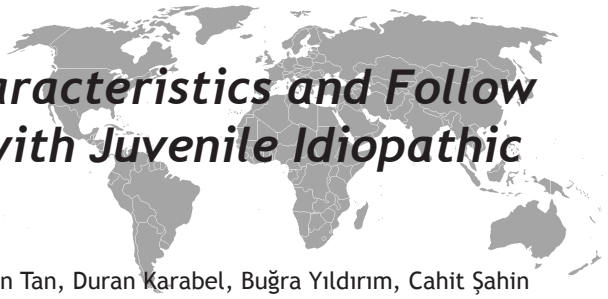
Clinical and Laboratory Characteristics and Follow Up Results of 121 Children with Juvenile Idiopathic Arthritis



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ABSTRACT

This study aimed to investigate the clinical and laboratory features of children with juvenile idiopathic arthritis (JIA) that followed up at Dicle University Hospital Department of Pediatrics. Totally, 121 (64 male, 57 female) children with the mean age of 10.0±4.1 (range, 1.5-1.8) years were included. The mean disease onset age was 7.9±3.8 (range, 0.8-15.4) years and the mean follow up period was 2.1±1.9 years. The percentages of JIA subtypes were as follows: Oligoarticular JIA 67 (55.4%), polyarticular 45 (37.2%), enthesitis related arthritis 5 (4.1%) and systemic JIA 4 (3.3%). The most common complaints were arthralgia (91.7%), fever (57.0%), fatigue (38.8%) and malaise (34.7%) and the most frequently involved joints were knee (74.4%), ankle (57.9) and wrist (48.8%). Complete remission were achieved in 28 (23.1%) and partial remission in 56 (46.3%), however 27 (21.3%) cases not responded to treatment satisfactorily. Significant risk factors for poor response to treatment with logistic regression were found as delay in treatment ≥6 months (Odds ratio, OR:11.1; p=0.006), existence of thrombocytosis (OR: 7.5; p=0.009) and early disease onset (age<5 years) (OR:18.1; p=0.004). In conclusion, JIA is a heterogeneous childhood disease with varied clinical manifestations. Early onset disease, delay in treatment and existence of thrombocytosis were the risk factors for an unfavorable outcome.

Key words: *Juvenile idiopathic arthritis, clinical findings, laboratory results, response to treatment*

Juvenil İdyopatik Artritli 121 Çocuğun Klinik ve Laboratuvar Özellikleri ve Takip Sonuçları

ÖZET

Bu çalışmada Dicle Üniversitesi hastanesi Pediatri bölümünde izlenen Juvenil İdyopatik Artrit'li (JİA) çocukların klinik ve laboratuvar özelliklerinin araştırılması amaçlandı. Yaş ortalaması 10,0±4,1 (aralık, 1,5-1,8) yıl olan, toplam 121 JİA'lı çocuk (64 erkek, 57 kız) çalışmaya alındı. Ortalama hastalık başlama yaşı 7,9±3,8 (aralık, 0,8-15,4) yıl, ortalama takip süresi 2,1±1,9 yıl idi. Juvenil İdyopatik Artrit alt tipleri sayı ve yüzdeleri; oligoartiküler JİA 67 (%55,4), poliartiküler 45 (%37,2), entezit ilişkili artrit 5 (%4,4) ve sistemik JİA 4 (%3,3) idi. En sık şikayetler eklem ağrısı (%91,7), ateş (%57,0), yorgunluk (%38,8) ve halsizlik (%34,7) idi. En sık etkilenen eklemler; diz (%74,4), ayak bileği (%57,9) ve el bileği (%48,8) idi. Tam remisyon 28 (%23,1) hastada, kısmi remisyon 56 (%46,3) hastada gözlenirken, 27 (%21,2) hasta tedaviye yeterli yanıt vermedi. Lojistik regresyon analizi ile, tedaviye başlamada ≥6 ay gecikme (OR:11,1; p=0,006), trombositoz varlığı (OR:7,5; p=0,009) ve hastalığın erken başlaması (□5 yaş) (OR:18,1; p=0,004) tedaviye yetersiz yanıt için anlamlı risk faktörleri olarak saptandı. Sonuç olarak JIA çocukluk çağının değişik klinik belirtilerle seyreden heterojen bir hastalığıdır. Hastalığın erken başlaması, tanı ve tedavide gecikme ve trombositoz varlığı olumsuz sonuç için anlamlı risk faktörleri olarak bulundu.

