Evaluation of the time of patients' admission to the tertiary pediatric rheumatology center for juvenile idiopathic arthritis

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Abstract

Aim: To determine the interval between disease onset and admission to pediatric rheumatology clinic of patients with juvenile idiopathic arthritis (JIA) and, to identify the factors that affect the admission time (AT) to rheumatology center.

Methods: We designed a retrospective observational study in children with JIA. The study variables were age, gender, JIA subtype, acute phase reactants (APR), disease activity scales, presence of a pediatric rheumatologist, and distance to a pediatric rheumatology center. Outcome parameter was the duration between onset of symptoms and first visit of rheumatologist. The parameters were evaluated with variance analysis and regression models.

Results: 198 patients (female:120 (60.6%)) were included. There were 112 (56.5%) patients in oligo-articular JIA, 27 (13.6%) in rheumatoid factor negative poly-articular JIA, 22 (11.1%) in enthesitis related arthritis (ERA), 29 (14.6%) in systemic-JIA, 4 (2%) in rheumatoid factor positive poly-JIA, two patients each in undifferentiated and psoriatic arthritis. The median AT in the systemic-JIA and other groups was 16 (IQR 10.5-27.5) and 71 (IQR 33.5-211) days, respectively. There was a significantly longer AT in the ERA group than others (p=0.005). We found a correlation between longer AT and older age, low back pain, enthesitis, and low erythrocyte sedimentation rate (ESR). In the multivariate analysis, only low ESR and enthesitis contributed an increase in AT [OR 2.05 (1.07-3.93), 6.22 (1.29-29.99)].

Conclusions: The older age, low back pain, enthesitis and low ESR contribute to the late AT. JIA requires high suspicion in children with poorly defined findings and low APR.

Keywords: Juvenile idiopathic arthritis; Admission time; Affecting factors

Key messages:

-In this study, admission time in JIA patients was acceptable, but most of the patients had a longer admission time.

-Symptoms such as the presence of enthesitis and low back pain should be warning signs for JIA in pediatric patients.

-In JIA, acute phase reactants are not always elevated.

Introduction

Juvenile idiopathic arthritis (JIA) is the most common chronic arthritis in childhood that begins before age 16 and persists for at least 6 weeks.[1, 2] A prolonged active illness affects most patients, which can lead to physical impairment and chronic joint damage. This disease leads physiological, psychological, and economic burden to the patient, parents, and society.[3] Therefore, the aim in treating all types of JIA is to prevent permanent joint damage and to improve life quality and range of motion. For this, 'early aggressive treatment' is recommended in the management of JIA.[4]

Duration of access to health care is important in disease progression. The Rheumatology Standards of Care for children and youth with JIA, which include the minimum level of care for children with JIA, were designed by the British Standards of Care for Pediatrics and Adolescent Rheumatology (BSPAR).[5] The pediatric rheumatology team should evaluate children within 10 weeks of the beginning of symptoms and/or 4 weeks after referral, as per established recommendations.

In our country, pediatricians or family physicians regularly follow children up to the age of 18. Our health policy provides free medical care for children. In the emergency department, patients can be examined without any limitations. However, pediatricians or other clinicians must provide direction for a pediatric rheumatologist's evaluation. In our center, a tertiary hospital, we evaluate referred patients in one week and inpatient consultations in one day. However, the admission time is highly variable. Therefore, the present study aimed to assess the admission time (AT) and the factors affecting this time in JIA patients.

Materials and Methods

Study design and participants

This retrospective study included 229 patients with JIA who were followed up in our pediatric rheumatology center between 2015 and 2021.

The inclusion criterion was a JIA diagnosis according to the International League Against Rheumatism[6] and all JIA subgroups were included [systemic JIA (SJIA), oligo-articular JIA (OJIA), rheumatoid factor (RF) positive poly-articular JIA (PJIA), RF-negative PJIA, enthesitis-related arthritis (ERA), undifferentiated JIA and psoriatic arthritis]. Thirty-one patients were excluded

from the study due to their comorbidities (who had previously been followed up in our department with diagnoses of familial Mediterranean fever, acute rheumatic fever, connective tissue disease, etc.), previous treatment for JIA at another center, and lack of medical data.

