

ORIGINAL ARTICLE

CHANGING CLINICAL PROFILE OF ACUTE RHEUMATIC FEVER
AND RHEUMATIC RECURRENCE

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Background: Clinical profile of acute rheumatic fever and rheumatic recurrence seems to have changed in countries where rheumatic fever is still endemic. The objectives of this study were to compare clinical profile and outcome of patients suffering initial and recurrent episodes of acute rheumatic fever in children. **Methods:** This prospective study was conducted in two tertiary care hospitals from January to June 2011. The diagnosis was based on the modified Jones criteria. Sixty children were included in the study, 15 having first episode of rheumatic fever and 45 with rheumatic recurrence. The severity of carditis was assessed by Clinical and echocardiography means. **Results:** Carditis was the commonest presentation in both first (80%) and recurrent attacks (100%). Arthritis was seen in 60% of children with first episode and in 26.7% with recurrence. The frequency of subcutaneous nodules, invariably associated with carditis, was very high (33.3% in the first and 48.3% in recurrent episodes). Carditis was generally mild during first episode (53.3%) and severe with rheumatic recurrence (55.6%). There was no death in either group. One patient with severe mitral regurgitation and rheumatic recurrence underwent mitral valve repair for intractable heart failure. **Conclusion:** Clinical profile of rheumatic recurrence and acute rheumatic fever has changed. Rheumatic recurrence is associated with severe carditis. Carditis is more common than arthritis even in the first attack. Sub-cutaneous nodules are a frequent finding invariably associated with carditis.

Keywords: Rheumatic Fever, carditis, nodules, clinical profile, Pakistan

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INTRODUCTION

Rheumatic fever is the leading cause of acquired heart disease in children and young adult's worldwide.¹ Rheumatic heart disease and acute rheumatic fever are endemic in Pakistan and one of the major causes of morbidity and mortality in children.²⁻⁴ Prevalence is one of the highest in the world, 21.9/1000 in urban slums of Lahore in a recent school survey and 5.6/1000 in rural population in a community survey.^{5,6}

The clinical profile of acute rheumatic fever and rheumatic recurrence differ markedly in different parts of the world, mild in developed countries.⁷⁻¹⁰ and severe in the developing world.¹¹⁻¹⁴ This inference has been drawn due to non-differentiation of initial episode from the recurrent cases of rheumatic fever. The clinical profile and severity of the disease is milder in patients with first episode as compare to those with recurrent episodes.¹⁵⁻²⁵ This may also be related to the fact that initial attacks with silent carditis are often missed and these unreported children presented with severe carditis as recurrence.²⁶⁻²⁸

There was an impression that clinical profile of acute rheumatic fever and rheumatic recurrence has changed especially with reference to frequency of arthritis in first episode, frequency of subcutaneous nodules and frequency as well as severity of carditis. We designed this study to compare the clinical profile of acute rheumatic fever in first and recurrent episodes, compare the severity of carditis in the first versus

recurrent episodes and look at the outcome of both groups in our set up.

MATERIAL AND METHODS

This study was conducted in the paediatric cardiology departments of two teaching hospitals of Lahore. Punjab Institute of Cardiology is a dedicated cardiac facility and The Children Hospital/The Institute of Child Health is a tertiary care paediatric hospital. We included all children up to 16 years of age presenting to these 2 hospitals with acute rheumatic fever. The diagnosis was based on modified Jones criteria.²⁹ We excluded children with associated diseases and established RHD with no activity. Those seen with the recurrent episodes were differentiated from those with first episode primarily on the basis of the history.

The period of study was from January 2011 to June 2011. The socio-demographic variables gathered were the age, sex, number of siblings, number of total family members, occupation and literacy. The socioeconomic status was based on socioeconomic status scale of Kupuswamy urban³⁰ which includes education, occupation and family income. The detailed information for all patients included a history, examination, 12 lead ECG, chest x ray, and laboratory tests (complete blood count, ESR, CRP, ASOT to seek evidence of previous streptococcal infection and blood cultures if necessary). We collected details from each patient and their family members. History of monoarthritis, arthralgia, skin rash and sore throat was

also elicited. Carditis was graded on the basis of following criteria:¹⁵

- No carditis: absence of sleeping tachycardia and cardiac murmur as a sign of valvitis confirmed by echocardiography.
- Mild carditis: was characterized by cardiac murmur, cardiothoracic ratio between 0.45 and 0.5, with no signs of congestive cardiac failure.
- Moderate carditis: was characterized by cardiac murmur, cardio-thoracic ratio between 0.60 and 0.70, no signs of frank congestive cardiac failure, and presence of signs of mild pulmonary arterial hypertension.
- Severe carditis: was characterized by signs of congestive heart failure, pulmonary arterial hypertension, and a cardio-thoracic ratio of 0.75 or more.

