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RESEARCH PAPER

Disease Activity States of Juvenile Idiopathic Arthritis in a Referral Centre in Bangladesh

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Abstract

Background: The clinical course of juvenile idiopathic arthritis (JIA) is unpredictable and characterised by periods of disease inactivity followed by active disease states with on or off medication.

Objectives: To assess the disease activity state of JIA patients in our centre and compare them with other available reports.

Methods: A retrospective cohort study carried out in the department of paediatrics, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka from July 2010 to December 2019 . A total of 1782 JIA patients, fulfilling ILAR criteria, who have completed at least three years of follow-up were enrolled in this study. Disease activity states were assessed according to Wallace's criteria.

Results: The mean age at presentation of disease was 8.33±4.8 years and M:F ratio was 1.4:1. Enthesitis related arthritis (ERA) was the commonest (38.0%) subtype, followed by systemic arthritis and RF–ve polyarthritis. Eighty-three percent of the JIA patients were treated with MTX followed by sulfasalazine (30.0%) and leflunamide (13.0%). Only 12.0% received biological agents and other drugs including thalidomide and tofacitinib. At 3 years follow-up, 39.2% had active disease and 60.7% had non-active disease states. Inactive disease states, clinical remission on medication (CRM) and clinical remission off medication (CR) were maintained by 27.1%, 20.1 %, and 13.3% of JIA patients respectively.

Conclusion: Most (60.7%) of the JIA patients maintained CRM, CR and inactive disease states. Active disease was found in 39.2% of JIA patients. The highest rate of remission was achieved in persistent oligoarthritis cases. RF+ve polyarthritis patients had the lowest remission rate.

Keywords: Active disease, Clinical remission on medication, Clinical remission off medication, Enthesitis related arthritis.

Introduction

Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease and is a significant cause of short and long-term morbidity in children.[1] The number of joint involvement and extra-articular features are the differentiating factors of JIA subtypes.[2] It is reported that, systemic JIA, RF+ve poly JIA and ERA tends to have higher disease activity and this patients have difficulty to achieve inactive disease compared to other subtypes.[3] Each subtypes differ in treatment, disease activity and outcome.

Few studies done in our neighboring country, India suggested that their demographic characteristics, disease profile and patterns of disease activity are different from studies reported from the USA and UK.[4,5] The North American and European JIA cohort recently observed an improved understanding of early disease course, management, and short-term outcome of this disease.[6] This cohort reported that early disease course and treatment response might predict the outcome more precisely. Recently, a Canadian study reported that 27 % of JIA patients in their cohort had active disease and 72 % had inactive disease at 3 years of follow-up.[7] A study done in BSMMU, Bangladesh in 2008 showed that, among 132 JIA children, more than 50% presented with long duration of disease and wrong diagnosis was found in about 64% of cases.[8] Among 415 JIA patients followed up in between, 2004-2012 at the same centre, it was reported that, about 49% patients had long duration of disease at presentation (>1 year) and about 26% had wrong diagnosis.[9] Comparison of those 2 studies done at the

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same centre, 6 years apart reflected gradually increasing level of awareness about JIA in Bangladesh. Later study also reported that, 68% of them achieved inactive disease state irrespective of subtypes and 51% maintained remission and 16.3% had relapse.[9]

Ethnic, geographic and socioeconomic factors could be the reasons for the difference between disease activity states of JIA and outcome in Asian and western countries. Lower standards of living, limited awareness and costly treatment could also be responsible for the different outcomes of JIA patients in this sub-continent.

Outcomes of JIA patients depend on JIA subtypes, presentation at disease onset and the presence of poor prognostic factors.[10] So, more emphasis is to be given on early diagnosis and initiation of treatment with disease-modifying anti-rheumatic drugs (DMARDs) and if needed biologics or alternatives, to achieve early remission. The present study aimed to assess JIA patients' disease activity states at 3 years follow up and compare them with other available reports.

