

# Rheumatic Fever in the Nazareth Area during the Last Decade

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## Abstract

**Background:** Acute rheumatic fever is considered a relatively uncommon disease in developed countries. Although cases are encountered in the Nazareth area in Israel, no systematic study of this disease has been done in the last 20 years.

**Objective:** To study the incidence and characteristics of acute rheumatic fever cases in the Nazareth area during the last decade.

**Methods:** Cases of acute rheumatic fever diagnosed according to the modified Jones criteria were identified in two hospitals in the Nazareth area during the 10 years. These two hospitals receive about 75% of non-obstetric referrals to the emergency room. Clinical, laboratory and treatment data of these patients were documented and the incidence of disease calculated. The population census in the Nazareth area was obtained from the Central Bureau of Statistics.

**Results:** Forty-four patients, with a mean age of 18 years, were identified. The mean annual incidence was 5 cases/100,000 population. Arthritis was found in 98% of the patients (migratory in 52%) and carditis in 34%, but only one patient had a subcutaneous nodule, and none had either erythema marginatum or chorea. Only one patient with carditis developed heart failure a few months later due to severe mitral stenosis.

**Conclusion:** Rheumatic fever in the Nazareth area is still manifest. The mean age of the patients was higher than found previously. In only half of the patients was the arthritis migratory, with other major manifestations of rheumatic fever found only rarely.

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Rheumatic fever is a type of reactive disease that occurs after pharyngeal infection by *Streptococcus* group A. Classically, it is characterized by self-limited, migratory, non-erosive arthritis appearing one or several weeks after the infection. Cardiac involvement accounts for the morbidity and mortality of the disease.

Since the turn of the last century until the 1970s, there was a continuous decline in the incidence of the disease in

western countries; however in the early 1980s episodes of epidemics in the USA were reported [1-5]. Currently, it is considered a relatively uncommon disease in developed countries. As in the western countries, epidemiological studies in Israel also showed a persistent decline in the incidence of acute rheumatic fever from the 1950s until the 1970s [6,7], although a report from the Negev area showed no clear decline in the incidence of acute rheumatic fever during the 1980s [8]. A recent report by a member of our team included six cases of acute rheumatic fever seen during one year in a local hospital in the Nazareth area, prompting us to review the new cases of rheumatic fever in the Nazareth area during the last decade [9].

## Materials and Methods

The Nazareth area includes the city itself surrounded by eight small villages — Eilut, Kanna, Reina, Tura'an, Yafa, Mashhad, Ein mahel, and Iksal. The area of Nazareth Ilit was excluded from the study. The entire population is indigenous Arab. The population in the Nazareth area is served by a relatively large hospital, the Central Emek Medical Center in the nearby city of Afula, as well as by three small local community hospitals — the Nazareth Hospital (the largest), the Holy Family Hospital, and the French Hospital.

In the Nazareth area rheumatic fever is considered a disease that requires hospitalization; we therefore assumed that the number of cases encountered in these hospitals is a good approximation of the total number of diagnosed cases in the area during the last decade. Due to different filing methods, only the medical records from the Central Emek Medical Center and the Nazareth Hospital could be evaluated. These two hospitals see about 75% of the non-obstetric referrals to the emergency room, according to the reports from the sick funds that cover the entire population. At the Central Emek Medical Center we used the code of 290 for acute rheumatic fever (International Classification of Diseases, ICD-9 coding system) to locate relevant files. At the Nazareth Hospital we reviewed the monthly listings of discharge diagnoses to locate charts with acute rheumatic fever or suspected rheumatic fever over the last decade. The population

census was obtained from the Central Bureau of Statistics in Israel.

All charts were reviewed by the first author of this study. The study group included patients who met the modified Jones criteria [10] and who had not developed any other rheumatic disease within 6 months of the diagnosis. Information on any other rheumatic disease was obtained from the outpatient chart, inpatient chart or by phone contact. Six patients with follow-up of less than 6 months could not be contacted. The diagnosis of carditis included either organic heart murmur not previously present, enlarged heart, congestive heart failure, pericardial friction rub, or signs of pericardial effusion. The incidence of rheumatic fever was calculated by dividing the number of observed cases by 0.75.

