Rheumatic Fever Management and Prevention in Pediatrics Still a Challenge

Nadia M. Fida, MD

Department of Pediatrics, Faculty of Medicine
King Abdulaziz University, Jeddah, Saudi Arabia
nadiafida@hotmail.com

Abstract. Rheumatic fever resulting from group A β-hemolytic Streptococcus infection continues to be a serious cause of morbidity and mortality in developing countries. Guidelines for diagnosis and prevention of rheumatic fever are reviewed. A systemic review of literature was performed. Arthritis followed by carditis and chorea, are the main manifestations of disease. Evidence of asymptomatic carditis has been increasing; however, abnormality identified by echo-doppler evaluation is not considered as criterion for diagnosis of rheumatic fever. No single laboratory test can confirm diagnosis; however, some tests help to characterize inflammatory process and provide evidence of streptococcal infection. There are a lot of gray cases. Diagnosis is difficult even with Jones Criteria. Carditis and arthritis are signs of other systemic illness, although the history is different. In the acute stage, if no thorough history has been taken, signs of carditis and arthritis are minimal and will mislead patient to seek late medical advice. Therefore follow-up is needed as patients are seen in the general clinic. They should receive an early referral to a pediatrician with a multidisciplinary approach wherein a cardiologist could help to identify any problem. Benzathine penicillin continues to be the best therapeutic option for treatment and secondary prophylaxis, due to its efficiency and low cost.

Keywords: Rheumatic fever, Streptococcus, Echocardiography, Prevention, and Diagnosis.

Correspondence & reprint request to: Dr. Nadia M. Fida,
P.O. Box 80215
Jeddah 21589, Saudi Arabia

Introduction

Acute rheumatic fever (ARF) was described 100 years ago by Walter Butler Cheadle, who offered a full description of the disease as we know it today: carditis, polyarthritis and chorea, as well as subcutaneous nodules and erythema marginatum[1]. It is an important worldwide health problem that causes structural and functional alterations of the heart. The treatment cost is very high due to repeated hospitalizations. In addition, the suffering caused to patients and relatives emphasizes negativity of the disease[2].

The disease continues to be a major cardiovascular health problem in areas of the developing world with limited resources and in communities with minority indigenous populations[3,4]. As many as 25-45% of cases worldwide appear in those nations. Certain climate features, such as cold temperature and humidity, favor streptococcal infections and, therefore, increasing frequency of RF. In addition, low socioeconomic status, unfavorable environmental conditions, malnutrition, poor hygiene, promiscuity and difficulty in accessing medical care have been associated with increasing incidence and prevalence of RF[5]. Although individuals of any age group may be affected, most cases are reported in persons aged 5-15 years. No sex predilection exists[6]. Even a conservative estimate of the incidence of RF suggests that at least 50,000 new episodes occur every year[7]. Turkey is one of the countries where the incidence of ARF and consequently the prevalence of rheumatic heart diseases [RHD] are still high (2–10/1000)[6]. In the past 50 years, ARF has emerged as a major contributor to cardiovascular morbidity in India[7]. Despite the paucity of information regarding secular trends, the few available community surveys indicate that there are at present more than 1 million patients with RHD. The prevalence of RHD in Saudi Arabia as reported by al-Sekait MA and his colleagues was 24 per 10,000 schoolchildren (6-15 years). The prevalence was higher in rural areas and in females[8]. The prevalence of rheumatic carditis worldwide varies from 0.55 to 11 per 1000[9].

Aim. This review of literature considers the factors that bear most importantly on the pathogenesis of acute rheumatic fever and on the strategies for its diagnosis, prevention and management.

Etiology and Pathogenesis

Although, RF has been known for many years to be consequent to streptococcal infection of the oropharynx, its pathogenesis is not completely understood. Genetic and epidemiological evidence suggests that there is a risk to the population. The nature of streptococcal antigens plays an important role in determining the history of the disease[5].

The finding that family members of RF patients have a higher probability of developing the disease, independent of environmental factors, has led to the hypothesis of a genetic predisposition[10]. However, the mode of inheritance is not yet known. During the 1980s and early 1990s the presence of alloantigens (not associated with the HLA system) had been described on the surface of B-cells. These antigens designated 883 and D8/17 could be detected in 72% and 100% of RF patients, respectively, and in 15% of normal individuals[11]. The D8/17 marker was also present in higher frequency in individuals with obsessive-compulsive disorders and Sydenham's chorea, than in controls groups[12].

