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# RHEUMATIC FEVER AND RHEUMATIC HEART DISEASES: EPIDEMIOLOGY, PREVENTION, TREATMENT AND REHABILITATION

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## EPIDEMIOLOGY OF RHEUMATIC FEVER

### In temperate climates:

The clearest relationship of group A streptococcal infection to rheumatic fever is found in studies of "closed" populations (such as military recruits) subject to epidemic streptococcal sore throat in temperate climates (11). Several firm concepts have emerged in these studies which may be summarized briefly:

1. When one selects patients who are ill with frank, exudative streptococcal pharyngitis due to certain common prevalent pharyngeal strains of virulent group A streptococci, rheumatic fever follows at a fairly predictable attack rate (approximately 3 percent) regardless of the age, race, or ethnic group studied and regardless of the year or season in which the study was made.

2. The major variables which are related to this attack rate in such studies are:

   a) The magnitude of the immune response to the antecedent streptococcal infection, and

   b) the duration of convalescent carriage of the organism.

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Weak ASO responses may be associated with acute rheumatic fever attack rates of considerably less than 1 percent, whereas strong responses may produce rates well in excess of 5 percent.

3. Rheumatic fever can be prevented following such infections by treatment with antibiotics which promptly and thoroughly eradicate the streptococcus from the pharynx.

Streptococcal infections are spread by intimate, person-to-person, airborne contact. Streptococci recovered from dust on floors, blankets and clothing are of very low infectivity. Close, intimate living conditions, however, represent the most dangerous setting for transmission of pharyngitis, particularly when extremes of seasons promote crowded indoor living conditions (5). Under such conditions, the explosive spread of a single group A streptococcal serotype is most impressive.

Sporadic streptococcal disease and rheumatic fever among school children in large cities of temperate zones

When one attempts to define more precisely the threshold of streptococcal pharyngitis required to produce rheumatic fever and turns to the study of endemic streptococcal disease in school children, the complexity of the problem of defining a streptococcal infection becomes very great. Studies made in Chicago school children, for example (14), showed that sore throats associated with positive cultures for group A streptococci resulted in rheumatic fever attack rates that varied greatly according to the clinical, bacteriologic and immunologic criteria of streptococcal disease. Thus, more than 800 untreated patients who had a positive throat culture for group A streptococci but who had only mild clinical manifestations, such as non-exudative pharyngitis, did not develop rheumatic fever although 40 percent of these had detectable streptococcal immune responses. The initial or acute phase streptococcal antibody titers in these patients were often relatively high (close to 300 ASO units, for example) suggesting frequent, small, antigenic stimuli, but the magnitude of the antigenic boost of each infection was on the average relatively weak. Furthermore, of the streptococcal strains isolated only 40 percent were typable for known M protein serotypes, and other studies of these strains showed them to have less virulence properties than epidemic strains (18).

Such observations drew attention to several possibilities concerning streptococcal pharyngitis and rheumatic fever. First, that a milder form of streptococcal infection, clinically and epidemiologically, might have much less potential for producing rheumatic fever. Second, the definition of a significant streptococcal infection is very difficult in a population of children in whom pharyngeal carriage of streptococci is relatively high, in whom repeated mild streptococcal infections are frequent, but in whom viral infection is by far the most frequent cause of upper respiratory symptoms, including sore throat. Although an increase in streptococcal antibodies between acute and convalescent phase sera is usually an acceptable criterion of streptococcal pharyngitis, some studies have pointed out the problem of excluding recent preceding streptococcal illness as a cause for a late-rising titer. When such infections are associated with prolonged pharyngeal convalescent carriage of streptococci, intercurrent viral upper respiratory infections may seem to be streptococcal in character when throat cultures are made (7).

Streptococcal disease in affluent communities in the temperate zones

The virtual disappearance of acute rheumatic fever among relatively affluent populations of North America and Europe, and especially in cities with few, if any, slums and with optimal housing conditions, is one of the dramatic events of recent medical history. Yet streptococcal pharyngitis in the school-age children of such communities continues to be relatively common, and assays of streptococcal antibody titers continue to show moderately high titers in these populations. Although much credit has been given to the generous dispensing of antibiotics to account for this change, the most casual survey of the therapeutic regimen prescribed by many physicians would reveal, in this author's experience, the use of far less than the optimal courses of penicillin required to prevent rheumatic attacks, at least from epidemic-type streptococcal pharyngitis.