## Results

Forty-six cases met the criteria for rheumatic fever. Two patients were excluded due to the development of juvenile rheumatoid arthritis in one patient and Behçet's disease in the other. Demographic data of the patients are shown in Table 1. Most of the cases occurred in the winter-spring period (data not shown). All of the 10 patients who provided information regarding the occupation of the head of the household were of low socioeconomic status.

The annual number of cases and calculated incidence of acute rheumatic fever in the Nazareth area during the last decade are shown in Table 2. Statistical analysis using the chi-square test to compare all the groups showed no significant difference in the standard incidence ratio between the groups. All patients were admitted with fever, 43 (98%) had arthritis, 15 (34%) had carditis, but only one patient had a subcutaneous nodule, and none of the patients had erythema marginatum or chorea.

Nearly all the patients with carditis had significant heart murmurs (14 of 15), mostly systolic, and all had findings on echocardiography (14/14), mostly mitral regurgitation.

Table 1. Demographic and clinical variables in 44 patients with acute rheumatic fever

Total no. of cases	44
Females	25 (57%)
Age (yr)	
Median	18
Range	5-35
People living in the same house	
Median	9
Range	7-13
Patients with previous sore throat	31 (70%)
Time from sore throat to RF symptoms (days)	
Median	12
Range	4-40
Patients who received antibiotics before RF	10 (23%)
Patients with previous RF	7 (16%)

RF = rheumatic fever

Table 2. Incidence of rheumatic fever in the Nazareth area over the last decade

Year	Population of the Nazareth area	No. of RF cases*	Calculated incidence of RF in the Nazareth area
1988	106,600	4	5.00
1989	109,900	7	8.49
1990	109,700	11	13.37
1991	113,200	3	3.53
1992	116,600	1	1.14
1993	120,500	2	2.21
1994	123,900	6	6.46
1995	129,900	7	7.18
1996	131,000	2	1.75
1997	135,000	1	0.99

\* Hospitalized in the Central Emek Medical Center in Afula and Nazareth Hospital.

One patient had pericardial effusion. Of the six patients with electrocardiographic changes, one patient had atrioventricular dissociation, two had first-degree and two had second-degree atrioventricular block (Wenckebach type), and one patient had idionodal rhythm and incomplete right bundle branch block. Nine of the 15 patients were less than 18 years old, the median age for all the patients, and 10 of the 15 patients were females. Among the 43 patients with arthritis, the first joint to be involved was the knee in 18 patients (42%) and the ankle in 17 (40%). Other joints were involved less frequently. The pattern of involvement was migratory in 14 cases (33%), additive in 13 cases (30%), and both additive and migratory in 2 cases (5%). Two patients (5%) had monoarthritis, and in 12 patients (27%) no pattern could be determined by chart review.

ECG abnormalities were also seen in seven patients without evidence of carditis. These included first-degree atrioventricular block (four patients), nodal rhythm with IRBBB (one patient), wandering atrial pacemaker (one patient), and IRBBB with peaked T waves (one patient).

## Laboratory findings

The laboratory results are shown in Table 3. Serotyping of the positive throat culture for *Streptococcus* group A was not done. Over the years, measurements of antistreptolysin-O antibody titers [11,12] and C-reactive protein [13,14] had been determined by different methods. All had elevated antistreptolysin-O antibody titers, and 36 (82%) had titers more than twice the upper normal limit. One patient with slightly elevated antistreptolysin-O antibody titer had a strongly positive test for anti-deoxyribonuclease B antibodies.

