January 2014

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Clinical and Biochemical Characteristics of Children with Juvenile Idiopathic Arthritis

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ABSTRACT

Objective: To determine the clinical and biochemical characteristics of children with Juvenile Idiopathic Arthritis (JIA) at a tertiary care centre in Karachi, Pakistan.

Study Design: A descriptive study.

Place and Duration of Study: Paediatric Rheumatology Clinic of The Aga Khan University Hospital (AKUH), Karachi, from January 2008 to December 2011.

Methodology: Clinical and laboratory profile and outcome of children less than 15 years of age attending the Paediatric Rheumatology Clinic of the Aga Khan University, Karachi with the diagnosis of Juvenile Idiopathic Arthritis according to International League against Rheumatism were studied. These children were classified into different types of JIA; their clinical and laboratory characteristics, response to therapy and outcome was evaluated.

Results: Sixty eight patients satisfying the criteria of International League against Rheumatism (ILAR) for Juvenile Idiopathic Arthritis were enrolled during the study period of four consecutive years, their age ranged from 9 months to 15 years. Mean age at onset was 6.45 ± 4.03 years while mean age at diagnosis was 7.60 ± 3.93 years. Polyarticular was the most predominant subtype with 37 (54%) patients, out of these, 9 (24%) were rheumatoid factor positive. An almost equal gender predisposition was observed. Fever and arthritis were the most common presenting symptoms, with only 2 patients presenting with uveitis.

Conclusion: The clinico-biochemical characteristics of JIA at the study centre showed a pattern distinct with early onset of disease, high frequency of polyarticular type and a higher rheumatoid factor (QRA) and ANA positivity in girls.

Key Words: Juvenile idiopathic arthritis. Rheumatoid. Autoimmune. Children. Pakistan.

INTRODUCTION

Juvenile Idiopathic Arthritis (JIA) describes a clinically heterogeneous group of arthritides of unknown etiology that begins before the 16th birthday and persists for at least 6 weeks.[1] JIA is the most common chronic rheumatic disease in children and is an important cause of short and long-term disability.[2] JIA encompasses several disease categories; each has different modes of presentation, clinical signs, and symptoms, and in some cases, genetic background.[3] Almost all children with arthritis report chronic or recurrent pain with restricted physical activity and limited use of upper limbs or hands. There is a scarcity of data and established registries reported prevalence varying between 16 and 150 per 100,000.[1] JIA has the potential to cause long-term disability and leave a lasting impact on the quality of life of affected children.

Different classification systems have been developed so far and are still being evolved. Most widely accepted classification worldwide is developed by the International League Against Rheumatism (ILAR). According to ILAR classification, JIA has been divided into eight different subtypes.[4] Nevertheless, despite a dramatic advance in the understanding of JIA subtypes, pathobiology and management, much remains to be done.[5]

New advances in pharmacologic treatments have shown robust results. Even though none of the available drugs has a curative potential, prognosis of JIA has greatly improved as a result over the years.[6] Early interventions with disease-modifying anti-rheumatic drugs may help minimize joint damage[7] and increase remission rates.[8] However, use of such drugs can be complex, particularly in terms of appropriate dosing and monitoring for possible adverse effects in children. Moreover, the long-term effects of these medications in children are still unexplained.[9]

International research networks of paediatric rheumatology have contributed to fostering the conduct of controlled clinical trials and also the development of validated outcome measures. JIA has been extensively studied in the Western population, but there is a dearth of local data about the disease profile. This study was consequently undertaken to determining the clinical and biochemical characteristics of JIA in children and their outcome over a period of 4 years.

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METHODOLOGY

This cohort descriptive study was carried out at The Aga Khan University Hospital (AKUH), Karachi, Pakistan. It included patients presenting to the specialist paediatric rheumatology clinic, from January 2008 to December 2011.

A retrospective review of file was done and information was collected via a structured proforma prepared for the study. Data pertaining to JIA subtype, gender, age at onset of symptoms and age at diagnosis, joint involvement, and laboratory parameters included inflammatory markers e.g. leucocytes, platelets, Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), presence or absence of rheumatoid factor (QRA) and Anti-nuclear antibody (ANA) positivity were collected. In addition, different therapeutic regimen offered and their response was also observed.

Detailed history from patients and their parents/ guardians were taken; a complete clinical examination including musculoskeletal examination was performed by the treating physician. Patients who satisfied the ILAR criteria of JIA were subsequently included in the study. Children having other possible causes of arthritis were excluded. Patients were then further classified according to ILAR classification of the disease into polyarticular rheumatoid factor positive or negative, oligoarticular persistent and extended, systemic-onset, psoriatic, enthesitis-related and undifferentiated JIA sub- types depending upon number of joints involved and other systemic features were included in the study.