Anahtar kelimeler: *Juvenil idyopatik artrit, klinik bulgular, laboratuvar bulguları, tedaviye yanıt*

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INTRODUCTION

Juvenile idiopathic arthritis (JIA) is chronic inflammatory disease that affects synovial membranes of joints and sometime extraarticular organs including liver, spleen, pleura and pericardium. The incidence of JIA is estimated as 2 to 20 cases per 100,000 children, with a worldwide prevalence of 16-150 per 100,000 children (1-4). JIA is a heterogenous group of autoimmune diseases and may lead to childhood disability. Early diagnosis of JIA is difficult and usually laboratory evidence of inflammation is available. The diagnosis of JIA is one of exclusion, obligating to rule out rheumatic, infectious and other potential causes of chronic synovitis (1, 6,7). Classification of JIA has changed over the years and different percentages and clinical characteristics of subgroups have been reported in various studies from particular areas of the world. Management of JIA is time-consuming and drug for treatment of JIA often have undesirable side effects (4, 8-11). Despite various previous studies on predictive factors for good or poor prognosis of JIA, no consensus available about the prognostic factors of the disease (12-14).

In this study we aimed to investigate clinical and laboratory features of our JIA patients and determine prognostic factors for poor or well response to treatment.

MATERIALS AND METHODS

The study group included 121 children with JIA (64 male, 57 female). The diagnosis of JIA was done according to the classification criteria set up by Task Force of Pediatric Standing Committee of International League of Associations for Rheumatology (ILAR) (6). Patients having arthritis due to any other systemic illnesses such as systemic lupus erythematosus, juvenile dermatomyositis or familial Mediterranean Fever were excluded. Age of patient, age at disease onset, age at diagnosis and duration of treatment delay were determined and recorded. Clinical symptoms and signs of patients such as arthritis, arthralgia, fever, fatigue, malaise and morning stiffness were searched and recorded.

Laboratory studies, including white blood cell count (WBC), platelet count, hemoglobin (Hb), hematocrit, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor (RF) and anti-nuclear antibody (ANA) were performed with standard methods. Some accepted normal limits for laboratory tests were as follows: ESR as <15 mm/h, CRP 0-5 mg/dl, peripheral leukocyte count 4000-10000/mm^3, platelet count 150-400·10^3/mm^3

The overall outcome was determined as three levels according to European League Against Rheumatism disease activity criteria (15): A) Complete remission- Clinical remission without disease activity, B) Partial remission- certain disease activity without abnormal joints, C) Non-remission (Continuous or repeating disease activity with abnormal joints). Following prognostic factors were investigated; gender, disease onset age, time from onset to regular treatment, number of involved joints, existence of anemia, thrombocytosis, high CRP or high ESR at diagnosis.

Drugs that given to JIA patients were naproxen sodium, indomethacin, methotrexate, sulfasalazine, etanercept, steroids and folic acid. Physiotherapy was offered to patients as either home exercise after initial coaching or encouragement physical activity at home. All JIA patients underwent periodic ophthalmologic examination for the existence of uveitis or cataract.

Statistical analysis

All statistical analyses were done using SPSS 11.5 (SPSS Inc., Illinois, Ca, USA). Categorical variables were expressed as numbers and percentages, and numerical data as mean plus minus standard deviations. Differences between groups were determined by Chi-square test, Student's t test or Mann-Whitney U test. Prognostic factors were examined by logistic regression analysis. P value of less than 0.05 was accepted as significant.

RESULTS

The study population included 121 children (64 male, 57 female) with JIA. The mean age of patients was 10.0±4.1 (range, 1.5-18) years. The mean age of disease onset was 7.9±3.8 (range, 0.8-15.4) years and the mean follow up period was 2.1±1.9 (range, 0.3-9.2) years. The mean duration for delay in diagnosis was 6.8±8.7 (median 5; range, 2-60) months.

Clinical and laboratory characteristics of patients are given in Table 1. JIA subtypes were as follows: Oligoarticular 67 (55.4%), polyarticular 45 (37.2%), enthesitis related arthritis (ERA) in 5 (4.1%) and systemic

***Table 1**. Clinical and laboratory characteristics of children with juvenile idiopathic arthritis*

	n (%)
Complaints	
Arthralgia	111 (91.7)
Fever	69 (57.0)
Fatigue	47 (38.8)
Malaise	42 (34.7)
Morning stiffness	23 (19.0)
Involved joint	
Knee	90 (74.4)
Ankle	70 (57.9)
Wrist	59 (48.8)
Hand finger	42 (34.7)
Elbow	36 (29.8)
Foot finger	27 (22.3)
Hip	23 (19.0)
Sacroilliac joint	12 (10.0)
Laboratory finding	
Increased CRP	86 (71.1)
Increased ESR	82 (67.8)
Thrombocytosis	64 (52.9)
Leukocytosis	49 (40.5)
Anemia	49 (40.5)

CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate

onset 4 (3.3%) (Table 2). Polyarticular JIA group included more girls (55.1%), while oligoarticular JIA subgroup had predominantly male patients (58.3%).

