ORIGINAL ARTICLE

Evaluation of children with juvenile idiopathic arthritis in southeastern Turkey: a single center experience

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Abstract

Background: The aim of this study was to investigate the disease characteristics of children with juvenile idiopathic arthritis (JIA) in southeast Turkey.

Methods: The International League of Associations for Rheumatology (ILAR) criteria were used to diagnose JIA. Hospital records of the Pediatric Rheumatology Unit, of the Dicle University Hospital, were reviewed retrospectively and demographic, clinical and laboratory data were recorded.

Results: Totally 213 children (103 boys, 110 girls), with an age range of 1.6-18 years were enrolled. The mean age of the disease onset was 8.1 years. Polyarticular type was the most common (42.3%) presentation. The frequencies of other JIA subtypes were as follows: oligoarticular 37.1%, systemic 8.9%, enthesitis-related arthritis (ERA) 10.8% and psoriatic arthritis 0.9%. The knees (74.2%) and ankles (54.0%) were the most commonly affected joints. Uveitis was found in 4.2% of patients. Anti-nuclear antibodies were positive in 11.7% and HLA-B27 in 2.8% of patients. Active disease was seen in 57 (26.7%) patients at the last visit.

Conclusion: In the present study, polyarticular JIA was the predominant subtype and there were fewer patients with positive ANA or uveitis compared to previous studies. Hippokratia 2015, 19 (1): 63-68.

Keywords: Juvenile idiopathic arthritis, disease characteristics, southeastern Turkey

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Introduction

Juvenile idiopathic arthritis (JIA) is one of the most common pediatric rheumatologic disorders. The etiology of JIA is unknown. The term JIA encompasses a heterogeneous group of diseases that are characterized by arthritis beginning before 16 years of age and lasting for at least 6 weeks[1,2]. Previously, JIA was called juvenile rheumatoid arthritis (JRA) by the American College of Rheumatology (ACR) and juvenile chronic arthritis (JCR) by the European League Against Rheumatism (EULAR). Currently it is called JIA, a term coined by the International League of Associations for Rheumatology (ILAR)[3]. JIA has a significant degree of morbidity and disability that negatively affects quality of life and daily activities[1,4]. The incidence and prevalence of JIA varies according to geography and ethnicity[5]. Studies have reported the incidence to be 2-20/100,000 and prevalence to be 7-400 per 100,000 children[6,7].

The clinical and laboratory findings of JIA vary between different populations[8,9]. Some studies reported that the disease is more widespread among children living in North America and Europe, compared to those living in Asia and Africa[10].

The heterogeneous nature of the disease, lack of a specific diagnostic test and discrepancies in the classification of the disease lead to difficulties when comparing patients from different ethnic origins and geographic regions.

The management of the disease is time-consuming and the drugs used to treat it frequently cause adverse effects[11,12]. Although there are previous studies on possible prognostic factors in JIA, there is no consensus on definite prognostic factors for the disease[13,14].

To our knowledge, there is no large previous study on JIA in southeastern Turkey. Therefore, in this retrospective study, we aimed to evaluate the clinical and laboratory features of children with JIA in southeastern Turkey. Another goal was to use the results of this study to compare the JIA disease manifestations in Turkey to those found around the world.

Patients and Methods

The study population included 213 children (103 male, 110 female) with JIA. Patients that had been diagnosed with JIA at the Department of Pediatric Rheumatology of the Dicle University Children's Hospital between 1998 and 2013 were identified. The hospital is the main referral center for southeastern Turkey. Medical records were reviewed retrospectively.

The classification criteria set up by the Task Force of the Pediatric Standing Committee of ILAR were used to diagnose JIA[15]. Patients were categorized into one of seven subgroups: oligoarticular arthritis, polyarthritis with rheumatoid factor, polyarthritis without rheumatoid factor, systemic arthritis, psoriatic arthritis, enthesitis-related arthritis (ERA) and undifferentiated arthritis[15]. Diagnosis of JIA was established based on the existence of chronic arthritis lasting longer than six weeks and absence of any other systemic disease that could explain arthritis development. Following six months of the first JIA diagnosis, if the number of involved joints was four or less, the disease was accepted as oligoarthritis, when five or more joints were involved, it was named as polyarthritis. Before the diagnosis, we performed infection studies including cultures and serology to exclude brucellosis, tuberculosis or any other infection. Bone marrow aspiration was performed in suspicious cases with monoarthritis prior to methotrexate treatment in order to exclude malignancy.

