



Original Articles

RHEUMATIC FEVER IN IRANIAN CHILDREN: CLINICAL AND PREVENTIVE ASPECTS

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ABSTRACT

A total of 70 children aged 6 to 15 years with rheumatic fever and completed in-hospital data were reviewed from 1988 to 1993. In 58.6% of patients this was the first attack of disease, while in 41.4% the episode represented a recurrence. Noncompliance of antimicrobial prophylaxis was noted in all of the subjects with recurrences. 61.4% of cases gave a previous history of sore throat, and inappropriate or inadequate antibiotics had been prescribed for all of them. Carditis had occurred in 76% of patients and 51% of them had developed heart failure. Congestive heart failure was three times more prevalent in recurrences than in initial attacks. The study showed an urgent requirement for a national training program for all health personnel (including doctors), along with the education of healthy children, patients, and their families in order to establish effective primary and secondary prophylaxis in this area.

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INTRODUCTION

The incidence of rheumatic fever (RF) in industrialized countries began to decline early in the twentieth century and is now well below 5 per 100,000 population per year.¹ The problem has not disappeared, however, as witnessed by recent sizeable outbreaks in the USA.^{2,3} In developing countries the incidence is likely to approach 27 to 100 per 100,000 in children. In India, an estimated 6 million children are affected by rheumatic fever and 250,000 new cases are seen each year among school-age youngsters.⁴ In developed countries the prevalence of rheumatic heart disease (RHD) in school-age children has been reported to be 0.6 to 0.7 per

1000. In developing countries, the prevalence of RHD is high, ranging from 1.2 to 18.6 per 1000.¹ A prevalence of RHD of 8/1000 has recently been reported among school children in Iran (unpublished data). The above data indicate that RF/RHD is the most common cardiovascular disease in children and young adults and remains a major public health problem in developing countries. The sequelae of RF are essentially limited to the heart and depend on the presence and severity of carditis.

Prevention of both initial and recurrent attacks of RF depends on control of group A beta-hemolytic streptococcal upper respiratory tract infections. Prevention of first attacks (primary prevention) is accomplished by proper identification and adequate antibiotic treatment of streptococcal pharyngitis. The individual who has suffered an attack of rheumatic fever is inordinately susceptible to recurrences following subsequent group A streptococcal upper respiratory tract

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infections and requires continuous prophylaxis in order to prevent recurrences (secondary prevention).

The present study was designed to verify the concept that improper treatment of streptococcal pharyngitis and inadequate or irregular secondary prophylaxis result in severe cardiac lesions in young children. The study was also performed to demonstrate the clinical profile and natural course of RF and to compare the features of initial and recurrent episodes of RF in children living in Iran.

PATIENTS AND METHODS

During a 5-year period from June 15, 1988 to June 15, 1993, seventy patients with RF were admitted to the pediatrics department of the Ayatollah Tudeghani Medical Center in Tehran. Diagnosis of RF was made according to Jones' criteria which was revised in 1988 by the World Health Organization.

Patients were carefully assessed at their initial presentation to determine if it was their first attack or a recurrence of RF. Children with established rheumatic heart disease (RHD) who had no evidence of current rheumatic activity at presentation were excluded. The patients who were readmitted during the period of study were not included again in order to avoid duplication. Two-dimensional and Doppler echocardiographic examinations were performed on each subject with a heart murmur. The following criteria for RHD were fulfilled: history, physical examination, chest X-ray, electrocardiography, echocardiography, and exclusion of other valvular diseases. Polyarthritides was diagnosed if it was migratory, involved several different joints and the joints were tender, red, warm, and swollen with limitation of movement. The diagnosis of carditis was made on the basis of the following manifestations: the presence of a murmur representing valve insufficiency, cardiomegaly, congestive heart failure (CHF), and pericarditis. Carditis was classified as mild in the presence of valvular insufficiency without cardiomegaly, moderate in the presence of cardiomegaly or combined mitral and aortic insufficiency, and severe if there was CHF or pericardial effusion. A PR interval was considered prolonged if it was more than 0.18 seconds in duration. Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and antistreptolysin O (ASO) titers were determined in each patient by standard methods.

RESULTS

There were 70 patients with RF during the 5-year period. The number of cases in each year are shown in Fig. 1. As can be seen in this figure the annual admission rate is relatively constant. Thirty-nine (55.7%) of the patients were boys and thirty-one (44.3%) were girls with a male to female ratio of

1.3:1. The age range was 6 to 15 years with a mean of 10.6 years. The age distribution of patients is shown in Table I, which reveals that the 9 to 14 year age group comprises 74.3% of subjects. In forty-one patients (58.6%) this was the initial attack of RF, while in twenty-nine (41.4%) the episode represented a recurrence. At the time of first admission, ten patients (14.3%) presented with their second, thirteen (18.6%) with their third, and six (8.5%) with their fourth or higher attack. There were three patients with recurrent yearly attacks. Noncompliance of antimicrobial prophylaxis was noted in all of the children with recurrences. Male-female ratios for initial and recurrent attacks were 21/20 and 18/11, respectively. Forty-three children (61.4%) recalled symptoms suggestive of pharyngitis within 1 month before the onset of RF. All but four of them had received an inappropriate or incomplete course of antibiotics such as ampicillin, amoxycillin, co-trimoxazole, gentamicin, and procaine penicillin for their sore throat. In the remaining 4 subjects, two had received erythromycin and the other two inadequate doses of benzathine penicillin.

