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Clinico–Immunological Profile in Juvenile Rheumatoid Arthritis–an Indian Experience

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Abstract. From a Pediatric Rheumatology Clinic 361 children diagnosed as juvenile rheumatoid arthritis (JRA) according to American Rheumatism Association-JRA criteria were studied retrospectively for their clinico-immunological profile. The mean age of onset in systemic, pauciarticular and polyarticular onset, JRA subtypes were 5.2, 6.8 and 7.2 years respectively. There was male preponderance in systemic and pauciarticular JRA. In seropositive polyarticular JRA, girls outnumbered boys. The frequency of occurence of systemic, pauciarticular and polyarticular disease was 87 (24%), 108 (30%) and 166 (46%) respectively. The systemic onset disease was dominated by extra-articular manifestations in terms of fever (100%), rash (57%), hepatomegaly (51%) and lymphadenopathy (25%). The pauci- and polyarticular illnesses were commonly dominated by joint involvement, morning stiffness, and in few patients, by extra-articular manifestations also. The joints were involved symmetrically. Most commonly involved joints in order of decreasing frequency were knee, ankle, wrist and elbow in all the subtypes. Anemia and leucocytosis were observed in majority with higher frequency in systemic onset JRA. The rheumatoid factor (RF) was present in 15% of polyarticular JRA. RF was also present in 7 and 9% of patients with pauciarticular and systemic subtypes respectively. The antinuclear antibody was positive in only 3 out of 66 patients in whom the test was carried out.

The demographic profile and trends in clinical features were similar to the studies reported on caucasian population with difference in the actual frequency of various clinical features.
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Key words : *Arthritis; Chronic arthritis; Juvenile rheumatoid arthritis (JRA); Juvenile chronic arthritis (JCA); Clinical features; Immunology.*

Juvenile rheumatoid arthritis (JRA), a syndrome of heterogenous clinical features, is the commonest rheumatologic disease in children. JRA is characterized by the presence of chronic synovitis and absence of other identifiable diseases known to be associated with arthritis. It is the leading cause of disability in children in the west[1,2]. It has been observed that clinical profile and immunological markers in non-caucasian children are different from white children[3-10]. There are only few studies describing clinical profile of JRA in Indian children. Notwithstanding the number of patients in these studies, the findings do suggest that the clinical manifestations, age and sex distribution are different from various series reported from USA and UK.

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We present our experience of 361 children with JRA over last 10 years.

Material and Methods

A retrospective study was carried out by analyzing the data of children with the diagnosis of JRA, attending the Pediatric Rheumatology Clinic (PRC) at All India Institute of Medical Sciences New Delhi, India, between 1986 and 1995. The diagnosis was based on the American Rheumatism Association Juvenile Arthritis Criteria (ARA-JAC)[11]. In brief, the criteria included (i) Onset of arthritis below 16 years of age (ii) Persistent arthritis of one or more joints for at least 6 weeks (iii) Exclusion of other diseases known to be associated with arthritis (iv) Classification into subtypes by onset based on the predominant clinical features in the first 6 months of onset of first symptom-(a) Systemic onset : joint involvement with persistent intermittent fever with or without rash or other organ involvement (b) Pauciarticular onset : arthritis in 4 or fewer joints during onset (c) Polyarticular onset : arthritis in 5 or more joints during onset[12,13].

In the clinic, a detailed clinical history was entered into the proforma with special reference to joint symptoms, fever, rash, low back pain, joint-stiffness and symptoms of iridocyclitis. The counting of total number of joints involved was done by the ARA criteria[14]. Briefly, each joint was counted individually, but the cervical spine, carpal joints of each hand and tarsal joints of each foot were counted as one joint each. The metacarpophalangeal (MCP), metatarsophalangeal (MTP), proximal interphalangeal (PIP) and distal interphalangeal (DIP) joints were counted individually. All patients were evaluated by an ophthalmologist for evidence of uveitis by regular slit lamp examination.

For comparative study, data was analyzed for each of the JRA onset subtypes for age and sex distribution, duration of illness at the time of presentation, mode of onset of the disease, presence of prominent clinical features, frequency of involvement of individual joints of upper and lower extremities-unilaterally (assymetrical) or bilaterally (symmetrical). The hematological parameters analyzed include presence of anemia, increased erythrocyte sedimentation rate (ESR, Westergren) and leucocytosis. Presence or absence of immunological markers like rheumatoid factor (RF) and antinuclear antibody (ANA) was also determined in limited number of patients in each JRA onset subtype.