Patients with inflamed joints due to other diseases such as malignancy, trauma, metabolic diseases, vasculitides, Behçet's disease, inflammatory bowel disease and other systemic illnesses (familial Mediterranean fever, systemic lupus erythematosus) were excluded. We also excluded children with post-infectious arthritis related to viral or bacterial infections including post-streptococcal arthritis and reactive arthritis.

Patients' age, sex, age at diagnosis, age at disease onset and length of delay in treatment, were collected for each patient. The clinical symptoms and signs of patients, such as arthralgias, arthritis, fever, fatigue, malaise and morning stiffness were identified and recorded. The treatment regimens such as nonsteroidal anti-inflammatory drugs (NSAIDs), methotrexate, systemic glucocorticoids, disease-modifying anti-rheumatic drugs (DMARDs) were obtained from the available records. Our first choice drugs were naproxen sodium and methotrexate for oligoarthritis and these drugs with addition of steroids in polyarthritis. Intraarticular steroid injection was chosen when there was oligoarthritis with normal acute phase reactants. We used systemic steroids for severe polyarthritis and systemic JIA. We used combination therapies with sulfasalazin, intravenous high dose pulse methylprednisolone and nonsteroid inflammatory agents for enthesitis related arthritis. Biologic agents were used in patients who did not respond to 3-6 months of DMARDS. Etanercept, anakinra, canakinumab or tosilizumab were used as biologic agents.

Laboratory data, including complete blood cell count, inflammatory markers such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were analyzed

Table 1. Clinical and laboratory data of the 213 children with JIA at initial presentation.

Laboratory findings	Patient numbers n (%)	Complaints	Patient numbersn (%)
Anemia	81 (38.0)	Arthralgia	209 (98.1)
Leukocytosis	54 (25.4)	Fever	111 (52.1)
Thrombocytosis	104 (48.8)	Fatigue	85 (39.9)
Increased ESR	156 (73.2)	Malaise	114 (53.5
Increased CRP	148 (69.4)	Morning stiffness	33 (15.5)
ANA positivity	25 (11.7)	Raynaud phenomenon	1 (0.5)
RF positivity	28 (13.1)		
§HLA B-27 positivity	6 (2.8)		

JIA: juvenile idiopathic arthritis, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, RF: rheumatoid factor, ANA: anti nuclear antibody, HLA-B27: human leukocyte antigen-B27, n: number, §Note that HLA-B27 test was done in only 47 of the 213 JIA patients.

Table 2. Comparison characteristics of children with JIA in different ethnicities.

	Southeast Turkey	India	Taiwan	South Africa	Western Europe	Spain
Female/male	110/103	98/137	88/107	39/39	1484/618	288/144
Age at onset (years)	8.6	12*	9.5*	7.3	5.4	5.2
Oligoarticular (%)	37.1	21	23	26.8	51	61.3
Polyarticular	42.3	29	16.4	40.9	32	10.0
Polyarticular RF (+) (%)	10.8	12	4.6	14	-	0.7
Polyarticular RF (-) (%)	31.5	17	11.8	26.9	-	9.3
Systemic (%)	8.9	8	18.9	7.7	16.4	8.8
ERA (%)	10.8	36	37.4	23	-	8.6
Psoriatic (%)	0.9	1	1.5	1.3	-	4.6
Uveitis (%)	4.2	-	6.7	-		12
ANA positivity (%)	11.7	-	33.3	4.5∞	-	57.6

JIA: juvenile idiopathic arthritis, RF (-): rheumatoid factor negative, RF (+): rheumatoid factor positive, ERA: enthesitis-related arthritis, ANA: anti-nuclear antibody, Values are presented as average, * mark means the median value. ∞ It should be noted that ANA test were performed only in 67 of 78 South African children with JIA.

