Juvenile idiopathic arthritis in a center in the Western Anatolia region in Turkey

Türkiye İç Batı Anadolu Bölgesi'ndeki bir merkezde jüvenil idiyopatik artrit

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The known about this topic

Juvenile idiopathic arthritis shows variances in terms of sex, age at the time of diagnosis, and treatment response by subtypes from region to region. Local studies show that these variances are associated with many causes including genetic and environmental factors.

Contribution of the study

In this study, the characteristics of patients with juvenile idiopathic arthritis were compared with national and international data, and structural differences and similarities of our region were examined. Enthesitis-related arthritis is the most common subtype. It was emphasized that enthesitis should not be overlooked on physical examination as enthesitis-related arthritis has the poorest prognosis in terms of diagnostic delay and treatment response.

Abstract

Aim: To demonstrate the demographic data, subgroup distributions, responses to treatment and outcomes of long-term follow-up in patients who were followed up and treated in our clinics with a diagnosis of juvenile idiopathic arthritis, and to compare these data with national and international data.

Material and Methods: The files of 116 patients who had been diagnosed as having juvenile idiopathic arthritis, were initiated on treatment and presented for regular follow-up visits between January 2012 and January 2018, were examined. Their demographic findings, treatments, active/inactive disease states (on-medication and off-medication) and treatment response states were evaluated.

Results: According to the International League of Associations for Rheumatology criteria, the subtypes were specified as enthesitis-related arthritis (n=38), oligoarticular (n=37), rheumatoid factor (-) polyarticular (n=17), systemic (n=15), rheumatoid factor (+) polyarticular (n=5), and psoriatic juvenile idiopathic arthritis (n=4). In total, the female/male ratio was found to be 1.5. The mean delay time between the first complaint and the diagnosis was found to be 5.7±5.2 months. The patients with systemic type were diagnosed at the earliest, while the patients with polyarticular and enthesitis-related subtypes were diagnosed at the latest. Thirty-two percent of the patients were treated

Öz

Amaç: Kliniğimizde izlem ve tedavi edilen jüvenil idiyopatik artrit tanılı hastaların demografik verilerini, alt gruplarına dağılımını, tedaviye yanıtlarını ve uzun dönem izlemlerini ortaya koymak, ulusal ve uluslararası veriler ile karşılaştırmaktır.

Gereç ve Yöntemler: Ocak 2012 ile Ocak 2018 tarihleri arasında jüvenil idiyopatik artrit tanısı alarak tedavi başlanan, düzenli kontrole gelen 116 hastanın dosyası incelendi. Demografik bulgular, aldığı tedaviler, aktif/inaktif hastalık (ilaçlı ve ilaçsız) ve tedaviye yanıt durumları değerlendirildi.

Bulgular: Uluslararası Romatoloji Derneği Birliği ölçütlerine göre jüvenil idiyopatik artrit alt tipleri 38 entezit ilişkili artrit, 37 oligoartiküler, 17 romatoid faktör (-) poliartiküler, 15 sistemik, 5 romatoid faktör (+) poliartiküler, 4 psöriatik jüvenil idiyopatik artrit olarak değerlendirildi. Toplamda kız erkek oranı 1,5 idi. İlk yakınma ile tanı konulması arasındaki gecikme süresi ortalama 5,7±5,2 aydı. En erken tanı alan sistemik tipte hastalar, en geç tanı alan hastalar ise poliartiküler ve entezit ilişkili alt tipte olanlardı. Hastaların %32'sine yalnızca metotreksat tedavisi verilirken, %38'ine ek biyolojik ilaçlar verildi. Her iki tedavi grubunda inaktif

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with methotrexate alone, and 38% were given additional biologic drugs. In both treatment groups, the time to achieve inactive disease was the shortest in the oligoarticular group and the longest in the enthesitis-related arthritis group. In the study period, 38 patients were in remission off-medication (the highest rate (53.3%) was observed in the systemic group) and 71 patients were in remission on-medication (the highest rate (70.2%) was observed in the oligoarticular group). Remission was obtained in 94% of the patients.