Effected joints with the decreasing order were knee, ankle, wrist, hand fingers, elbow, foot fingers, hip and sacroiliac joint with the percentages from 74.4% to 10.0% (Table 1). Uveitis was found in 8 (6.6%) of patients

***Table 3**. Anti-inflammatory drugs given to patients and patient outcome of patients at last control*

Drugs	n (%)
Non-steroids	85 (70.2)
Methotrexate	77 (63.6)
Steroids	32 (26.4)
Sulfasalazine	21 (17.4)
Others (Etanercept, cyclosporine etc.)	7 (5.8)
Patient satisfaction	
Partial remission	56 (46.3)
Complete remission	28 (23.1)
Mild improvement	10 (8,3)
Very few improvement	12 (9.9)
No remission	15 (12.4)

***Table 2**. Juvenile idiopathic arthritis subtypes of patients*

JIA subgroups	n (%)
Oligoarticular JIA	67 (55.4)
Polyarticular RF (+)	10 (8.3)
Polyarticular RF (-)	35 (28.9)
Systemic JIA	4 (3.3)
ERA	5 (4.1)

RF: Rheumatoid factor, ERA: Enthesitis related arthritis

which all of them had oligoarticular arthritis.

There were no differences in the ratios of anemia and elevated inflammatory markers between oligoarticular and polyarticular JIA subgroups (data not shown, $p>0.05$). However, polyarticular subgroup had more frequent fatigue (61.2% vs. 23.6%; $p<0.001$), malaise (53.1% vs. 15.3%; $p<0.001$), anorexia (61.2% vs. 22.2%; $p<0.001$), morning stiffness (28.6% vs. 12.5%; $p=0.027$) and low-grade fever (70.8% vs. 48.6%; $p=0.016$) compared with the oligoarticular subgroup.

The most frequently used anti-inflammatory drugs were non-steroid anti-inflammatory drugs (NSAID, naproxen, ibuprofen or indomethacin) (70.2%), methotrexate (63.6%), and steroids (26.4%) (Table 3). Complete remission was achieved in 28 (23.1%) patients and partial remission in 56 (46.3%). Others (18.2%) followed up with mild and very few improvements and no-remission achieved in 12.4% of patients (Table 3).

Abnormal laboratory test results at hospital admission were as follows: leukocytosis in 50 (41.0%) patients, thrombocytosis in 64 (52.9%), high ESR in 82 (67.8%), high CRP in 86 (71.1%) and anemia in 49 (40.5%) (Table 1). The mean ESR level was 38.0±31.5 (range, 2-120) mm/h, mean WBC 10.4±4.2 (range, 4.6-37.0) ×103/ml, platelet count 437±157 (range, 156-1164) ×103/ml, hemoglobin level was 11.1±1.7 (range, 7-16) g/dl and hematocrit level was 33.0±4.7 (range, 16-47).

Patients were divided according to treatment response subgroups as sufficient response group (Complete and partial remission) (n=84) and insufficient response group (no remission or few or mild improvement) (n=37). There were significant differences between sufficient and insufficient response groups in the frequencies of anemia ($p=0.019$) and thrombocytosis ($p<0.001$) (Table 4).

Table 4. *Comparisons of factors that associated with response to treatment (n (%).*

	Sufficient response (n:84)*	*Insufficient response** (n:37)*	*p value*
Anemia			
Yes	*23 (27.4)*	*19 (51.4)*	*0.019*
No	*61 (72.6)*	*18 (48.6)*	
Thrombocytosis			
Yes	*30 (35.7)*	*26 (70.3)*	*<0.001*
No	*54 (64.3)*	*11 (29.7)*	
Oligoarticular	*28 (33.3)*	*23 (62.2)*	*0.027*
Polyarticular	*56 (66.7)*	*14 (37.8)*	
Age of JIA onset			
<5 years	*14 (16.7)*	*18 (48.7)*	*<0.001*
5-9 years	*26 (31.0)*	*11 (29.7)*	
>9 years	*44 (52.3)*	*8 (21.6)*	
Delay in diagnosis			
≤3 months	*33 (82.5)*	*7 (18.9)*	*<0.001*
3-6 months	*30 (81.1)*	*7 (18.9)*	
≥6 months	*21 (47.7)*	*23 (62.2)*	

