The distribution of juvenile idiopathic arthritis in the eastern Mediterranean: results from the registry of the Turkish Paediatric Rheumatology Association

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Abstract

Objective

To analyse the demographics, main clinical and laboratory features and subtype distribution of juvenile idiopathic arthritis (JIA) in an eastern Mediterranean country, based on a multicentre registry.

Methods

Between March 2008 and February 2009 with this cross-sectional study, consecutive patients seen with JIA in selected centres were registered through a web-based registry. All patients were classified according to the International League of Associations for Rheumatology (ILAR) criteria.

Results

There were 634 patients with a mean age of 11.84±4.66 years and the female/male ratio was 1.2. The distributions of JIA patients according to onset of disease were as follows: systemic 92 (14.5%), oligoarticular extended 26 (4.1%), oligoarticular persistent 234 (36.9%), rheumatoid factor (RF) positive polyarthritis 20 (3.2%), RF negative polyarthritis 129 (20.3%), enthesitis-related 120 (18.9%), psoriatic 13 (2.1%). The frequency of uveitis was 15.7% among all of the oligoarthritis patients. Anti-nuclear antibody (ANA) was positive mainly among the oligoarticular onset patients. Twenty-one patients also had Familial Mediterranean fever (FMF). Among systemic JIA patients, the frequency of macrophage activation syndrome (MAS) was 15.2% (n=14). At the end of the mean follow-up of 7.6±4.4 years, 305 (48.1%) patients were defined to have inactive disease on medication, and 106 (16.7%) were completely free of any disease symptoms without medication.

Conclusion

Enthesitis related arthritis had a high frequency whereas psoriatic arthritis was very rare compared to other series. We suggest that there are certain differences in the characteristics of JIA in our eastern Mediterranean population. Thus, genetic studies need to be assessed in these populations separately and findings of genome wide association studies need to be confirmed in different populations.

Key words

Turkish registry, juvenile idiopathic arthritis, ILAR classification, uveitis, macrophage activation syndrome.

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Introduction

Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease in the world. Studies from different countries have shown that the prevalence as well as the distribution of subtypes varies in different ethnic groups (1-4). In previous studies from Turkey, it has been reported that the prevalence of JIA was similar to Western countries (5, 6). However, there is no reliable multicentre study that outlines the distribution of subtypes of JIA patients in Turkish children. Recent studies from different countries have shown that some subtypes such as oligoarticular extended and psoriatic JIA were more frequent in populations of European origin whereas some other JIA subtypes were more prominent in other ethnic groups (7).

The population of Turkey is Caucasian. The mainland of the country Anatolia has harboured ancient civilisations such as the Lykians, Phonecians, Troyans and Hitites. A major migration to Anatolia came from the Baltic region around 2500 BC. Along with the Indo-European branches many migrations from the Middle East and Mesopotamia in pre-Biblical times have also occurred. We have undertaken a nationwide multicentre cross-sectional study to define the distribution of the subtypes of JIA patients as described by International League of Associations for Rheumatology (ILAR) in Edmonton (8). We selected the major referral centres in Ankara and Istanbul receive the majority of the patients from all over the country and we have also included centres from different parts of the country that take care of patients with paediatric rheumatic diseases to represent the population better. This study provides the first reliable data from the country.

Material and methods

With this cross-sectional study, data of the JIA patients were collected through a web-based registry in selected centres between March 2008 and February 2009. Patients were consecutively enrolled in each centre and each patient was classified according to the ILAR criteria (8). The principal investigators from each centre were invited to a meeting to review the classification criteria and to practice data entry to the registry. Paediatric centres of the following nine referral centres participated in the study: Hacettepe University Medical School, Gülhane Military Medical Academy School of Medicine, Cerrahpaşa University Medical School, Dokuz Eylül University Medical School, Gazi University Medical School, Erciyes University Medical School, Akdeniz University Medical School, Gaziantep University Medical School, Göztepe Training and Research Hospital. These centres were selected since they were referral centres and their overall patient population would provide a good representation of the Turkish patients.

All centres were asked to register consecutive JIA patients that had been followed for at least 6 months. This was decided in order to differentiate the disease course of oligoarticular patients. Data at the time of the last visit was entered to the online registry based in Hacettepe University School of Medicine. Registered data included demographic features, medical history, and initial features including physical examination, laboratory tests and current medical treatment. Initial physical examination findings and registered clinical parameters included number and type of joints (small or large) involved at disease onset, presence of systemic features, signs of enthesitis and sacroiliac tenderness (Tables I and II). Uveitis was defined according to "Standardisation of Uveitis Nomenclature (SUN) Working Group criteria" (9). Both active and previous episodes of uveitis were registered at the time of enrolment.