The most important antigenic structures of the Streptococcus is proteins M, R and T located in the external layer of the bacterial cell wall. The difference in protein M determines the different serotypes of group A *B-hemolytic streptococci*. In addition, protein M has potent antiphagocytic activity resulting from immunoglobulin binding through non-immune mechanism. Serotypes association with RF include M1, M3, M5, M6, M14, M18, M19 and M24[5].

Patients with ARF have high levels of antibodies to M protein, and this may act as like a superantigen, including an exaggerated immune response and autoimmunity[13]. It is thought that following apparent convalescence of non-treated streptococcal pharyngitis, breakdown products of the Streptococcus with molecular similarity to human tissues are recognized by the immune system, initiating an autoimmune response. This is the basis of the theory of cross- reactivity of molecular mimicry by which the host would promote self-injury due to the presence of common antigenic sequences in their tissues and those of Streptococcus[14]. According to this theory, common epitopes alter the immune system's ability to distinguish self from non-self. More recently, it has been shown that streptococcus shares antigenic similarity with circulating lymphocytes and certain HLA molecules[15]. A study carried

out in Brazil revealed the presence of antibodies to ribosomal protein of the central nervous system in patients with Sydenham's chorea which was associated with activity[16].

The presence of high levels of immune complexes has been observed in the sera and joints of patients with active RF[17]. CD4^{+}T lymphocytes are increased in ARF in association with decreased CD8^{+}T lymphocytes and increased levels of interleukins (Ils)[18]. The presence of CD4^{+} and CD8^{+} lymphocytes within the whole thickness of the valvular wall, as well as the expression of vascular cell adhesion molecule (VCAM-1) on valvular endothelial wall, may indicate an important role for these elements in the pathogenesis of rheumatic carditis[19]. Badr-Eldin, hypothesized that the primary factor in the pathogenesis of RF was alteration in the function of mononuclear phagocytes. According to this hypothesis, phagocytic abnormalities permit persistence of circulating immune complexes[20].

The presence of decreased CD8^{+}T and increased CD4^{+}T cells in addition to increased antibody production and immune complex formation, would create a vicious cycle[5].

Problematic Isolated Major Manifestations

Carditis

It is characterized by inflammation of the pericardium, myocardium and endocardium. It is the most severe clinical manifestation of RF and can lead to valvular heart disease, cardiac failure or even death. Carditis occurs in approximately 40-50% of patients at the first attack[9]. Pericarditis occurs in 5-10% of patients. Abnormalities on electrocardiogram (ECG) and chest radiography can be observed; however, the best way to make the diagnosis is the echocardiography. Myocarditis occurs in 10% of patients. It may present with signs and symptoms of cardiac failure. Isolated myocarditis is also rare[21]. Endocarditis, the most frequent form of cardiac involvement, can be asymptomatic or present with a cardiac murmur[22]. Murmurs present during the acute phase do not indicate a permanent valvular defect, and in the majority of cases, they are transient. The most frequently affected valves are in the following: mitral, aortic, tricuspid and pulmonary[5].

Isolated Polyarthritis

Where ARF is uncommon, the diagnosis of isolated polyarthritis is problematic because of the large differential diagnosis[21]. Arthritis is observed in 60-80% of patients[23]. Arthritis, frequently migrating, transient and self-limiting, usually involves large joints. It typically lasts 2-3 days in each joint, and 2-3 weeks in total, disappearing without Squelea[5]. Polyarthritis is, however, recognizable early on in the a rheumatic attack when streptococcal antibodies are at peak elevation. Therefore, the absence of a significant increase in Group A streptococcal (GAS) antibodies at the onset of polyarthritis is a useful negative predictor of the diagnosis of ARF, and it suggests reactive arthritis due to another infection, such as rubella, Lyme disease, the enteric organisms causing Reiter's disease, ankylosing spondylitis, and so forth. When GAS antibodies are increased, however, the diagnosis of ARF remains presumptive, requiring months of close observation, because such elevations may have been only coincidental GAS infections that were not causally related[21].