Materials and Methods

This retrospective study was carried out at the paediatric rheumatology clinic, department of paediatrics, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka from July 2010 to December 2019. Usually each week 50-60 new children with suspected rheumatic diseases attended this clinic. Paediatric rheumatologists diagnosed these new patients according to the ILAR classification criteria and after starting treatment, these patients were followed up regularly. All the data were maintained both electronically (web-based) and in files.JIA patients were classified at the time of diagnosis and reclassified after completing the initial six months. Patients who had arthritis due to other than JIA were excluded from the study. A total of 1782 JIA patients were enrolled and subsequently 196 children were excluded due to incomplete follow-ups. Follow-ups were done initially at 4-6 weeks interval and then 3 monthly. Some patients (depending on disease severity and complications), needed more frequent follow-up.

Informed consents were taken from all parents/ attendants or patients before enrollment. A pretested questionnaire was used to collect the relevant data. History and clinical examination findings regarding musculoskeletal system, and other systemic examinations, including eye findings were recorded. Relevant laboratory findings including complete blood count with ESR, SGPT, serum creatinine, rheumatoid factor (RF), anti-nuclear antibodies (ANA) and human leukocyte antigen (HLA)-B 27 status were also recorded at the time of diagnosis. RF was tested twice, at least three months apart during the first 6 months of the disease. HLA-B27 was tested in all male patients with arthritis or enthesitis over 6 years of age and in all patients (male or female) with ERA like presentation. Eye examination was done by an ophthalmologist for assessment of uveitis.

Medications used by each patient, including non-steroidal NSAIDs, DMARDs e.g. methotrexate (MTX), sulfasalazine, leflunomide and biological DMARDs (etanercept, infliximab, tocilizumab), thalidomide and tofacitinib were also recorded. Oral, intra-venous and intra-articular steroid (IAS) injections were also documented. IAS injections were recorded as the number of visits for each joint injection during this follow-up period.

JIA disease activity states, including active disease, inactive disease, CRM and CR were assessed at the initial visit and subsequently at the follow-up visit. Inactive disease, CRM and CR were collectively termed as non-active disease.[3] Wallace criteria was adopted to define inactive disease and clinical remission in JIA patients.[11] Inactive disease was defined as no active arthritis; no fever, rash, serositis, splenomegaly, or generalized lymphadenopathy attributable to JIA; no active uveitis; normal ESR or C-reactive protein and physicians global assessment of disease activity indicate no disease activity. Remission on medication was defined as at least six continuous months of inactive disease on medication. Clinical remission off medication was defined as 12 months or more of inactive disease without medication.[11]

Data were checked, verified, and analysed by SPSS (statistical program for social science). Descriptive data were expressed as mean, SD, frequency and percentage.

Results

Among the 1586 enrolled JIA patients who completed 3 years of follow-up,59.0% were male and 41.0% were female, with a male: female ratio being 1.4:1. Mean age at presentation and age at final follow-up visit were 8.33±4.8 years and 11.13±2.7 years respectively. Duration of illness at presentation was more than 12 months in 48.6% of the patients. RF and ANA positivity were found in 5.7% and 6.9% cases respectively. HLA-B27 was found positive in 34.6 % of patients, of which 89.5 % had ERA (table I).

Table I: Baseline characteristics of JIA patients (n=1586)

Characteristics		Ratio and mean± SD
Male: Female		1.4:1
Age at onset years (years)		8.33 ± 4.8
Age at follow-up visit (years)		12.71 ± 14.97
Disease duration at follow-up visit (years)		3.20 ± 0.8
Duration of illness		
Age at presentation	Frequency (n)	Percentage (%)
6 weeks to 6 months	286	18%
7 months to 12 months	530	33.4%
More than 12 months	771	48.6%
Serological lab test		
RF –positive	91	5.7%
ANA (IF) -positive	111	6.9%
HLA –B 27 positive	584	34.6%

Frequencies of JIA subtypes among the patients are shown in Figure1. ERA was the most common subtype (38%), followed by systemic JIA (17%) and RF negative polyarthritis (15%).