Data was entered, validated and analyzed using Statistical Package for Social Sciences (SPSS) version 19.0. Mean and standard deviation were expressed for numerical variables while frequencies and percentages were expressed for categorical variables.

As per Ethical Review Committee (ERC) guidelines at The Aga Khan University Hospital (AKUH), the study protocol was granted exemption (1935-Ped-ERC-11).

RESULTS

A total of 68 patients with the clinical diagnosis of JIA were included. The gender distribution was almost equal 33:35 (M: F 0.9:1) except in the systemic onset where the female ratio was almost double than the male (M: F 1:2). The minimum age of presentation was 9 months while the maximum age was 15 years. The mean age at onset of disease was 6.45 ± 4.03 years. The mean age at diagnosis was 7.60 ± 3.93 years; with systemic onset JIA being the youngest 4.43 ± 2.55 followed by poly- articular subtype 7.80 ± 3.82 while oligoarticular subtype were 8.59 ± 4.08 respectively. There were three peaks of age of presentation at 3, 6 and 12 years   (Figure 1).

Polyarticular subtype was the predominant type (n=37, 54% cases) in this study, out of which 9 (24%) were QRA positive with male to female ratio of 3:6. Oligoarticular was the second common subtype (n=19,
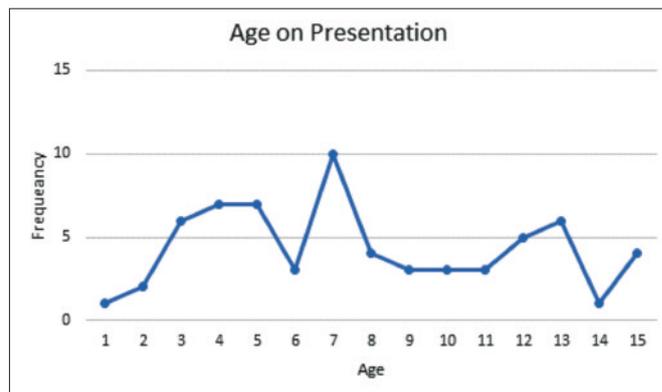

Figure 1: JIA -Age at presentation.

28%). Among them, 7 were extended subtype, all males and QRA positive. Nine (13%) patients were of systemic onset subtype. There were 2 cases of enthesitis-related arthritis and one with psoriatic arthritis.

Knee was the most frequently involved joints in all three types of JIA followed by ankle with a collective frequency of almost 80%. Wrist, elbow, metacarpo-phalangeal, proximal and distal inter-phalangeal joints are the other joints involved in decreasing order of frequency mostly in polyarticular type.

Various laboratory parameters in patients with JIA are shown in Table 1. Most of the biochemical markers were elevated in systemic onset and polyarticular type JIA. Complete blood count showed that overall 39 (57%) patients were anemic (hemoglobin < 10 g/dl) at presentation, among them the majority was systemic onset and polyarticular subtypes with the frequency of 8 (89%) and 22 (60%) respectively. White cell counts were raised (> 11,000/mm^3) in a total of 23 (34%) patients; 67% of these were of systemic onset type. Twenty nine (43%) had thrombocytosis (platelet count > 45000/ cumm) with the preponderance of systemic onset type 8 out of 9 (89%). Other acute phase reactants, including ESR and CRP, were also raised in most of the patients with the frequency of 52 (77%) and 50 (74%) respectively. It was observed that almost all patients with systemic onset type had high ESR and CRP (Table I). Overall positivity of rheumatoid factor was 22 (32%). Among them, majority 42% of patients were of oligoarticular types. ANA was positive in 11 (16%) patients with significant female predominance (M:F = 2:9); majority of them (6) were also of oligoarticular type while 4 of polyarticular and only one patient with systemic onset type had ANA positive.

Outcome was analyzed as response to therapy at the time of last follow-up. Mean follow-up was 27.5 months with the duration ranged from 4 to 45 months (Table II). The Carol Wallace criterion were applied based on Delphi questionnaire which defined 3 stages of disease: inactive disease, clinical remission on medication, and clinical remission off medication.[17]

Table I: Laboratory parameters in JIA.