Post Streptococcal Reactive Arthritis (PSRA)

What is at issue is whether to recognize PSRA as a separate disease from the polyarthritis clearly associated with RF[24]. The characteristics of PSRA that are not typical of ARF are persistence of arthritis for several months, non-migratory polyarthritis, and poor response to non-steroidal anti-inflammatory drugs (NSAIDs), and in adults, an apparent predilection for female patients. Thus, some authors claim that PSRA does not meet published Jones Criteria and should therefore be excluded[25]. Brief textbook descriptions of the typical polyarthritis of ARF, however, such as those described in the Jones guidelines as "almost always migratory" and "lasting 4 weeks" are helpful guidelines, but they are not necessarily a mandatory requirement for the diagnosis of ARF. Indeed, Jones Criteria have been "required" only in rigorous clinical trials to assure homogeneity of patient cohorts. Some patients with PSRA developed rheumatic valvular disease after several years of follow up— indeed, in some reports, the rates were as high as 7% in children with PSRA[25]. Although the numbers of the reported cases of so-called PSRA are still rather few and not always similarly defined, they warrant further study.

Sydenham's Chorea

It may occur as an isolated manifestation, and frequently recurs following new streptococcal pharyngitis. After puberty, it is almost entirely limited to women. Like polyarthritis, it is most often evanescent—over in a few weeks—but occasionally, it may be stubborn and persist for many months. The pathogenesis of chorea, which is similar to the synovitis of polyarthritis, seems to be associated with immune complex disease produced by non-destructive auto-antibodies localized to the basal ganglia and striatal system of the brain[26].

Laboratory Investigations

Many of the patients diagnosed as having ARF during these epidemics had no recognizable prodrome that would have brought them to medical attention. A history of symptomatic pharyngitis was often absent. It is important to remember that the throat culture is frequently negative by the time rheumatic fever develops. These facts emphasize the need to consider ARF in the appropriate clinical setting and use the streptococcal enzyme tests to establish a diagnosis. Chronic rheumatic heart disease was common in young children who presented with carditis[27].

Documentation of Inflammation

Leukocytosis with neutrophilia and mild to moderate anemia are found. Hemologlobin levels below 90g/L are usually associated with severe carditis. Lymhocytosis and severe anemia suggest a differential diagnosis that includes leukemia and sickle cell anemia[27]. Acute phase reactants are always elevated at the onset of acute RF. The erythrocyte sedimentation rate (ESR) is elevated in the first weeks of the disease, and higher levels are found among patients with cardiac involvement. C-reactive protein (CRP) is elevated at the onset of the acute phase and tends to disappear at the end of the second or third week. Both ESR and CRP are affected by anti-inflammatory medications. Acid alpha-l-glycoprotein and alpha-2-globulin are elevated in the acute phase of the disease and remain elevated for a prolonged time. Their levels are not influenced by anti inflammatory medications and they have been used to monitor RF activity[27].

Detection of Streptococcal Infection

Group A *Streptococcus* is isolated by culture of throat swab in only 15-20% of patients. This may be due to both the latency period between infection and the onset of RF symptoms as well as the prior use of antibiotics. Non-invasive carriage of Group A *streptococcus* contributes to the low sensitivity of throat culture in diagnosing a preceding infection. Rapid antigen detection tests from throat swabs have the same limitations as cultures with specificity of 95% but lower sensitivity[28].

Elevated titers of anti-streptolysin O (ASO) confirm invasive streptococcal infection, but approximately 20% of patients with RF may not have this antibody. In these cases, determination of anti-hyaluronidase, anti-deaoxyribonuclease B (Anti-DNAse B) and/or anti-streptokinase antibodies may be essential for the diagnosis of recent infection. However, in most developing countries only the ASO test is available in public hospitals. Therefore, serial determinations of ASO at 15-day intervals are recommended. The Streptozyme test simultaneously detects several antibodies to the streptococcus; however, it has not been shown to have any advantage over the ASO titer[5].

Chest Radiograph and Electrocardiogram (ECG)

The chest radiograph and ECG may be abnormal in only 30% of patients with carditis. The chest radiograph usually shows cardiomegaly only in patients with myocarditis or moderate to severe pericardial effusion. On ECG, repolarization abnormalities characterized by prolonged PR and cardiac output (QT) intervals can be observed. These abnormalities are not unique to RF and could be present in Systemic Juvenile Idiopathic Arthritis or Systemic Lupus Erythematosus. A persisting, prolonged PR interval is usually a manifestation of cardiac fibrosis rather that an active process, whereas a persisting prolonged QT interval is a manifestation of severe disease and has a less favorable outcome. Low-voltage QRS complexes and abnormalities of the ST interval may be seen with pericarditis[5].

