The Hallmarks of Rheumatic Fever in Developing Countries (Pakistan and Afghanistan)

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Abstract

Rheumatic fever (RF) is a multisystem disorder resulting from post streptococcal infection. It reflects a generalized vasculitic process with the following features: (1) rheumatic arthritis (significantly affecting the large joints), (2) carditis, (3) rheumatic chorea, (4) erythema marginatum, and (5) subcutaneous nodules. In this study, we observed these features singly or in variable combinations. Initially, acute rheumatic fever with carditis, in some untreated cases, progressed to chronic rheumatic heart disease, with devastating outcome.

Key words: Rheumatic fever, Pakistan, Afghanistan, developing countries, carditis, rheumatic heart disease, rheumatic arthritics

Introduction

We undertook a comparative study among the indigenous population of the North West Frontier region of Pakistan (NWFP) and the immigrant population in the border region of Pakistan near Afghanistan. These regions are associated with sharp seasonal outbursts of cold climatic conditions. Table 1 presents a comparison of the incidences of acute rheumatic fever between these two populations.

In a study from New Zealand, annual incidence of rheumatic fever (RF) in one section was 3.1 per 100,000 (0.031/1,000) population, whereas in the underprivileged regions incidence rates were nearly 46.1 per 100,000 population (0.46/1,000) [1].

The high rates of RF in the study area may be due to the failure of the medical care delivery system to provide secondary prophylaxis for this health lingering problem, thereby resulting in untreated patients developing severe carditis and chronic valvular heart disease.

This paper describes the epidemiology, clinical features, diagnosis, and treatment of RF, with particular emphasis on treatment in developing countries.
nations and areas where ready access to medical care may be lacking. In developed countries RF has declined in incidence over the past 4 to 6 decades, in underdeveloped countries it is still one of the most important cause of cardiovascular morbidity and mortality [2]. We also present primary and secondary prophylaxis options available in the absence of medical facilities or for patients with low socioeconomic status.

**Epidemiology of Rheumatic Fever**

Group A beta hemolytic streptococcal infection is the most common bacterial cause of tonsillopharyngitis. Those harboring Group B infection are more likely to have enlarged tonsils and tender enlarged anterior cervical lymph nodes. See Figure 1.

Most patients with rheumatic fever are aged 5-16 years, but, in sporadic cases, the disease has been observed even in the elderly [3]. Unhygienic living and low socioeconomic status have been identified as the most important triggering factors [4].

**Pathogenesis**

Streptococcal infection of the pharynx is the prerequisite for rheumatic fever; there is a latent period of two to six weeks between infection and development of disease [5]. Figure 2 shows the structure of group A beta hemolytic streptococcus (GABHS).

The outer coat of the streptococcus consists of several proteins. Protein M is the most important with regard to the virulence of the pathogen. It is presumed that antigenic similarity exists between human and bacterial antigens, namely, the group-specific carbohydrate of group A streptococcus with glycoprotein of the heart valves and the streptococcal M protein, sarcolemal protein, or other component of myocardial cell. Various ethnic groups react to streptococcal antigens differently depending upon the location of protein marker on the surface of human leucocyte antigen (HLA) [6].

In normal subjects with uncomplicated infection, the body response is different from the hyperresponsiveness as observed in rheumatic fever. Black patients with rheumatic fever have higher frequencies of HLA expression denoted as HLA-DR2, whereas the leucocyte marker found in patients of European origin with rheumatic fever is expressed as HLA-D4 [7].

**Pathology**

As a generalized vasculitic process, rheumatic fever involves edema of the ground substance, with fibrinoid deposition aggregates of lymphocytes, plasma cells, and a few neutrophils around the fibrinoid deposition, followed by a breakdown of collagen fibers. On advancement, the fibrinoid complex results in the development of a pathognomonic avascular lesion characteristic of the rheumatic fever, known as Aschoff’s body, with perivascular distribution [8]. In the heart, the brunt of the lesion is on the left side; often, endocardium is involved, and sometimes all the three layers may be affected. In the acute stage, edema and cellular infiltration of the valve leaflets/chordae tendineae have been observed, resulting in incomplete closure of the valves. Later, chronic inflammatory changes result in fibrosis, thickening, deformities of the leaf-
lets, and shortening of the chordae tendineae, terminating in valve stenosis and incompetence.