Results

A total of 361 children were included in the study—206 boys and 155 girls. Eighty seven patients had systemic, 108 had pauciarticular and 166 had polyarticular onset illness. There was male preponderance in systemic and polyarticular JRA but the sex distribution was almost equal in pauciarticular JRA. The male to female ratio in seropositive (RF Positive) polyarticular JRA was 3 : 8. The mean age of onset of 3 subtypes was 5.2, 6.8 and 7.2 years for systemic, pauciarticular and polyarticular diseases respectively. The youngest patient was 4 months old and was suffering from systemic JRA (Table 1).

The mean duration of illness in systemic JRA was 2.8 years, in pauciarticular 3 years and in polyarticular onset JRA 2.9 years. The onset of illness was acute in 60%, 33% and 40% of children with systemic, pauci-

TABLE 1. Age at Onset, Sex and Subtypes of Juvenile Rheumatoid Arthritis

JRA subtype	Total children N (%)	Boys N	Girls N	Male : Female Ratio	Age of onset (years) Mean	Range
Systemic	87 (24)	53	34	1.55	5.2	0.5-12
Pauciarticular	108 (30)	55	53	1.03	6.8	1-15
Polyarticular	166 (46)	98	68	1.44	7.2	0.35-14
Total	361	206	155			

articular and polyarticular illnesses respectively. The predominant clinical features in systemic onset disease included fever (100%), joint pain/swelling (100%) rash (57%), hepatomegaly (51%) and lymphadenopathy (25%). In polyarticular disease, the prominent clinical features were joint pain/swelling and joint-stiffness. The systemic features such as fever, hepatomegaly and lymphadenopathy were present in few cases. In pauciarticular disease also, the predominant features were joint pain/swelling and stiffness. Eye involvement was present in 12 (3%) children, out of whom 5 had polyarticular, 5 had pauciarticular JRA and 2 were classified as systemic JRA (Table 2).

The distribution of joint involvement in upper and lower extremities is given in Table 3 and 4 respectively. In majority of children, the joint involvement was symmetrical.

Hemoglobin of less than 10 g/dl was observed in one-third of poly- and

TABLE 2. Clinical Features in JRA

JRA subtype Clinical features	Systemic N = 87	Pauciarticular N = 108	Polyarticular N = 166
Joint pain and Joint swelling	87 (100)	108 (100)	166 (100)
Morning stiffness	30 (34)	54 (50)	94 (57)
Fever	87 (100)	11 (10)	25 (39)
Rash	50 (57)	2 (2)	2 (1)
Uveitis	2 (2)	5 (5)	5 (3)
Lymphadenopathy	22 (25)	10 (10)	13 (8)
Hepatomegaly	44 (51)	13 (12)	37 (22)
Splenomegaly	17 (20)	3 (3)	8 (5)
Subcutaneous nodule	3 (3)	0	0
Erythema nodosum	1 (1)	0	0
Clinically evident pericardial effusion	7 (8)	0	1 (0.6)

Figures in parentheses indicate percentages.

Table 3. Join Involvement in JRA : Upper Extremity

Joints involved	Systemic (N = 87)		Pauciarticular (N = 108)		Polyarticular (N = 166)	
	Asymmet	Symmet	Asymmet	Symmet	Asymmet	Symmet
Shoulder	4 (4)	17 (20)	3 (3)	1 (1)	8 (5)	23 (14)
Elbow	7 (8)	22 (25)	10 (10)	9 (9)	23 (14)	50 (30)
Wrist	5 (5)	33 (38)	5 (5)	17 (17)	15 (9)	61 (37)
Metacarpo-phalangeal (MCP)	5 (5)	19 (22)	2 (2)	7 (7)	10 (6)	35 (21)
Proximal inter-phalangeal (PIP)	4 (4)	19 (22)	2 (2)	9 (4)	9 (5)	35 (21)
Distal interphalangeal (DIP)	3 (3)	19 (22)	2 (2)	4 (4)	8 (5)	33 (20)

Asymmet = Asymmetrical, Symmet = Symmetrical
Figures in parentheses are percentages.