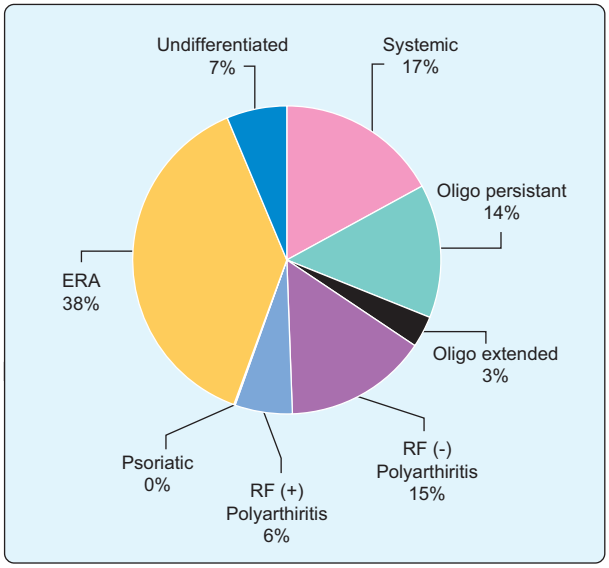

Figure 1: Subtypes of juvenile idiopathic arthritis (JIA)

Non-steroidal anti-inflammatory drugs (NSAIDs) were used as first-line treatment in all categories (100%). The most commonly used disease-modifying anti-rheumatic drug (DMARDs) was MTX (83.4%), followed by sulfasalazine and leflunomide (table II). During the study period, 26.4 % of the patients received intra-articular steroid (IAS) injections of which majority had oligoarthritis subtype. Short course oral steroid was given in 39.7% of JIA patients. Intravenous steroid injection was used mainly (90.0%) in systemic arthritis. Cyclosporine was given in 5 sJIA patients who were diagnosed as macrophage activation syndrome (MAS). Only 12.1% of patients received biological DMARDs and alternatives (thalidomide and tofacitinib) in this study. Among them, thalidomide was used in 54.6% of sJIA patients. Other biological agents (etenercept, tocilizumab (TCZ), infliximab) including tofacitinib were used in few cases.

The disease outcomes, including active disease, inactive disease, clinical remission with medication (CRM), and clinical remission off medication (CR) among JIA subtypes were also recorded (figure 2). In this study, 39.2 % of JIA cases had active disease and 60.7% had non-active disease states. Among non-active disease states, inactive disease was maintained in 27.2%, CRM in 20.1% and CR in 13.3% of patients. Highest frequency of clinical remission was achieved in persistent oligoarthritis and lowest in RF +ve polyarthritis cases.

Table-II: Medication history for JIA patients (n=1586)

Name of the drug	Total n (%)	ERA n=603	Oligo JIA Persistent n =225	Oligo JIA Extended n=38	Poly JIA Poly RF +ve n=89	JIA RF - ve n=251	SJIA n=269	Unclassified n=111
NASIDs	1586 (100%)	461 (76.4%)	165 (73.3%)	37 (97.3%)	69 (77.5 %)	172 (68.5 %)	214 (79.5%)	70 (63.06 %)
Oral steroid	631 (39.7 %)	157 (26.03%)	25 (11.1 %)	22 (57.8%)	53 (59.5 %)	133 (52.9 %)	194 (72.1%)	47 (42.3%)
Intra-articular steroid	419 (26.4%)	36 (5.9 %)	124 (55.1%)	35 (92.1%)	41 (46.06%)	68 (27.09%)	89 (33.08%)	26 (18.01%)
MTX	1323 (83.4 %)	481 (79.7 %)	111 (49.3%)	38 (100%)	89 (100%)	251 (100%)	269 (100%)	84 (75.6%)
Sulfasalazine	486 (30.64%)	471 (78.1%)	0 (0%)	02 (5.2%)	08 (8.98%)	0 (0%)	0 (0%)	05 (4.5%)
Leflonamide	220 (13.8%)	0 (0%)	0 (0%)	0 (0%)	49 (55.5%)	151 (60.05%)	0 (0%)	20 (18.07%)
Etanercept	16 (1.0%)	12 (1.99%)	0 (0%)	0 (0 %)	4 (4.49 %)	0 (0 %)	0 (0 %)	0 (0 %)
Infliximab	02 (0.12%)	2 (0.33%)	0 (0%)	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)
Thalidomide	117 (9.6%)	0 (0%)	0 (0%)	0 (0 %)	0 (0%)	0 (0%)	117 (54.6%)	0 (0 %)
Tocilizumab	28 (2.2 %)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	28 (13%)	0 (0%)
Tofacitinib	30 (1.8%)	15 (2.48%)	0 (0%)	2 (5.2%)	7 (7.8%)	3 (1.19%)	03 (1.11%)	0 (0%)

