	22 (27.8%)	7 (25.9%)	11 (19.3%)
>10 years (n, %)	4 (36.4%)	27 (12.8%)	5 (27.8%)	12 (21.4%)	4 (5.1%)	7 (25.9%)	6 (10.5%)
Ongoing treatment							
Steorid (n, %)	3 (27.3%)	59 (28%)	5 (27.8%)	19 (33.9%)	25 (31.6%)	6 (22.2%)	15 (26.3%)
cDMARD (n, %)	5 (45.5%)	113 (53.6%)	12 (66.7%)	35 (62.5%)	36 (45.6%)	15 (55.6%)	56 (70.9%)
Methotrexate (n)	5	105	10	30	32	15	17
Leflunomid (n)	-	7	2	4	6	1	-
Cyclosporine (n)	–	–	-	–	–	–	1
Azathioprine (n)	-	3	-	1	-	-	-
Salazopyrin (n)	-	3	–	–	12	1	-
bDMARD (n, %)	5 (45.5%)	62 (29.4%)	8 (44.4%)	22 (39.3%)	38 (48.1%)	12 (44.4%)	17 (29.8%)
Anakinra (n)	-	-	-	-	-	-	1
Canakinumab (n)	-	-	-	-	-	-	10
Etanercept (n)	5	37	5	16	18	9	4
İnfliximab (n)	-	3	-	-	2	1	-
Adalimumab (n)	-	20	2	2	17	2	3
Tocilizumab (n)	-	2	1	1	1	-	4

bDMARD, biologic-disease modifying-antirheumatic drug; cDMARD, conventional-disease modifying-antirheumatic drug; JIA, Juvenile idiopathic arthritis; RF, Rheumatoid factor.

dermatitis (n = 28, 6.1%), allergic asthma (n = 14, 3.1%), migraine (n = 10, 2.2%), food allergy (n = 6, 1.3%), autoimmune thyroiditis (n = 6, 1.3%), PIDs (n = 5, 1.1%), vitiligo (n = 5, 1.1%), allergic urticaria (n = 5, 1.1%), inflammatory bowel disease (n = 5, 1.1%), congenital heart disease (n = 4, 0.9%), scoliosis (n = 3, 0.7%), vesicoureteral reflux (n = 3, 0.7%), epilepsy (n = 3, 0.7%), type 1 diabetes mellitus (DM) (n = 2, 0.4%), Hirschsprung disease (n = 1, 0.2%), cystic fibrosis (n = 1, 0.2%), neural tube defect (n = 1, 0.2%), deafness (n = 1, 0.2%), astrocytoma (n = 1, 0.2%), down syndrome (n = 1, 0.2%), retinitis pigmentosa (n = 1, 0.2%), hypertension, (n = 1, 0.2%), Wilms tumor (n = 1, 0.2%), idiopathic thrombocytopenic purpura (n = 1, 0.2%), cerebral palsy (n = 1,