Is, then, the change in incidence of rheumatic fever in such modified epidemiologic settings a matter of a quantitative change in the virulence of rheumatogenic organisms or is there, perhaps, also a qualitative change in the prevalent strains of pharyngeal streptococci in such cultures? The latter question raises an old issue (19, 12). Are there streptococcal strains that are non-rheumatogenic? If so, under what epidemiologic conditions are they prevalent?

Rheumatogenic and nephritogenic streptococci: "Skin streptococci"

The epidemiology of streptococcal infections in warm climates has become of greater interest in recent times because of the increasing awareness of the frequency of streptococcal skin infections (22). It is now clear that the common type of skin sore which results from secondary infection abrasions, insect bites and other types of skin trauma, and which is associated with poverty and unhygienic living conditions is a streptococcal infection. Staphylococci overgrow the crusted surface of such lesions and have, in the past, confused the etiology of this kind of pyoderma (3). Furthermore, as epidemic streptococcal pharyngitis has come under better control, epidemics of acute glomerulonephritis observed in recent years have been found primarily in populations in which pyoderma is prevalent in children. Thus, the careful studies at the Indian reservations of Minnesota - Red Lake and Cass Lake (20), in Trinidad (9), in southern USA (3, 1), and in Israel (10), have identified so-called "new" serotypes of streptococci which seem to have a predilection for skin residence. Moreover, the transmission of such organisms seems to be from skin to throat, rather than vice-versa (22), and throat carriage of so-called "skin strains" is a common feature of populations in which pyoderma is prevalent.

The remarkable feature of streptococcal pyoderma and its complicating acute glomerulonephritis is the complete absence of acute rheumatic fever following such infections, despite the frequent concomitant throat carriage of these organisms. Furthermore, from studies of pharyngitis in these populations, it appears that although isolation of these "skin" strains from the throat is common, the streptococcal immune response is considerably less vigorous than that observed following pharyngeal infections with the better-studied "throat strains" (1).

Such observations have led to the concept that acute glomerulonephritis requires an antecedent infection by a strain of streptococci that has nephritogenic potential, the infection may be either of the skin or of the throat, and it does not cause rheumatic fever. We have termed such strains "non-rheumatogenic" (19). Conversely, the well-recognized pharyngeal serotypes which have caused most epidemics of rheumatic fever (e.g. types 1, 5, 6, 19, 24, etc.) have not caused acute glomerulonephritis and do not appear to cause common streptococcal pyoderma.

A further distinction between the two types of infections is the difference in the immune response. Streptococcal pyoderma, with or without acute glomerulonephritis, produces relatively feeble ASO and anti-NADase titers, whereas the response of anti-DNAse B and antihyaluronidase is vigorous (22).

In view of the foregoing discussion, those who attempt studies of acute rheumatic fever in warm climates harbouring populations prone to pyoderma must be prepared to interpret pharyngeal carriage of streptococci and ASO responses with awareness of the admixture of the streptococcal strains which may be present. In the southern USA, seasonal variation demonstrates strikingly the dissociation of the two diseases - acute glomerulonephritis prevalent in summer and acute rheumatic fever in late fall and winter (Figure 1). In tropical climates, however, such seasonal distinction is not present, at least not to the same degree, and both diseases may be superimposed throughout the year.

Variations of epidemiologic settings in the tropics which predispose to acute rheumatic fever

Because there is little firm evidence to support an effect of climate per se on the pathogenesis of acute rheumatic fever, one should consider the role of climate as but another variable which can affect the conditions promoting the rapid spread of pharyngeal streptococci of rheumatogenic potential. If this thesis is valid, we should be able to interpret most of the variations observed in the prevalence of rheumatic fever and rheumatic heart disease in various parts of the world. Furthermore, to date there is no particular race or ethnic group that is either more or less susceptible to streptococcal pharyngitis or to either of its non-suppurative sequels, and the role of genetic factors in the development of either of these complications is a limited one (16).

Because the most consistent predisposing epidemiologic factors for rheumatic fever appear to be crowded living conditions, close person-to-person contact, and indequate treatment and prevention of streptococcal infections, a survey of the prevalence of acute rheumatic fever and rheumatic heart disease in certain tropical populations should clearly

reflect the effect of these factors. The World Health Organization Regional Office for the Western Pacific held a seminar in Manila in 1968 on the prevention and control of cardiovascular disease due to infections (23) at which the subject of rheumatic heart disease in the region received particular attention.

The seminar emphasized the remarkable variation in cultures, ethnic groups and geographical features of the region. Regardless of such variables, rheumatic fever and rheumatic heart disease was identified as a major problem only in areas where crowding, large families, low socio-economic conditions, increasing urbanization, rapid industrialization, and changing ways of life were most striking.