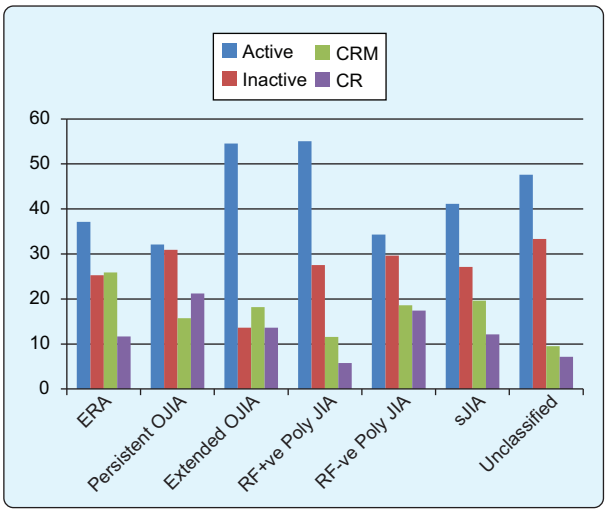

Figure 2: Juvenile idiopathic arthritis – category specific outcome (n=1219)

Discussion

This retrospective study was carried out to assess the disease activity states of JIA cases at 3 years follow up. Findings of this study were also compared with other relevant studies from different countries.

Similar to previous Bangladeshi studies, this study also found male predominance with a male: female ratio of 1.4:1.[8,9] Indian studies also reported similar results.[4,5,12] Females were predominant in Europeans and North American studies.[13] Socio-cultural context could be the factors behind this male predominance .The mean age at presentation was 8.33 years with more than 48% of patients having >one year disease duration at presentation, which was similar to the previous studies from this center.[8,9] The age at presentation and age at onset in the Bangladeshi cohorts appeared comparatively higher in all the subtypes of JIA which were comparable to the reports from India and Singapore.[12,14] Median age of onset was lower in the European and American cohorts compared to the present study.[15] Lack of awareness, wrong or delayed diagnosis and ethnicity could be the reasons for the late presentations.

In the present study, ERA was found to be the commonest (38.0%) subtype of JIA. This finding was different from our previous studies where polyarticular RF negative JIA was most common, but similar to the studies conducted among Taiwanese children.[3] Kunjir V et al in their study in India and Tanya M et al in their study in Singapore also reported ERA as the main subtype where 36% and 32.8% cases respectively had ERA in their series.[12,14] But studies done in Europe, North America and Africa showed that oligoarthritis represented the largest JIA subtypes.[16-19] Similar to other studies conducted in the South and Southeast Asian region, frequency of oligoarthritis was low in the present study.[12,20] Al Hemairi et al in their cohort from Saudi Arabia reported sJIA as the most common JIA subtype (36.5%).[21] In the present study, systemic arthritis was 17.5%, which is in agreement with reports from different countries.[12,14,17,19] The reasons behind the difference between the JIA subtypes could be due to genetic, environmental and ethnic variations among regions. Sample bias in different study places may also play some role.

The treatment strategy was based on the treatment recommendation consensus guidelines for JIA, though due to logistical constrains, it was not always possible to adhere this guideline.[22,23] Our practice was to start MTX for our polyarticular diseases including polyarthritis, extended oligoarthritis, systemic arthritis and peripheral arthritis predominant ERA patients. Majority of the patients received MTX (83.4%) in this study which was similar to reports from other SEA countries, African and Middle East countries but differed from North American and European data.[15] A prospective Canadian cohort reported 1104 children with JIA, where majority received NSAIDs (88%) followed by DMARDs (55%), biologics (16.4%) and systemic corticosteroids within 6 months of diagnosis.[24] About 98% of the JIA patients received NSAIDs in a Swedish cohort which was also similar to our study.[25] In the present cohort,100% of JIA patients received NSAIDs. Biological agents were prescribed in a small number of patients in this cohort which was similar to SEA regional reports.[15] But these agents were more commonly prescribed in the European and North American cohorts. Most of the biological agents and other alternatives including thalidomide and tofacitinib in our cohort were used in the systemic arthritis followed by ERA and RF +ve polyarthritis cases. Thalidomide (poor man biological) was added to 54.6% of sJIA patients who were refractory to conventional DMARDs, due to economic constraints. Islam MM et al. in a study from our country reported thalidomide as safe and effective.[26] The study findings showed that after adding thalidomide, arthritis significantly improved in 55% and 73% of the patients at 6 and 12 months respectively.[26] Majority of sJIA patients improved with thalidomide in the present series and only 13% of them who didn't show good response, were treated with TCZ. Vilaiyuk et al in their study from Thailand reported that majority (32.5%) of their systemic JIA patients were added TCZ.[27]

