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ORIGINAL ARTICLE

The long-term follow-up of patients with oligoarticular juvenile idiopathic arthritis: a single-centre experience

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ABSTRACT

Aim To evaluate the clinical course and outcomes of oligoarticular juvenile idiopathic arthritis (JIA) patients from 2003 to 2021, identifying factors linked to severe disease and complications.

Methods We analysed 208 oligoarticular JIA patients followed at Cerrahpaşa Medical School, using medical records. Continuous variables were compared with the Mann-Whitney U test, and logistic regression was applied to identify predictors of severe disease and damage.

Results Among 208 patients (68.75% female), the average treatment duration was 45 months. The knee was the most affected joint (82.6%), followed by the ankle (50.4%). The initial mean Juvenile Arthritis Disease Activity Score (JADAS) score was 18, decreasing to 3 at the last visit. Juvenile Arthritis Damage Index (JADI) score averaged 0.64. Limited range of motion was observed in 34.13% patients. Uveitis was the most common extra-articular complication (14.9%), with higher biologic use in these patients ($p<0.001$). Disease severity correlated with initial and final JADAS ($p<0.001$) and JADI ($p<0.001$). Regression analysis linked elbow involvement ($p=0.000$) and adalimumab use ($p=0.001$) to disease sequelae. MEFV gene mutations were found in 10.9% of patients. Based on the Wallace criteria, 85% were in remission with medication, 6.25% had inactive disease, and 8.6% achieved drug-free remission.

Conclusion: Oligoarticular JIA generally has a mild course and good prognosis. However, elbow involvement and biologic use are associated with more severe disease and sequelae. Uveitis is the most common extra-articular complication.

Keywords: arthritis, biologics, damage, oligoarticular JIA

INTRODUCTION

Juvenile idiopathic arthritis (JIA) represents the most commonly seen chronic rheumatic disease in paediatrics. The diagnosis is established based on the International League Against Rheumatism (ILAR) criteria, which include age at onset <16, chronic arthritis for at least 6 weeks and exclusion of other conditions including infection and malignancy (1-3). According to the ILAR classification criteria, the disease is subdivided into 7 subtypes with oligoarticular JIA representing the most common JIA subtype worldwide, seen in 10-50% of JIA patients (4).

In a recent study performed among the Turkish population, the oligoarticular JIA was reported as the most frequent JIA subtype, seen in 38-40% of all JIA patients (5-7). Oligoarticular JIA, generally seen among female patients younger than 6 years of age, is subdivided into two subgroups: persistent (≤4 joints affected during the disease course) and extended (after the initial 6-month period, the total number of affected joints >4) (7) . Typically, the disease presents with monoarthritis with a favourable prognosis and low frequency of functional disability (8). Anti-nuclear antibody (ANA) positivity, seen in 70-80% of patients, represents the main risk factor for the development of uveitis. Uveitis, rather than arthritis, is the main disability factor in ANA positive patients' group (9). The extended disease form is characterized with more severe clinical course with potential complications and sequalae (9-11).

Growth retardation, functional disabilities and orthopaedic problems, although rarely seen, could significantly disturb the life quality of patients (12). Still, the lack of data on clinical follow-up and outcome makes the prognosis of the disease unclear. There is a striking need for long-term prospective studies that would enlighten the long-term prognosis and complications of oligoarticular JIA (12,13).

Since there is no biological marker defining the inactive disease, the decision on disease activity is based on physical examination and laboratory criteria including markers of inflammation such as C-reactive protein and erythrocyte sedimentation rate (14-16). The Juvenile Arthritis Disease Activity Score (JADAS) and Juvenile Arthritis Damage Index (JADI)(15-16) are proposed for the measurement of disease

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activity and disability in JIA. The Wallace criteria for defining clinical inactive disease are used in clinical practice in order to evaluate the disease outcome and treatment response (17-18).
In the last 2 decades, there have been significant developments in JIA treatment, with timely introduction of biologics, which became more affordable worldwide and markedly influenced the disease prognosis. Still, there is a proportion of patients who do not reach the drug-off medication, despite the appropriate treatment (19-22).
The aim of this study was to evaluate the clinical course and outcome of patients with oligoarticular JIA to evaluate potential factors contributing to more severe clinical course and a risk of disease complications.

PATIENTS AND METHODS

Patients and study design

Patients diagnosed according to the ILAR criteria for oligoarticular JIA(3,4), followed up at Cerrahpasa Medical School, Department of Pediatric Rheumatology were included in the study. Initially, a total of 290 oligoarticular JIA patients, of which 216 (74.5%) females, followed up in the time period 2003-2021 were regrouted. Of them, 82 (28.3%) were further excluded: 30 (10.3%) due to incomplete medical documentation, 26 (8.9%) due to short follow-up period (<3 months), seven (2.4%) due to irregular follow-up, and 19 (6.5%) patients due to transition to adult rheumatologists. At the time of the study those patients were followed-up at adult rheumatology department so we could not reach their medical documents. All patients followed at the Pediatric Rheumatology Department at the time of the study were included.
Infections, malignancies and mechanic/orthopaedic problems were excluded. None of the patients included in the study was initially misdiagnosed as JIA, since the inclusion criteria required exclusion of other possibilities. Finally, 208 patients were selected for further evaluation.
The study was approved by the Ethical Committee of Istanbul University-Cerrahapaşa, Cerrahpaşa Medical School, Turkey.