Echocardiography (EC) and Doppler Methods

Most cases of rheumatic carditis are not severe enough to be symptomatic, and the diagnosis of isolated carditis has previously

depended on auscultation alone[29]. Approximately 80% or more of the cases of mitral regurgitation detected by EC are also readily diagnosed by the auscultation of experienced clinicians. The remaining "subauscultatory" cases are those with the mildest degree of mitral or aortic regurgitation. The sensitivity of EC may detect degrees of valvular regurgitation within physiologic range; however, they are not functionally significant, especially in children and in very thin, active individuals with highly elastic valve leaflets and rings. Although EC, particularly accompanied by Doppler studies, offers greater sensitivity and specificity for the assessment of valvular regurgitation, it need not be considered essential for the diagnosis of RF by experienced primary care physicians, especially in settings where the disease is common and medical resources are limited[21,30]. Nonetheless, cardiologists proficient in echo-Doppler technology now use this method routinely to distinguish abnormal from physiologic valve leaks more sensitively and accurately than by auscultation alone. Whether the Jones Criteria should be modified to incorporate these techniques is being debated with differences of opinion tempered by considerations of availability and cost benefit of EC to developing countries, since outcomes of the treatment and management of such minimal valvular inflammation may not differ significantly, whether they are detected or not[30].

In his Harvey lecture at the end of the eighteenth century, William Cheadle proposed that each major manifestation of ARF represented part of a single larger syndrome[30]. In the 1960s, when antistreptolysin O and other GAS antibody titers generally became available to clinical laboratories, a committee of the American Heart Association (AHA) revised the Jones Criteria, suggesting that the criteria, particularly those for polyarthritis, could be strengthened by including evidence of antecedent GAS infection. Some limitations were emphasized — circumstances in which a diagnosis of ARF may be made without strict adherence to the Jones criteria, which are, after all, but general guidelines. By then, antibody titers may have decreased to normal levels and the minor manifestations of systemic inflammation (fever, erythrocyte sedimentation rate, C reactive protein, *etc*.) may have abated[29].

Most patients with recurrent RF fulfill the Jones criteria, but in some patients, the diagnosis of a recurrence is less obvious[21]. The Jones

Criteria, therefore, apply more readily to initial attacks, and more diagnostic latitude is sometimes needed to interpret recurrent carditis in patients with preexisting rheumatic heart disease. The steps in the evolution of the modification of the Jones criteria have been reviewed recently in detail[30].

How Can We Prevent Rheumatic Heart Disease?

As cited by the AHA the best defense against rheumatic heart disease is to prevent rheumatic fever from ever occurring. By treating strep throat with penicillin or other antibiotics, doctors can usually stop acute rheumatic fever from developing.

Secondary Prevention

For prevention of rheumatic recurrences, continuous antibiotic prophylaxis is now recommended by health authorities throughout the world[31]. Monthly injections of 1.2 million units of benzathine penicillin G are the most stringent regimen. In some populations with a high prevalence of RF; however, some observers have reported that the last week of the month is not completely covered by this regimen, and they choose to administer it every 3 weeks[32]. In a community in which RF has not appeared for many years, patients who have had polyarthritis alone and who reach adult life without rheumatic valvular disease are at lower risk. Penicillin prophylaxis has been safely suspended after several years of treatment when rheumatogenic streptococci have been shown to have disappeared from the community[33].

Treatment

Antibiotic therapy can be initiated before laboratory results are available. Treatment should be discontinued if test results are negative. The Infectious Diseases Society in America (IDSA) notes that rheumatic fever can be prevented even if treatment is postponed for up to nine days after symptom onset.

Because of proven safety and efficacy, narrow spectrum, and low cost, penicillin remains the treatment of choice for patients who are not allergic to the drug. Once-daily amoxicillin therapy could become an alternative regimen if the results of preliminary investigations confirm

efficacy. In young children, amoxicillin is often used in place of oral penicillin V. For recurrent acute pharyngitis, Benzathine penicillin G 1.2 million units intramuscularly remains the treatment of choice for prophylaxis and is administered every 3 or 4 weeks[34]. For patients who have carditis but no residual heart disease, prophylaxis is continued for 10 years or into adulthood (whichever is longer). Those patients who have residual heart disease from carditis are treated at least until age 40 or may receive lifelong prophylaxis.