Initial laboratory tests including complete blood count, erythrocyte sedimentation rate (ESR), testing for ANA, RF and HLA-B27 were carried out in respective university laboratories or two selected laboratories in Ankara and Istanbul. Increased ESR was defined as >20mm/h, leukocytosis and anemia were defined relative to age. Thrombocytosis was defined as platelets >450000/mm^3. A titer of 1:80 was chosen as a cut-off point for ANA positivity for at least two positive results at least 3 months apart.

Table I. Demographics and clinical characteristics of the patients (n. (%)), and (mean ± standard deviation)

	Systemic	Oligoarticular		Polyarthritis RF positive	Polyarthritis RF negative	Enthesitis-related	Psoriatic	Whole cohort
		Extended	Persistent					
No.	92 (14.5)	26 (4.1)	234 (36.9)	20 (3.2)	129 (20.3)	120 (18.9)	13 (2.1)	634
Age (years)	10.61±4.76 (1–18)	9.38±5.02 (2–18)	9.85±4.34 (3–18)	14.60±3.83 (1–18)	13.02±4.18 (1–18)	15.33±2.88 (4–18)	13.08±3.64 (8–18)	11.84±4.66 (1–18)
Female/Male	43/49	20/6	160/74	16/4	81/48	24/96	10/3	354/280
Disease duration (years)	4.97±3.79 (1–12)	4.38±2.94 (1–11)	3.86±2.95 (1–16)	3.85±3.41 (1–12)	5.22±3.61 (1–16)	3.82±2.66 (1–14)	5.54±3.53 (1–15)	4.35±3.25 (1–16)
Number of involved joints*	4 (0–36)	7 (5-10)	2 (1-4)	9 (5-38)	8 (4-43)	2 (0-14)	4 (1-10)	3 (0-43)
Small joint involvement	52 (56.5)	16 (61.5)	22 (9.4)	18 (90)	105 (81.4)	23 (19.2)	6 (46.2)	242 (38.2)
Large joint involvement	76 (82.6)	24 (92.3)	227 (97.0)	19 (95.0)	121 (93.8)	113 (94.2)	0	580 (91.5)

* Values are presented as medians (min–max)

Table II. Physical examination and laboratory findings of the patients on their initial diagnosis except uveitis (n (%))

	Systemic	Oligoarticular		Polyarthritis RF positive	Polyarthritis RF negative	Enthesitis-related	Psoriatic	Whole cohort
		Extended	Persistent					
No. (%)	92 (14.5)	26 (4.1)	234 (36.9)	20 (3.2)	129 (20.3)	120 (18.9)	13 (2.1)	634
Fever	90 (97.8)	3 (11.5)	9 (3.8)	2 (10.0)	17 (3.2)	4 (3.3)	2 (15.4)	127 (20.0)
Lymphadenopathy	42 (45.7)	0	4 (1.7)	1 (5.0)	4 (3.1)	0	1 (7.7)	52 (8.2)
Uveitis	2 (2.2)	4 (15.4)	37 (15.8)	0	8 (6.2)	8 (6.7)	3 (23.1)	62 (11.6)
Pericarditis	24 (26.1)	0	0	0	1 (0.8)	0	0	25 (3.9)
Hepatosplenomegaly	47 (51.1)	1 Z(3.8)	8 (3.4)	0	7 (5.4)	0	0	63 (9.9)
Thrombocytosis	59 (64.1)	14 (53.8)	47 (20.1)	5(25)	60 (46.5)	23 (19.2)	5 (38.5)	213 (33.6)
ESR >20 mm/h*	91.60±29.56 (2–143)	47.42±28.12 (4–162)	42.19±28.76 (13–100)	52.20±25.56 (4–130)	59.39±35.37 (8–125)	44.08±31.90 (4–130)	56.77±30.73 (12–125)	54.05±35.02 (2–162)
ANA positivity n (%)	0	15 (57.7)	121 (51.7)	8 (40.0)	30 (23.3)	4 (3.3)	3 (23.1)	191 (30.1)
HLA-B27	NA	NA	NA	NA	NA	76(63.3)	NA	
RF+	NA	0	0	20 (100)	0	0	0	20 (3.1)

* ESR was presented as mean ± standard deviation

Each centre was asked to register the treatment received at the last visit. This cross-sectional study was approved by the local ethics committee in each and every centre. The individual participant written consent was obtained.