Methods

All data were obtained from patients' medical histories: demographic features, age at disease onset, age at diagnosis, age at participation of the study, family history, type and count of joints involvement, disease duration, time to remission, disease activity, the number of joints with sequalae, presence of uveitis, duration of treatment, used non-biologic/biologic disease modifying antirheumatic drugs (DMARDs), initial/ JADAS (15-16), JADI (15-16), and juvenile arthritis disease, the application of intra-articular steroids (IAS).
JADAS measures JIA activity using four components: physician's and parent/patient global assessments (0–10 scale), active joint count (up to 71), and optionally erythrocyte sedimentation rate (ESR) (0–10). Higher scores indicate greater disease activity.
JADI assesses long-term joint (JADI-A) and extra-articular (JADI-E) damage. JADI-A scores 36 joints (0–2 per joint), while JADI-E evaluates systemic damage (0 or 1 per organ). It distinguishes permanent damage from disease activity.
The initial laboratory findings were recorded: ESR, C-reactive protein (CRP), positivity and the level of anti-nuclear antibody (ANA)(15-16).

Statistical analysis

Categorical variables were expressed as numbers (percentage). Continuous variables were given as mean±SD (standard deviation) or median (minimum-maximum) according to their distribution as measured by the Kolmogorov-Smirnov test. Categorical variables were compared using the $\chi 2$ test or Fisher's-exact test, if available. Continuous variables were compared using the Mann-Whitney U test. Logistic regression analysis was performed to determine which variables were predictive. The $p<0.05$ was used as significant.

RESULTS

Out of a total 208 included patients, 143 (68.75%) were female (Table 1). The initial ANA positivity was present in 164 (78.8%) patients. Eighteen (8.6%) patients had a family history for rheumatologic disease. The average length of the treatment was 45 months (range 1-240 months), with the first remission lasting for an average of 3 months (range 1-22 months). The knee was the most commonly affected joint, in 172 patients (82.6%), followed by the ankle, 105 (50.4%).

Table 1. Demographic characteristics of patients with oligoarticular juvenile idiopathic arthritis

Characteristic	No (%) of patients
Female	143 (67.75)
Family history of rheumatic disease	18 (6.6)
	Median (Min.-Max.) (months)
Age at disease onset	41 (4-192)
Age at diagnosis	48 (5-195)
Duration of follow-up	54.5 (4-252)
Duration of treatment	46 (1-240)

The mean age at arthritis onset was 41 months (range 4-192 months). During the mean follow-up period of 54 months (range 4-252 months), mean frequency of the disease attack was 3 (range 0-21). The mean initial JADAS score was 18 (10-31) vs. 3 (0-21) at the last examination.
The mean JADI score was 0.64 (min.0-max. 4) with 93 (44.7%) patients having JADI score >0 (Table 2).

Table 2. Clinical characteristics and outcome of patients with oligoarticular juvenile idiopathic arthritis

Characteristic	No (%) of patients
ANA positivity	164 (78.8)
Affected joint	
Knee	172 (82.6)
Ankle	105 (50.4)
Elbow	37 (17.7)
Uveitis	31 (14.9)
Outcome	
Remission with medication	177 (85)
Remission without medication	18 (8.6)
Inactive disease	13 (6.25)
Activity score	
Initial JADAS	18 (10-31)
Last JADAS	3 (0-23)

ANA, Antinuclear Antibody; JADAS, Juvenile Arthritis Disease Activity Score

The limited range of motion (ROM) was present in 71 (34.13%) patients during the follow-up. The most common extra-articular disease complication was uveitis, seen in 31 (14.9%) patients. Biologic treatment was added to 79 (37.9%) patients. The biologic usage was significantly higher in patents with uveitis compared to those without uveitis ($p<0.001$).

No significant correlation between ANA positivity and uveitis was found ($p=0.081$).

In nonparametric correlation analysis, when compared with JADI, the age of onset of complaints, follow-up time, time to first remission, number of activations, number of joints with sequelae, duration of treatment, length of methotrexate use, duration of the use of etanercept and adalimumab were significant ($p<0.05$). Elbow involvement and biological use were significant when compared to JADI in Mann Whitney test analysis. Regression analysis of all significant data showed that elbow involvement ($p=0.000$) and adalimumab ($p=0.001$) use were significant in terms of JADI sequelae.

The intra-articular steroids (IAS) were applied in 122 (58.6%) patients. The mean frequency of IAS application was 1.42 per patient. (min. – max. = 0- 9). The frequency of IAS application was significantly correlated with initial JADAS score ($p=0.022$).

Disease modifying anti-rheumatic drugs (DMARDs) had been used by majority of patients, 201 (96.6%). The methotrexate was the most performed initial DMARD, followed by leflunomide used in 11 (5.29%) patients, who had intolerance or adverse for the methotrexate treatment. In the course of the therapy, 79 (37.9%) biologic agents were included: etanercept in 57 (72.15%) and adalimumab in 22 (27.84%) patients. All patients with uveitis were treated with adalimumab. The usage of biologic drugs was significantly correlated with initial JADAS score, final JADAS score and JADI score ($p<0.001$, $p=0.011$, and $p<0.001$, respectively).

