Sequelae of the Initial Attack of Acute Rheumatic Fever in Children from North India

A Prospective 5-year Follow-up Study

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SUMMARY We determined the outcome of acute rheumatic fever in 85 children from North India who had received regular antistreptococcal prophylaxis after their first attack. By the end of the 5-year follow-up, 33 patients had rheumatic heart disease. Mitral insufficiency, the most common valvular lesion, appeared in 91% of the patients, whereas mitral stenosis developed in only 18%. Initial carditis, congestive heart failure, cardiac-megaly or moderate-to-severe mitral insufficiency significantly increased the risk of rheumatic heart disease ($p < 0.001$). The recurrence rate of acute rheumatic fever in children who received continuous prophylaxis was 0.006 per patient-year. Most recurrences (92%) mimicked the first attack and produced further cardiac damage in five patients with carditis and in one patient with chorea. Cardiac status during the first attack of rheumatic fever and the continuity of prophylaxis were the major determinants of outcome. Statistical comparisons disclosed that with continuous prophylaxis, the prevalence rate, evolution and clinical spectrum of the sequelae of acute rheumatic fever in children from India do not differ significantly from those in the West.

ACUTE rheumatic fever (ARF) is generally believed to be more severe in India and neighboring countries than it is in the West.\(^1\) This opinion is controversial, primarily because of the divergent reports of the disease from the Indian subcontinent. For example, De Silva\(^2\) and Padmavati\(^3\) emphasized the paucity of severe manifestations of ARF in children from Sri Lanka (Ceylon) and New Delhi, respectively. In contrast, Roy et al.\(^4\) reported a much higher incidence of carditis and congestive heart failure, and concluded that ARF occurred in a more severe form in North India than in the West. High frequencies of cardiac involvement have been reported from South India,\(^5\) Iran,\(^6\) Pakistan\(^7\) and Egypt.\(^8\)

All but one of these studies, however, were retrospective, and no clear distinction was made in the analysis of first compared with recurrent attacks or with regard to the frequency of major manifestations of the disease.\(^9\) When we undertook a prospective study in a general pediatric outpatient clinic that served a large section of New Delhi and adjacent states, and admitted all patients with a first attack of ARF, the relative frequencies of major manifestations of the disease were very similar to the spectrum prevalent in the West.\(^10\)

Our findings then raised the question as to whether the sequelae of the first attack of ARF in children from India were truly different from those reported elsewhere. The purposes of this article are to report results from a prospective 5-year follow-up of these patients, with emphasis on the sequelae of ARF and factors that may contribute to residual rheumatic heart disease (RHD), and to compare our findings with those from the West.

Materials and Methods

Patient Population

The original study comprised 102 children who had a first attack of ARF. The description of this patient group, the results of the initial evaluation and the diagnostic criteria for ARF and carditis that were used, have been reported elsewhere.\(^10\)-\(^12\) Of this group, 85 children, 52 boys and 33 girls, 5–12 years old (mean 8.7 years), returned to the cardiac clinic and entered our 5-year prospective study.

Management of ARF (Initial Attack)

Soon after admission to the original study, each patient received a single intramuscular injection of...
0.6–1.2 million units of benzathine penicillin to eradicate streptococci.

Depending on the presenting features of each child, antiinflammatory therapy was given as recommended by Markowitz and Gordis1 on the basis of U.K.-U.S. Joint Reports on ARF.14,18 Patients who had congestive heart failure4* received decongestive therapy with digitalis and diuretics in addition to antiinflammatory therapy.

After the initial eradication of streptococcal infection, antistreptococcal prophylaxis* consisting of monthly intramuscular injections of 1.2 million units of benzathine penicillin was started for each child.

Follow-Up Studies

After discharge from the hospital, each patient was examined monthly for the first 6 months, at 9 and 12 months, and then every 6 months for the remainder of the study. At each visit, a careful history was taken with particular attention to evidence of sore throat, recurrence of ARF and compliance with prophylaxis. In addition, chest roentgenograms, ECGs and throat cultures were obtained, and erythrocyte sedimentation rates, antistreptolysin-0 titers and C-reactive protein were determined.

During follow-up examinations, mitral insufficiency was graded as mild if patients had an apical systolic murmur that was transmitted toward the left axilla but had no apical or basal diastolic murmur or cardiomegaly; moderate if the apical systolic murmur was conducted to the left axilla and to the back, with mild cardiomegaly; or severe if the patient also had an apical middle-diastolic rumble, clinical or radiologic evidence of cardiomegaly, and radiologic or electrocardiographic evidence of left atrial enlargement.17

The criteria for diagnosis and treatment of ARF recurrences during the follow-up were similar to those used during the initial attack.

Analysis of Data

The patients were divided into two groups. Group A included children without cardiac involvement during the initial attack, subgrouped as those with isolated joint involvement or isolated chorea. Group B included children with carditis subgrouped as those with joint involvement, chorea, carditis alone, or congestive heart failure, with or without pericarditis.

Patients with carditis were also subgrouped according to the nature of the initial heart murmur and were assessed for subsequent changes in cardiac status.