Table 2. Comorbidities of the Patients by Their Disease Subtypes

	Extended Oligoarticular JIA (n = 11)	Persistent Oligoarticular JIA (n = 211)	RF Positive Polyarticular JIA (n = 18)	RF Negative Polyarticular JIA (n = 56)	Enthesitis Related Arthritis (n = 79)	Psoriatic Arthritis (n = 27)	Systemic JIA (n = 57)
Comorbidity count							
None (n, %)	9 (81.8%)	147 (69.7%)	13 (72.2%)	39 (69.6%)	53 (67.1%)	14 (51.9%)	34 (59.6%)
One (n, %)	2 (18.2%)	52 (24.6%)	4 (22.2%)	13 (23.2%)	23 (29.1%)	9 (33.3%)	18 (31.6%)
Two (n, %)	-	9 (4.3%)	-	3 (5.4%)	3 (3.8%)	4 (14.8%)	5 (8.8%)
Three (n, %)	-	3 (1.4%)	1 (5.6%)	1 (1.8%)	-	-	-
Atopic diseases							
Allergic rhinitis (n, %)	1 (9.1%)	14 (6.6%)	1 (5.6%)	5 (8.9%)	6 (7.6%)	1 (3.7%)	9 (15.8%)
Allergic asthma (n, %)	-	5 (2.4%)	-	1 (1.8%)	2 (2.5%)	1 (3.7%)	5 (8.8%)
Allergic urticaria (n, %)	-	2 (0.9%)	1 (5.6%)	1 (1.8%)	-	-	1 (1.8%)
Atopic dermatitis (n, %)	-	12 (5.7%)	-	4 (7.1%)	5 (6.3%)	5 (18.5%)	2 (3.5%)
Food allergy (n, %)	-	3 (1.4%)	1 (5.6%)	1 (1.8%)	1 (1.3%)	-	-
Autoimmune diseases							
Autoimmune thyroiditis (n, %)	-	2 (0.9%)	1 (5.6%)	2 (3.6%)	-	1 (3.7%)	-
Autoimmune hepatitis (n, %)	-	1 (0.5%)	-	-	-	-	-
Type 1 DM (n, %)	-	1 (0.5%)	-	-	1 (1.3%)	-	-
ITP (n, %)	-	1 (0.5%)	-	-	-	-	-
Vitiligo (n, %)	-	4 (1.9%)	-	-	-	1 (3.7%)	-
Malignancies							
Wilms tumor (n, %)	-	-	-	-	-	1 (3.7%)	-
Astrocytoma (n, %)	-	1 (0.5%)	-	-	-	-	-
Neurological diseases							
Migraine (n, %)	-	4 (1.9%)	-	2 (3.6%)	2 (2.5%)	-	2 (3.5%)
Epilepsy (n, %)	-	3 (1.4%)	-	-	-	-	-
Pseudotumor cereri (n, %)	-	-	-	-	-	-	1 (1.8%)
Cerebral palsy (n, %)	1 (9.1%)	-	-	-	-	-	-
Neural tube defect (n, %)	-	1 (0.5%)	-	-	-	-	-
Gastrointestinal diseases							
Hirschsprung disease (n, %)	-	-	-	-	1 (1.3%)	-	-
IBD (n, %)	-	2 (0.9%)	-	-	2 (2.5%)	-	1 (1.8%)
Others							
ADHD (n, %)	-	17 (8.1%)	2 (11.1%)	5 (8.9%)	5 (6.3%)	2 (7.4%)	4 (7%)
PIDs (n, %)	-	2 (0.9%)	1 (5.6%)	-	1 (1.3%)	1 (3.7%)	-
Cystic fibrosis (n, %)	-	1 (0.5%)	-	-	-	-	-
CHD (n, %)	-	1 (0.5%)	-	-	1 (1.3%)	1 (3.7%)	1 (1.8%)
Scoliosis (n, %)						2 (7.4%)	1 (1.8%)
Deafness (n, %)	-	-	-	1 (1.8%)	-	-	-
VUR (n, %)	-	1 (0.5%)	-	-	1 (1.3%)	-	1 (1.8%)
Down syndrome (n, %)	-	1 (0.5%)	-	-	-	-	-
Retinitis pigmentosa (n, %)	-	-	-	-	1 (1.3%)	-	-
Hypertension (n, %)	-	-	-	-	-	1 (3.7%)	-

ADHD, attention-deficit hyperactivity disorder; CH, congenital heart disease; CF, cystic fibrosis; DM, diabetes mellitus; IBD, inflammatory bowel disease; ITP, idiopathic thrombocytopenic purpura; JIA, juvenile idiopathic arthritis; PIDs, primary immune deficiencies; RF, rheumatoid factor; VUR, vesicoureteral reflux.

Table 3. The Frequencies of Any Comorbidities, Atopic Diseases, Autoimmune Diseases, and ADHD in Females, Children Under Biologic Treatment, and in Children with Systemic JIA, or ANA Positivity

	Any Comorbidity			Atopic Diseases			ADHD			Autoimmune Diseases		
n, (%)	Yes (n = 150)	No (n = 309)	*P*	Yes (n = 75)	No (n = 384)	*P*	Yes (n = 35)	No (n = 424)	*P*	Yes (n = 15)	No (n = 444)	*P*
Gender			.292			.147			1			1
Female	88 (58.7)	197 (63.8)		41 (54.7)	244 (63.5)		22 (62.9)	263 (62)		9 (60)	276 (62.2)	
Male	62 (41.3)	112 (36.2)		34 (45.3)	140 (36.5)		13 (37.1)	161 (38)		6 (40)	168 (37.8)	
ANA			.732			.500			.570			1
Positive	63 (42)	135 (43.7)		35 (46.7)	163 (42.4)		13 (37.1)	185 (43.6)		6 (40)	192 (43.2)	
Negative	87 (58)	174 (56.3)		40 (53.3)	221 (57.6)		22 (62.9)	239 (56.4)		9 (60)	252 (56.8)	
Disease			.243			.109			1			.235
Systemic	23 (15.3)	34 (11)		14 (18.7)	43 (11.2)		4 (11.4)	53 (12.5)		0 (0)	57 (12.8)	
Non-systemic	127 (84.7)	275 (89)		61 (81.3)	341 (88.8)		31 (88.6)	371 (87.5)		15 (100)	387 (87.2)	
Treatment			.715			.872			.188			.271
Biological	57 (38)	112 (36.2)		27 (36)	142 (37)		17 (48.6)	152 (35.8)		3 (20)	166 (37.4)	
Nonbiological	93 (62)	197 (63.8)		48 (64)	242 (63)		18 (51.4)	272 (64.2)		12 (80)	278 (62.6)	

ADHD, attention-deficit hyperactivity disorder; ANA, anti-nuclear antibody.