The cardiac findings were confirmed by echocardiography performed by experienced operators in paediatric echocardiography (MS, AR). The echocardiographic criteria were agreed on by all cardiologists before the scans were performed.

Treatment during admission, duration of stay and outcome were also analyzed. Approval of study was taken from hospital ethical committee.

Continuous variables were assessed by percentages, means and standard deviations. Student's t test and the chi square test were used for comparative analysis. A *p*-value of less than 0.05 was considered as significant.

RESULTS

Sixty children were diagnosed as acute rheumatic fever, 15 (33%) had first episode and 45 (66%) had recurrence of rheumatic fever. The mean age of patients with first episode was 8.3±2.5 years as compared to 11.7±2.3 years with recurrent episodes (*p*<.005). The male to female ratio was 1:1.5 in first episode group compared to 1:1.2 in rheumatic recurrence. Twenty (33.3%) children belonged to urban areas as compare to 40 (66.7%) to rural areas.

Majority of patients (n=32, 53.3%) belonged to poor socioeconomic group. Prior to referral to tertiary care centre, 66% (n=10) of the patients with first episode had been treated by general practitioner. Twenty nine percent (n=13) of the patients with rheumatic recurrence had been treated by general practitioner, 4.4 % (n=2) in district general hospitals and 64.4% (n=29) were in follow up at a tertiary care hospitals. The comparison between baseline characteristics of both groups is shown in table-1.

Carditis was present in 80% (n=12) of those suffering their first episode and 100% (n=45) in those having recurrent episodes (*p*<0.001). The carditis was mild in first episode 53.3% (n=8) and severe in recurrent episodes 55.6% (n=25) (*p*<0.001) (Table-2).

Pericarditis was present in 6.66% of those having a first episode, compared to 8.88% for those with recurrent episodes. Pulmonary arterial hypertension was only noted in patients with recurrent episodes, 15.5% (n=7) (*p*<0.001). Atrial fibrillation was only seen in 13.3% (n=6) of those having recurrent episodes (*p*<0.001).

Isolated mitral regurgitation (MR) was found in 66% of patients having first episode, but was found in only 6% of those with recurrent episodes. Aortic regurgitation (AR) in combination with mitral regurgitation was detected in 6% of patients having first episode, but in 26% of patients having recurrent episodes. Stenotic lesions were found only in those suffering recurrent episodes. All the findings were more severe in patients having recurrent episodes. (Table-3).

Arthritis was more frequent during the initial attack, 60% (n=9), compared to 26.7% (n=12) in those having recurrent episodes (*p*<0.05).

There was no past history of chorea in patients with rheumatic recurrence. None of the patients had chorea during initial attack of RF or rheumatic recurrence during the study period.

These are firm, round, painless and freely mobile nodules usually 0.5–2.0 cm in diameter that occur in crops over the elbows, wrists, knees, ankles and rarely at spinous process of the vertebrae. Sub-cutaneous nodules were invariably associated carditis. These were present mainly at elbows and knees and at spinous process of the vertebrae in one patient with rheumatic recurrence. Sub-cutaneous nodules were more frequent in those with recurrent episodes 48.3% (n=21) compared to first episode 33.3% (n=5) (*p*=0.179).

This was not observed in any patient with ARF or rheumatic recurrence.

Fourteen (93%) of patients having their first episode had history of fever, compared to 77.8% (n=35) of those suffering recurrent episodes in the absence of another cause of fever (*p*=0.178). Duration of fever was comparable in both groups as 14±3 days in first episode and 16±2 days in those recurrent episodes. Fever was generally low grade in both groups.

Arthralgia was a common finding but was only considered as minor criteria when polyarthritis was not taken as major criteria. This was found in 20% (n=3) of those suffering initial attack, compared to 28.8% (n=13) of those with recurrent episodes (*p*=3).

A past history of sore throat could be elicited in 66.66% (n=10) of children with first episode, compared to 35.55% (n=16) of those with recurrent episodes (*p*<0.05). Sore throat was treated by general practitioners prior to the presentation in tertiary care hospitals with antipyretics and oral antibiotics.

Blood cultures were done where infective endocarditis was suspected but were not positive in any

patient with ARF or rheumatic recurrence. The mean total leukocyte count was comparable in both groups as $11 \pm 5.5 \times 10^3 / \mu\text{L}$ in first episode and $11.7 \pm 4.26 \times 10^3 / \mu\text{L}$ in patients having recurrent episodes. All children had erythrocyte sedimentation rates of more than 12 mm in initial 1st hour. The mean rate was 59 ± 33 mm in the first hour of those having initial episode, compared to a mean of 54 ± 34 mm in patients having recurrent episodes. The anti-Streptomycin O Titer was 200 i.u. in 40 % of patients with first episode compared to 62.2% in children having recurrent episodes, between 200 and 400 i.u. in 53.3% compared to 31.1% and more than 400 i.u. in 6.7% of both with first and recurrent episodes.