Conclusion: Enthesitis which is the remarkable finding of enthesitis-related arthritis, should not be overlooked in routine physical examination. Awareness of enthesitis can contribute to the prevention of diagnostic delay in children with enthesitis-related arthritis.

Keywords: Antirheumatic drugs, juvenile idiopathic arthritis, methotrexate

zamana geçiş süresi en kısa oligoartiküler, en uzun entezit ilişkili artrit grubundaydı. Çalışma döneminde 38 hasta ilaçsız iyilik hali (en yüksek oran %53,3 ile sistemikte), 71 hasta ilaçlı iyilik hali (en yüksek oran %70,2 ile oligoartikülerde) olarak izlenmekteydi. Hastaların %94'ünde iyilik hali sağlandı.

Çıkarımlar: Entezit ilişkili artritin dikkat çekici bulgusu olan entezitin rutin fizik muayenede göz ardı edilmemesi gerekmektedir. Entezit farkındalığı, entezit ilişkili artritli çocuklarda tanı gecikmesinin önlenmesine katkıda bulunabilir.

Anahtar sözcükler: Antiromatizmal ilaç, jüvenil idiyopatik artrit, metotreksat

Introduction

Juvenile idiopathic arthritis (JIA) is among the most common rheumatic diseases of childhood and has been described as a chronic inflammatory synovitis. It is a heterogeneous disease that lasts for at least six weeks with an onset before the age of 16 years, and is diagnosed after excluding other known causes of arthritis. Different classification systems have been developed. The final classification system was updated by the International League of Associations for Rheumatology (ILAR) in 2011 and classified seven subgroups including systemic, oligoarticular (persistent and extended), enthesitis-related, polyarticular rheumatic factor (RF)-positive, polyarticular RF-negative, psoriatic, and unclassified arthritis (1). The prevalence and incidence of JIA depend on genetic and environmental factors, and may show significant variance among different societies. The prevalence of juvenile rheumatic arthritis has been reported as 0.007–4.01 in 1000 children, and its annual incidence has been reported as 0.008–0.262 per 1000 children (2).

The incidences of JIA subtypes, age at the time of diagnosis, sex, and responses to drugs show variance in studies conducted worldwide and in different regions of Turkey (3–13). In this study, we aimed to examine the incidences of JIA subgroups and treatment responses in patients with JIA in our Pediatric Rheumatology Clinic that follows up patients presenting from some provinces of the Inner Western Egean region (Denizli, Uşak, Afyon) and Mediterranean region (Burdur, Isparta, Antalya), and the patients' demographic clinical characteristics. The results of our patient population were compared with national and international data.

Material and Methods

In this retrospecitve cohort study, the files of 116 patients who were diagnosed as having JIA, who were initiated treatment and attended regular follow-up visits between January 2012 and January 2018, were examined. Ten patients who did not attent regular follow-up visits were not included in the study. At the time of diagnosis, other causes leading to arthritis including post-inflammatory arthritis, systemic inflammatory diseases, malignancy, and metabolic diseases were exluded. During the JIA subgroup classification, the ILAR criteria were used at the time of diagnosis and when reclassification was made after six months' treatment was completed (1). The patients' demographic data (JIA subtype, age, sex, age at the time of diagnosis, diagnostic delay, follow-up period) treatments, and treatment periods were recorded. Positivity for antinuclear antibody (ANA), rheumatoid factor (RF), and human leukocyte antigen 27 (HLA B27) was examined in all patients. An ANA titer of 1/100 measured using immunoflourescence was considered positive. Two rheumatoid factor values measured with an interval of 3 months in a six-month period above 10 U/L were considered significant. Human leukocyte antigen B27 was evaluated as positive and negative. All patients were examined by an opthalmologist every six months in terms of uveitis. Ultrasonography was performed in patients who had peripheral joint involvement, and magnetic resonance imaging (MRI) was performed in patients who had inflammatory back pain or sacroileitis findings. Familial Mediteranean fever (FMF) was interrogated according to childhood FMF criteria (14) in all patients and MEFV gene analysis was requested; colchicine treatment was initiated when the clinical picture was compatible. Treatments, treatment durations, and responses were evaluated in association in all patients. Considering active disease and inactive disease (clinical remission on- and off-medication) states at the time of final visit, and the time to reach inactive disease was recorded. Inactivity status was evaluated according to the Wallace criteria (15) [absence of active arthritis, absence of fever-rash-serositis-splenomegaly-diffuse lymphadenopathy, absence of uveitis, normal erythrocyte sedimentation rate (ESR) and C-reactive protein, lower visual analogue scale score compared with the previous value, shorter duration of morning stiffness (less than 15 minutes)]. Inactive disease while using medication for at least six months was defined as status of clinical remission on medication. Presence of inactive disease for at least 12 successive months' treatment was defined as status of clinical remission off-medication.