0.2%), autoimmune hepatitis (n = 1, 0.2%), and pseudotumor cerebri (n = 1, 0.2%). Comorbidities of the patients by their disease subtypes are given in Table 2.

Selected Disease Groups

In order to perform further analysis, certain disease groups were established. Those with allergic rhinitis, allergic asthma, allergic urticaria, atopic dermatitis, and food allergy were considered to have atopic diseases (n = 75, 16.3%). Those with autoimmune thyroiditis, vitiligo, type 1 DM, idiopathic thrombocytopenic purpura, and autoimmune hepatitis were considered to have autoimmune diseases (n = 15, 3.3%). In addition to these groups, patients with ADHD (n = 35, 7.6%) were also added into further analysis.

Those with systemic JIA and without, those with ANA positivity and without, those who were under biological treatment and those who were not, and females and males were compared to each other in terms of the frequencies of any comorbidity, atopic diseases, autoimmune diseases, and ADHD. There was no significant difference. However, none of the patients with systemic JIA had any of the autoimmune diseases. On the other hand, all of the patients with PIDs (n = 5) had ANA positivity. Detailed data are given in Table 3 and Figure 2.

DISCUSSION

We evaluated our JIA patients in terms of all comorbidities, excluding the rheumatic ones, cross-sectionally. The most common subtype was persistent oligoarticular JIA. Almost one-third of our patients had at least 1 comorbidity. The most common 3 comorbidities were allergic rhinitis, ADHD, and atopic dermatitis. Comorbidities were most commonly seen in those with psoriatic arthritis; nearly half had at least one. Although none of the patients with systemic JIA had any autoimmune diseases, there was no significant difference between them and non-systemic JIA patients regarding the frequency. None of the patients under biological treatment had malignity,

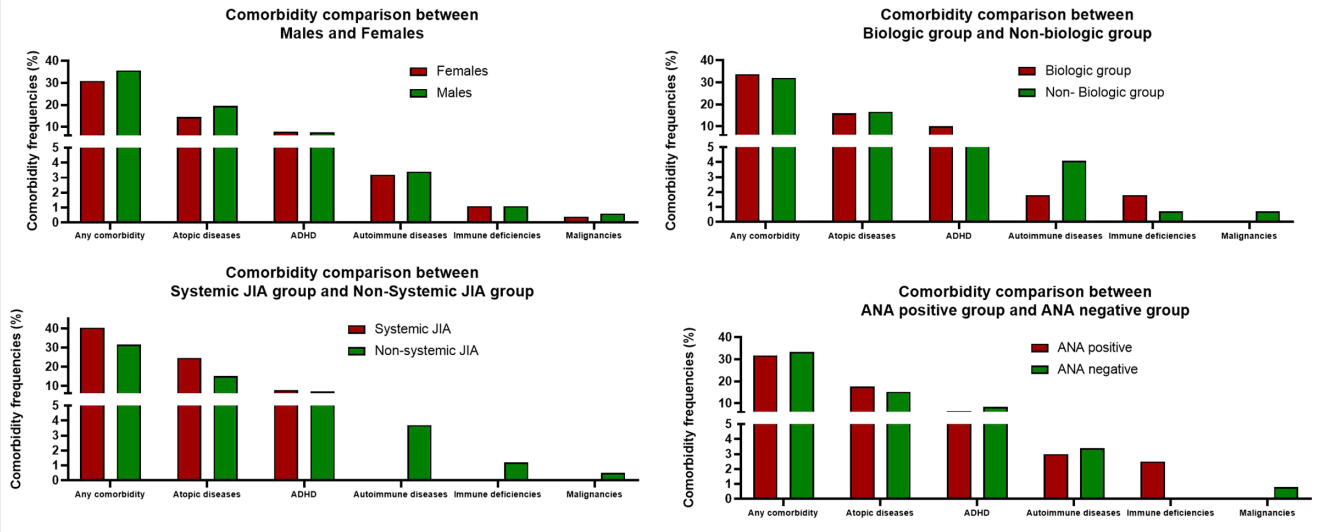

Figure 2. Comorbidity group comparisons between males and females, biologic group and non-biologic group, systemic group and non-systemic group, and anti-nuclear antibody positive and anti-nuclear antibody negative group.

and autoimmune diseases were less common in this group of patients. While there is no significant difference regarding ANA positivity between those with autoimmune diseases and those without, all patients with PIDs were ANA positive.