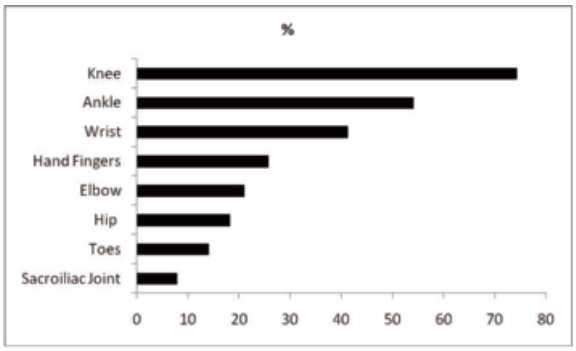

Figure 1. The frequencies (%) of affected joints at initial presentation in the 213 children with juvenile idiopathic arthritis.

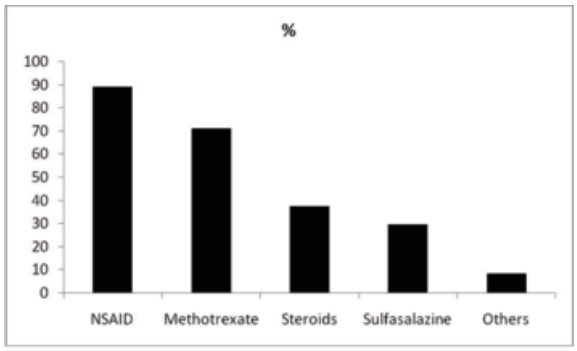

Figure 2. The frequencies (%) of given drugs in the 213 children with juvenile idiopathic arthritis during the study period. NSAID: nonsteroidal anti-inflammatory drug.

using standard methods. Also, patients were tested for rheumatoid factor (RF), anti-nuclear antibody (ANA) and human leukocyte antigen-B27 (HLA-B27). The HLA-B27 assay consisted of a polymerase chain reaction with sequence-specific primer analysis techniques. The ANA was measured using the immunofluorescent antibody method. RF was measured using the nephelometric method (Beckmann coulter IMMAGE-8000, Brea, U.S.A). ANA titers >160 IU/mL and values of RF >20 U/mL were classified as positive. In order to be classified as RF-positive disease, RF had to be positive on at least two occasions during the first six months of disease onset.

In order to check for the presence of uveitis, ophthalmologic examinations with slit lamp were regularly performed.

Patients were divided into subgroups according to disease activity: active disease or inactive disease. Disease activity was assessed according to the criteria published by Wallace *et al*[16]. Inactive disease included the following: no active arthritis, a normal ESR or CRP level, no fever, rash, serositis, splenomegaly or lymphadenopathy associated with JIA, no active uveitis, and/or a documented physician assessment that classified the disease as inactive. Active disease was divided into two groups: clinical remission on and off medications (CRM and CR, respectively). CRM was defined as at least six continuous months of inactive disease with medication. CR was defined as a minimum of 12 months of inactive disease without the use of anti-arthritis and anti-uveitis medications. Possible prognostic clinical factors (sex, disease onset age, inflamed joints, treatment) and hematological factors such as thrombocytosis and anemia were investigated. Also, we examined patients with a high ESR or high CRP at the time of diagnosis. The patients' drug treatments (naproxen sodium, methotrexate, steroids, sulfasalazine, etanercept etc.) and their responses to drug treatment were assessed in detail. Moreover, the patients were recommended to do physiotherapy that included exercise and stretching.

This study was approved by the Institutional Review Board University of the Dicle School of Medicine. Written informed consent was obtained from each participant and/or from his or her legal caregivers prior to enrolling in the study.

Statistical analysis

All statistical analyses were performed using SPSS (Statistical Package for Social Sciences) version 15.0 for Windows (SPSS, Inc., Chicago, IL). Categorical variables were expressed as counts and percentages. Independent samples t test or Mann Whitney U test were used for comparison of numerical data of patients and the controls. Chi-square test was used for comparison of nominal or ordinal variables. Prognostic factors were examined by logistic regression analysis. A p value of less than 0.05 was accepted as statistically significant.