**Complete or partial remission, **No remission, few or very few improvement, ESR: Erythrocyte sedimentation rate*

Response to treatment was significantly different between oligoarticular and polyarticular JIA subgroups in favor of polyarticular subtype. Oligoarticular JIA group had significantly higher frequency of insufficient response (44.8%) compared with polyarticular JIA group (20.0%) (p=0.027). The frequency of insufficient response was significantly higher in age below 5 years compared with age over 9 years (48.7% vs. 21.6%, respectively; p<0.001) (Table 4). Delay in diagnosis and starting treatment ≥6 months was found to be associated with significantly more frequent poor outcome compared with delay ≤3 months and 3-6 months (62.2% vs. each 18.9%, respectively; p<0.001) (Table 4). No significant differences were found in the mean disease onset age, follow up period, hematocrit, platelet count, CRP and WBC between JIA subgroups (data not shown, p>0.05).

Logistic regression analysis revealed that delay in diagnosis and treatment of JIA [Odds Ratio, OR:11.17 (Confidence Interval, CI: 1.98-63.16) , p=0.006], and existence of thrombocytosis [OR:7.35 (CI:1.63-33.12), p=0.009], and early onset disease (before age of 5 years) [OR:18.4 (CI:2.13-70.41), p=0.004] are factors associated with an unfavorable outcome; however, polyarticular involvement [OR:0.08 (CI:0.01-0.45), p=0.004] and late onset disease [OR:0.05 (CI:0.01-0.37), p=0.004] were found as predictors of a favorable outcome.

DISCUSSION

Juvenile idiopathic arthritis is the most common chronic rheumatic disease of childhood. Children with JIA suffered from chronic pain and frequently experience important daily life limitations. The disease generally has a life-long course and relapsing symptoms with increased acute phase markers. Sometimes JIA can lead to limited joint movements and even disability (5). JIA is not a sole disease instead it is a group of diseases that included at least 6 subtype according to new ILAR classification (6). These subgroups are oligoarticular, polyarticular, ERA, systemic onset JIA, psoriatic arthritis and undifferentiated arthritis. Additionally oligoarticular and polyarticular subtypes had even subgroups within them.

In present study, we evaluated 121 children with JIA and found subgroups as follows: Oligoarticular 55.4%, polyarticular 37.2%, ERA 4.1% and systemic JIA 3.3%. No patient had psoriatic arthritis. Although a study from Nigeria reported polyarthritis as the most common and systemic form as the rarest subtype; two studies from China reported systemic arthritis and ERA as the most common subtypes of JIA (9-11). In our study, polyarticular arthritis was the most common subtype and ERA and systemic onset JIA were the rarest subtypes. Generally, oligoarticular JIA has been reported as the most common subtype accounting 50% to 60% of cases with a peak

age of onset between 1 and 3 years. Knees and ankles are most commonly affected and at presentation and 50% of patients had monoarthritis (5,8). Our patients with oligoarthritis showed joint involvements with the percentages within oligoarthritis group as follows: knee (70.8%), ankle (51.4%), wrist (26.4%), hip (16.7%), elbow (15.3%) and sacroiliac joint (10.0%). Our patients with monoarthritis constituted 20.8% of cases in oligoarthritis subgroup.

Polyarticular JIA accounts for 25% to 40% of JIA and is subdivided in to RF positive and RF negative subgroups (5). Girls with polyarthritis account twice the number of boys. Similar to most rheumatic diseases the frequency of polyarticular JIA is twice in girls compared with boys, reflecting the female predominance (5,8). Our oligoarticular JIA subgroup had predominantly male patients (58.3%), while polyarticular group included more girls (55.1%) as in concordant with the percentages of subgroups that reported in the literature (1-4).

Polyarticular JIA patients may have constitutional symptoms such as fatigue, anorexia, weight loss, anemia, elevated inflammatory markers, morning stiffness and low-grade fever (5). Although, no differences were found in the ratios of anemia and elevated inflammatory markers between our oligoarticular and polyarticular JIA subgroups; polyarticular subgroup had more frequent fatigue, malaise, anorexia, morning stiffness and low grade fever compared with the oligoarticular subgroup, in consistent with the literature.