Systemic corticosteroid was added in 51% of JIA children as bridging therapy in the present study, which was similar to the reports from SEA and Middle East countries.[15] One-third of our JIA patients received IAS injection mostly in the oligoarthritis subtype, which were higher than North and Latin American reports (12.2– 25.6%), but lower than that of northern (73.5%) and southern (52.6%) Europe.[15] Majority of our systemic JIA patients (90%) required systemic corticosteroid which was comparable with the findings from Singapore and Thailand.[14,27]

Analysing the disease activity states, the present study found that,39.2% and 60.7% of cases had active disease states and non-active disease states respectively. Among non-active diseases, 27.2 % of patients had inactive disease. CRM and CR was maintained by 20.1% and 13.3 % patients respectively. A Chinese study showed that 47% of their cases achieved remission off medication and 48% of them were maintaining partial or non-remission.[28] In a Nordic cohort, 49.8 % of JIA patients achieved remission. Among them, 9.3% maintained CRM and 40.5% CR.[29]

A Singaporian cohort reported that, with early use of biological and traditional treatment,78% of patients had no active arthritis.[14] In the Research in Arthritis in Canadian Children emphasizing Outcomes (ReACCh-Out) cohort, the inactive disease was found in 45% within one year, increasing to 95.2 % at five years.[24] Our study had a total of three years follow up, so it may be expected that after 5 years of follow up, our JIA patients may achieve higher remission rate. Moreover, use of biological DMARDs in this cohort was much lower because of logistic constrains. That could be another important reason behind this lower remission rate.

Shenoi et al in their review reported that when MTX was used alone, inactive disease was found only in about 12% of patients but 20-45% of children achieved remission in combination with steroids and other DMARDs (hydroxychloroquine, or sulfasalazine).[30] Unaffordable biological agents, late and severe disease states and poor drug compliance could be the reasons for non-achievement of inactive disease. Humayun et al in their study from Bangladesh reported that 12.9% of JIA patients had poor drug compliance.[31] Main reasons for poor drug compliance were financial crisis, lack of awareness and difficulty in transportation. Episode-wise data were not documented in this study, but a good number of patients developed active disease states after achieving remission. In our previous study, relapse was found among 16.3% of JIA patients in two years of follow-up period.[9] Wallace et al. in their study reported that 40% to 69% of children had the probability of flaring within 2 years after attaining CR.[32]

In the present study, the highest and lowest number of clinical remission was achieved among persistent oligoarthritis and RF +ve polyarthritis patients. These findings are consistent with the results of Taiwanese and Nordic studies.[21,33] Similar observation was also reported by Guzzman et al. where oligoarthritis

achieved the highest remission, and children with RF +ve polyarthritis had the lowest remission.[24]

The majority of JIA patients in this study may represent our country data, because this centre is the largest paediatric tertiary care center where paediatic rheumatology service was accessible for the last 16 years and most of the cases are referred from all over the country. JIA diagnosis was validated for every patient, and the same group of paeditric rheumatologists made the validation, diminishing inclusion bias. Treatment protocol was almost consistent with current practice recommendations.[2,22] Retrospective nature of this study was the main limitation and episode wise data recording was not sufficient to document the joint involvement. Delayed referral and severe presentation including deformities and contractures at presentation were other limitations of this study.

Conclusion

This JIA cohort showed the predominance of ERA, increased prevalence in boys and long duration of disease at presentation. These characteristics of JIA patients were similar with SEA countries but differed from western countries. About 39.0% of patients had persistent active disease states and the rest maintained non active disease state in this study. Disease activity was significantly higher in the RF+ve poly JIA and extended oligoarthritis JIA patients which matched with the western data.

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