Advanced knowledge of comorbidities in children with inflammatory rheumatic conditions, which generally cause multisystem involvement, would be very helpful for us to arrange our multi-disciplinary approach and determine the prognosis. On this purpose, Yildiz et al[17] evaluated the comorbidities in children with familial Mediterranean fever (FMF). They did not exclude rheumatic diseases and showed nearly one-fifth of the patients to have co-existing diseases. The most common ones following JIA were asthma and Henoch–Schonlein purpura.

However, there is a scarce data regarding the children with JIA on this issue. In an adult study conducted with patients with rheumatoid arthritis, comorbidity was extremely common, with 75%.[18] In another adult study evaluating JIA patients under biological treatments, 62% of them had at least 1 comorbidity. The most common ones were uveitis, allergic rhinitis, and migraine.[19] However, those receiving biological treatment might be more likely to have comorbidities due to their possible refractory disease courses and more intense treatment regimens. In our study, 32.7% of the patients had co-existing diseases. We assumed that the facts that we included the patients regardless of their treatments, that we excluded the ones with more than one rheumatic disease, that we did not take into account disease-related conditions such as uveitis, and that we included only children and young adults were responsible for the relatively lower comorbidity frequency in our study. However, if we put uveitis aside, allergic rhinitis was the most common one in our study, either.

Although it is highly heterogeneous and poorly understood, autoimmunity that is mostly induced and maintained by the various elements of the adaptive immune system is the main pathogenetic mechanism for most of the subtypes of JIA.[20] Autoimmune diseases are characterized by tissue damage caused by autoreactive immune cells and certain antibodies, triggered by various environmental factors and epigenetic alterations in genetically susceptible hosts.[21] It has been previously shown that those with 1 autoimmune disease are more likely to develop a second one.[22] The accumulation of certain autoimmune diseases in some individuals is of interest and suggestive of genetic background. In favor of this sight, a strong association was shown between JIA and variants in TNFAIP3, STAT4, and C12orf30 regions that known to be associated with numerous autoimmune diseases.[23]

In our study, 3.3% of the patients had at least 1 concomitant autoimmune disease. Although several studies focused on one single autoimmune condition in JIA patients, there is a lack of data regarding all autoimmunities in this group. A recent study showed that while 15.2% of JIA patients had either clinical autoimmunity or elevated autoantibodies, only 4.2% of the total, similar to our finding, had a clinical autoimmune disease. While they showed Sjögren's disease as the most common autoimmune comorbidity, it was autoimmune thyroiditis in our study.[24] As aforementioned, we excluded rheumatic diseases.

Contrary to most subtypes of JIA, autoinflammation driven by mainly innate immune system elements rather than autoimmunity is prominent in systemic JIA pathogenesis.[25-28] Therefore, we hypothesized that autoimmune diseases would be more common in patients with non-systemic JIA than in patients with systemic JIA. Although we did not find a significant difference, none of the systemic JIA patients had any autoimmune condition. In a recent study, the prevalence of celiac disease and autoimmune thyroiditis were evaluated in JIA patients, and akin to our finding, none of the systemic JIA patients had any of them, possibly due to the pathogenetic differences of systemic subtype from the others.[16]

Type 1 diabetes mellitus (T1DM) is an autoimmune disease caused by the autoantibody-induced destruction of pancreatic beta cells, resulting in decreased insulin production and hyperglycemia.[29] It was shown by using the Poisson regression model that type 1 DM is significantly more common, with a prevalence of 0.5%, and onsets significantly earlier in JIA patients compared to the general population.[30] Similarly, 0.44% of our patients had type 1 DM. Hydroxychloroquine and anti-tumor necrosis factor (anti-TNF) agents were previously shown to reduce the risk of DM in adult patients with rheumatoid arthritis.[31-33] In our cohort, there were two patients with type 1 DM. One with ERA was in remission, but the other with persistent oligoarticular JIA was receiving etanercept.