JIA sub-type	Systemic onset (n=9) (%)(overall%)	Poly articular (n=37) (%)(overall%)	Oligoarticular (n=19) (%)(overall%)	Psoriatic/enthesitiis related arthritis (n=3) (%) (overall%)	Overall n = 68 (%)
HB < 10 g/dl	8 (89)	22 (60)	9 (47)	-	39 (57)
WBC counts > 11,000/cu mm	6 (67)	12 (32)	5 (26)	-	23 (34)
Platelet (> 450,000/cu mm)	8 (89)	19 (51)	3 (16)	-	29 (43)
ESR (> 20 mm/hr)	8 (89)	29 (78)	15 (79)	-	52 (77)
CRP (> 1)	9 (100)	27 (73)	14 (74)	-	50 (74)
QRA +ve	2 (22)	12 (32)	8 (42)	-	22 (32)
ANA +ve	1 (11)	4 (11)	6 (32)	-	11 (16)

Table II: Outcome of different types of JIA.

	Systemic onset (n=9)	Polyarticular (n=37)	Oligoarticular (n=19)	Psoriatic / enthesitis related arthritis (n=3)	Overall (%)
Remission off medication	5	14	10	3	32 (47.1%)
Remission on medication	1	7	4	-	12 (17.6%)
Active disease	-	3	1	-	4 (5.8 %)
Expired	1	2	-	-	3 (4.4 %)
Lost to follow-up	2	11	4	-	17 (25%)

Table III: Comparative clinical and biochemical characteristics of JIA in various studies.

	AKU	Lahore[10]	India[13]	Bangladesh[14]	Turkey[15]	United Kingdom[11]	Germany[12]
Number	68	91	74	132	196	572	172
Female: Male	35:33	49:42	26:48	34:89	94:102	384:188	118:54
Mean age of onset	6.45	10.76	6.4	7.5	6.9	-	-
Systemic onset (%)	13	4.4	14.9	6.8	15.3	14.7	17.4
Polyarticular (%)	54	44	37.8	47	37.2	24.7	28.7
Oligoarticular (%)	28	51.6	47.3	34.1	34.1	43.7	27.3
QRA (%)	33	48.4	2.7	5.3	8.1	5.2	2.9
ANA (%)	15	-	1	-	14.2	33	41.2
Psoriatic arthritis (%)	1.5	-	-	1.5	1	7.5	4.6
Uveitis (n)	2	-	1	12	4	114	21

The overall response rate to therapy was 86% (n=44) out of 51 patients who continued to follow in the clinic. Among those, 32 (62.5%) had clinical remission off medication and 12 (23.5%) had clinical remission on medication while 4 (8%) still had the active disease in their last follow-up. Best response was seen in oligoarticular persistent subtype while worse in polyarticular subtypes who are QRA positive. Seventeen (25%) were lost to follow-up due to accessibility, as they were from remote areas of the country. Three patients died, one with systemic onset type who subsequently develop macrophage activation syndrome. Two cases of polyarticular type died because of systemic tuberculosis and acute leukemia respectively. Two patients of systemic onset subtype presented with pericardial effusion, one of them require drainage while 2 patients of oligoarticular subtype develop uveitis both of them were ANA positive but none of them experienced visual loss. None of our patient developed amyloidosis.

DISCUSSION

Juvenile idiopathic arthritis is not an uncommon disease in children. Various characteristic of the disease have been widely studied in the developed countries; only few studies have been published from developing countries especially South Asian nations. So far, only one study is available from Pakistan which observes the pattern of juvenile idiopathic arthritis.[10]

Gender distribution in this study showed almost equal male to female ratio. (M: F =0.9:1) except in systemic onset JIA, where there were more females than males, in line with local data available from Pakistan;[10] it also corresponds well with the studies done in European countries like UK and Germany.[11,12] However, data from neighbouring countries like India, Bangladesh and Turkey report a significant male preponderance.[13-15]

The mean age at onset of the disease was 6.45 ± 4.03 years and the mean age of diagnosis was 7.60 ± 3.93 years. The age at onset in these children was comparatively younger than in the other studies which was 6.9 years in Turkish children,[15] 10.7 years as described by Nighat *et al.*[10] and 11.8 years in African children,[16] but comparable with an Indian study.[13] Among different subtypes, systemic onset JIA presents quite early at 4.3 ± 2.57, while oligoarticular presented at 7.00 ± 4.66 years.

The time elapsed from the onset of symptoms to the actual diagnosis was 1.15 years. This delay in diagnosis might be due to fact that such patients initially are dealt

by family physicians and referred to the general paediatricians after a couple of months of exhaustive treatment when symptoms do not settle. In addition, numbers of patients of oligoarticular JIA were initially treated as septic arthritis or rheumatic fever. Also, few of these patients were initially managed by the orthopaedic surgeons and had joint aspirate and synovial biopsy done before referral to rheumatology services.