The study was conducted in accordance with the principles of the Helsinki Decleration and approved by the local ethics committee (30.10.2018/20 and 16.04.2019/08).

Table 1. Demographic properties of the patients

	Total n=116	Oligoarticular JIA n=37	Enthesitis-related arhtirits n=38	Polyarticular JIA n=22	Systemic JIA n=15	Psoriatic JIA n=4	p
Female/male n/n	71/45	25/12	22/16	15/7	7/8	2/2	
Mean age (years)	12.9±4.7	10.4±4.8	15.4±3.1	14.6±4.9	10.5±3.9	16.1±1.0	p_1<0.001 p_2<0.001
Mean age at the time of diagnosis (years)	10.1±4.5	7.6±4.5	12.6±3.0	10.6±4.9	8.4±4.2	12.6±1.9	p_1<0.001
Diag-nostic delay time (months)	5.7±5.2	3.4±3.4	7.4±5.5	8.9±5.4	1.7±1.6	4.0±3.5	p_1<0.001
Follow-up time (months)	24.5±17.8	20.7±16.7	24.2±17.6	30.1±18.1	22.9±18.7	37±22.5	
Positive family history, n (%)	13 (11.2)	4 (16.7)	7 (25)	2 (11.1)	–	–	

Comparison was not made because the numbers of patients with psoriatic JIa and systemic JIA were low. JIA: Juvenile idiopathic arthritis

Written informed consent was not obtained because the study had a retrospective design.

Statistical Analysis

The data were analyzed using the SPSS 24.0 (IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp.) package program. Continuous variables are expressed as mean±standard deviation and median (minimum and maximum values). Categorical variables are expressed as numbers and percentages. The compatibility of the data with normal distribution was examined using the Shapiro-Wilk test. Kruskal-Wallis variance analysis was used for the comparison of the differences of independent groups (Mann-Whitney U test with a Bonferroni correction for binary examinations). Differences between categorical variables were examined using Chi-square analysis. A p value of <0.05 was considered statistically significant.

Results

Thirty-eight of 116 patients with JIA were classified as having enthesitis-related arthritis (ERA), 37 were classifed as oligoarticular JIA, 17 were classifed as RF(-) polyarticular JIA, 15 were classified as systemic JIA, five were classifed as RF(+) polyarticular JIA, and four were classifed as psoriatic JIA. Definite subtype classification was made once again one month after the diagnosis, and two patients were observed to have transformed from oligoarthritis to extended oligoarthritis type. Female sex was predominant in the subgroups excluding psoriatic JIA. The mean age at the time of diagnosis was found as 10.1±4.5 years, the mean follow-up time was found as 24.5±17.8 months, and female sex was predominant (female/male: 1.57). The highest mean age was found in the patients who had ERA, followed by polyarticular JIA, oligoarticular JIA, and