Twenty-three (10.9%) patients had a pathogenic Mediterranean Fever (*MEFV)* gene mutation. There was no significant correlation between presence of *MEFV* mutation and initial JADAS score, final JADAS score and JADI score. However, we found a significant correlation between the frequency of JIA application and the presence of underlying MEFV gene mutation ($p=0.025$).

When analysing patients according to the Wallace criteria for defining clinical inactive disease, majority of patients were in remission with medication, 177 (85%. Thirteen (6.25%) patients had inactive disease, while 18 (8.6%) had remission without medication.

DISCUSSION

A chronic anterior uveitis, which is the most common form, is generally asymptomatic in its initial stages (23).The most common extraarticular manifestation in our cohort was uveitis, similarly to the data of previous studies (24-27).

Although an ANA positivity has been reported as a risk for the development of uveitis (3, 8-11), we did not find a significant correlation between the ANA positivity and uveitis. This could be possibly explained by the high positivity of ANA oligoarticular form of the JIA (3), which characterised our cohort.

Over the past decade, randomized controlled trials (RCT's) of biologic agents have demonstrated their efficacy in controlling joint disease in JIA (20). The same drugs were also used in the treatment of JIA associated uveitis, and in our study, a biological agent was added to the treatment in 70.96% of the patients diagnosed with uveitis. The biologic usage was significantly higher in patents with uveitis.

The IAS was applied in 58.6% patients. DMARDs were used in most cases (96.6%), with methotrexate as the primary choice, leflunomide in 5.29% patients (due to methotrexate intolerance), biologic agents in 37.9% patients (mainly etanercept - 72.15%, and adalimumab - 27.84%). Our findings align with a recent study, where 84% patients received conventional DMARDs, primarily methotrexate (89%), and 45.2% were prescribed biologics, with etanercept being the most common (32%) (27).

Our results showed that the usage of biologics was significantly correlated with initial JADAS score, final JADAS score and JADI score. Despite the recommendation of the American College of Rheumatology (ACR) for the treatment of JIA (20), non-steroidal anti-inflammatory drugs (NSAIDs) were used in none of our patients as an initial treatment. This could be explained by the fact that our centre represents the tertiary medical centre with patients being referred from the general paediatricians. Therefore, patients referred had been already treated with NSAIDs before being admitted to our hospital.

It is well known that Turkey is an endemic country for Familial Mediterranean Fever (FMF), which could be associated with JIA (28). Since the study was performed among the Turkish population, we investigated the frequency of underlying FMF in our cohort.

Despite the significant developments in JIA treatment during the last two decades based on the introduction of biologics in the routine treatment (27), there is still a certain proportion of patients that remains unresponsive (30).

Although the frequency of remission increases with increasing disease duration, there remains a high burden of the disease in JIA (30); less than 50% of patients achieved a drug-free remission during the 10-year follow-up (29-31). The probability of drug-free remission varies significantly with a disease-onset type, being best for oligoarticular JIA, at approximately 50% (32). In a paediatric study from the pre-biologic era using the Wallace criteria for remission, 59% patients were in clinical remission off medication, 7% were in remission on medication and 34% had active disease at 30-year follow-up (33). In a longitudinal study from Nordic countries, significantly more patients (70%) were off medication after 18 years of follow-up compared to after 8 years (59.7%). However, the number of patients in remission did not increase (52% off medication versus 51% on medication) (34). In a study from Sweden, only 40.0% of the follow-up years, with a median follow-up time of 8 years, were free of arthritis or uveitis (35). In our study, the percentage of patients with remission on medication was even higher, which could be possibly explained by the shorter follow-up.

In our study, regression analysis showed that elbow involvement and adalimumab use were significant in terms of JADI – sequelae. This is similar to previous studies reporting the involvement of an upper limb at the disease onset as a predictor of a severe clinical course (18). Again, the Research in Arthritis in Canadian Children Emphasizing Outcomes (ReACCh-Out) cohort reported that JIA subtype, active joint count and pattern of joint involvement at enrolment could predict a severe disease course, which is in concordance with a previous study (36).

This study provides data on clinical course and major prognostic findings of patients with oligoarticular JIA during a mid-term follow-up. Still, all our patients were followed-up in the area of biologic anti-rheumatic drugs. Therefore, we could not

perform comparison between the pre- and post-biologic area among the patients.

Our study has some limitations. The number of patients is too limited, and data were collected retrospectively. Moreover, we were not able to provide data for each drug separately regarding the time to treatment initiation. Prospective studies with higher patients' number including other JIA subtypes would provide more relevant data.

In conclusion, the oligoarticular JIA is characterized with mild clinical course and a good prognosis. The elbow involvement and the biologic use was related to more severe disease course and development of sequalae. Uveitis represented the most common extra-articular disease complication. Further prospective studies in different geographic regions are required to support our findings.

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