The distribution of major manifestations among children with their first attack and in those with their second or higher attacks are summarized in Table II. Arthritis occurred in thirty-three (80.5%) of the 41 cases with an initial attack and in eleven (38%) of the 29 patients with a recurrence. Carditis was present in twenty-six (63.4%) of the 41 cases with an initial episode and twenty-seven (93%) of the 29 children with recurrence. A total of fifty-three patients (76%) developed carditis and forty-four (63%) had arthritis. One patient exhibited erythema marginatum in addition to carditis and arthritis in the initial attack group. There were no cases of chorea or subcutaneous nodules. During the study period two cases of chorea had been seen in the outpatient clinic who did not need admission and were therefore not included in the study. Various forms of valvular involvement in the 53 cases with carditis are demonstrated in Table III. Twenty-four (92.3%) of 26 children with first attacks had signs of mitral insufficiency, while two had combined mitral and aortic insufficiency. Sixteen (59.3%)

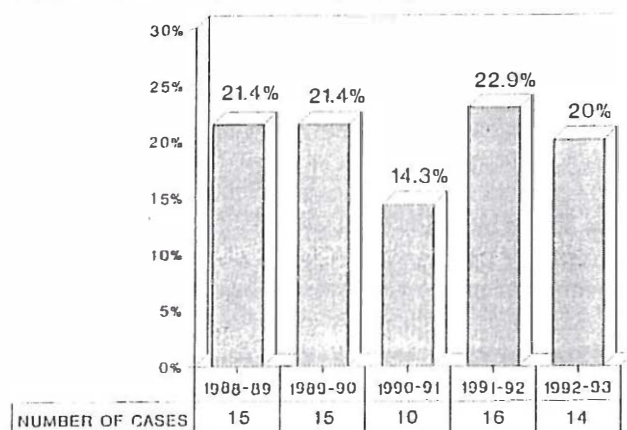


Fig. 1. Number of cases admitted each year.

Table I. Age distribution of patients.

| Age Group (year) | Number of Cases | Percent |
|------------------|-----------------|---------|
| 6-8 | 14 | 20% |
| 9-11 | 27 | 38.6% |
| 12-14 | 25 | 35.7% |
| > 14 | 4 | 5.7% |

Table II. Distribution of major manifestations in first and recurrent attacks of rheumatic fever.

| Major Criteria | First Attack (n = 41) | Recurrent Attacks (n = 29) | Total (n = 70) |
|----------------------|-----------------------|----------------------------|----------------|
| Arthritis | 33(80.5%) | 11 (38%) | 44(63%) |
| Carditis | 26(63.4%) | 27 (93%) | 53(76%) |
| Chorea | - | - | - |
| Erythema marginatum | 1(2.4%) | - | 1(1.4%) |
| Subcutaneous nodules | - | - | - |

Table III. Valvular involvement in patients with first and recurrent attacks.

| Cardiac Lesions | First Attack (n = 26) | Recurrent Attacks (n = 27) | Total (n = 53) |
|-----------------|-----------------------|----------------------------|----------------|
| MI | 24 (92.3%) | 16 (59.3%) | 40(75.5%) |
| MI + MS | - | 4 (14.8%) | 4(7.5%) |
| MI + AI | 2 (7.7%) | 5(18.5%) | 7(13.2%) |
| MI + MS + AI | - | 1(3.7%) | 1(1.9%) |
| MI + AI + TI | - | 1(3.7%) | 1(1.9%) |

MI: Mitral incompetence

MS: Mitral stenosis

AI: Aortic incompetence

TI: Tricuspid incompetence

Table IV. Severity of cardiac involvement in patients with first and recurrent attacks.

| Severity of Carditis | First Attack (n = 26) | Recurrent Attacks (n = 27) | Total (n = 53) |
|----------------------|-----------------------|----------------------------|----------------|
| Mild | 17 (65.3%) | 2 (7.4%) | 19(35.8%) |
| Moderate | 2 (7.7%) | 5 (18.5%) | 7 (13.2%) |
| Severe | 7 (27%) | 20 (74.1%) | 27 (51%) |

established rheumatic heart disease had isolated mitral incompetency, while a further 4 also had some degree of mitral stenosis. Combined aortic and mitral valve disease was present in five children. Isolated mitral stenosis and isolated aortic incompetence were not seen in any of our patients. Overall, mitral insufficiency was the most common valvular involvement and occurred in forty cases (75.5%). Three out of 27 patients with RHD underwent prosthetic valve replacement.