Definitions

The interval the onset of symptoms and the initial visit to the pediatric rheumatology department was computed as AT. In the SJIA group, admission within 15 days was recognized optimal AT because of a potentially fatal complication such as macrophage activation syndrome. In other JIA subgroups, less than 10 weeks was recognized ideal AT by BSPAR standards.

There are pediatric rheumatology departments in 18 out of 81 cities in our country, and approximately 100 pediatric rheumatologists work in these departments. However, our two largest cities, Istanbul and Ankara, are where most of our pediatric rheumatologists are located. There are no pediatric rheumatologists in cities with a population under 750,000. Ankara is both the capital and the 2nd largest city, and there are no pediatric rheumatologists in the surrounding cities. In addition, patients often admission to the nearest pediatric rheumatology center. For this reason, the surrounding cities of Ankara were categorized as rural areas. There are a small number of patients who were evaluated by a pediatric rheumatologist in other cities before admission to our center. In this study, patients who were previously evaluated by a pediatric rheumatologist in other cities were excluded.

Data collection

Demographic, clinical, and laboratory data [complete blood count (CBC), erythrocyte sedimentation rate (ESR) C-reactive protein (CRP), anti-nuclear antibody (ANA), RF, HLA-B27] of patients were recorded. The 10 cm visual analog score (VAS) and JADAS 27 was used to all patients at admission. The patient's pain was assessed using a 0 to 10 cm VAS. Higher scores indicated more severe pain.

We evaluated the relationship between age at diagnosis, gender, symptoms, number of involved joints, affected joints, uveitis, acute phase reactants, city of residence, distance from the center, presence of a pediatric rheumatologist, and AT. In the SJIA group, <15 days for shorter AT and >15 days for longer AT were used. In other JIA subgroups, <70 days and >70 days were used for shorter and longer AT, respectively. The factors affecting the AT were investigated. The distances of the rural area to Ankara were recorded. The distances to the cities were calculated from Ankara using a distance map provided by the Ministry of Transport and Infrastructure.

Ethics committee approval was received for this study, from the scientific and ethics committee of our hospital (approval number: E2-21-410; approval date: 21.04.2021).

Statistical Analysis

IBM SPSS Statistics for Windows, version 25 (SPSS Inc, Chicago, IL, USA) was used to perform statistical analysis. The variables were investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov-Simirnov/Shapiro-Wilk's test) to determine whether they are normally distributed. Continuous variables that do not have normal distribution were expressed as median [interquartile range (IQR)]. Categorical variables were summarized as counts (percentages). The Chi-square test was used to compare categorical variables and Mann-Whitney U-test was used to compare non-normally distributed continuous variables. The possible factors identified with univariate analyses were entered into the logistic regression analysis to determine independent predictors of delay in admission to rheumatology outpatient clinic. Hosmer-Lemeshow goodness of fit statistics were used to assess model fit. The odds ratios (OR) and their 95% confidence interval (CI) obtained in the adjusted regression analysis were calculated. The statistical significance level was accepted as a p-value <0.05.

Results

Patient characteristics

One hundred ninety-eight patients were included in the study. There were 120 (60.6%) females. The median age at the onset of symptoms was 7.8 years (0.7-16.7). Most of the patient group had OJIA (n=112, 56.5%) (persistent, extended). There were 27 (13.6%) patients with RF negative PJIA patients, 22 (11.1%) with ERA, 29 (14.6%) with SJIA, 4 (2%) with RF positive PJIA, 2 (1%) with undifferentiated JIA, and 2 (1%) with psoriatic arthritis. There were 157 (79.3%) patients living in the city center. 41 of the patients (20.7%) lived in various regions of the country. The pediatric department conducted the initial evaluations for 138 patients (69.6%). 60 patients (30.4%) visited the orthopedics, cardiology, physical therapy and rehabilitation, and pediatric emergency departments. The median AT in the SJIA and other groups was 16 (IQR 10.5-27.5) and 71 (IQR 33.5-211) days, respectively.