systemic JIA (Table 1). The ages at the time of diagnosis were significantly different from each other among the subgroups (p<0.001). The mean ESR value at the time of diagnosis was found as 78.2 mm/h (the highest value) in the systemic JIA group and 48.2 mm/h (the lowest value) in the ERA group. The mean diagnostic delay time was found as 5.7±5.2 months. In this regard, it was found that the patients in the systemic JIA subgroup were diagnosed the earliest and the patients in the polyarticular and ERA groups were diagnosed the latest (Table 1). In addition, the diagnostic delay times in the subgroups were significantly different from each other (p<0.001). The longest follow-up time was found in the polyarticular JIA type and the shortest follow-up time was found in the oligoarticular JIA type (Table 1). A positive familial history was found in 11.2% of the patients, and the highest rate of positive familial history was found in the ERA subgroup (25%) (Table 1). The percentage of anti-nuclear antibody (ANA) positivity was found as 62.2% in the oligoarticular group. In the whole patient group, this percentage was found to be approximately 44%. Rheumatoid factor was found to be positive in 22.7% of the patients with polyarticular JIA. HLA B27 was found to be positive in 21.1% of the patients with enthesitis-related arthritis. Uveitis developed in three (2.6%) patients; two of these patients were diagnosed as having oligoarticular JIA and one was diagnosed as having RF-negative polyarticular JIA. MEFV gene mutation was tested in 62 patients who had a prediagnosis of FMF. Additional colchicine treatment was initiated in 16 (13.7%) children because the clinical picture was compatible with the criteria of FMF. The M694V gene mutation, which is the most common gene mutation in this patient group, was found homozygously in six patients (Table 2). In the oligoarticular JIA group, the most commonly in-

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Table 2. MEFV mutations in the patients with juvenile idiopathic arthritis and familial Mediterranean fever

	Enthesitis-related arthritis	Oligoarticular JIA	Polyarticular JIA	Psoriatic JIA
M694V homozygous	4	2	–	–
M694V heterozygous	1	1	1	1
M680I heterozygous	1	–	–	–
M694V heterozygous and M680I heterozygous (Compound heterozygous)	1	–	–	–
V726A heterozygous	–	1	–	–
E148Q heterozygous	2	–	–	–
R202Q heterozygous	1	–	–	–
Total	10	4	1	1

JIA: Juvenile idiopathic arthritis

Table 3. Drug use and drug use times

	Total n=116	Oligoarticular JIA n=37	Enthesitis-related arthritis n=38	Polyarticular JIA n=22	Systemic JIA n=15	Psoriatic JIA n=4	p
Metho-treaxate alone, n (%)	81 (69.8)	27 (72.9)	28 (73.6)	19 (86.3)	7 (46.6)	4 (100)	
Time to transition to inactive disease in patients who did not use biologic drug (months)[abc]	4.2±3.5	3.1±2.9	5.6±4.3	4.6±3.4	2.5±0.5	3.5±0.7	*p<0.001
Number of patients who used biologic drug, n (%)	38 (32.7)	10 (27)	12 (31.6)	9 (40.9)	5 (33.3)	2 (50)	
Time to transition to inactive disease following use of biologic drug (months)	2.1±1.1	1.5±0.5	2.3±0.8	2.0±0.7	2.0±0.7	4.0±4.2	
Time of usage of biologic drug (months), Mean (Median)	14.3±12.5 (10.0)	10.1±9.0 (5.0)	15.9±13.8 (10.5)	20.6±14.8 (20.0)	9.2±9.6 (6.0)	11.0±9.0	

a: Comparison was not made, because the number of patients who used methotrexate was low among systemic JIA subjects; b: Comparison was not made, because the number of patients with psoriatic JIA was 4; c: Time to transition to inactive disease in the patients who did not use biologic drug; JIA: Juvenile idiopathic arthritis; *p: Oligoarticular JIA-enthesitis-related arthritis

volved joint was found to be the knee joint with a rate of 73%, and the ankle was the second most commonly involved joint (10.8%). For radiodiagnostic examinations, the patients with JIA who had active arthritis were evaluated using joint ultrasonography. The diagnosis of enthesitis-related arthritis was evaluated using MRI in patients who had inflammatory back pain or sacroileitis findings.