Results

The study population consisted of 213 children (103 boys, 110 girls) with JIA. The female to male ratio was 1.06. Although, there was male preponderance in ERA subgroup (65.2%); oligo- and polyarthritis groups had more female patients. However, no statistically significant difference was found in male/female ratio between subgroups (p>0.05, data not shown). The mean age of onset was 8.1 years (range 8 months-15.4 years; median 8.6 years) and the mean age of the patients was 11 ± 3.95 (range 1.6-18) years. The mean time interval between the onset of the disease and diagnosis was 4.7 ± 2.9 (median

Table 3. Disease activity of the 213 children with JIA in Southeast Turkey.

	Oligoarticular n (%)	Polyarticular RF(+) n (%)	Polyarticular RF(-) n (%)	Systemic n (%)	ERA n (%)	Psoriatic
Active disease	24 (30.4)	6 (26.1)	17 (25.3)	6 (31.6)	4 (17.4)	-
Inactive disease						
CRM	36 (45.5)	12 (52.2)	32 (47.8)	8 (42.1)	11(47.8)	1 (50)
CR	19 (24.1)	5 (21.7)	18 (26.9)	5 (26.3)	8 (34.8)	1 (50)
Total	79 (100)	23 (100)	67 (100)	19 (100)	23 (100)	2 (100)

JIA: juvenile idiopathic arthritis, RF (-): rheumatoid factor negative, RF (+): rheumatoid factor positive, ERA: enthesitis-related arthritis, CRM: clinical remission on medication, CR: clinical remission off medication, n: number.

4; range 2-22) months. The overall follow-up duration was 11 months or more from the beginning of the disease (median 2 years; range 11 months-9.2 years). The disease onset age was under five years in 50 (23.5%) patients, between 5 and 10 years in 83 (39.0%) and over 10 years in 80 (37.5%) patients.

The most common initial presenting symptoms/complaints were arthralgias in 209 (98.1%), fever in 111 (52.1%), fatigue in 85 (39.9%), malaise in 114 (53.5%), morning stiffness in 33 (15.5%) and Raynaud phenomenon in 1 (0.5 %) patient (Table 1). Table 1 shows the clinical characteristics of the patients. The frequencies of fatigue, anorexia, weakness and morning stiffness were significantly higher in polyarthritis group compared with other groups ($p<0.05$, data not shown). The frequency of anemia was changed from 31.6% to 49.3% in subgroups with the most frequency in polyarthritis group. The JIA subtypes were as follows: oligoarticular in 79 (37.1%), polyarticular rheumatoid factor (RF) positive in 23 (10.8%), polyarticular rheumatoid factor (RF) negative in 67 (31.5%), systemic arthritis in 19 (8.9%), enthesitis-related arthritis (ERA) in 23 (10.8%) and psoriatic arthritis in 2 (0.9%) patients. No patients were classified as undifferentiated arthritis. The distribution of the JIA subtypes is listed in Table 2.

The most affected joints were knee and ankle. Figure 1 summarizes the affected joints of the patients. Polyarticular JIA was the most common subtype (90 patients; 42.2%), 23 of them were RF positive and 67 were RF negative. There was no difference in the gender ratios between the subtypes of polyarticular JIA ($p>0.05$).

Oligoarticular JIA was the second most common type (79 patients; 37.1%). Thirty-nine of the oligoarticular JIA patients (49.4%) were male. Uveitis was found in 9 (4.2%) patients and of these patients, six had oligoarticular arthritis and three had ERA. ANA was positive in 16 (20.2%) patients with oligoarticular arthritis.

There were no differences in the hemoglobin (Hb) levels and ratio of elevated inflammatory markers between oligoarticular and polyarticular JIA subgroups (data not shown, $p>0.05$). The laboratory characteristics of the patients are shown in Table 1. Twenty-five (11.7%) out of 213 patients tested positive for ANA, twelve ANA-positive patients were boys. A positive RF was found in 28 (13.1%) patients. Forty-seven patients were tested for HLA –B27 and only 6 (2.8%) patients were positive. In our study population, three children with JIA developed macrophage activation syndrome (MAS). No mortality was seen. All patients gave good response to pulse methylprednisolone and intravenous cyclosporine treatment.