Table 4. Joint Involvement in JRA : Lower Extremity

Joints involved	Systemic (N = 87)		Pauciarticular (N = 108)		Polyarticular (N = 166)	
	Asymmet	Symmet	Asymmet	Symmet	Asymmet	Symmet
Hip	4 (4)	8 (8)	4 (4)	3 (3)	17 (10)	10 (6)
Knee	8 (9)	46 (53)	24 (24)	38 (38)	27 (16)	83 (50)
Ankle	11 (13)	42 (48)	27 (27)	22 (22)	22 (14)	83 (50)
Metatarso phalangeal (MTP)	0	8 (9)	5 (5)	2 (2)	13 (8)	18 (11)
Proximal interphal-angeal (PIP)	0	8 (9)	4 (4)	2 (2)	12 (7)	18 (11)
Distal inter phalangeal (DIP)	0	8 (9)	4 (4)	1 (1)	12 (7)	18 (11)
Cervical spine	0	8 (9)	4 (4)	1 (1)	0	10 (6)
Temporomandibular	0	3 (3)	0	0	0	0

pauciarticular JRA each, but was present in nearly half (52.3%) of systemic JRA children. ESR of more than 20 mm was present in almost all the cases and leucocytosis of more than 10,000/dl was observed in more than half the patients (Table 5).

The data for IgM rheumatoid factor was available for 157 patients. It was positive in 14.9% patients with polyarticular disease. Antinuclear antibodies were positive in 3 patients; 2 had polyarticular and one had pauciarticular disease (Table 6).

Table 5. Hematological Parameters in JRA

JRA onset subtype	Anemia (Hb < 10 g/dl)			Increased ESR (> 20 mm)			Leucocytosis (> 10,000/dl)		
	Total	No.	%	Total	No.	%	Total	No.	%
Systemic	65	34	52.3	55	55	100	59	40	67.8
Pauciarticular	53	19	35.8	56	51	91.1	56	38	67.9
Polyarticular	95	34	35.8	98	94	95.9	95	49	51.6

Table 6. Rheumatoid Factor and Antinuclear Antibody in JRA

JRA onset subtype	Rheumatoid factor			Antinuclear antibody		
	Total patients	Positive No.	%	Total patients	Positive No.	%
Systemic	42	4	9.5	23	0	-
Pauciarticular	41	3	7.3	22	1	4.5
Polyarticular	74	11	14.9	31	2	6.5

Discussion

Chronic arthritis in childhood shows very diverse clinical pattern. Differences in the criteria for inclusion or exclusion of arthritic diseases make it difficult to study comparisons on the frequency, natural history and the disease outcome. The clinical, radiological, immunogenetic and therapeutic aspects of JRA have been extensively studied and detailed particularly from North American and European countries. On the contrary, reports on JRA from developing countries are scarce. Lack of availability of meticulously compiled data on JRA in India is a major limiting factor even for roughly estimating the prevalence and incidence of JRA in this region of the world. Present study being hospital based in a tertiary-care health centre, therefore the figures for relative frequency of occurence of JRA may not represent its prevalence in the community. Similarly, the clinical features may also represent a projected more severe illness because of referral bias in favour of severe cases rather than a true picture. The mean age of onset in systemic, pauciarticular and polyarticular JRA was 5.2, 6.8 and 7.2 years respectively. The similar figures from studies on caucasians are 3.1-6.3 years for systemic JRA, 3.1-7.13 for pauciarticular and 5.3-8.8 years for polyarticular JRA[12-16]. The data reported in Indian studies is slightly on higher side[6,7,17]. This can be explained by selection bias in these studies which were reported from immunology clinics providing services mainly to adult patients. Overall, there was male preponderance in the present study. Gender bias in favour of boys is a prevalent social reality in India and its influence on the trends of present study cannot be entirely ruled out. Nevertheless, in seropositive polyarticular disease, girls out. numbered

boys. However, Khuffash *et al*[18] reported an equal male-female ratio in this serologic subtype in Kuwaiti children under 12 years of age with juvenile chronic arthritis (JCA). Male predominance has been reported in systemic and pauciarticular JRA. A study by Uppal *et al*[19] from our institute but from adult immunology clinic, also reported a higher male to female ratio of 1.3 : 1 in 23 North-Indian juvenile onset Still's disease cases. However, most studies report female preponderance in polyarticular JRA except studies from South Africa, Thailand and South India where even in polyarticular JRA, a male preponderance was observed. The relative frequency of three subtypes has been comparatively studied in Indian and Western series (Table 7). A study on North Indian children[17] carried out as a part of MD thesis at our hospital shows that systemic JRA consists of about 21% of patients, polyarticular 19% and pauciarticular 16%. In this study, two new categories were also observed. One was seronegative progressive erosive arthritis in 11% and other an unclassifiable seronegative spondarthropathy-entheseopathy syndrome in 33% of patients. The former was characterized initially by pauciarticular onset with subsequent increase in number of joints involved and progressive deforming arthritis during the course of disease. In the unclassifiable seronegative spondarthropathy-entheseopathy syndrome, the children presented with inflammation at the site of tendoachilles insertion or arthritis predominantly involving joints in lower half of body[17]. The similar division was not possible in our study because we followed ARA-JRA criteria for subclassification.