ERA frequency has been reported as 1-10% in different countries. Because the symptoms and signs of ERA were relatively less than other subtypes and disease progression is relatively slow, it can be easily misdiagnosed. ERA constituted 4.1% of our study group in compatible with the percentages that reported in the literature (1, 3-8).

Macrophage activation syndrome (MAS) is an uncommon but potentially life-threatening syndrome seen in systemic JIA. Clinical features of MAS include fever, pancytopenia, liver failure, coagulopathy with hemorrhage or thrombophilia, encephalopathy, and seizures. In two of our patients macrophage activating syndrome developed and successfully treated with early diagnosis and intravenous high dose steroids.

The mean CRP, ESR and leukocyte count were found to be increased in active phase of our patients. Additionally, elevated levels of acute phase markers were found in 40.5% to 71% of our patients. However, no differences were found between subgroups of our JIA patients in the viewpoint of the mean levels of acute phase reactants and in the percentages of high-level acute phase reactants. The active period of JIA is always together with an increase in acute phase reactant levels including WBC, ESR, and CRP (8). However, in JIA patients inflammatory markers (CRP or ESR) may be normal in the setting of active disease and the clinician may be falsely reassured that the patient does not have active disease (5).

Rheumatoid factor has been found as positive in 85% of rheumatoid arthritis, while only 5-10% of JIA patients had positive RF test results. In some countries, positive RF ratio was reported as 25-34% of JIA children (8). In our study group, RF was found as positive in 8.3% of patients and these patients constituted a subgroup of polyarticular subtype.

In our study group, complete remission was achieved in 23.1% of overall patients. Partial remission, which means certain disease activity without abnormal joints, was achieved in 46.3% of our JIA patients. Response to treatment in our patients was significantly better in polyarticular subtype compared with oligoarticular subtype. Complete and partial responses were found in 80% of our polyarticular JIA patients, while 55.2% of our oligoarticular patients had good response to treatment. In contrast with the previous reports, more frequent good response in our polyarticular JIA compared with oligoarticular ones, may be result from differences in patients compliance to treatment. More dramatic response to treatment in polyarticular subgroup may result in better compliance and resultant long-term well response to treatment. Ravelli et al. (12) reported the remission rates of JIA in various subtypes as follows; systemic JIA 33-38%, persistent Oligoarthritis 47-73%, extended Oligoarthritis 12-35% and RF (+) polyarthritis as 0-15%.

Rheumatoid factor positive polyarticular JIA accounts for only 5% to 10% of JIA. Seropositive polyarticular JIA patients have early onset, aggressive, erosive and symmetrical polyarthritis. Disease onset is typically seen in children older than 8 years with 90% of female predominance (1,5). In consistence with the literature, male/female ratio of our 10 polyarticular RF (+) JIA patients was 3/7, however, contrast to literature 6 of these patients had good response to treatment.

Although many efforts have been spent to find predictive factors for poor prognosis in JIA, no consensus have

been reached on this issue yet. Fantini et al. (13) stated that both onset age and gender had no effects on JIA prognosis, but complete remission was likely to be in infants younger than 1 year old. Flat et al. (14) suggested that elevated ESR, extensive and symmetrical arthritis, early onset and female gender were early predictive factors for an unfavorable outcome in JIA. In our study group, poor prognosis or insufficient response to treatment were found together with early onset disease, delay in diagnosis and starting effective treatment after 6 months and existence of thrombocytosis. Late onset disease and contrast to other reports polyarticular arthritis were found as predictors of favorable outcome in our patient group.

JIA is mainly treated with combination of anti-inflammatory and immunomodulatory agents and with physical therapy. Treatment should be initiated early and a biological agent should be added when therapy was not effective (1,5,8). We used non-steroid anti-inflammatory drugs in 70%, methotrexate in 64%, sulfasalazine in 17% and biological agents in 6% of our patients.

In population-based series of JIA patients, uveitis occurs in 10-15%, with predominantly in patients with oligoarticular arthritis (16). Uveitis was found in approximately 7% of our JIA patients with oligoarthritis.

In conclusion, JIA is a heterogeneous childhood disease with variable clinical and laboratory features. Response to treatment was associated with certain subtypes of the disease, early or late onset of the disease, delay in diagnosis and treatment and presence or absence of thrombocytosis and anemia. Further prospective studies are needed to achieve early diagnosis, detect prognostic factors and more effective treatment modalities in children with JIA.

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