About 10% of the patients benefited from non-steroidal anti-inflammatory treatment. Intraarticular injections were performed in 25 patients and a second intraarticular injection was performed in 11 patients. Initiation of steroid treatment was needed in 21 patients. Four of these patients had oligoarticular JIA, seven had ERA, two had polyarticular JIA, and eight had systemic JIA. Eight patients with systemic JIA and one patient with polyarticular JIA needed high-dose steroid treatment. Methotrexate was used in a total of 108 patients. Methotrexate treatment alone was given in about 32% of patients. Among the patients treated with methotrexate alone, the inactive time transition was the shortest in the systemic JIA group, while the longest was in the ERA group. There was a statistically significant difference between oligoarticular JIA and ERA (Table 3). Biologic drugs were used in

Table 4. Rates for disease recurrence, active disease, and on-drug/drug-free remission

	Total n=116	Oligoarticular JIA n=37	Enthesitis-related arthritis n=38	Polyarticular JIA n=22	Systemic JIA n=15	Psoriatic JIA n=4
Disease recurrence n (%)	41 (35.3)	17 (45.9)	9 (23.7)	7 (31.8)	5 (33.3)	3 (75)
Drug-free remission n (%)	38 (32.7)	9 (24.3)	12 (31.6)	7 (31.8)	8 (53.3)	2 (50)
On-drug remission n (%)	71 (61.2)	26 (70.2)	21 (55.2)	15 (68.2)	7 (46.7)	2 (50)
Active disease, n	7	4	3	–	–	–

JIA: Juvenile idiopathic arthritis

38.2% (n=38) of patients. Following biologic drug use, the shortest transition time to the inactive period was found in the oligoarticular JIA group, and the longest time to the inactive period was found in the ERA group (Table 3). Modification in biologic drugs was needed in four patients (three patients with poliarticular JIA, one patient with psoriatic JIA). Although the use of biologic drugs was needed for a longer time period in patients who had polyarticular JIA (median 20 months), this duration was shorter in the systemic JIA group (median 6 months). Among the biologic drugs, etanercept was used in 21 patients, adalimumab was used in 11 patients, anakinra and canakinumab were used in three patients, tosilizumab was used in two patients, and inflixsimab was used in one patient.

Disease recurrence was observed during the follow-up period in 35% of patients (most commonly in the oligoarticular JIA group) (Table 4). When the final outcomes following treatment were examined, it was found that remission on and off medication was provided in 109 of the patients (94%). Among seven patients who were in the active period, four had oligoarticular JIA and three had ERA. During the study, the presence of inactive disease for at least 12 consecutive months off-medication following completion of treatment (drug-free remission) was found in 38 patients (32.7%). In the systemic JIA group, this percentage was found to be higher (53.3%) compared with the other groups. At the final follow-up visit, 71 patients had had inactive disease for at least six months while receiving medical treatment (on-drug remission) and the percentage of on-drug remission was higher (70.2%) in the oligoarticular JIA group compared with the other groups (Table 4).

In our study group, macrophage activation syndrome due to systemic JIA developed in only one patient, and the disease was controlled with high-dose steroid treatment and successive treatment with steroids. Amyloidosis did not develop in any patient.