**Clinical Features**

Arthritis, as a major manifestation of rheumatic fever, is found in almost 80% patients. It affects large joints in an asymmetrical fashion with migratory pain, swelling (see Figures 3 and 4), and limitation of movement, sometimes awakening the patient during sleep. The pain is usually out of proportion to swelling. Joint involvements, in order of frequency, include shoulder, elbow, wrist, knee, ankle, and hip. Pain lasts for one to five weeks without any residual deformity. A dramatic response to therapeutic dose of salicylates is characteristic [9].

Carditis is another clinical feature of rheumatic fever. The incidence is 40%-50%, and the condition is often asymptomatic, detected when patient is seeking medical help for arthritis. The rheumatic process usually remains active in carditis for three to six months, with development of endocarditis, affecting the mitral valve in 70%-80% of cases (detected by the Carey Coombs short mid diastolic murmur in the mitral area), aortic valves in 25%-30% of cases, and tricuspid/pulmonary valves in < 5% of cases [10]. In rheumatic fever with heart involvement, myocarditis is associated with endocarditis detected by radiological evidence of cardiomegaly, congestive heart failure manifested by dyspnea, with tachypnea, and with pulmonary edema. In still others, carditis manifests as pericarditis diagnosed by pericardial rub or by fluid in the pericardium on echocardiography. In some cases, less specific signs may serve

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*Figure 3.* Joint swelling characteristic of rheumatic arthritis. Inflammation of synovial membranes and narrowing of the joint spaces are also observed.

*Figure 4.* Joint swelling distinguishing feature of rheumatic arthritis.

*Figure 5.* Frontal radiograph of the chest shows a convexity in the region of the left atrium indicating left atrial enlargement from mitral stenosis. The patient was swallowing barium at the time of the exposure.
as evidence of carditis, such as prolongation of the P-R interval to greater than 0.04 sec (Figure 6), changing quality of heart sounds, sinus tachycardia present even during sleep, and arrhythmia. Echocardiographic studies have revealed minute abnormalities of the mitral valve present in almost 20%-25% of patients having no audible heart murmur [11].

Chorea is found in almost 10% of patients with rheumatic fever, is more common in girls than in boys, and has been observed both alone and, in some cases, with carditis [12]. A long incubation period (two to six months) accounts for diagnostic difficulties resulting from normal serum antistreptolysin O titer (ASO) and Erythrocyte Sedimentation Rate (ESR) results. In addition to displaying choreiform movements, patients may also be depressed, apathetic, or easily provoked. The principal features in Sydenham’s chorea are generalized and/or unilateral involuntary movements [13]. Such movements occur at rest, may start suddenly or gradually, and are exacerbated by stress. However, these disappear during sleep. Generally, the patient has hypotonia, coordination problems, gait disturbances, and speech impairment, resulting in severe disruption of daily activities.

Erythema marginatum is a fourth feature of rheumatic fever. It occurs in 4%-5% patients, alone or with carditis, and lasts for several weeks [14]. It manifests as pink macules which, on spreading, take on a geographical appearance with serpiginous margins and a fading center (Figure 7). These have been observed on all parts of the body except the face and may last from a week to several months.

Rheumatic nodules (Aschoff’s body), in common research experience, have been seen in 1 of every 200 patients with rheumatic fever. They appear in groups over bony prominences and in association with severe carditis [15].

Aschoff’s body derives from the larger lymphatic vessels, and the central core is composed of precipitated lymph and necrotic protoplasm.