The other clinical manifestations reported in systemic JRA with variable clinical frequency include myocarditis, and features involving central nervous system, pulmonary, pleural and renal systems, and severe vasculitis. These features were not observed in our patients on clinical examination. Since our study is a retrospective analysis, possibility of missing these rare clinical manifestations cannot be ruled out. These features were indeed observed, though infrequently, in a prospective study in Indian children[17].

Extra-articular manifestations were more commonly present in systemic onset JRA. Frequency of skin rash in systemic JRA observed in the present study was 57% and Uppal *et al*[19] also reported it in

TABLE 7. Relative Frequency of Disease Subtypes in Various Studies

Authors	Year	No. of patients	Systemic %	Pauciarticular %	Polyarticular %
Brewer[2]	1970-82	100	43	29	28
Haffejee[8]	1975-82	60	15	37	48
Parivisutt[9]	1978-84	55	25	27	47
Malaviya[6]	1978-81	82	9	34	57
Porkodi[7]	1984-86	100	10	49	41
Khuffash[18]	1990	108	29	29	42
Present study	1986-95	361	24	30	46

44% of juvenile onset Still's disease cases from the similar population. These figures are lower than 90-96% documented in white children but more than the figure of 10% in black children. Lymphadenopathy and splenomegaly were encountered in only 25% and 20% of the present study patients and 39% and 35% of cases in study by Uppal *et al*[19] respectively, in contrast to the higher figures of 76-86% and 33-75% respectively reported in literature. However, hepatomegaly was observed in 51% which is similar (57%) to one reported by Uppal *et al*[19]. The comparative figures from western series are about 20-40%[12-16]. Clinically evident pericarditis was observed in our study in 7 patients of systemic onset JRA. It has been reported that on routine echocardiographic evaluation asymptomatic (subclinical) pericarditis is especially common in children which is generally not diagnosed on routine clinical examination[20]. Joint involvement was present in all systemic JRA cases in first 6 months of onset of illness. In most of the cases, the joint involvement was symmetrical. The knee joints were most commonly involved followed by ankle, wrist and elbow. This is similar to the observation in western series[12-14] except that hip joint was involved uncommonly in the present series.

The extra-articular manifestations in polyarticular and pauciarticular JRA were much less than systemic JRA. The manifestations were less in frequency in comparison with the similar studies from west[12-16]. In the present study, iridocyclitis was observed in 12 patients-pauciarticular 5, polyarticular 5 and systemic disease 2. The overall incidence of iridocyclitis as reported in literature varies from 8 to 34%. It occurs more commonly in pauciarticular illness, in girls and in association with presence of antinuclear antibodies. In the present study, the incidence of iridocyclitis was less, female preponderance and poor association with presence of ANA are similar to the observations of other studies on non-caucasian population[3-10,17]. The pattern of joint involvement in pauci-and polyarticular JRA was similar to the studies on caucasian children[12-16].

The laboratory investigations showed increased incidence of anemia in systemic as compared to polyarticular and pauciarticular subtypes. The ESR was invariably increased in all subtypes. Increased ESR has been found to correlate well with the disease activity. These trends are similar to other studies with minor difference in frequency because of limited information available in our study.

The information for RF was available in 157 patients. It was positive in 15% of polyarticular cases, and 7% and 9% in pauciarticular and systemic diseases respectively. A low and variable frequency of RF has been reported in pauciarticular and systemic diseases by other authors also. A possibility of false positive test due to nonspecific reaction to various infections cannot be ruled out. Further, no data is available on the prevalence of RF in the community in India. The very low positivity of ANA in JRA as observed by us has also been reported by other studies on non-caucasian children[3-10]. A study from Saudi Arabia[21] has shown similar clinical profile to western JRA children. However, data from these studies need careful interpretation because most of them are retrospective studies and the reports on RF and ANA status were not available for all the patients.

We conclude that there is no major difference in the profile of JRA between

caucasian and North Indian children. The demographic manifestations in our study were similar to caucasian population with some difference in the actual frequency. The study further emphasizes that occurrence of rash and lymphadenopathy in systemic onset JRA is particularly less common in this part of the world as evident from other reports also[7,19]

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