In terms of disease characteristics, 37 (54%) were polyarticular with oligoarticular being the second commonest 19 (28%). Systemic onset JIA being the least frequent 9 (13%) subtype. The same sequence was observed in Turkey, Bangladesh and Germany in contrast with the studies from Lahore, India and UK where oligoarticular was most frequent subtype. One limitation of the study was the large selection bias as there was a high frequency of polyarticular subtype in these children. That might be due to the fact that these children perhaps had an extended oligoarticular phase due to delay in referral to the paediatric rheumatologist.

Knee and ankle were the most frequently affected joints accounting for an 80% of the cases in both poly and oligoarticular subtypes. Other joints that were involved, in order of frequency were the wrist, elbow, shoulder, metacarpo-phalangeal, inter-phalangeal and hip joints. This is comparable to data reported in other studies by Seth et al., Aggarval et al. and Singh et al.[13,18,22]

Ninety percent of cases of uveitis occur within 4 years of diagnosis of JIA.[23] The incidence of uveitis is quite high among children of developed countries like UK and Germany but considerably low among children of south Asian countries. Similar trend was seen in this study as well, where only 2 patients had uveitis; both had oligoarticular subtype with ANA positivity. One possible reason for this could be the delay in diagnosis of the development of uveitis in our set up, where many general practitioners would by-pass it as a simple conjunctivitis. We recommend regular screening by an ophthalmologist. Newly diagnosed patients are ideally screened within 6 weeks of diagnosis.[24]

The QRA factor positivity generally predicts the unfavourable outcome and poor response to therapy. QRA factor among these children was undoubtedly higher (32%) than that reported from neighbouring and other parts of the world (Table III).[11-15] These findings were reflected in another study available from Pakistan 48.4% which indicates that one-third to half patients of JIA from Pakistan are QRA positive.[10] Long-term follow-up of these patients will estimate the significance of QRA positivity in our population as these patients responded surprisingly well to treatment despite positive QRA factor. ANA prevalence in current study was 16% which is comparable with the Turkish population but quite low in contrast to other European studies.[11,12,15]

NSAIDs were used as the most commonly prescribed drugs in our patients. Naproxen and ibuprofen were preferred in majority of the patients due to easy availability and better tolerance; indomethacin was also used in a few patients as the first line agent. Methotrexate was the second preferred agent used mostly in polyarticular subtype and in a few cases of oligoarticular extended and systemic onset subtypes, who showed poor or no response to NSAIDs in 4 - 6 weeks time. Corticosteroids were used in all patients of systemic onset type while in few patients with polyarticular and extended oligoarticular subtypes, where inadequate response to NSAIDs and methotrexate were observed. Thomas et al. reported a standardized mortality ratio for females of 5.1 and males of 3.4.[25] In 2010, this is reported to have reduced to 0.57 (males and females combined).[26] Combination therapy of two or more drugs such as, NSAIDs with methotrexate, NSAIDs with steroids or NSAIDs with methotrexate and steroids was required in selected cases of polyarticular QRA positive and extended oligoarticular subtypes. Sulphasalazine and hydroxychloroquine were used mostly in patients with polyarticular disease with QRA positive as an adjunctive therapy with NSAIDs and methotrexate. We did not observe any major side effects that would require discontinuation of the medicines. Most patients experienced mild to moderate gastrointestinal discomfort with nausea and vomiting mainly with methotrexate and sulphasalazine. These symptoms were successfully managed with gastro-protective agents in the form of antacids and proton pump inhibitors. Folic acid supplements were used in all patients requiring methotrexate.

The high rate of loss to follow-up could also be attributed to the fact that most of our patients hailed from a lower socioeconomic background and the cost of transport from their areas to the main city was quite high.

Introduction of the biologic agents in the management of JIA opens a new era in the prognosis and long-term outcome of the disease and the better future prospects.[19-21] Unfortunately, we did not use biological agents in any of our patient because of the various reasons. Only few studies are available regarding the efficacy and safety of these agents in paediatric age group, therapy is quite expensive and not widely available in Pakistan. Few patients who remain have active disease despite of aggressive management are the best candidates for biologic therapy in this study.

CONCLUSION

It can be safely concluded from our study that the clinical and biomedical characteristics of Pakistani children are somewhat different from those of European and other neighbouring countries. We feel that there is still deficiency in understanding of the diagnosis and optimal

care of JIA. We recommend early referral and multi-disciplinary approach for these patients to ensure prompt treatment, thereby improving their long term follow-up and outcome. There is still a need of further research on JIA from the country to enhance our understanding about the clinical and biological characteristics of JIA and also measure the long term outcome with reference to impact on growth and health of our children.

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