Statistical analysis

Statistical analysis was done by using SPSS version 15.0. Mean±standard deviation, median, minimum and maximum values, and percentages and numbers were used to express all the data.

Results

A total of 634 JIA patients enrolled in the study. The mean age of the patients at the time of study and mean age of the disease onset were 11.84±4.66 (1.0–18.0 years) and 7.69±4.41 (1–11 years), respectively. The female/male ratio was 1.2 (354/280). The distribution of JIA patients according to the onset were as follows: systemic 92 (14.5%), oligoarticular extended 26 (4.1%), oligoarticular persistent 234 (36.9%), RF positive polyarthritis 20 (3.2%), RF negative polyarthritis 129 (20.3%), enthesitis-related arthritis (ERA) 120 (18.9%), psoriatic 13 (2.1%) (Table I). Distribution of joint involvement was as expected for each subtypes (Table I).

Uveitis was most frequent among oligoarticular onset disease although it was occasionally present in other onset types as well. The frequency of uveitis was 15.7% among all of the oligoarthritis patients. ANA positivity was 61.2% in patients with uveitis. ANA was positive in more than half of the patients with oligoarticular type onset. Based on registered initial laboratory results, anemia was present in 52.8% (335/634) of the JIA patients. The mean ESR among the JIA patients was 54.05±35.02mm/h (2–162mm/h). HLA B27 was present among 63.3% of the patients with enthesitis related arthritis (Table II).

In 21 patients (3.3%) familial Mediterranean fever and in 3 patients (0.5%) in-

Table III. Distribution of JIA subtypes in children of Turkish and another descent (%).

JIA subtype	Turkish registry (n=634)	European [7] (n=599)	Asian [7] (n=50)	German [18] (n=1085)	England [4] (n=507)	Latin American[13] (n=110)
Systemic	14.5	13.1	12	10	5.3*	3.6
Oligoarticular						
Persistent	36.9	30.1	26	40	45.9	70.9
Extended	4.1	11.8	2	16		
RF negative polyarticular	20.3	23.1	20	16.8	13.4	16.4
RF positive polyarticular	3.2	2.2	4	3.2	2.3	
Enthesitis-related	18.9	7.6	24	86.3		
Psoriatic	2.1	12.1	8	66.9		
Other						9.1

*In another study from the United Kingdom, Fife *et al*. reported a ratio of sJIA as 10% (17).

flammatory bowel disease were present as concomitant disorders. Current medical treatment of the patients was as follows: 349 (55.0%) were on non-steroidal anti-inflammatory drug (NSAID) treatment, 290 (45.7%) were receiving methotrexate (MTX), 121 (19.1%) were still on steroids, 103 (16.2%) received salazopyrin (all ERA patients), and 74 (11.7%) were on anti-TNF treatment at the time of the data entry.

At the end of the mean follow-up of 7.6±4.4 years from the time of diagnosis, 305 (48.1%) patients were defined to have inactive disease on medication, and 106 (16.7%) were completely free of any disease symptoms without medication. Thirty patients (4.7%) had complications in our cohort: 14 had infections and 14 had macrophage activation syndrome of which almost all had systemic onset JIA. Among systemic JIA patients, the frequency of MAS was 15.2% (n=14).

Discussion

This is the first multicentre study demonstrating the distribution of JIA subtypes and the characteristics of the disease in the eastern Mediterranean. Epidemiological studies in JIA show different sex ratios according to ethnicity. Our cohort indeed had a lower female: male ratio (1.27:1) as compared to the European origin (7:3), North American origin and Latin American origin (9:1). The ratio was similar to that reported in patients of Asian (1:1) origin (7, 10). We are unable to comment on this further other than to say that this may be due to ethnic reasons and maybe the higher rate of ERA.

It has been shown that the subtypes of JIA have different distributions in different ethnic groups (Table III) (11-15). The characteristics of JIA have been mainly defined from the North American or European populations in which the majority of patients are oligoarticular, and about 10% of the patients have systemic JIA. On the other hand, oligoarticular onset is less frequent among African American and Asian children (16). The differences between several ethnic groups may stem from environmental and/or genetic factors. Distribution of the JIA subtypes in the European *versus* non-European ethnic origins has recently been published from a country with mixed ethnic population (7). Subtype distributions in this study were similar to the relevant reports on the subject (1-4, 11-14). The non-European populations in this study were Asians, Indians, Arabs, Hispanics and native North Americans. When we compare the distribution of subtypes in our Turkish cohort with those reported in this mixed ethnic population (7), the rates of extended oligoarthritis and enthesitis related subtypes are in between those expected in European and non-European populations (Table III). Persistent oligoarthritis and systemic onset types had a similar rate to Europeans while psoriatic arthritis was very rare. Although Adib *et al*. (4) have found the rate of sJIA as 5.3%, in the United Kingdom Fife *et al*. (17) have reported a rate of 10%. Similarly, according to the German National Rheumatologic Database, the proportion of sJIA was 10% (18).

