ORIGINAL ARTICLE

Juvenile Rheumatoid Arthritis

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Abstract

Objective: To determine the spectrum of clinical presentation, laboratory parameters and drug therapy in patients with Juvenile Rheumatoid Arthritis (JRA).

Study Design: Case series.

Place and Duration of Study: The Children's Hospital and The Institute of Child Health, Lahore, from October 2008 to October 2011.

Methodology: All patients who fulfilled the American College of Rheumatology criteria for JRA were enrolled. Their clinical features, investigations done and treatment received for JRA were noted. Statistical analysis of data was done on SPSS version 16.0 for obtaining descriptive statistics.

Results: Out of 185 patients, 50.3% (n = 93) were females; 54% (n = 100) were between 10 – 15 years of age. Polyarthritis was found in 71.9% (n = 133) followed by oligoarthritis (22.7%, n = 42) and systemic onset disease (5.4%, n = 10). Morning stiffness (78%) and fever (68%) were the most common clinical presentations. All patients with systemic onset disease had fever (n = 10) followed by skin rash, hepatosplenomegaly and lymphadenopathy. Uveitis was found in 2 patients, and both belonged to the oligoarticular group. Rheumatoid factor was found in 10.27% (n = 19) of all patients. All patients were given non-steroidal anti-inflammatory drugs (NSAIDs). Disease modifying agents (methotrexate) were given to 43.8% (n = 81). Steroids were used in 61% (n = 113) of patients either with NSAIDs alone or NSAIDs plus methotrexate.

Conclusion: Disease profile of JRA at the study centre showed that polyarthritis is the commonest type. Recognition of subtypes will help in planning the management of these patients.

Key words: *Juvenile rheumatoid arthritis (JRA). Rheumatoid factor (RF). Methotrexate. Disease modifying anti-rheumatic drugs (DMARD's).*

INTRODUCTION

Juvenile rheumatoid arthritis (JRA) is characterized by chronic synovitis of peripheral joints manifesting as soft tissue swelling and effusion. It almost certainly comprises of a number of entities, characterized principally by arthritis of appendicular joints, each of which has distinct modes of presentation and may have same or different causes.[1]

The incidence of JRA is approximately 13.9/100,000 children/year among children 15 years or younger, with an overall prevalence of approximately 113/100,000 children. There is a need for increased identification and referral of children with arthritis to paediatric rheumatology treatment centres. Different racial and ethnic groups appear to have varying frequencies of the subtypes of JRA. One study reported that black American children with JRA were older at presentation and less likely to have elevated antinuclear antibody (ANA) titers or uveitis.[2] The exact incidence and prevalence of this disease in children is not available from Pakistan. Various studies from India described somewhat different profile in this subcontinent as compared to the West.[3-6]

The present study was conducted to evaluate the spectrum of clinical presentation, laboratory parameters and drug therapy required in patients with JRA seen at a tertiary care dedicated children's hospital.

METHODOLOGY

This cross-sectional study was carried out at The Children's Hospital and The Institute of Child Health, Lahore, over a period of 3 years, from October 2008 to October 2011. All consecutive patients who fulfilled the American College of Rheumatology (ACR) criteria of JRA were enrolled in the study. ACR criteria include age less than 16 years, signs of arthritis in one or more joints, disease duration 6 weeks or longer, onset type defined in first 6 months (i) polyarthritis: when 5 or more inflamed joints; (ii) oligoarthritis: when less than 5 joints and (iii) systemic onset disease: arthritis with characteristic fever and exclusion of other forms of juvenile arthritis.[2]

Data collected at first clinical visit included age, gender, number of joint involvement, associated systemic features like morning stiffness, fever, rash, lymphadeno-

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pathy or hepatosplenomegaly. Type of arthritis was assigned according to ACR criteria. Clinical uveitis was diagnosed by slit lamp examination by ophthalmologist. Relevant laboratory data was noted including, haemoglobin (Hb), total leukocyte count (TLC), platelet count (PLT), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and presence of rheumatoid factor (RF) and antinuclear antibodies (ANA). Patients were treated with non-steroidal anti-inflammatory drugs (NSAIDs), steroids and methotrexate as per protocol and course of their disease was followed in outpatient clinic (Rheumatology Clinic).

Statistical analysis of data was done on Statistical Package for Social Sciences (SPSS) version 16.0. Distribution of patients in three types was described in percentages. Gender ratio was described in numbers in all three types. Mean age was determined and age distribution in various subgroups was determined to identify the most common age at presentation. Frequency and percentages of clinical features, laboratory parameters and drug treatment were made in three subtypes and described in tabulated form.

RESULTS

A total of 185 patients were enrolled. Out of which 133 (71.9%) were in polyarticular JRA group, 42 (22.7%) were in oligoarticular JRA group and 10 (5.4%) were in systemic onset disease. Among all, 50.3% (n = 93) were female. Male to female ratio (M:F) in numbers was 61:72, 24:18, 7:3 in polyarticular JRA, oligoarticular JRA and systemic onset disease respectively. The mean age at presentation was 10.45 $\pm$ 3.55 years with the youngest patient one year and the oldest patient 16 years of age. Distribution of age at presentation was such that 16 patients (8.6%) were less than 5 years, 56 patients (30.3%) were between 5-10 years, 100 patients (54.1%) were between 10-15 years and 13 patients (7%) were more than 15 years.