Immune dysregulation disorders are generally characterized by a breakdown in the balance between the effector and regulatory components of the immune system, resulting in inappropriate immune responses, including autoimmunity and increased susceptibility to infections.[34] Defining the patients with autoimmune diseases accompanied by PIDs would help identify the patients with immune dysregulation whose diagnoses are relatively tough to set.[35] However, there is insufficient data regarding JIA patients on this issue. There were 5 patients with PIDs in our cohort. Two of them had selective immunoglobulin (Ig) A deficiency. Although 3 of them have no certain diagnosis, their immune globulin levels were found to be lower when they were screened because of common respiratory infections prior to their anti-rheumatic medication were started, they had benefits from the monthly intravenous immunoglobulin (IVIG) treatment, and therefore, they had been considered to have PIDs by the immunologists. All of the patients with PIDs had ANA positivity which is a suggestive tool for autoimmunity. One of the strongest messages to us is that these 3 patients require further genetic investigations. Selective IgA deficiency is the most common PIDs and has previously been shown to be associated with numerous autoimmune conditions, including JIA.[36-40]

While T-helper 2-related cytokines dominate the pathogenesis of atopic diseases, T-helper 1-type cytokines are prominent in JIA pathogenesis.[41,42] Therefore, atopic diseases were thought to hinder autoimmune disease development.[43] Likewise, one of our hypotheses was atopic diseases would be rare in our patients. However, atopic diseases were the most common comorbidity group in our patients, and they were seen in 16.3% of them. In an adult study performed on JIA patients, allergic disease frequency was higher than even in our one. Almost a quarter of the patients had any of them.[19] An adult study revealed that there is no inverse relation between atopic diseases and

autoimmune disorders.[44] Besides, it was suggested that highly increased serum IgE levels significantly enhance the risk of autoimmune diseases.[45] Hence, we suggest that the relationship between atopy and autoimmunity is quite complex and not as simple as T-helper 1/T-helper 2 theory.

Pro-inflammatory cytokines and inflammatory markers are increased in children with ADHD and correlated with the disease severity.[46-48] Therefore, we considered children with inflammatory rheumatic diseases more likely to have ADHD than the general population. Consistently, ADHD was found to be significantly more common in children with FMF.[49] However, no such data are evaluating JIA patients on this issue. Attention-deficit hyperactivity disorder was seen in 7.6% of our patients. A community-based study from our country reported the prevalence of ADHD with impairment as 12.4%.[50] Our relatively low results can be explained by the fact that the previous one was a screening study while we presented those already diagnosed in our study.

Another conundrum regarding JIA patients is malignity. Although malignity is common and a major concern in JIA patients, it remains unclear whether the reason is the disease itself or its medication, particularly biological treatments.[51] In our cohort, 2 patients had malignity, one with Wilms tumor and the other with astrocytoma. None of them were under biological treatment and never had. Only 1 patient had malignity in another study evaluating JIA patients in terms of malignity, and he was under biological treatment.[52]

There are noteworthy limitations in our study. First, we did not evaluate the disease activities of our patients that would contribute to developing comorbidity. Second, we have no healthy control group to compare. Third, we did not evaluate the intervals between the comorbidity onset, and neither JIA onset nor medication was started. Fourth, associated factors with the frequency of malignancies and PIDs could not be measured due to the limited number of cases.

In conclusion, we sought to identify the non-rheumatic comorbidities in our JIA patients and found that almost one-third had at least one. This finding might be very helpful to us in planning our multi-disciplinary approach to our patients. The main strength of the study is that this is the first one evaluating all comorbidities, except rheumatic conditions in children and young adults with JIA, as far as we know. In contrast with the previous common sense that suggests that atopic diseases might be rare in children with autoimmune diseases, the most common comorbidities in our study were atopic diseases. Attention-deficit hyperactivity disorder, believed to be more common in chronic inflammatory diseases, is the second most common comorbidity, and its frequency in JIA patients was evaluated for the first time in our study. None of our patients with systemic JIA had an autoimmune disease. This finding is in line with the pathogenetic difference between the systemic subtype and the other subtypes of JIA. All our JIA patients with PIDs had ANA positivity which supports the idea that they also have autoimmunity in addition to immune deficiency. Therefore, we suggest that immune dysregulations should be considered in all JIA patients with a history of common infections, particularly if they are ANA positive.

Ethics Committee Approval: The study was approved by İstanbul University-Cerrahpaşa Institutional Review Board (04/04/2018-127814).

Informed Consent: A written informed consent was obtained from all the participants included in this study and no identifying information of any participant was included in this article.

Peer-review: Externally peer-reviewed.

Author Contributions: Data Collection and/or Processing – F.H., V.G., B.H., E.A., E.K.K., C.D.; Analysis and/or Interpretation – F.H., V.G., B.H., E.A., E.K.K., C.D.; Writing Manuscript – F.H., M.Y., A.G., A.A., A.A., S.S., K.B.; Critical Review – O.K.

Declaration of Interests: The authors have no conflict of interest to declare.

Funding: This study received no funding.

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