Discussion

In studies conducted worldwide, it has been found that the distribution of demographic findings including age, sex, age at the time of diagnosis, and the frequency of subgroups, vary in patients with JIA. The reasons for this variance include genetic factors, social status, living environment, and recent desrciption of the diagnostic criteria in more detail (2). Although oligoarticular JIA is the most common subtype in Europe and North America, ERA was observed to be the most common subtype in Asia and Middle East countries (3–5). This shows that genetic and environmental factors play a special role. In the first study conducted by Kasapçopur et al. (9) according to the ILAR criteria in Turkey, systemic JIA was observed most commonly, whereas Demirkaya et al. (10) found that oligoarticular JIA was observed most commonly and the percentage of ERA was higher compared with Western populations in a large-scaled study that they conducted in subsequent years. There is a similar status in the Mediterranean and Southeastern Anatolia regions (11, 12). In a recent study conducted by Çakan et al. (13) in the region of Istanbul, the similar percentage of oligoarticular JIA and ERA was associated with the fact that our country was a transition region between Europe and Asia. In our study, we found that the percentages of oligoarticular JIA and ERA were close to each other, similar to large cities (Table 5). These results confirm that the ERA subgroup is more common in our country compared with Europe and America. Although the female/male ratio was found to be equal in previous studies in our country, we found that the female ratio was higher (Table 5). In previous studies, ERA was reported to be common especially in male patients (16); however, we found that the percentage of female patients was also high in the ERA group in our study (Table 5). The female/male ratio was found as 1.5 in all patients, but this ratio was 1.3 for ERA. In FMF, which is observed commonly in our country, signs similar to ERA in association with arthritis, inflammatory back pain and enthesopathy may be observed, and this should be considered in the differential diagnosis (17–19).

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Table 5. Demographic porperties in studies conducted in Turkey and comparison of the subtypes of juvenile idiopathic arthritis

	Our study (Denizli)	Çakan et al. (İstanbul) (13)	Demirkaya et al. (Ank.-İst.-İz.) (10)	Yılmaz et al. (Adana) (11)	Şen et al. (Diyarbakır) (12)	Kasapçopur et al. (İstanbul) (9)
Number of patients (n)	116	265	634	196	213	198
Mean age at the time of diagnosis (years)	10.1±4.5	9.9±4.9	11.8±4.6	6.9±3.7	11±3.9	6.6±4.1
Female/male ratio	1.57	1.05	1.2	0.92	1	0.86
Rate of uveitis (%)	2.6	4.5	15.7	2	4.2	10.1
Rates of JIA subtypes (%)						
Oligoarticular JIA	31.9	32.9	41	34.1	37.1	23.2
RF positive polyarticular JIA	4.3	3.8	3.2	6.6	10.8	3.5
RF negative polyarticular JIA	14.7	13.5	20.3	30.6	31.5	17.2
Enthesitis-related arthritis	32.8	32.9	18.9	10.3	10.8	21.7
Psoriatic JIA	3.4	1.9	2.1	1	0.9	5.6
Systemic JIA	12.9	13.2	7.3	15.3	8.9	26.3

Ank.: Ankara; İst.: İstanbul; İz.: İzmir; JIA: Juvenile idiopathic arthritis; RF: Rheumatic factor

The association of FMF with JIA has been found with a rate of 3–8% in studies conducted in our country, and the association with juvenile spondyloarthropathy has been reported with a rate of 3–10% (17–20). In our study, ten patients had both FMF and ERA among 38 patients who were diagnosed as having ERA according to the ILAR criteria, and five of these ten patients were female. The mutations of these patients are shown in Table 2. Excluding three patients who were found to have heterozygous E148Q and R202Q, which are considered polymorphisms, four of the remaining seven patients who had significant mutations were male and three were female. All these seven patients had enthesopathy and radiologically confirmed sacroileitis. These patients had the diagnostic criteria and clinical characteristics of both ERA and FMF. If we consider all seven patients with significant mutations as having FMF and sacroileitis, the percentage of female patients does not change (20 of the remaining 31 patients were female and 11 were male). Therefore, the main reason for the predominance of female sex in the ERA group was the fact that the percentage of female patients was generally high in our whole study group.