PREVENTION

The implementation of preventive measures for first attacks (primary prevention) and recurrences (secondary prevention) of rheumatic fever is more complex than the simple facts of prevention suggest. The best programmes for rapid and routine diagnosis of sore throats by throat cultures have often been mounted in communities in which rheumatic fever does not seem to be a problem at all. The streptococcal strains in such places have become attenuated, and the disease sporadic (17). Contrariwise, only the poorest medical care and surveillance of respiratory infections are available to some of the most severely affected groups. The global nature of streptococcal pharyngitis and the seemingly irreducible human reservoir of pharyngeal carriers of virulent strains, however, make it incumbent upon all communities to limit the exposure and the spread of this disease by scrupulous adherence to the principles of rheumatic-fever prevention. It is the duty, therefore, of every community, whether or not it has a serious streptococcal-disease problem, to assess its own programme for rheumatic-fever prevention and to decide how to meet the recommended standards for such programmes.

The most knowledgeable advice available to all physicians and health workers in all communities, here and abroad, concerning how rheumatic fever prevention may best be implemented can be found in the recent report of the Inter-Society Commission for Heart Disease Resources, established

jointly by the American H art Association and the US Public Health Service's Regional Medical Programmes, which appointed a study group of rheumatic fever and rheumatic heart disease to help to fulfil the Commission's purpose of "developing guidelines for the evaluation of medical facilities and services in the prevention, diagnosis, treatment, and rehabilitation of patients with cardiovascular disease"(13). The rheumatic fever study group's report is both an elegant blueprint for action by the community and a perceptive compendium of the specific problems that must be overcome if a programme is to be effective. An outline of the major principles are enumerated as follows:

Primary prevention

1. The community should identify the professional group that can serve as a committee on streptococcal disease - rheumatic heart disease and should fix responsibility for the prevention programmes upon an agency with the best potential for the job - usually the local health department.

2. The community should be able to estimate the size of its problem by readily available sources of data (such as hospital discharges, health records, and surveys).

3. Reliable, inexpensive and efficient throat culture services must be provided (21). For a patient with acute sore throat, we need to know simply, "is the culture positive for hemolytic streptococci?" If not, the trouble and expense of antibiotics can be spared.

4. Treatment of streptococcal pharyngitis must be adequate to eradicate the organism. It is still difficult to convince the profession that a single injection of 0.6 to 1.2 million units of benzathine penicillin G intramuscularly is optimal treatment. The alternative of 10 days of oral penicillin G (200,000 - 250,000 units b.i.d.) or, for penicillin-allergic persons, of erythromycin (.5 Gm. b.i.d.) is dependent upon unpredictable patient fidelity (2).

5. Medical students, physicians, nurses and other professionals should be taught streptococcal microbiology adequately in a clinical context by departments of medicine, paediatrics and community medicine.

6. Once a primary prevention programme is developed in the community, the leaders should present their case directly to the public through all available communications media.

7. School-oriented programmes, particularly in overcrowded schools in the centre city and those in other high-risk areas, provide excellent opportunities for children with symptomatic pharyngitis to be examined and to have a throat culture made by any available trained personnel either trained volunteers or school nurses or other paid public health workers.

8. Community surveillance for streptococcal infections is very helpful to set the appropriate index of suspicion for dealing with patients with pharyngitis, to determine when a symptomatic contact should have throat cultures made, or even to determine when mass prophylaxis with penicillin should be given.

Secondary prevention (prevention of recurrent rheumatic attacks)

1. Establish a rheumatic fever registry.

2. Provide prophylactic drugs: The most efficient regimen for continuous prophylaxis against group A streptococci is a monthly intramuscular injection of 1.2 million units of benzathine penicillin. The disadvantages and discomfort of this regimen have to be weighed against the individual patient's susceptibility to recurrences. Those with rheumatic heart disease, recent rheumatic fever, and exposure to an environment in which the incidence of streptococcal infection is frequent deserve the most effective protection. As a second choice, prophylaxis may be administered orally with either 1 Gm. of sulfadiazine daily in a single dose or 200,000 units of penicillin given twice daily on an empty stomach. The duration of continuous prophylaxis cannot be fixed arbitrarily for all patients, although the safest generalization is that it be continued indefinitely. Certainly, those under the age of 18 years should receive a continuous prophylactic regimen. A minimum period of 5 years is recommended for patients who develop rheumatic fever without carditis over

the age of 18. The decision to continue prophylaxis beyond this period should take into account a number of variables. Patients with rheumatic heart disease are more susceptible to reactivation of rheumatic fever if they contract a streptococcal infection. Moreover, patients who have had carditis in a previous attack are much more likely to suffer carditis again in a subsequent attack. Climate, age, occupation, household situation, cardiac status, and length of time since the previous attack are all significant variables which influence the risk of recurrence. The decline in recurrence rates with increasing age is due to: (a) decreased rate of streptococcal infection, and (b) decrease in the rate of rheumatic reactivation following streptococcal infection in older rheumatic subjects. Despite this decreased rate, however, the risk of rheumatic recurrence in adults remains relatively high when the streptococcal disease encountered is severe or epidemic.