Non-steroidal anti-inflammatory drugs (NSAID, naproxen, ibuprofen or indomethacin) (89.2%) were the most frequently used drugs, followed by methotrexate (71.4 %) and steroids (37.6 %). Figure 2 shows the types of drug treatment.The frequencies of given drugs were NSAID in 82.6-92.4% patients, methotrexate in 57.0-95.7%, sulfasalazin in 17.4-38.8%, and steroids in 25.3-78.9% in different subgroups of JIA patients. Sixteen patients received etanercept.

Active disease was seen in 57 (26.7%) patients at the last visit. Inactive disease was achieved in 156 (73.2%) patients. A hundred of the patients were CRM (46.9 %) and 56 (26.2%) were CR (Table 3).

Discussion

JIA is not a single condition, but rather it is a heterogeneous group of disorders characterized by arthritis of unknown etiology that manifests itself before the age of 16 years and persists for at least six weeks[2]. It is one of the most common inflammatory diseases in childhood and is a major cause of disability[17].

The female/male ratio in JIA varies between studies. In previous reports from Western societies, girls outnumbered boys. The present study showed a female predominance, similar to what has been described in the European and Latin American populations[18]. In previous studies, the mean age at onset ranged between 4.1 and 10.3 years[19]. In our study, the age at onset was higher than in European and American patients[18] but was lower than reported in small studies of Asian (China and India) patients[20,21]. As noted in previous studies, the knee and ankle joints were the most commonly involved joints in our patients[22].

JIA is a heterogeneous group of several disease subtypes and the incidence of the subtypes varies in different populations. The present study found that polyarthritis was the most common subtype, which was followed by oligoarthritis. Systemic and psoriatic arthritis were the rarest subtypes. These findings are in line with other studies from Asian and non-European countries[23,24]. In contrast, oligoarthritis has been reported as the most common type in Western populations[25]. However, some Asian countries have reported different subtypes as being most common. In China, ERA was the most common subtype[20], while in Japan systemic arthritis was the most frequent[24].

Enthesitis-related arthritis is a form of undifferentiated spondyloarthropathy. In Chinese and Indian studies, the frequency of ERA has been found to be quite high (37%, 36%, respectively)[20] while the incidence of ERA is significantly lower in Western populations (7%-13%)[26,27]. In 47 of our patients, HLA-B27 was tested for and only six patients were HLA-B27 positive, all of whom were ERA patients. ERA constituted 10.8% of our study group, which is similar to what has been found in Western countries and Turkey. These results suggest that there may be ethnic differences in the prevalence of the JIA subgroups.

Testing positive for ANA has been reported as a risk factor for the development of uveitis, especially in patients with oligoarticular arthritis[28]. In our study, 11.7% of patients tested positive for ANA. This ratio is quite low when compared with European and North America populations[25]. Although our ANA positivity ratio is quite low when compared with European and North America populations, Nordal *et al* reported ANA positivity as 27.4% in a long term Nordic Cohort[27]. However, previous studies have also found a low prevalence of ANA positivity in Turkey[29,30], Zambia, South Africa, and India[31]. We think

our low frequency of ANA positivity may be partially resulting from insufficiencies of our laboratory facilities in the past years, since our study is retrospective. Our results together with the similar results from Zambia, South Africa and India also may indicate variations in ANA positivity according to different geographic areas and ethnicities.

In previous studies, the incidence of uveitis has been reported to be between 10 to 20%, but in our study, only nine patients had uveitis[27]. These findings were consistent with earlier studies of children with JIA from Turkey[30]. Uveitis was observed in 4.2% of our patients, six of which had oligoarticular arthritis and three had ERA. ANA positivity has been considered to be an important prognostic factor. In contrast, in our study no difference was detected in terms of active and inactive disease with regards to ANA positivity. This result may be due to the small number of ANA-positive patients.