It was also noteworthy that enthesitis related arthritis (18.9% in the Turkish population) was almost thrice as common as in the European (7.6%) and English populations (6.3%), though much less common than the Asian (24%) population (4, 7, 10). These figures may reflect the indigenous character of the Turkish population. On the other hand, HLA-B27 has a rather lower rate than expected among the enthesitis related arthritis patients. Yazıcı *et al*. (19) reported that the prevalence of HLA-B27 (by latex agglutination) was 8/268 (3%) among healthy controls in the Turkish population, comparable to other populations. Thus, other unknown genetic and/or environmental factors may play a role in the pathophysiology of high ERA rates.

Figures from different centres that were included in this study were similar. This was probably due to the fact that the centres in Ankara and Istanbul are referral centres and they receive patients from all over the country, and only about 5–10% of their patients are local. This fact also suggests that the presented data reflects the demographics of the whole country, although we were not able to include all the centres from Turkey.

Oligoarticular-onset JIA is characterised by early onset asymmetric arthritis with a high frequency of ANA positivity, and these patients have a high risk for the development of uveitis (20-24). Various rates have been reported for uveitis in JIA. Reininga *et al*. (10) reported 153 patients with JIA from Netherlands, and 27 of them developed asymptomatic anterior uveitis (17.6%). ANA positivity in their study was detected more frequently in JIA patients

with uveitis (66.7%) than in JIA patients without uveitis (48.6%). In one study from Italy, uveitis developed in 62 patients (20.1%) of whom 57 had oligoarticular, 3 had polyarticular, and 2 had systemic-onset JIA (25). In another study from Germany, the prevalence of uveitis was 12%, and it was observed more frequently in oligoarthritis both in extended (25%) and persistent (16%) subgroups (26). Among 234 children diagnosed with JIA in Spain, prevalence of uveitis was 7.3% (27). On the other hand, uveitis is quite rare in Asian and African populations (28). In our whole cohort, the frequency of uveitis was 11.6% (62 patients) which is similar to those reported from European populations. Uveitis was detected in 37 (15.8%) and 4 (15.4%) of the persistent and extended oligoarticular JIA populations, respectively. In initial reports from Turkey, uveitis was thought to be rarer however; this was obviously due a lack of multidisciplinary approach in the past. Higher rate of uveitis once again shows the importance of collaboration with an ophthalmology team among others, in the care of these children.

Anemia was common in all subgroups although it was more pronounced among systemic onset patients. However, the rate of iron deficiency anaemia in the school age children in our country varies in different regions ranging from 5.4–27.6% which may explain the high rate of anaemia among our patients (29, 30). As expected thrombocytosis was frequent among systemic onset patients.

ANA positivity in our oligoarticular JIA population was 71.2%. ANA positivity has been reported as 82.6% and 73.4% among oligoarticular patients in two separate groups of European oligoarticular onset patients (7, 23). The frequency of ANA positivity in our population was similar to those reported in the European populations.

The presented data also outlines the treatment strategies in the country. While NSAIDs and MTX are widely used, use of biologics may be less than expected. Minden *et al*. (31) performed a study to estimate the cost of JIA in the national paediatric rheumatologic database in Germany. They recorded that 10% of all JIA patients were under biologics. In our cohort the use of biological agents was 11.7% at the time of the data entry. This is probably due to the strict bureaucratic measures involved in their use.

Macrophage activating syndrome was seen in a substantial number of systemic onset JIA patients (32). MAS has become a well-recognised problem in systemic JIA, and the figures reflect the awareness of this entity among Turkish paediatricians.

JIA is an important disease in the eastern Mediterranean population and this is the first multicentre study showing the characteristics of JIA patients in the eastern Mediterranean. The presented figures should alert the health authorities about the scope of the problem. We suggest that the subtype distribution reflects the characteristics of our population that are somewhat different from Western Europe and quite different from the Middle East, Asia and Africa. These figures probably reflect the indigenous character of the Turkish population. Thus genetic studies need to be assessed in these populations separately and findings of genome wide association studies need to be confirmed in different populations.

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