**Diagnosis**

Since there is no specific diagnostic test for rheumatic fever, diagnosis is mainly based on clinical grounds [16-18]. The Jones Criteria of 1944, employed as guiding principles for the diagnosis of acute rheumatic fever, were modified by American Heart Association in 1992 and reconfirmed in 2000. Nevertheless, over the past several years, progress in numerous areas has prompted a re-examination of the conventional Jones criteria. The primary focus is now on the diagnostic role of using echocardiography with Doppler (ED), a technique introduced in the revision of Jones criteria of 1992. Numerous studies from a broad range of clinical circumstances have suggested that, in the absence of overt carditis, ED has become the definitive diagnosis tool for carditis in RF, even in the ab-
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Figure 9. Mitral stenosis: There is progressive thickening, scarring of mitral leaflets and chordae, with some degree of left ventricle enlargement.

Figure 10. Mitral regurgitation: Structural changes of mitral valve, thickening of valve leaflet with a restricted leaflet tip characteristic of mitral valve regurgitation.

Figure 11. Aortic stenosis: Thickening of the valve leaflets causing variable degree of stenosis of valve orifice.

Figure 12. Aortic regurgitation: with evidence of incompetent valves.

Furthermore, ED has become a cornerstone in the worldwide screening program to evaluate the prevalence of rheumatic heart diseases. Carditis is considered the major clinical manifestation of RF based on the auscultatory findings of murmurs, either of mitral or aortic regurgitation, or both. In reality, carditis is pancarditis and involves all layers of the heart, including the endocarditis, myocarditis, and pericardium. In Gewitz et al.’s [19] Revised Jones Criteria for acute RF under the current circumstances, ED results are considered as part of the diagnostic criteria for confirmation of carditis in patients suspected of RF; this method conclusively supported diagnosis of carditis. Therefore, ED should be performed in all cases of confirmed and suspected RF among patients from moderate- to high-risk populations with RF and heat murmurs, or with heart murmurs only [20]. ED is also recommended for patients with RF but with no evidence of carditis.

In addition to the concern with the appropriate role of ED in RF, the Revised Jones Criteria of 1992 raised questions about treating monoarticular arthritis of RF with non-steroidal anti-inflammatory drugs before diagnosis; this has been considered in major manifestations of arthritis in selective high-risk populations [21]. At the present time, suspicion that monoarthritis may be part of the RF spectrum is likely to be reserved for patients in moderate- to high-risk populations. The addition of polyarthralgia as a major manifestation of auscultatory findings.

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is applicable only for moderate- or high-incidence populations after careful consideration and exclusion of other causes of arthralgia, such as autoimmune, viral, or reactive arthropathies [19,20].

Further, the following guidelines may be considered in diagnosing rheumatic fever:

- Major criteria: arthritis, carditis, chorea, erythema marginatum, and rheumatic nodules
- Minor criteria: Polyarthralgia; fever; previous history of rheumatic fever/heart disease; raised level of ESR, leucocyte count or C-reactive protein; prolonged P-R interval; and evidence of preceding streptococcal infection (increased antistreptolysin O, positive throat culture for group A streptococcus, anti-DNAase)

When rheumatic fever cannot be diagnosed with two major or one major and two minor criteria, the following guidelines are used for diagnosis:

a. Evidence of preceding streptococcal infection is not required when
   1. chorea is present and all other causes of chorea have been excluded and
   2. the patient has carditis from insidious or late onset and no other cause has been found.
   b. Otherwise, evidence of preceding streptococcal infection is required.

**Rheumatic Recurrence**

In a stable patient with rheumatic heart disease, the presence of one criterion or of fever, arthralgia, and raised ESR and leucocyte count strongly suggest presumptive diagnosis of recurrence [22,23].

**Differential Diagnosis**

The following are to be excluded before a diagnosis of rheumatic fever can be made: rheumatoid arthritis, osteomyelitis, Brucella arthritis, hereditary recurrent polyserositis, and sickle cell polyarthropathy.

**Complications**

Potential complications include arrhythmia, pericarditis with effusion, rheumatic pneumonitis, and congestive heart failure.