The severity of carditis is presented in Table IV. Among the 26 children with carditis in their initial attack and the 27

children with carditis in their recurrent attack of RF, cardiac involvement was considered mild in 17(65.3%) and 2(7.4%) and severe in 7 (27%) and 20 (74.1%) cases respectively. Of the 53 children with carditis, seven (13.2%) showed CHF in their first attack and twenty (38%) in recurrent attacks. CHF was three times more common in recurrent than in initial episodes. One patient (an 8 year old girl) in the first attack group developed pericarditis in addition to CHF. Bacterial endocarditis (BE) was associated with heart failure in 3 children with recurrent attacks. Two had positive blood cultures for coagulase-positive *Staphylococcus aureus*, and the other for *Streptococcus viridans*. One of the two children with *Staphylococcus aureus* BE died while the other required prosthetic valve replacement. There were two known deaths among the 70 subjects (2.9%), both in children with established RHD. Causes of death were intractable CHF and pulmonary edema due to severe myocardial fibrosis and dysfunction in a 12 year old girl and BE in a 9 year old boy. Aspirin hepatotoxicity was observed in two patients in the first attack group which resolved after withdrawal of the drug.

The minor diagnostic criteria included fever in 68%, arthralgia in 14% and prolonged PR interval in 18% of the 70 cases with RF. Leukocytosis was noted in 56% of the children. ESR was greater than 60 mm/h in sixty-seven (95.7%) of the patients and more than 90mm/h in nearly half of these. CRP was positive in 52 patients (74%), and evidence of a preceding streptococcal infection, suggested by an ASO titer of greater than 333 Todd units/mL, was found in all but 2 patients who had insidious carditis. The titer was more than 500 units/mL

5 patients (7%) had positive throat cultures for group A β -hemolytic streptococci. Only 14 patients (20%) had regular clinical follow-up and the remaining 56(80%) were lost to follow-up.

DISCUSSION

RF is most frequently observed in the age group most susceptible to group A streptococcal infection, i.e. children from 5-15 years of age. In this study children from 9 to 14 years of age comprised 74.3% of the subjects. Carditis is present in 40-80% of patients with RF,⁵ and when there is cardiac involvement the incidence of residual heart disease is directly proportional to the severity of the carditis. 75% of patients with CHF during the initial attack will have chronic valvular disease after 10 years. On the other hand, when cardiac findings are limited to a systolic murmur, only about 25% of the patients are left with residual heart disease. Recurrences of rheumatic fever markedly influence the prognosis. Recurrences are more likely when the initial attack occurs early in life and when the attack includes carditis. They are more apt to occur in the years immediately

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after an attack, in patients with residual heart disease, and in those with previous recurrences.⁶ Carditis was the most common presenting symptom in this study. Half of the 53 children with carditis presented with CHF, and CHF was three times more common in recurrences than in first attacks. At their first admission, about one-third of a total of 70 cases presented with their third or higher recurrence with RHD already in its chronic form. CHF and recurrent acute rheumatic carditis were their most common presenting features. This is in accordance with previous studies.^{7,8} Mitral insufficiency was the most common valvular lesion in both groups of children with either initial or recurrent episodes of RF in the present study. This is also in agreement with the findings of previous studies.^{2,7,9} Early significant development of mitral stenosis has been reported in several developing countries.^{10,11,12} We didn't detect any cases of pure mitral stenosis in this series. There were four cases of mixed mitral incompetence and stenosis in the recurrent attack group. No cases of isolated aortic insufficiency were found. Five of the 7 patients with combined mitral and aortic valve insufficiency were boys. Isolated involvement of the aortic valve is rare and tricuspid valve or pulmonary valve involvement is also reported to be unusual in the literature.

Aspirin hepatotoxicity was observed in two of our patients, both of them boys. Hepatotoxicity of anti-rheumatic doses of salicylate therapy has been reported previously.¹³

RF is a nonsuppurative sequel of group A streptococcal upper respiratory tract infection. Physicians and public health authorities must depend upon the accurate diagnosis and treatment of group A streptococcal pharyngitis and prevention of recurrent infections in known rheumatic cases in order to prevent the crippling effects of RF and RHD. In developing countries intramuscular benzathine penicillin is the recommended method for both primary and secondary prevention. It is regrettable that in the present study 43 children with suggestive symptoms of sore throat received inappropriate or inadequate primary prophylaxis and all of the 29 children with repeated episodes received their secondary prophylaxis irregularly. A study of prescribing practices in childhood sore throat carried out in Northern India¹⁴ revealed widespread ignorance regarding the correct choice and appropriate duration of antimicrobial therapy. The authors concluded that there was an urgent need for continuing medical education and on-the-job training programs for all categories of medical personnel, including

pediatricians. It seems that the same suggestion is highly recommended in Iran.

In conclusion this study highlights the fact that the high incidence of RF and the severity of RHD in developing countries is due to lack of prevention. Strict adherence to prophylactic regimens will significantly reduce the incidence and severity of this problem.

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