The median time from the onsent of initial symptoms to diagnosis was found as 4.6 months in a study conducted in England (21), 6.7 months in the study conducted by Çakan et al. (13) in Istanbul, and 5.7 months in our study, varying by subtypes (Table 1). In previous studies, it was reported that pediatric patients with systemic JIA reached medical care in the shortest time and were diagnosed be-

cause they had poorer general status and higher inflammatory markers at the time of onset of symptoms. In this group of patients, families seek medical attention earlier as they are more anxious because of the predominance of fever. It has been stated that normal ESR in association with joint pain causes diagnostic delay in children (21). In our study, the highest mean ESR value was found in the systemic JIA group and the shortest mean ESR value was found in the ERA group. The shortest diagnostic delay time was found in the systemic JIA group because of these factors. The reason that patients with polyarticular JIA are diagnosed latest may be the fact that families consider symmetrical and multiple joint pain, which generally occur in polyarticular JIA, as growing pains and delay seeking medical attention. A similar situation also occurs in ERA and the sign of enthesitis may be overlooked in primary healthcare institutions.

ANA positivity was found as 62.2% in the oligoarticular group among our patients, which is similar to the percentage found in a study conducted in Turkey in previous years (9). In our study, HLA B27 was found to be positive in 21.1% of the patients with ERA, and this percentage was found as 63.3% in a countrywide study (10). In a study in which two separate patient groups (one group with FMF in association with sacroileitis, and the other group with juvenile spondyloarthropathy) were compared, HLA B27 positivity was found as 26.7% in the first group and 86.6% in the second group (22). In the same study, HLA B27 positivity was found with a lower rate in spondyloarthropa-

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thy observed in FMF compared with spondyloarthropathy observed in ERA, enthesitis and axial involvement were found with a lower rate and acute- phase reactants were found to be higher (22). In the study conducted by Gülhan et al. (23), on the other hand, it was reported that the frequency of MEFV mutations was increased in patients with HLA B27-negative ERA, and this might be one of the genetic factors. In addition, it was stated that FMF, which is observed commonly in our country, might overlap with juvenile spondyloarthropathy at the same time (20). In our study, there were seven patients who were diagnosed as having both FMF and ERA, and possessed significant mutations. HLA B27 was found to be positive in one of these patients and enthesopathy was more prodominant compared with sacroileitis in the remaining patients. Human leukocyte antigen B27 positivity is expected, especially in individuals with a significant family history. In our study, this percentage was found as only 25%; the highest rate of positivity of family history was found in the ERA group. When pediatric FMF criteria were interrogated in the patients who had a positive family history, however, none of them raised suspicion, and no significant mutations were found in any of these patients when MEFV gene mutations were examined.

A diagnosis of FMF was made with a rate of 3.3% in the JIA group in a study conducted throughout Turkey (10). In our study, FMF was diagnosed with a rate of 13.7%. The MEFV gene mutation was studied in our patients who presented with symptoms of arthritis and whose clinical pictures were compatible with FMF according to the pediatric FMF criteria. M694V, which is the most common gene mutation, was found in six patients, homozygously (Table 2). This may be related to the high prevalence of FMF in the population in our region. According to our clinical experiences, FMF is observed most commonly in the province of Uşak in the Internal Western Egean region, and resistant FMF cases are also observed most commonly in this province. Among six patients who had homozygous M694V, four had a diagnosis of ERA and two had a diagnosis of oligoarticular JIA. In the patients who had a diagnosis of enthesitis-related arthritis, sacroiliac joint tendency was present in addition to arthritis or enthesitis as determined according to the ILAR criteria, and sacroileitis was confimed using MRI. These patients met both pediatric FMF criteria and the ILAR ERA criteria. One of these four patients had HLA B27 positivity and the remaining three had a positive first-degree family history of HLA B27 positivity-related disease. Morning stiffness and monoarthritis lasting longer than six weeks in two patients who had a diagnosis of oligoarticular JIA, were not compatible with the clinical picture of prolonged arthritis of FMF.