Evaluation of the variables affecting the admission time

SJIA patients:

Children's hospitals' inpatient services provided follow-up care for all SJIA patients. A pediatrician examined each patient at least once during this time. In addition, all patients had received various antibiotic treatments. The mean duration of a consultation with pediatric rheumatology was 16 (10.5-27.5) days. In 15 (51.7%) patients, pediatric rheumatology consultation was required for longer than 15 days. The median age of symptom onset was 5.1 (2.7-9.7) years, and there were 12 patients (41.4%) who were female. Gender and age of symptoms onset had no effect on AT (p=0.096, p=0.47).

Twenty-two patients (75.9%) lived in Ankara and 7 (24.1%) patients lived in different cities. The rural region's median distance from the city was 407 (234-1002) km. The center where 24 (82.8%) patients resided had a pediatric rheumatologist. Table 1 is a summary of the assessment of the variables influencing the AT in the SJIA group.

Patients were evaluated before and after 15 days, and the median ESR was 83 mm/h (61-98), and 80 mm/h (60-113), respectively (p=0.65). Median CRP values were 8.3 mg/L (4.2-13.9) and 10 mg/L (5.9-18) at evaluation time shorter and longer than 15 days, respectively (p=0.42).

The other JIA patients:

The other JIA groups included 169 patients and 108 (63.9%) patients were female. The median AT was 71 (33.5-211) days (~2.4 months). Ninety-two patients (54.4%) had AT than longer 10 weeks. Fifty-one (55.4%) of patients were female. The median age of symptom onset was 8.7 (4.8-12.5) years. The median age of symptom onset was 7.7 (3.1-11.8) and 9.8 (5.2-12.8) years in patients with AT shorter and longer 10 weeks, respectively. The AT was longer in the elderly patients (p=0.006).

One hundred thirty-five (79.8%) patients resided in the city center. There was no relationship between the place of residence and the AT (p=0.059).

The ERA group had the longest AT [median 338 days (11-1737)]. The ERA group's AT was noticeably longer than the other groups' ATs (p 0.001). Figure 1 illustrates the AT in the JIA subgroups.

Eleven (6.7%) of the patients had low back pain, while 9 (10.7%) of the 11 had delayed admission. The AT was significantly delayed for patients with low back pain (p=0.034). Sacroiliitis

and enthesitis were higher in this group, respectively (p=0.044, *p*<0.004). AT and evaluation of clinical findings are shown in Table 2.

Median ESR and CRP values were 22 mm/h (9-41) and 2.1 mg/dL (0.6-6.3), respectively. 53 (31.4%) patients had positive ANA, 18 (10.7%) patients had positive HLA-B27, and 4 (2.3%) patients had positive RF.

In the multivariate analysis, in addition to gender and age of onset of symptoms, variables for which there was a significant difference in univariate analyses (p 0.100) or a difference that was almost significant were also considered. Sacroiliitis was not included in the model due to its strong correlation with enthesitis and low back pain. Therefore, it was found that low ESR and the presence of enthesitis at the time of diagnosis increased the probability of delay in admission [OR 2.05 (1.07-3.93), 6.22 (1.29-29.99), respectively] in logistic regression analysis that included gender, age of symptom onset, enthesitis, and ESR. The analysis results are shown in Table 3.

Activity scales

The patient's median VAS was 8 (8-10). According to VAS at admission, 25 (12.6%) patients had moderate activity and 173 (87.4%) patients had high activity. The median VAS was 9 (5-10) in the group with less than 10 weeks of admission, and 8 (5-10) in the group with a longer AT. There was a significant correlation between lower vas score and longer AT (p=0.001).