The prevalence of RF positivity in children with JIA (5-10%) was lower when compared to children with seronegative disease. The RF test should be performed in polyarticular JIA since it has prognostic value[32]. In the present study, 13.1% of patients were positive for RF and 82.1% of these patients had polyarticular JIA. Seropositive polyarticular JIA is an aggressive and erosive subtype that inhibits the growth of the affected joints and can lead to growth retardation. The disease is more common in girls and frequently the age of onset is over 8 years. Consistent with previous reports[1,33], in the present study, the age at disease onset in seropositive children was frequently more than 8 years of age (56.6%) and the male/female ratio was 10/13.

The presentation of children with systemic JIA is variable, because unlike other subtypes, extra-articular features are more prominent than joint involvement. Extra-articular features include fever, hepatosplenomegaly, rash and lymphadenopathy. In this study, 8.9% of patients had systemic JIA. These results are consistent with other reports from India (8%) and South Africa (7.7%). However, this ratio is lower when compared to Western European countries[31].

MAS is a rare but a life-threatening complication of systemic JIA. In patients who develop MAS, fever, leukopenia, thrombocytopenia, hypofibrinogenemia, liver failure and encephalopathy can be seen. In this study, three children with JIA developed MAS. In the literature, the mortality related to MAS has been reported to be between 8 to 22%[33,34]. Intravenous high dose steroids, followed by low dose steroids and cyclosporine successfully treated MAS in all three children.

ESR and CRP are useful inflammatory markers that may be indicative of disease activity in JIA. Nevertheless, the value of these markers in active disease is variable. ESR is a useful marker for monitoring disease activity[3,11]. In the present study, the percentages of patients with elevated levels of ESR and CRP were 73.2 and 69.4%, respectively. However, the average values of the acute phase markers did not differ between the JIA subgroups in our patients.

Anemia associated with chronic disease can be seen in JIA. Anemia was found in 38% of our patients. Leukocytosis is common in active JIA and thrombocytosis can be seen especially in the systemic subtype. Leukocytosis and thrombocytosis were found in 25.4% and 48.8% of the patients in our study, respectively. Forty-two percent of patients with systemic JIA had leukocytosis and 63.1% had thrombocytosis. In this study, the white blood cell and platelet counts were elevated in most of the systemic JIA patients, which is similar to previous reports[35].

Previous studies show that active disease occurs in between 24-60% of JIA patients[19]. In our study, 26.7% of JIA patients had persistent disease activity. In this study, active disease was seen in 30.4% of the oligoarticular subtype whereas 23% of the polyarticular patients had active disease. Consistent with previous studies, we observed that the oligoarticular subtype was more likely to respond to treatment than the polyarticular subtype[13]. This result can be attributed to better compliance and better long-term response to treatment.

The main goal of JIA treatment is to prevent systemic involvement, ensure normal growth, physical development, to avoid disease relapse and to control the disease symptoms[36]. Despite major advances in the treatment of JIA, non-steroidal anti-inflammatory drugs (NSAIDs) are still the mainstay of treatment, followed by methotrexate and steroids. In recent years, biological agents have been shown to improve disease prognosis and to reduce disease burden[37]. In this study, the majority of patients received NSAIDs as an initial therapy. Other drugs that were used with decreasing frequency were methorexate, steroids, sulfasalazine and biologic agents in our patients.

There were some limitations to our study. First, this study was hospital-based, second it is possible the data may be incomplete and incorrect due to the retrospective study design and finally, the HLA-B27 test was not performed in all patients.

Conclusion

To our knowledge, this study is the largest reported cohort of children with JIA in southeastern Turkey. The clinical manifestations of JIA in our patients were different than in other international studies. Our study was able to show that Turkish children are at a higher risk than children from Western countries for developing polyarticular disease. Also this study showed that there is a lower prevalence of ANA positivity and JIA-related uveitis in children in southeastern Turkey. When taken together, the results of the study suggest that immunogenetic and environmental factors may have an important role in the prevalence of JIA subgroups among different ethnic groups. Further prospective genetic and immunologic studies are needed to better define the clinical phenotypes of the disease, prognostic factors and more effective treatment modalities in different geographic and ethnic groups in patients with JIA.

Conflict of interest

Authors report no conflict of interest. Authors alone are responsible for content and writing of the paper.