Treatment of JIA is sophisticated, and includes drug treatment, appropriate nutrition, patient and parent education, and physical therapy. The aim of treatment in JIA is to prevent the outcomes of the disease including vision loss, growth retardation, joint damage, joint contractions, and functional limitation by controlling inflammation. Although methotrexate has been safely used in the treatment of JIA for years, it was reported to be ineffective in about 30% of patients (24). When methotrexate is ineffective, biologic drugs prevent the development of disease status in the early phases of the disease. In recent years, the use of biologic drugs has enhanced complete remission, as well as preventing chronic joint damage and disability. In our clinic, we needed to add biologic drugs to treatment in patients who were clinically unresponsive despite use of methotrexate for at least three months. In our study group, approximately one-third of all patients responded to methotrexate treatment alone, and we had to add biological drugs to treatment in another one-third portion of the patients. In the study conducted by Demirkaya et al. (10), approximately 46% of the patients used methotrexate and 12% used biologic drugs. This study was conducted between 2008 and 2009 during which the use of biologic drugs was initiated. By contrast, our study was conducted between 2012 and 2018 when the use of biologic drugs became widespread. In the same study, the rate of remission on medication (48%) was found to be approximately three-fold higher compared with the rate of remission off medication (16%). In our study, the rate of remission on medication was found to be approximately two-fold higher compared with the rate of remission off medication. However, the rate of active patients was found to be considerably low (6%). These ratios may show variance when patients are followed up for a longer period of time because JIA is characterized by remission and activation periods, and additional treatments are needed from time to time.

In our study, the lowest treatment response was found in the ERA groups in both patient groups who used methotrexate and biologic drugs. In a retrospective study conducted with 2571 patients with JIA by the Childhood Arthritis and Rheumatology Research Alliance (CARRA), greater pain intensity and poorer health status were reported in the ERA group compared with the other JIA subtypes (25). In a study conducted by Donnithorne et al. (26), it was found that transition to inactive disease was more unsuccessful in the ERA group among patients with JIA in whom anti-TNF treatment was initiated. In our study, the longest time to transition to inactive disease following the use of biologic drugs was found in the ERA group. In our study, the enthesitis-related arthritis group was the most problematic JIA subgroup in terms of frequency, di-

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agnostic delay, and treatment response. Diagnostic delay may especially arise from the fact that patients associate their symptoms with different diseases, and the finding of enthesitis is not much recognized in medical practice.

At the final follow-up visit, one-third of patients had inactive disease without medication for at least 12 consecutive months after ceased treatment. Again, this percentage was found to be 28% in a recent similar study (13). In terms of inactive disease without medication (at least 12 consecutive months), among the subtypes the patients with systemic JIA had the highest ratio (approximately half of these patients). About two-thirds of the patients had inactive disease with medical treatment for at least six months at the final follow-up visit. Among the subtypes, in terms of inactive disease with medication, oligoarticular JIA patients had the highest ratio (70.2%). In the study conducted by Guzman et al. (27), it was reported that patients who had oligoarticular JIA reached success with the highest remission rate (53%), and patients who had RF-positive polyarticular JIA reached the lowest level of remission.Macrophage activation syndrome is one of the complications that develop in systemic JIA, and it occurs secondary to hemophagocytosis. Pancytopenia, reduced ESR, and reduced fibrinogen level, hypertriglyceridemia, and hyperferritinemia are observed. Another complication related to systemic JIA is amyloidosis. In our country, the rate of amyloidosis was found as 10% in studies conducted before the initiation of use of biologic drugs (8); it still occurs albeit rarely at the present time (13). The fact that amyloidosis was not observed in any of our patients, and macrophage activation syndrome related to systemic JIA developed in one patient together with a low activation rate, may have arisen from the early initiation of treatment.

The lower number of patients (116) compared with other studies conducted in our country is a limitation of our study. However, the number of pediatric rheumatology clinics that perform regular patient follow-up is newly increasing. Therefore, these data may gain importance in a regional aspect.

In conclusion, JIA shows variances in terms of sex, age at the time of diagnosis, diagnostic delay status, and treatment response by subtype from region to region. Countrywide multi-center studies are needed in this area.

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