All patients were severe activity on the JADAS 27 scale. The median JADAS 27 was 22.9 (12-40.4) in patients with an AT shorter than 10 weeks, and 18.6 (11-40.4) in patients with an AT longer than 10 weeks. There was a correlation between low JADAS 27 score and delated admission (p=0.001).

Discussion

This study analyzed how long JIA patients with symptoms waited before visiting a pediatric rheumatologist for the first time, as well as the factors that contributed to this delay. We observed that SJIA patients were hospitalized, but 15 (51.7%) patients were consulted to the pediatric rheumatologist after more than 15 days. We also found that most patients (54.4%) in the other JIA group, which included OJIA, RF positive and negative PJIA, ERA, undifferentiated, and psoriatic arthritis, admitted to a pediatric rheumatologist after more than 10 weeks. In all JIA sub-category, the ERA group had longer AT. We detected a longer AT in patients with older age, low back pain, sacroiliitis and enthesitis. In addition, we determined that only low ESR and enthesitis were effective on AT in the analysis performed.

Early diagnosis and treatment are very important in prognosis and survival in JIA[7]. However, the AT varies based on the patient or other conditions. Therefore, it is important to determine the ideal AT and the factors influencing late admission. Studies were designed to evaluate the variables influencing late admission and the post-referral waiting period. Additionally, some countries have provided guidelines based on their own health standards.[5,8] The UK aimed to standardize access to health in children with the BSPAR standards. By these standards, a JIA patient should reach a pediatric rheumatologist no later than 10 weeks after symptom onset or 4 weeks after referral.[5] In our study, we evaluated the time from symptom onset to admission. In the other non-SJIA subgroups, the median AT was 71 days (2.36 months). This rate is 5.5 months in the UK[9], 3-3.3 months in France[10,11], 3 months in Germany[12], 3.8 months in Canada[13], 4.1 months in India[14], and relatively in our study, AT was acceptable by BSPAR standards. However, although the median AT was 2.4 months, approximately half of the patients had late AT.

Also, in our study SJIA patients were consulted to the pediatric rheumatology department close to the ideal time. The prolonged fever in these patients followed in the inpatient service may have alerted the clinicians. Nevertheless, some patients were consulted to the pediatric rheumatology for more than 15 days. Exclusion of infection, malignancy and other inflammatory diseases may contribute to the prolongation of this period.

Additionally, in our study, patients with enthesitis, sacroiliitis, and low back pain had higher AT. Similarly, Aoust L et al. observed that 66% of patients in the ERA group had enthesitis and that the time to diagnosis was prolonged in this group.[10] Pediatricians and other clinicians may have difficulty assessing children's complaints of lower back and entheses pain as they may not be able to express their complaints clearly. On the other hand, adolescents are better able to describe and localize their pain, so the clinician can identify the characteristics of the pain in more detail. In addition, the findings can be attributed to diseases such as trauma, avascular necrosis, transient synovitis, and posture problems. Another study reported a longer AT in extended OJIA. Furthermore, this study recommended patients with musculoskeletal problems whose likely causes of arthritis were ruled out should be referred to a pediatric rheumatologist within two to three weeks.[15]

Freychet C *et al.* reported that older age, enthesitis and joint pain in the long AT, and joint swelling, claudication, high ESR/CRP, and positive ANA in the short AT were effective.[11] According to our results, there is no relationship between joint swelling, a positive ANA, and AT. However, the AT was prolonged by older age, enthesitis, and low ESR. This result indicates that high ESR and CRP alert clinicians. However, high ESR and CRP are not usually found in JIA. In addition, family and physicians may detect limping and swollen joints in young children earlier.

However, family and clinicians may bring less attention to non-painful swollen joints in the older group. Therefore, a higher degree of suspicion is necessary for diagnosis.