References

1. Ravelli A, Martini A. Juvenile idiopathic arthritis. Lancet. 2007; 369: 767-778.
2. Martini A, Lovell DJ. Juvenile idiopathic arthritis: state of the art and future perspectives. Ann Rheum Dis. 2010; 69: 1260-1263.
3. Kim KH, Kim DS. Juvenile idiopathic arthritis: Diagnosis and differential diagnosis. Korean J Pediatr. 2010; 53: 931-935.
4. Martini A, Ruperto N: Quality of life in juvenile idiopathic arthritis compared to healthy children. Clin Exp Rheumatol. 2001; 23: 1-7.
5. Saurenmann RK, Rose JB, Tyrrell P, Feldman BM, Laxer RM, Schneider R, et al. Epidemiology of juvenile idiopathic arthritis in a multiethnic cohort. Arthritis Rheum. 2007; 56: 1974-1984.
6. Helmick CG, Felson DT, Lawrence RC, Gabriel S, Hirsch R, Kwoh CK, et al; National Arthritis Data Workgroup. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part I. Arthritis Rheum. 2008; 58: 15-25.
7. Gowdie PJ, Tse SM. Juvenile idiopathic arthritis. Pediatr Clin N Am. 2012; 59: 301-327.
8. Aggarwal A, Misra R. Juvenile chronic arthritis in India: is it different from that seen in Western countries? Rheumatol Int. 1994; 14: 53-56.
9. Schwartz MM, Simpson P, Kerr KL, Jarvis JN. Juvenile rheumatoid arthritis in African Americans. J Rheumatol.1997; 24: 1826-1829.
10. Weiss JE, Ilowite NT. Juvenile idiopathic arthritis. Pediatr Clin North Am. 2005; 52: 413-442, vi.
11. Huang H, Qian X, Yu H, Li J, Zhang Y. Clinical analysis in 202 children with juvenile idiopathic arthritis. Clin Rheumatol. 2013; 32: 1021-1027.
12. Qin Z, Jiang X, Lin Y. Clinical characteristics of 228 cases with juvenile idiopathic arthritis. J Applied Clinical Pediatrics. 2008; 21: 12-17.
13. Ravelli A. Toward an understanding of the long-term outcome of juvenile idiopathic arthritis. Clin Exp Rheumatol. 2004; 22: 271-275.
14. Fantini F, Gerloni V, Gattinara M, Cimaz R, Arnoldi C, Lupi E. Remission in juvenile chronic arthritis: a cohort study of 683 consecutive cases with a mean 10 year followup. J Rheumatol. 2003; 30: 579-584.
15. Petty RE, Southwood TR, Manners P, Baum J, Glass DN, Goldenberg J, et al; International League of Associations for Rheumatology. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. J Rheumatol. 2004; 3: 390-392.
16. Wallace CA, Ruperto N, Giannini E; Childhood Arthritis and Rheumatology Research Alliance; Pediatric Rheumatology International Trials Organization; Pediatric Rheumatology Collaborative Study Group. Preliminary criteria for clinical remission for select categories of juvenile idiopathic arthritis. J Rheumatol. 2004; 3: 2290-2294.
17. Horneff G, Schmeling H, Biedermann T, Foeldvari I, Ganser G, Girschick HJ, et al; Paediatric Rheumatology Collaborative Group. The German etanercept registry for treatment of juvenile idiopathic arthritis. Ann Rheum Dis. 2004; 63: 1638-1644.
18. Gutierrez-Suarez R, Pistorio A, Cespedes Cruz A, Norambuena X, Flato B, Rumba I, et al; Pediatric Rheumatology International Trials Organisation (PRINTO). Health-related quality of life of patients with juvenile idiopathic arthritis coming from 3 different geographic areas. The PRINTO multinational quality of life cohort study. Rheumatology (Oxford). 2007; 46: 314-320.
19. Adib N, Silman A, Thomson W. Outcome following onset of juvenile idiopathic inflammatory arthritis: I. frequency of different outcome. Rheumatology (Oxford). 2005; 44: 995-1001.