**Treatment**

Bed rest is indicated until the basic parameters (temperature, resting pulse rate, ESR, and ECG) have returned to a normal level. Aspirin has been advised at a dose of 80-100 mg/kg/day in four divided doses to achieve serum level of 20-30 mg/dl total for a duration of four to six weeks [24,25]. Then the dose is tapered as determined by the fall of ESR level to avoid rebounds. The corticosteroid prednisolone can be used at 2 mg/kg/day in four divided doses for two weeks, and then tapered over six to eight weeks for a total of 16 weeks. In rheumatic heart disease with heart failure, prednisolone must be started earlier and supplemented with frusemide. For treatment of choreiform movements, anxiolytics are used. Haloperidol at 0.05 mg/kg/day or diazepam at 15-20 mg in four divided doses can be prescribed, slowly reducing the dose once choreiform moments are controlled [26,27].

**Prophylactic Treatment**

**Primary Prophylaxis**

In the event that pharyngitis throat culture excludes antecedent group A streptococcal infection and treatment of the positive case is required, primary prophylaxis will avoid unnecessary aggressive antibiotics in the negative cases. In remote regions with high incidence of pharyngitis/rheumatic fever, there may be no facility for culture test and/or the cost of test may not be affordable or the patient may be unwilling to test. The strategy of treating all such pharyngitis patients is by one injection of benzathine penicillin (1.2 million units for all those above 30 kg body weight and 0.6 million units for all under 30 kg body weight); this is the best and most practical strategy (Refshauge & Kalisch, 2012). Additionally, an oral form of medication, namely phenoxymethypenicillin, may be used for 10 days at a dose of 250 mg four times daily for patients with body weight ≥ 20 kg and 125 mg four times daily for those under 20 kg body weight [29]. For patients allergic to penicillin, erythromycin is useful; for adults, 250 mg four times daily, or 20-40 mg/kg for children < 25 kg body weight is indicated [30,31].

**Secondary Prophylaxis**

In patients who have previously had rheumatic fever, subsequent streptococcal infection may precipitate recurrence of the fever. This may precipitate cardiac damage, even if damage was escaped previously, or further cardiac damage on a heart already affected. Secondary prophylaxis consists of one intra-
muscular injection of benzathine penicillin (BPG) monthly or, for patients who escaped carditis previously, one BPG at three to four weekly interval in higher endemic regions. Prophylaxis is typically continued for five years, but patients with carditis in the initial episode of rheumatic fever must continue monthly BPG for 25 years [32]. Additionally, for patients with rheumatic carditis, presurgical intervention must be advised with a short course of additional broad-spectrum antibiotic to avoid the chances of bacterial endocardritis.

In a 15-year follow-up study, patients given regular BPG prophylaxis at four weekly interval with dosage determined by the patient’s weight had a 60% lower rate of recurrence than nontreated patients [33,34]. More frequent (twice-weekly) BPG injections yielded nearly 52% additional reduction in the risk of recurrence of rheumatic fever and a 43% reduction in streptococcal throat infections. This might explain the shorter serum lifespan of BGP. The irregular schedule of prophylactic treatment found in more than half of the study population was found to result in 60% higher incidence of rheumatic fever compared with the rest of population [35]. Survey results indicated that the primary causes of irregular secondary prophylaxis were fear of painful injection, insufficient socioeconomic status to afford the long-term purchase of BPG, lack of self-reliance in treatment, insufficient counseling, and inability to travel to primary care facilities located at long distances. Moreover, in some cases, the false impression of relief from rheumatic fever symptoms may lead patients to prematurely abandon continuation of secondary prophylaxis. Failure to set the duration of treatment is therefore an important factor responsible for irregular secondary prophylaxis or discontinuation of secondary prophylaxis. On follow up, morbidity/mortality rates were significantly lower in patients following regular secondary chemoprophylaxis, particularly the shorter BPG protocol [36].

Conclusion

For the treatment and follow up of rheumatic fever, implementation of a registry is warranted. During the follow up treatment, patients should be asked to report any change of address and/or any adverse reaction noticed during the course of treatment. Patients and their relatives should be strongly instructed to adhere to treatment protocols, because non-adherence is the main cause of treatment failure/recurrence. The main concern in the use of secondary chemoprophylaxis is lack of education on the part of the patients, which could prevent adherence to treatment protocols. Close monitoring of patients under treatment is key for successful treatment.

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