Among all patients, morning stiffness (77.8%) and fever (67.6%) were the most common clinical presentations in all types of JRA. Involvement of small joints, temporomandibular joint and spine were mainly seen in polyarticular JRA and systemic onset disease. Fever was present in all patients of systemic onset disease followed by skin rash, hepatosplenomegaly and lymphadenopathy (Table I). Uveitis was found in 2 patients (1.08%); both were male and belonged to oligoarticular JRA sub-type.

Rheumatoid factor (RF) was positive in 19 (10.27%) patients. Out of all sero-positive patients, 95% (n=18) were in polyarticular JRA sub-type. None of the patients in systemic onset disease was RF positive. Systemic onset disease was the commonest type associated with anaemia, leukocytosis, thrombocytosis, increased ESR and CRP (Table II). None of the patients was anti-nuclear antibodies (ANA) positive.

Non-steroidal anti-inflammatory drugs (NSAIDs) were used in all patients either alone or in combination with steroids and methotrexate. Disease modifying agents (DMARD's) were used in 81 patients (43.8%). Out of these 81 patients, 74 (91.3%) were in polyarticular group. Steroids were used in 113 patients (61%) either with NSAIDs or NSAIDs plus methotrexate (Table III).

Table I: Clinical features in juvenile rheumatoid arthritis subtypes.

	Oligoarthritis (n = 42)	Polyarthritis (n = 133)	Systemic onset disease (n = 10)	Total (n = 185)
Morning stiffness	26 (61.9%)	111 (83.5%)	7 (70%)	144 (77.8%)
Fever	24 (57.1)	91 (68.4)	10 (100%)	125 (67.6%)
Large joints	42 (100%)	133 (100%)	10 (100%)	185 (100%)
Small joints	2 (4.8%)	105 (78.9%)	7 (70%)	114 (61.6%)
Spine	0 (0%)	73 (54.9%)	5 (50%)	78 (42.2%)
Temporomandibular joint	0 (0%)	20 (15%)	2 (20%)	22 (11.9%)
Skin rash	0 (0%)	6 (4.5%)	7 (70%)	13 (7%)
Hepatomegaly	3 (7.1%)	5 (3.8%)	7 (70%)	15 (8.1%)
Splenomegaly	1 (2.4%)	2 (1.5%)	8 (80%)	11 (5.9%)
Lymphadenopathy	0 (0%)	05 (3.8%)	03 (30%)	8 (4.3%)

Table II: Laboratory parameters in juvenile rheumatoid arthritis subtypes.

	Oligoarthritis (n = 42)	Polyarthritis (n = 133)	Systemic onset disease (n = 10)	Total (n = 185)
Anaemia (Hb <10 g/dl)	14 (33.3%)	38 (28.57%)	08 (80%)	60 (34.05%)
*TLC >10,000/cu mm	12 (28.5%)	57 (42.85%)	09 (90%)	78 (42.16%)
Platelet count > 400/cu mm	16 (38.1%)	65 (48.8%)	06 (60%)	87(47.02%)
**RF positivity	01 (2.38%)	18 (13.53%)	00 (0%)	19 (10.27%)
†CRP Positivity	15 (35.7%)	46 (34.58%)	04 (40%)	65 (35.13%)
††ESR >20 mmHg	21 (50%)	72 (54.13%)	08 (80%)	101 (54.59%)

**TLC = Total leukocyte count; **RF = Rheumatoid factor; †CRP = C-reactive protein; ††ESR = Erythrocyte sedimentation rate.*

Table III: Drug therapy in juvenile rheumatoid arthritis subtypes.

	Oligoarthritis (n = 42)	Polyarthritis (n = 133)	Systemic onset disease (n = 10)	Total (n = 185)
NSAIDs* alone	29 (69%)	37 (27.8%)	01 (10%)	67 (36.2%)
NSAIDs+ Methotrexate	00 (0%)	05 (3.8%)	00 (0%)	05 (2.7%)
NSAIDs+Steroid	10 (23.8%)	22 (16.5%)	05 (50%)	37 (20%)
NSAIDs+ Methotrexate+ Steroid	03 (7.1%)	69 (51.8%)	04 (40%)	76 (41.1%)

**NSAIDs = Nonsteroidal anti-inflammatory drugs.*

DISCUSSION

Juvenile rheumatoid arthritis (JRA) is not an uncommon disease in children and far exceeds the estimated prevalence when objective criteria are used and an examination is performed by an experienced paediatric rheumatologist.[7] Reviews of 34 epidemiological studies showed that 0.07 – 4.01 per 1000 children worldwide are affected.[8] The true incidence and prevalence in our country is not known. Published data are difficult to compare because of varying referral patterns, the heterogeneity of disease, its evolution over time, differences in classification criteria, dissimilarity of

source populations. Substantial geographic and ethnic differences are present with regard to age at onset, relative frequencies of onset types and immunological markers.[1,9-11]