Certain characteristics of the entire group were analyzed for their prognostic value: the presence or absence of cardiomegaly, congestive heart failure and recurrences of ARF and, in children with recurrences, compliance or noncompliance with antistreptococcal prophylaxis.

Studies from the West14,18-22 consisted of patients who had received continuous antistreptococcal prophylaxis, which has a major impact on the outcome of rheumatic fever.15 The recurrence rate of ARF during 5 years of follow-up and prevalence rate of RHD after 5 years were therefore determined only for patients who had received continuous prophylaxis. The recurrence rate was expressed as the number of recurrences per patient follow-up year and the prevalence rate was expressed as the percentage of cases after 5 years. Like ours, all Western studies in the comparison included a follow-up of at least 5 years.

The statistical significance of differences between groups was tested by Fisher’s exact test.20 Differences in the recurrence rates of ARF per patient year in the comparison were tested for significance by the index-of-dispersion statistics, as described by Cox and Lewis;24 the difference in prevalence rates was tested for significance by the chi-square test.

Results

Prevalence Rate of Rheumatic Heart Disease

Among the 85 patients, 33 (39%) had RHD at the end of the 5-year period (table 1). Of the 65 who received continuous prophylaxis, 23 had RHD (prevalence rate 35.4%). The prevalence rate of RHD was significantly higher among patients who presented with carditis rather than isolated chorea or joint involvement: 66% vs 23% or 0% (p < 0.001, table 1). Similarly, RHD was more common in children who initially presented with cardiomegaly (75% of those with vs 12% of those without cardiomegaly, p < 0.001), congestive heart failure (86% of those with vs 30% of those without heart failure, p < 0.001), or moderate-to-severe mitral regurgitation (72% of those more severely affected vs 33% of those with mild regurgitation or 8% of those with no heart murmur, p < 0.001).

Thirty of the 45 patients who initially had carditis had heart murmurs at the end of the 5-year follow-up (table 2). The murmurs had worsened in eight, were unchanged in 17 and decreased in intensity in five. Mitral regurgitation was the most common valvular lesion, occurring in 29 patients (91%). Mitral regurgitation was the sole manifestation of RHD in 25 patients (78%) and was associated with mitral stenosis in three patients and with aortic insufficiency in one patient. Mitral stenosis was present in three other patients; of particular interest was its insidious development in two girls 2 and 4 years after the first attack of ARF that presented as chorea; both patients received continuous prophylaxis and ARF did not recur. In another patient, mitral stenosis was associated with aortic regurgitation. None of the patients had evidence of aortic stenosis or involvement of the tricuspid or pulmonary valve.

Recurrence of Acute Rheumatic Fever

ARF recurred 24 times in 22 of the 85 patients. All seven recurrences in patients with isolated joint involvement and six of seven recurrences in patients with chorea mimicked the first attack and were not associated with RHD. The exception was a patient who initially had isolated chorea, then had a recurrence of chorea and carditis and subsequently had residual RHD that persisted through the end of the follow-up period. Each of the 10 recurrences among patients who initially had carditis mimicked the first
TABLE 1. Relation Between Severity of Cardiac Involvement During Initial Attack of Acute Rheumatic Fever and Cardiac Status After a 5-year Follow-up

<table>
<thead>
<tr>
<th>Cardiac involvement during initial attack</th>
<th>Cardiac status at 5 years</th>
<th>RHD (n)</th>
<th>Normal (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>(%)</td>
<td>(%)</td>
</tr>
</tbody>
</table>

Group A: No cardiac involvement
Isolated joint involvement 27 0 (0) 27 (100)
Isolated chorea 13 3 (23) 10 (77)
Subtotal 40 3 (8) 37 (92)

Group B: Patients with carditis
1. No heart failure or pericarditis
   Mild MR 9 3 (33) 6 (67)
   Moderate MR 17 11 (65) 6 (35)
   Severe MR 5 4 (80) 1 (20)
   Subtotal 45 30 (66)* 15 (34)
2. Congestive heart failure or pericarditis
   14 12 (86) 2 (14)
   Subtotal 45 30 (66)* 15 (34)
   Total 85 33 (39) 52 (61)

*Prevalence rate of RHD was significantly higher in patients with carditis than in patients with either isolated joint involvement or isolated chorea (p < 0.001 by Fisher's exact test).

Abbreviations: ARF = acute rheumatic fever; RHD = rheumatic heart disease; MR = mitral regurgitation.

attack and was followed by RHD that persisted through the end of the study. Recurrence of carditis produced further cardiac damage in five of these patients, including two whose heart murmur completely disappeared 2-3 months before the recurrence.