3. Establish follow-up programmes to ensure patient fidelity to the prophylactic regimens. The follow-up should be devoted most vigorously to those at highest risk for recurrences - namely, those with rheumatic heart disease, with recent rheumatic fever (within 5 years), and with exposure to conditions of highest streptococcal-disease prevalence.

4. Make available to the community medical consultations, clinics, and laboratory facilities for rheumatic patients.

5. Mount a continuing programme of physician and community education for the needs of the rheumatic fever patient.

## TREATMENT

There is no specific cure for rheumatic fever, and no known measures change the course of the attack. Good supportive therapy, however, can reduce the mortality and morbidity of the disease.

Chemotherapy

After rheumatic fever is first diagnosed, a course of penicillin should be given to eliminate group A streptococci. This is advisable even if bacteriologic examination yields throat cultures negative for streptococci, since the organisms may be present in areas inaccessible to swabs. It is preferable to administer penicillin parenterally. An effective course is either a single injection of 1.2 million units of benzathine penicillin intramuscularly or 600,000 units of procaine penicillin intramuscularly daily for 10 days. Attempts to reduce ultimate heart damage by administering penicillin early in the acute rheumatic attack in larger doses have not been successful to date. After completion of the therapeutic course of penicillin, continuous protection from reinfection with streptococci should be provided by instituting one of the prophylactic regimens described later.

Suppressive therapy

Both corticosteroids and salicylates are of considerable value in controlling the toxic manifestations of rheumatic fever, in contributing to the comfort of the patient, and in combating anorexia, anemia, and constitutional symptoms. In severe rheumatic carditis associated with heart failure, such nonspecific anti-inflammatory effects may reduce the burden upon the labouring heart. Occasionally, they may tilt the balance in favour of survival of a critically ill patient. Corticosteroids are more potent than salicylates in suppressing acute exudative inflammation, and some patients in whom salicylates fail to control the disease respond quickly to relatively large doses of corticosteroids. Whether or not intensive corticosteroid therapy instituted early in the first rheumatic attack can reduce the degree of ultimate cardiac scarring is a point which is still somewhat at issue in patients with relatively mild cardiac involvement. Where carditis is more severe, all carefully controlled studies fail to reveal any clear superiority of corticosteroids over aspirin in terms of modifying the duration of the acute disease or residual heart damage after five years of follow-up. However, there is still considerable variation in the recommendations concerning the use of these agents.

Most authorities now use salicylates rather than corticosteroids to treat children with rheumatic fever but with no evidence of carditis, since the prognosis for recovery without permanent stigmas in such cases is greater than 95 percent. If signs and symptoms are not adequately suppressed by salicylates, corticosteroids are substituted. Patients with mild carditis are probably given corticosteroids in most instances, although it is in such cases that there is the greatest disagreement about their value. Patients with severe carditis are usually treated promptly with corticosteroids, particularly if heart failure is evident, in which case parenteral doses of mercurial diuretics are given and salt intake is restricted.

No arbitrary schedule of doses of corticosteroids or salicylates is recommended, although they should be adequate to achieve prompt symptomatic improvement. Salicylates are usually given as acetylsalicylic acid in a total daily dose initially of 0.15 g per kg (1 grain per pound) of body weight, up to a maximum daily dose of 10 g. Corticosteroids are usually started in doses comparable for different analogues to that of 10 to 15 mg. of prednisone every 6 hours. The duration of treatment should be guided by the expected course of the disease and by the severity of the rheumatic process in the individual case. Because most rheumatic attacks last 6 weeks, treatment should be continuous at least for this period, with doses tapered during the last 2 weeks. Should clinical symptoms relapse (rebound phenomenon), an additional 4 to 6 weeks of treatment is advised. In stubborn attacks, such courses may have to be repeated several times. Weekly tests for C-reactive protein in the blood and for the erythrocyte sedimentation rate are useful in following the healing process, particularly when treatment with corticosteroids or salicylates is gradually withdrawn. With adequate suppressive doses, the C-reactive protein should disappear from the blood, and the erythrocyte sedimentation rate should decrease. Reappearance of C-reactive protein and an increase in the ESR upon withdrawal of treatment indicate continued rheumatic activity unless other causes of inflammation are present.