Bed rest was advised for all children. Injections Benzathine penicillin was given to all patients. Aspirin was given in the dose of 100 mg/kg/day, being reduced to 75 mg/kg/day after 2 weeks. Steroids were administered to 6 (40%) patients with first episode mainly for abdominal pain and vomiting and in fifteen (33.33%) patients with recurrent episodes, for severe heart failure, toxemia, abdominal pain, vomiting and pericarditis ($p=0.13$). Diuretics and Digoxin were given to all patients with carditis. Aggressive vasodilator therapy, such as angiotensin converting enzyme inhibitors, was used in severe carditis complicating recurrent episodes, used in 15% of patients. Inotropic support was used in 4% of patients, and sodium nitroprusside in 10%. Children having uncontrolled congestive cardiac failure underwent surgery.

Duration of hospital stay was similar in patients with initial attack having carditis and recurrent episodes, being 19.4 ± 20.5 days in acute rheumatic fever compared to 21.5 ± 10 days in recurrences ($p=.08$). Two patients with polyarthritis having initial attack were treated on outdoor basis.

One patient with recurrent episodes underwent surgery for severe intractable mitral regurgitation (mitral valve repair). There was no death in either group. All patients could be discharged home.

Table-1: Comparison of Baseline Characteristics between Acute Rheumatic Fever and Recurrent Episodes

Basic Characteristics	ARF (n=15)	Recurrence (n=45)	p-Value
Age (years)	8.3±2.5	11.7±2.3	<.005
Male: Female ration	1:1.5	1:1.2	0.38
Poor Socioeconomic status	6 (40%)	26 (57.7%)	0.42
Average income (US \$)	97.89	81.25	0.5
Family members sharing a room	7	10	0.01
Rural to urban ratio	1:0.8	1:0.4	0.22
School attendance at presentation	15 (100%)	43 (93%)	0.09
Treatment prior to admission	10 (66%)	44 (97.5%)	<0.001
Duration of symptoms in days-mean (range)	30 (7-120)	41 (6-180)	0.032

Table-2: Comparison of severity of carditis between acute rheumatic fever and recurrent episodes

Severity of Carditis	ARF	Recurrence	p-value
No Carditis	13.6%	0%	<0.001
Mild Carditis	53.2%	4.4%	<0.001
Moderate Carditis	33.2%	40%	0.74
Severe Carditis	0%	55.6%	<0.001

Table-3: Comparison of valvular lesions between acute rheumatic fever and recurrent episodes

Valvular lesion	ARF	Recurrence	p-value
MR	66.66% (n=10)	6.66% (n=3)	<.001
AR	6.66% (n=1)	0% (n=10)	<.001
MR+AR	6.66% (n=1)	26.66% (n=12)	<.001
MR+AR+TR	0% (n=0)	53.33% (n=24)	<.001
MS	0% (n=0)	0% (n=0)	-
MS+AR	0% (n=0)	2.22% (n=1)	<.001
MS+MR+AR	0% (n=0)	4.44% (n=2)	<.001
MS+MR+AR+TR	0% (n=0)	2.22% (n=1)	<.001

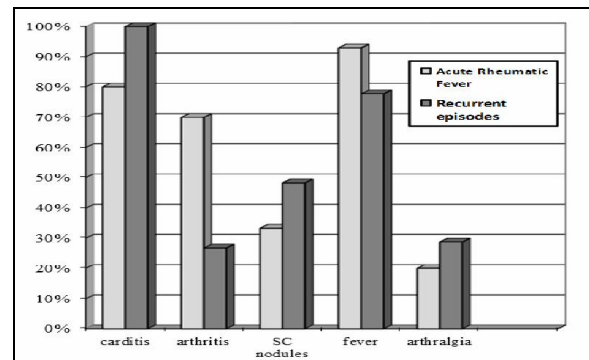


Figure-1: Clinical Profile of Acute Rheumatic Fever versus Recurrent episodes

DISCUSSION

In this prospective study, we have documented that clinical profile of first episode of rheumatic fever and rheumatic recurrence seems to have changed in Pakistan. We registered approximately thrice as many patients suffering recurrent episodes compared to those seen after their first episode.