Twenty-two recurrences in 20 patients were related directly to omissions of antistreptococcal prophylaxis for 2-4 months. Thus, there were only two recurrences of ARF among 65 patients who received continuous monthly prophylaxis for 5 years, yielding a recurrence rate of 0.006 per patient-year. This recurrence rate did not differ significantly from values for similarly treated children in five comparable Western studies by Wood et al. and others (p > 0.05, table 3). Similarly, the prevalence rate of RHD in our study (35.4%) was not significantly different

TABLE 2. Evolution of Rheumatic Heart Disease in Children with Carditis After 5-year Follow-up

<table>
<thead>
<tr>
<th>Cardiac status during initial attack of ARF</th>
<th>Cardiac status during follow-up</th>
<th>No. of pts</th>
<th>No. change</th>
<th>Decrease in murmur</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carditis and joint involvement</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild MR</td>
<td>7</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Moderate MR</td>
<td>19</td>
<td>10</td>
<td>3</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Severe MR</td>
<td>6</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Subtotal</td>
<td>32</td>
<td>12</td>
<td>6</td>
<td>3</td>
<td>11</td>
</tr>
<tr>
<td>Carditis and chorea</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild MR</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Moderate MR</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Severe MR</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Subtotal</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Isolated carditis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild MR</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Moderate MR</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Severe MR</td>
<td>9</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Subtotal</td>
<td>11</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>45</td>
<td>17</td>
<td>8</td>
<td>5</td>
<td>15</td>
</tr>
</tbody>
</table>

Abbreviations: RHD = rheumatic heart disease; ARF = acute rheumatic fever; MR = mitral regurgitation.
from that in the Western studies (p > 0.05). During the 5-year follow-up, evidence of heart disease disappeared in 15 of 45 patients (33%) who had a heart murmur during the initial attack. This percentage compares favorably with the 26–62% in groups reported by Feinstein et al.22 and others.14, 20, 21

Discussion

ARF has a world-wide distribution and continues to be a major cause of heart disease in young children and adolescents in many countries.1, 5, 23 The disease and its sequelae are believed to have substantial geographic variability, with a higher incidence of severe cardiac involvement in some countries.1 Rapid development of mitral stenosis with severe pulmonary hypertension within 6–12 months after the first attack of ARF is reported to be more common among Indian children.4, 5, 20 Still lacking, however, is the evidence of a difference in the response to streptococcal infection or in the virulence of the pathogen itself, either of which could account for the apparent geographic variations in ARF or its sequelae.

Previous studies from India4–5, 20 were retrospective and included patients who were referred for evaluation of heart disease. Most children did not receive regular antistreptococcal prophylaxis, and no information was available about their cardiac status during the initial attack of ARF and the number and type of ARF recurrences. The paucity of such information severely limits the comparative value of these studies.8 Moreover, without regular prophylaxis, carditis during the initial attack greatly increases the risk of recurrent carditis and further heart damage. Thus, the higher incidence of severe cardiac involvement in the previous studies from India4–5, 20 most likely reflects the end result of multiple insults to the heart in children without adequate prophylaxis against recurrent streptococcal infection and its sequelae.

RHD developed in 33 of 85 children in our study. Mitral insufficiency was the most common valvular lesion, occurring in 91%, whereas mitral stenosis developed in 18%. The more frequent occurrence of juvenile mitral stenosis in previous reports from India is in sharp contrast to our observations and may be related to several factors. For example, the relative scarcity of hospital beds and the tertiary nature of the institutions where earlier data were collected invariably favor hospitalization of the sickest patients. In addition, the fact that there are more children than adults in India and neighboring countries may also favor the observation of unusual complications in children. The wide discrepancy between our findings and the less favorable results from the past, therefore, seem to stem from an inadvertent bias in previous patient selection rather than from a true geographic variation in the sequelae of ARF in childhood.

The mimicking nature of recurrence of ARF and its impact on residual cardiac status is well recognized. None of the recurrences in children with initial joint involvement produced RHD in our study. In contrast, in patients with initial carditis, each recurrence involved the heart and produced further cardiac damage in five of 10 patients, including two patients whose heart murmur had disappeared 2–3 months before the recurrence. These observations are in full accord with those of Feinstein et al.27, and Kuttner and Mayer28 that carditis is more likely to recur in patients who have cardiac involvement during the first attack and that each mimicking recurrence may further damage the heart. Of special interest are the two girls with chorea alone in whom mitral stenosis subsequently developed insidiously despite continuous antistreptococcal prophylaxis and no recurrences. Aaron et al.29 reported similar sequelae to "pure" chorea among children in the West.

Heart murmur disappeared completely in 5 years in
about one-third of our patients. This was most common in those with a grade I apical systolic murmur and least common in patients who initially had heart failure. Heart murmur persisted in all patients with aortic insufficiency or mitral stenosis.

Our observations establish that the evolution, spectrum and the prevalence rate of sequelae of ARF do not differ between children from India and those from the West, provided that continuous antistreptococcal prophylaxis is maintained after the first attack. The strict maintenance of antistreptococcal chemoprophylaxis is essential in preventing recurrences of ARF in children throughout the world, particularly in overcrowded areas where a majority of the pediatric populations reside. Faithful compliance with this regimen will undoubtedly remain the strongest defense against ARF1, 8, 20, 21 until an effective primary preventive vaccine is available for the rheumatogenic strains of Streptococcus. 32, 33

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