## Treatment and course

Patients who had arthritis but no carditis (29 patients) were initially treated with aspirin, usually at a dosage of 1

ECG = electrocardiography

IRBBB = incomplete right bundle branch block

Table 3. Laboratory data of patients with acute rheumatic fever

Laboratory parameter	Results	No. of patients tested
Antistreptolysin-O antibody titer	↑	All
Positive throat cultures (patients)	3	All
Anti-DNAase B	↑	1
Erythrocyte sedimentation rate (mm/h)		All
Median	95	
Range	45–140	
C-reactive protein	↑	All
White blood cells (/ml)		All
Median	10.3x10 <sup>3</sup>	
Range	4.6–17.3	
Antinuclear antibody	–	33
Rheumatoid factor	–	38
C3 (mg/dl)		19
Median	112	
Range (normal 70–170)	75–185	
C4 (mg/dl)		19
Median	24	
Range (normal 15–45)	16–45	
Antibodies to <i>Brucella</i>	–	25
Hepatitis B surface antigen	–	18
Antibodies to <i>Chlamydia</i>	–	1
Liver function tests	Mildly ↑ in one patient	All
White cell count (/ml) (from knee synovial fluid)		2
Mean	14,800	
Urine analysis	Mild proteinuria and hematuria in 2 patients	All

↑ elevated

g q.i.d. (range 0.75–1.5 g q.i.d.). Corticosteroids were added later in two patients — on account of ECG changes in one, and continuous musculoskeletal pain in the other patient who was pregnant. Generally, the fever subsided within 1–5 days, but mostly within 48 hours. Joint symptoms were usually markedly relieved within 1–5 days. During the hospital stay three patients had new joint involvement that responded to either increasing doses of aspirin or further follow-up on the same dose.

Among the 43 patients with arthritis, frank arthritis after discharge reappeared in 5. This was attributed to non-compliance in four, and to the rapid tapering of corticosteroids in the fifth patient. The arthritis responded to the resumption of treatment in all cases.

Treatment for the 15 carditis patients consisted of aspirin only in 6 patients, corticosteroids in 4, and both aspirin and corticosteroids in 5. The usual corticosteroid dose was 40–60 mg of prednisone administered in divided doses for 2 weeks, then slowly tapered and stopped after 4–6 weeks. The fever and joint symptoms in the six patients who were treated with aspirin only were ameliorated within a few days. One patient, who had diastolic murmur and mild to moderate mitral stenosis on admis-

sion and was discharged on aspirin 1 g q.i.d., was readmitted 2.5 months later with pulmonary edema due to severe mitral stenosis with a mitral valve area of 1.1 cm<sup>2</sup>. There was no evidence of recurrent rheumatic fever, and this patient underwent balloon valvuloplasty 8 months later. The remaining five patients had mild cardiac findings. Four patients were treated with corticosteroids only, resulting in amelioration of fever and joint symptoms within 1–2 days. There was a resolution of the hyperdynamic hearts within a few days, and improvement in the murmur grade from one week to a few months. Repeated echographic studies revealed an improvement after a period ranging from months to years. In two of the five patients treated with a combination of corticosteroids and aspirin, the aspirin was routinely added while the dosage of the corticosteroids was tapered. The three remaining patients were initially treated with aspirin. Corticosteroids were added due to enlarging left ventricle in one patient, pericardial effusion in another, and persistence of conduction defect in the third patient. Improvement was later noted in all of them.

All the ECG conduction abnormalities reverted to a normal sinus rhythm within 2 days to 2 months. One patient had spontaneous reappearance of second-degree atrioventricular block one year after recovery, which reverted spontaneously to normal sinus rhythm the next day.

As prophylactic treatment, all 44 patients received either penicillin V-K 200,000 IU b.i.d., or benzathine penicillin G 1.2 million IU monthly. Some of them, however, especially those on oral prophylactic treatment, were non-compliant

## Discussion

Since the turn of the last century until the 1970s there has been a steady decline in the incidence of rheumatic fever in western countries. The reported incidence of this disease in the USA at the end of the 1970s was 2/100,000 [1]. This decline is attributed to many factors, including penicillin treatment and prophylaxis, improvement in health services and social conditions, as well as a change in the virulent serotypes of *Streptococcus* group A over the years. However, epidemics did occur in the years 1984–89 [1–5], and it was found that in these epidemics the serotypes of the *Streptococcus* group A were more virulent and that the patients belonged to the middle class.