The frequency of carditis was high (86.6%) even in the first attack of rheumatic fever. This finding is fairly high compared to reports in the past in developed countries⁷⁻¹⁰ as well as developing world^{10,16-19}. A similar study from Pakistan found that carditis was less frequent in those with first episode, at 64% compared to 96% in those suffering recurrent episodes ($p<0.05$).¹⁵ This may also be related to the fact that initial attacks with silent carditis are missed²⁶⁻²⁸ and these unreported children presented with carditis as main feature and were taken as initial attack of acute rheumatic fever based on history. The nature of carditis, however, was mild in our study when compared to recurrent episodes. This finding is similar to that observed in the past locally and internationally.^{7-10,15-19} In India, two different studies, more than a decade apart, found that the course of first episode was mild.^{16,19}

Studies from Middle East have also demonstrated the mild nature of carditis.^{10,17,18} In Pakistan, a similar study also confirmed mild carditis in ARF when compared to recurrent episodes¹⁵. In this study the carditis was mild in 29.8% of patients with first episode, compared to 10.6% in those having recurrent episodes, moderate in 26.3% compared to 53.8% and severe in 5.3% of those with initial attack compared to 31.8% of those with recurrent episodes ($p<0.05$). Severe carditis was only observed in those with recurrent episodes. Thus, if no distinction was made between those having first episode compared to those with recurrent episodes, then patients diagnosed with ARF according to the modified Jones criteria would present with severer disease, with the dominant feature as carditis, and would resemble the studies from most of the developing countries in the past.²⁰⁻²⁵

Polyarthrititis was more common during the first episode, at 60%, compared to 26.7% in those having recurrent episodes ($p<0.05$). Similar data has been reported from Indian subcontinent. Arthritis was present in 67.6% patients with first episode, compared to 48.66% in those having recurrent episodes in a large study reported from India³¹ and 61.4% in cases of, compared to 36.5% in those suffering recurrent episodes in a study from Pakistan¹⁵. Data from Middle East however, reports a higher frequency of arthritis in the first episode. Polyarthrititis was a presenting feature in 79% cases with ARF in Kuwait¹⁰ and 90% in a study from Qatar¹⁷. Another similar study from Saudi Arabia, found that polyarthrititis was the main presenting feature in 76% cases of ARF.¹⁸ Thus literature review shows that arthritis is still more common than carditis in initial episode in most parts of the world. In our country, however, our study has again shown a higher frequency of carditis when compared to arthritis in first episode of rheumatic fever, an observation already reported from Pakistan.¹⁵

Subcutaneous nodules despite being major criteria are seen less frequently as manifestations of ARF in the developing as well as developed countries.³¹⁻³⁸ Our study does not support this finding. Sub-cutaneous nodules were more frequent in those with recurrent episode compared to first episode. Such a high frequency of subcutaneous nodules has never been reported in the literature. This may partly be related to a high frequency of carditis in our study and invariable association of subcutaneous nodules with carditis. This however would not explain a frequency of 33% in first and almost 50% in recurrent episodes. Subcutaneous nodules are an immunological reaction and a genetic predisposition is the most likely explanation for such a high association.

Erythema marginatum was seen neither in patients with ARF nor in recurrent episodes. Erythema marginatum is rare, being reported in less than 2% of

patients in Aboriginal Australians and children of developing countries.³¹⁻³⁸ It may be missed due to delayed presentation in tertiary care hospitals, as well as evanescent nature and lack of associated symptoms, particularly in dark skinned people.

The comparison of the socioeconomic status of our cases showed that all the children belonged to lower socioeconomic communities. Very few belonged to lower middle and none to high-income group. It can, of course, be argued that only poor patients come to the public hospitals. Both the hospitals were major tertiary care hospitals where large numbers of patients are from the middle or lower middle class. Most of patients came from the urban slums, where sanitation and hygiene is poor. The houses are Over-crowded, with 9-10 persons living in single house, which consists of one or two rooms. When we compared the socioeconomic parameters in those with recurrent episodes with those seen after their first episode, we noted that those with recurrent episodes came from even overcrowded poorer families. Our study showed that acute rheumatic fever is endemic in the urban slums, where the adverse socioeconomic and environmental factors are aggregated. Preventive measures should therefore be undertaken to these areas.

Majority of our children were initially treated by general practitioners and local hospitals which caused a significant delay in their presentation in tertiary care hospitals. The preventive strategies should be directed to these care providers if we want to control rheumatic fever in our community. Government and non- government programs of health education should be actively involved in teaching primary and secondary prevention of rheumatic fever, as hospital-based programs are unlikely to control acute rheumatic fever.³⁹⁻⁴⁰

CONCLUSION

Clinical profile of ARF and rheumatic recurrence has changed in Pakistan. Carditis is more common than arthritis even in the first attack although mild in majority. Sub-cutaneous nodules are a frequent finding invariably seen with carditis. Recurrence is associated with severe carditis.

AUTHOR'S CONTRIBUTION

AMS: Data collection, results analysis, manuscript. MS: Results analysis, manuscript and corrections. AUR: Results analysis, manuscript

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