Also, in a recent study, short AT was defined as <3 months. This study demonstrated that the distance between the residence and the center is significant in AT.[14] In our study, we defined the ideal AT as 10 weeks or less. Living in the city center or rural area, distance from the city center, and presence of a pediatric rheumatologist had no effect on the short AT.

There are few studies on the relationship between disease activity and admission/referral times. A recent study found no correlation between the VAS score and the referral time.[16] In our study, patient VAS and JADAS 27 scores were evaluated at admission. Patients with low VAS and JADAS 27 had the late AT detected.

The most studies have shown that many factors affect the AT.[16,17] According to these research' findings, social, organizational, and disease-specific characteristics all have an impact on health services. In addition, studies have reported that insufficient training and skills related to the musculoskeletal system may affect the results. The authors recommended increasing education on musculoskeletal assessment and increasing awareness of JIA.[18,19]

This study has some limitations. The first is a single center and retrospective study. The results of the study reflect local data and may not be applicable to other regions of the country. Additionally, the socioeconomic and educational status of the families could not be analyzed due to the retrospective design of the study. Finally, the number of physicians who examined patients until they were referred to a rheumatologist, as well as their tenure in the profession, were not considered.

As a result, our hospital had an acceptable AT that met BSPAR standards. However, a late AT was present in over half of the patients. In this study, older age, low back pain, enthesitis, and low ESR all contributed to late admission. In addition, low disease activity was also found to be effective in the late AT. Therefore, symptoms that children cannot adequately defined (such as enthesitis, low back pain) should be evaluated more carefully in terms of JIA. It should also be noted that normal APR does not rule out JIA.

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Tables and Figures

Table I: Clinical and demographic findings of the SJIA patients

SJIA group	AT <15 days n=14	AT>15 days n=15	P
Female, n (%)	8 (57.1)	4 (26.7)	0.096
Symptom onset age, years, median (IQR)	5.9 (3.3-10)	4.1 (1.8-9.4)	0.47
Living in Ankara, n (%)	12 (85.7)	10 (66.7)	0.39
Presence of a pediatric rheumatologist, n (%)**	12 (85.7)	12 (80)	1.0
Referring clinic, n (%)			
Pediatrics	14 (100)	15 (100)	
The others (pediatric emergency, physical therapy, and rehabilitation, orthopedic, and cardiology)	0	0	
Symptoms, n (%)			
Fever duration, days, median (IQR)	18 (15-20)	20 (15-30)	0.23
Morning stiffness	8 (57.1)	9 (60)	0.87
Skin eruption	11 (78.6)	11 (73.3)	1.0
LAP	5 (35.7)	8 (53.3)	0.34
HSM	10 (71.4)	11 (73.3)	1.0
Serositis			
Pleuritis	3 (21.4)	0 (0)	0.10
Pericarditis	3 (21.4)	2 (13.3)	0.65
Myocarditis	1 (7.1)	0 (0)	0.48
Joint swelling, n (%)	13 (92.9)	12 (80)	0.598
Arthritis, n (%)			
Knee	7 (50)	5 (33.3)	0.36
Ankle	7 (50)	6 (40)	0.588
Wrist	6 (42.9)	3 (20)	0.24
Elbow	0	4 (26.7)	0.1
Small joints	1 (7.1)	1 (6.7)	1

SJIA: systemic juvenile idiopathic arthritis, AT: admission time, LAP: lymphadenopathy, HSM: hepatosplenomegaly