As in the western world, the incidence of acute rheumatic fever in Israel declined steadily until the 1970s when the incidence was 2 cases/100,000 population in the Jewish population and about 7 cases in the non-Jewish population [6,7]. The decline in incidence was attributed mainly to the improved social conditions of the population. Since then there have been very few reports on rheumatic fever in Israel. One study evaluating all cases of acute rheumatic fever in the pediatric wards of the Soroka Medical Center in the Negev area found no evidence of decline in the incidence of acute rheumatic fever during

the 1980s. In our study in the Nazareth area, the average annual incidence of rheumatic fever during the last decade was 5 cases/100,000 population. There was no significant difference in the incidence between the years.

Many of our patients lived in crowded conditions, and all the patients who reported household income were of low socioeconomic status. On average, compared to other areas of the country, the standard of living of the Nazareth area population is lower, the populace is less educated, the sanitary conditions are poorer, and there is more overcrowding. Therefore, the figures from our study cannot be extrapolated to other areas of the country or to other developed countries, but our findings clearly suggest that efforts are still needed to reduce the incidence of rheumatic fever in areas with low socioeconomic status, even in developed countries.

The median (and mean) age was 18 years, which is higher than the classic age (5–15 years). In the last wave of epidemics in the USA, the mean age was also high. In one study from one of the developing countries in Asia, the mean and median age of all the patients with acute rheumatic fever diagnosed between the years 1990 and 1995 was 12.7 and 12 years respectively [15]. The reason for this shift is unclear. In Israel, since day-care centers are prevalent and conditions in schools are crowded, this shift probably represents differing sensitivities to the virulent strains of the hemolytic streptococci. Unfortunately, strain typing was not done. Only three patients had positive throat culture for *Streptococcus* group A, which might have been due to antibiotic treatment before the swabs were obtained or to the swabs not being taken correctly.

The time that elapsed between the onset of throat symptoms and that of rheumatic fever symptoms in our patients ranged from 4 to 40 days, which is similar to that reported previously [16]. This suggests the need for public health measures to increase the use of throat cultures in the Nazareth area. Those who developed rheumatic fever more than 5 weeks after the appearance of pharyngeal symptoms probably had pharyngeal re-infection prior to rheumatic fever [17].

All but one patient had arthritis. Joint involvement becomes more common with the increasing age of the patient with rheumatic fever [18]. In only half of the patients on whom we had information regarding the pattern of involvement, the type of involvement was migratory, and in about 40% it was additive. With increasing age the duration of arthritis may also be longer, allowing extra time for the involvement of other joints while the previously affected one is still markedly inflamed [19].

Fifteen patients (34%) had carditis. The incidence of carditis is inversely related to age, and in one study less than a third of the patients aged 14 years and above had carditis [20]; in fact 9 of the 15 patients with carditis in our series were less than the median age of 18 years.

The antistreptolysin-O antibody titer is the most important test for the diagnosis of rheumatic fever. This

test has 50–90% sensitivity and 90% specificity, and can differentiate between streptococcal throat infection and carrier state [21]. All the patients in our series had elevated titers.

Patients with arthritis responded well to aspirin. The recommended dose of aspirin is 100 mg/kg/day for 2 weeks, followed by 65 mg/kg/day for a further 6 weeks. In some patients, serum acetyl salicylic acid levels were obtained, but the dosage adjustment was determined according to the patients' clinical status. The patients with carditis (n=6) who were initially treated with corticosteroids had a benign clinical course. In contrast, of the nine patients who were initially treated with aspirin alone, four showed either no improvement or a deterioration in the cardiac findings and one patient progressed rapidly to severe mitral stenosis. Although corticosteroids are traditionally indicated in severe cardiomegaly or heart failure, we believe that despite the lack of controlled clinical trials it might be prudent to add corticosteroids to the treatment of all those with carditis.

Finally, prophylaxis is a vital factor in the management of rheumatic fever, although there is still debate regarding the required duration of prophylaxis. Moreover, compliance is improved when intramuscular injection of benzathine penicillin G is given.

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