20. Shen CC, Yeh KW, Ou LS, Yao TC, Chen LC, Huang JL, et al. Clinical features of children with juvenile idiopathic arthritis using the ILAR classification criteria: A community-based cohort study in Taiwan. J Microbiol Immunol Infect. 2013; 46: 288-294.
21. Kunjir V, Venugopalan A, Chopra A: Profile of Indian patients with juvenile onset chronic inflammatory joint disease using the ILAR classification criteria for JIA: a community-based cohort study. J Rheumatol. 2010; 37: 1756-1762.
22. Weiss JE, Ilowite NT. Juvenile idiopathic arthritis. Pediatr Clin N Am.2005; 52: 413-442, vi.
23. Saurenmann RK, Rose JB, Tyrrell P, Feldman BM, Laxer RM, Schneider R, et al. Epidemiology of juvenile idiopathic arthritis in a multiethnic cohort: ethnicity as a risk factor. Arthritis Rheum. 2007; 56: 1974-1984.
24. Fujikawa S, Okuni M. Clinical analysis of 570 cases with juvenile rheumatoid arthritis: results of a nationwide retrospective survey in Japan. Acta Paediatr Jpn. 1997; 39: 245-249.
25. Merino R, De Inocencio J, Garcia-Consuegra J. Evaluation of ILAR classification criteria for juvenile idiopathic arthritis in Spanish children. J Rheumatol. 2001; 28: 2731-2736.
26. Modesto C, Anton J, Rodriguez B, Bou R, Arnal C, Ros J, et al. Incidence and prevalence of juvenile idiopathic arthritis in Catalonia (Spain). Scand J Rheumatol. 2010; 39: 472-479.
27. Nordal E, Zak M, Aalto K, Berntson L, Fasth A, Herlin T, et al. Ongoing disease activity and changing categories in a long-term nordic cohort study of juvenile idiopathic arthritis. Arthritis Rheum. 2011; 63: 2809-2818.
28. Shin JI, Kim KH, Chun JK, Lee TJ, Kim KJ, Kim HS, et al. Prevalence and patterns of anti-nuclear antibodies in Korean children with juvenile idiopathic arthritis according to ILAR criteria. Scand J Rheumatol. 2008; 37: 348-351.
29. Kasapcopur O, Yologlu N, Ozyazgan Y, Ercan G, Caliskan S, Sever L, et al. Uveitis and anti nuclear antibody positivity in children with juvenile idiopathic arthritis. Indian Pediatr. 2004; 41: 1035-1039.
30. Yilmaz M, Kendirli SG, Alt?ntas DU, Karakoc GB, Inal A, Kilic M. Juvenile idiopathic arthritis profile in Turkish children. Pediatr Int. 2008; 50: 154-158.
31. Weakley K, Esser M, Scott C. Juvenile idiopathic arthritis in two tertiary centres in the Western Cape, South Africa. Pediatr Rheumatol Online J. 2012; 10: 35.
32. Shin YS, Choi JH, Nahm DH, Park HS, Cho JH, Suh CH. Rheumatoid factor is a marker of disease severity in Korean rheumatoid arthritis. Yonsei Med J. 2005; 46: 464-470.
33. Kahn P: Juvenile idiopathic arthritis: an update for the clinician. Bull NYU Hosp Jt Dis. 2012; 70: 152-166.
34. Sawhney S, Woo P, Murray KJ. Macrophage activation syndrome: a potentially fatal complication of rheumatic disorders. Arch Dis Child. 2001; 85: 421-426.
35. Tsai HY, Lee JH, Yu HH, Wang LC, Yang YH, Chiang BL. Initial manifestations and clinical course of systemic onset juvenile idiopathic arthritis: a ten-year retrospective study. J Formos Med Assoc. 2012; 111: 542-549.
36. Beresford MW, Cleary AG, Foster HE, Hutchinson E, Baildam EM, Davies K; UK MCRN/Arthritis Research UK Paediatric Rheumatology Clinical Studies Group; British Society of Paediatric and Adolescent Rheumatology. Comment on: Developing standards of care for patients with juvenile idiopathic arthritis.Rheumatology (Oxford). 2010; 49: 2227-2229.
37. Moorthy LN, Peterson MG, Hassett AL, Lehman TJ. Burden of childhood-onset arthritis. Pediatr Rheumatol Online J. 2010; 8; 8: 20.