** *A public hospital with pediatric rheumatologist*

Table II: Clinical and demographic findings of the other JIA patients

The other groups (OJIA, PJIA, ERA), n=169	AT <70 days n=77	AT>70 days n=92	P
Female, n (%)	57 (74)	51 (55.4)	0.257
Symptom onset age, years, median (IQR)	7.7 (3.1-11.8)	9.8 (5.2-12.8)	**0.006**
Living in the Ankara, n (%)	64 (83.1)	71 (77.1)	0.501
Presence of a pediatric rheumatologist, n (%)**	66 (85.7)	73 (79.3)	0.54
Referring clinic, n (%)			1
Pediatrics	52 (67.5)	61 (66.3)	
The others (pediatric emergency, physical therapy, and rehabilitation, orthopedic, and cardiology)	26 (33.7)	30 (32.6)	
Symptoms, n (%)			
Low back pain	2 (2.5)	9 (9.7)	0.034
Joint pain	60 (77.9)	72 (78.2)	0.85
Morning stiffness	32 (41.5)	50 (54.3)	0.07
Joint swelling, n (%)	69 (89.6)	71 (77.1)	0.014
Knees	61 (79.2)	62 (67.3)	0.09
Ankles	33 (42.8)	40 (43.4)	0.87
Wrists	19 (24.6)	15 (16.3)	0.24
Elbows	8 (10.3)	7 (7.6)	0.59
Small joints	13 (16.9)	14 (15.2)	0.83
Sacroiliitis	5 (6.5)	16 (17.3)	**0.03**
Enthesitis	1 (1.3)	14 (15.2)	**0.001**
Hip involvement	9 (11.6)	16 (17.3)	0.28
JADAS 27	22.9	18.6	0.001
VAS	9	8	0.001

OJIA: oligo-articular juvenile idiopathic arthritis, PJIA: poly-articular juvenile idiopathic arthritis, ERA: enthesitis related arthritis, AT: admission time, VAS: Visual analog score

*** A public hospital with pediatric rheumatologist*

Table III: Factors affecting the admission time

Admission time >70 days (non- SJIA group)	**Univariate analysis**		**Multivariate analysis**	
	OR (95% CI)	**P**	**OR (95% CI)**	**p**
Gender (M□F)	1.45 (0.76-2.76)	0.258	1.11 (0.56-2.21)	0.760
Symptom onset age	1.06 (0.99-1.14)	0.080	1.04 (0.97-1.12)	0.282
Enthesitis (Yes□No)	7.23 (1.58-33.16)	**0.011**	**6.22 (1.29-29.99)**	**0.023**
ESR≤25 □ ESR>25 mm/h	2.04 (1.09-3.82)	**0.025**	**2.05 (1.07-3.93)**	**0.031**

M: male, F: female, ESR: erythrocyte sedimentation rate, OR:Odds ratio

**The possible factors identified with univariate analyses were entered into the logistic regression analysis to determine independent predictors of delay in admission.*

Figure 1- The Admission time in JIA subgroups

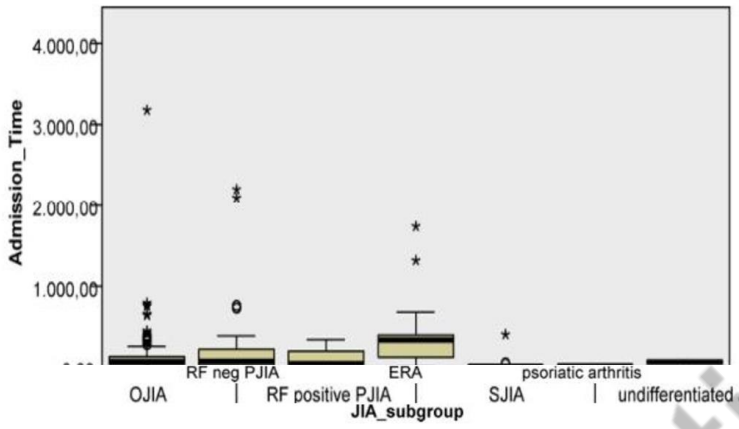

Fig 1: The Admission time in JIA subgroups

**OJIA: Oligo-articular juvenile idiopathic arthritis, RF: Rheumatoid factor, PJIA: Poly-articular juvenile idiopathic arthritis, ERA: Enthesitis related arthritis, SJIA: Systemic juvenile idiopathic arthrit*