REHABILITATION

Course and prognosis of acute rheumatic carditis

Proper rehabilitation of patients recovering from rheumatic fever and rheumatic carditis requires intimate knowledge of the "natural history" of the disease. The best available information of the evolution of rheumatic heart disease has been obtained from recent long-term follow-up studies of patients having antistreptococcal prophylaxis in whom the features of the acute rheumatic attack were carefully documented and analyzed by standardized criteria (4, 15).

These studies demonstrate that patients who have rheumatic fever without evidence of carditis (at least 50 percent in most series) rarely have rheumatic heart disease when examined five years later. Obviously, therefore, patients without significant cardiac murmurs require no intensive effort to prevent cardiac sequelae by prolonged bedrest or prolonged restriction of physical activity.

In addition, these studies show that certain manifestations which have been considered by some to be indicative of "carditis" (such as prolongation of the P-R interval and T wave changes in the electrocardiogram; arrhythmiasis; and slight or equivocal evidence of "cardiac enlargement") may have a benign prognosis. Unless these manifestations are associated with significant murmurs they cause little harm. Moreover, the prognosis differs markedly with the degree of cardiac involvement, as reflected by the intensity and the kind of heart murmurs and by the presence of congestive heart failure. Thus, in one study (4) of patients having "probable valvulitis" (a diagnosis based upon the presence of a loud, apical systolic blowing murmur radiating to the axilla) approximately 25 percent had rheumatic heart diseases five years later. Of those who had "unmistakable valvulitis" (manifested by a diastolic murmur, either mitral or aortic), 67 percent had rheumatic heart disease five years later. Similarly, in the "cooperative study" (6) the incidence of rheumatic heart disease five years after the acute attack was directly related to the severity of acute rheumatic carditis, as follows: 4 percent in patients with no carditis

during the acute attacks; 18 percent in those with soft organic apical systolic murmurs only; 32 percent in those with louder organic apical systolic murmurs; 52 percent in those with diastolic murmurs; and 70 percent in those with congestive heart failure of pericarditis.

Regulation of physical activity

Knowledge of the features of acute rheumatic fever which influence the prognosis for the development of cardiac stigmata is the most useful guide to the amount of physical activity which may be permitted the patient during the attack and during convalescence. In the absence of carditis, strict bedrest is unnecessary after the first few weeks of the disease if the acute manifestations (polyarthritis, fever, chorea) are suppressed or have abated. Such patients may be permitted sedentary activities until suppressive anti-rheumatic therapy is terminated. Relapses, if any, usually occur within two weeks of discontinuing the treatment or occasionally as late as four weeks afterward. Sydenham's chorea may appear still later. In general, if no relapse is evident one month after discontinuing therapy, or two months at the very most, the attack may be considered to have ended. We have never observed spontaneous reactivation of acute rheumatic fever after this period of time unless new streptococcal infection has intervened (15).

Therefore, the patient without carditis may resume full activity two months after the attack has ended. If carditis was a feature of the attack, but murmurs have disappeared, full activity may be resumed after six months of observation have confirmed the continued absence of heart disease. In patients with residual cardiac murmurs, the dynamics of the lesion and size of the heart usually determine future restrictions of activity.

CONCLUSIONS

Rheumatic fever is a complication of streptococcal pharyngitis which can occur in all races and ethnic groups throughout the world. Although the pathogenesis is still unproved, there is a strong correlation between acute rheumatic fever and the severity of streptococcal pharyngitis, clinically, epidemiologically, and immunologically. The ubiquity of streptococcal strains, their variation in virulence, and their qualitative differences, particularly between "skin" and "throat" strains, have made the study of streptococcal epidemiology complex. It is now apparent, however, that pyoderma-producing streptococci of nephritogenic potential do not cause rheumatic fever.

TABLE I

SUMMARY OF ASO TITERS IN FILIPINOS[1]

| | Mean Titer u/ml | % >200u | Ave.Rise u/ml | % Pts. with rise of >200u |
|---|---|---|---|---|
| Acute rheumatic fever | 419 | 72 | 303 | 65 |
| Convalescent strep throat | 229 | 40 | 167 | 32 |
| Controls | 110 | 24 | - | - |

[1] Data extracted from report of Limson, et al (8).

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