According to American College of Rheumatology (ACR) criteria JRA is divided into three subtypes. This categorization not only helps in diagnosis but also for the follow-up of subsequent treatment plans for the patients. In this study polyarticular JRA is the commonest type. However, some studies done in Asian countries found different results. In Kingdom of Saudi Arabia and Japan systemic onset JRA was the most common type.[12,13] Polyarticular JRA was the most common type in Sri Lanka.[14] Another study conducted at a tertiary care hospital in Lahore showed 51.6% patients were having polyarticular JRA and 44% were having oligoarticular JRA.[15] Similar patterns of disease were found from various studies in India.[4,5,16,17] While it is different from West where oligoarthritis and systemic onset disease is more prevalent as compared to polyarthritis.[18-21] The reason may be that all studies from Pakistan, India and Sri Lanka were hospital based studies while studies from the Western countries were community based and are not comparable with each other. Secondly, polyarticular JRA is more severe type, patients with this type might attend the tertiary care hospital for management and that might have been reflected in these hospital based studies. This is evident from a community based study in Bangladesh which showed 60% patients with oligoarticular JRA which is consistent with Western literature.[22] However, this is not similar to the hospital based study done in Bangladesh,[23] as well as in many Asian countries.[4,5,14-17]

In the Western literature, the most frequently reported age of onset of JRA is 1 – 3 years and it is more common in female as compared to male.[1,2] In this study and many regional studies, males were either equal or more in number as compared to females.[3,4,6,17] Similarly, late age at presentation was seen in this study as well as from another Pakistani study and various Indian studies.[3,4,6,16,17] The reason may be the ethnic and geographic similarity of both populations, or biological characteristic of the disease in this subcontinent. Another reason may be male gender predominance in South East Asians where females are given less importance and usually not brought to the hospitals. This is true as all were hospital based studies. Different scenario in a community based study in Bangladesh where female to male ratio was equal in polyarticular JRA.[22]

It is known that fever and morning stiffness are the most common presenting symptoms of all types of JRA.[1,2] This is true in this study as well as other studies from India.[3,13] In patients with systemic onset disease, fever was a constant feature followed by rash, hepato-splenomegaly and lymphadenopathy in this study. Moreover, anaemia, leukocytosis and thrombo-cytosis were significantly found in systemic onset disease. This is consistent with various studies from both India and West.[1-4,13] Uveitis was reported in only 2 patients in this study. Uveitis is closely related with antinuclear antibodies (ANA) positivity. In this study, ANA was 100% negative. The explanation to this is that all ANA levels were done by indirect hemagglutination method. Low frequency of uveitis and low rate of ANA positivity were also reported in Sri Lanka and India,[3-6,14] which again show some geographic and genetic variation of the disease in this subcontinent.

Rheumatoid factor (RF) positivity is associated with onset of the disease in an older child with polyarticular JRA sub-type (approximately 8%), the development of rheumatoid nodules, and with a poor overall prognosis and eventual functional disability. In this study, RF positivity is seen in 10.27% among all types of JRA. Seth *et al*. and Parkodi *et al*. in India reported 15% and 9.7% seropositivity respectively,[4,6] while Selvaag *et al*. in Norway reported 4.1% sero-positivity.[24] The reason may be difference in geographic population under study. In this study sero-positivity was significantly associated with polyarticular JRA sub-type. Some studies from India and the West showed very high seropositivity with polyarthritis.[16,25] The reason may be the inclusion of more patients with polyarthritis as compared to other types.

The long-term treatment of children with JRA is initiated and subsequently modified according to disease subtype, severity of the disease, specific manifestations of the illness, and response to therapy. The objective of treatment is to keep the child in a pattern of adaptation that is as normal as possible and to accomplish this goal with minimal risk of adverse effects. Non-steroidal anti-inflammatory drugs (NSAIDs) were the mainstay of treatment in all types of JRA in this and in various studies.[3,11] Naproxen and Ibuprofen were the drugs used in this study. The study from Chandigarh reported safe and effective response with salicylic acid.[3] Disease modifying anti-rheumatic drugs (DMARD's) like methotrexate was used in patients who had poor response to NSAIDs or clinical deformities. This is consistent with various studies.[3,11,14] Steroids were used in many studies as short course, intra-articular and topical for uveitis.[3,11] Biological agents are newer therapeutic agents in the management of JRA. The use of biological agents in the management of JRA will not only improve the outcome but also help the children in having active and fruitful life for community. Further studies on reasons of different presentation in our setup are needed. Moreover, a prospective study for the utility of newer therapeutic agents in management of JRA should be done.

CONCLUSION

Polyarticular JRA sub-type is the commonest type in this hospital based study. Recognition of these different sub-types is useful in the diagnosis and long-term management of these patients. Treatment according to the sub-types and induction of newer therapeutic agents in the management of JRA will prevent morbidity.

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