Patients with severe carditis are often treated with corticosteroids, but studies of the effects of corticosteroids in the treatment of rheumatic carditis have shown conflicting results[27]. A 2003 meta-analysis from the Cochrane database concluded that there was no significant difference in outcome when corticosteroids and aspirin treatment were compared. This prophylactic regimen does not substitute for the standard bacterial endocarditis prophylaxis required for patients who have rheumatic heart disease.

Cost-Effect

In Tompkins' assumption, the cost of acute rheumatic fever and RHD per patient is estimated to be fourteen thousand six hundred seventy-four US dollars ($14,674.00)[35]. In 1993, North *et al.* obtained an intensvice analysis of the cost of acute RF and rheumatic heart disease in Auckland, New Zealand obtaining an average per patient cost in was nineteen thousand two hundred twenty-six NZ Dollars (NZ$19,226.00)[36]. If North's estimate is converted into USD and adjusted at 3.5% annual inflation rate, the cost per patient in 1997 is estimated to be eighteen thousand six hundred US dollars (US$18,600.00). In this analysis, the cost of ARF and RHD is estimated at twenty thousand US dollars (US$20,000.00).

Kenneth H. Webb, recommended a high-sensitivity antigen test strategy than the treat-all strategy[37]. Use of the high-sensitivity antigen test was the least expensive of the strategies using a diagnostic test, in terms of total (encounter plus complication) costs. In terms of cost per streptococcal complications prevented, the high-sensitivity antigen test strategy was also the most cost-effective under most circumstances currently seen in the United States.

Summary and Conclusion

In the near future the burden that heart failure will impose on the emerging economies is likely to increase dramatically. There is an urgent need for properly conducted population-based studies in Saudi Arabia to establish the true size of the problem and the relative importance of the different etiologies'. This will help to inform appropriate health policy within these countries. Preventive and public health strategies will need to be specific to the local epidemiological characteristics. As countries go through epidemiological transition and undergo socio-economic development, the epidemiology is likely to become increasingly similar to that of Western Europe and North America.

Finally, what can we look forward to in the future? There are some obvious limitations in our ability to completely eradicate rheumatic fever with antibiotics. There has been progress in purifying and characterizing streptococcal M protein, the antigen that elicits antibodies that confer immunity to the streptococcus. However, the availability of a vaccine is not imminent.

Progress has also been made in identifying a genetic marker for rheumatic fever susceptibility. The genetic marker could be useful to identify susceptible individuals in families with a history of rheumatic fever.

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الحمى الروماتيزمية عند الأطفال .. الوقاية والعلاج تبقى من التحديات !

نادية محمد فدا

قسم طب الأطفال، كلية الطب، جامعة الملك عبدالعزيز

جـــدة – المملكة العربية السعودية

المستخلص. السيرة المرضية: حمى الروماتزم الناتجة عن المجموعة [أ] المكورة العقدية المتعلقة بحل الدم-B العدوي تستمر لتصبح سببًا هامًا للمرض والوفيات في البلدان النامية. وتم استعراض القواعد الإرشادية للتشخيص والوقاية من الحمى. تم عمل مراجعة منهجية للمادة المطبوعة. الالتهاب المفصلي المصحوب بالتهاب القلب والكوريا/الزفن تعتبر المظاهره الرئيسية لهذا المرض. وهناك بينة لتزايد حالات التهاب القلب اللاّ أعراضي، لذلك فإن الحالات الشاذة التي تم تحديدها بواسطة تقييم إيكو دوبلر echodoppler لا تعتبر معيارًا لتشخيص حمى الروماتزم، لأنه لا يوجد هناك اختبار مخبري يمكن أن يثبت هذا التشخيص. لذلك فإن هناك بعض التجارب تساعد على تحديد خصائص العملية الالتهابية وتقديم بينة ودليل لعدوى المكورة العقدية. توجد هناك العديد من الحالات الغامضة التي يصعب معها التشخيص حتى مع معايير جونز. يعتبر التهاب القلب والالتهاب المفصلي إشارات وعلامات لمرض بدني كلي آخر علمًا بأن السيرة المرضية مختلفة. في المرحلة الحادة إذا لم يتم أخذ سيرة مرضية شاملة فإن علاقات التهاب القلب والالتهاب المفصلي تصبح أصغر ما يمكن ويتأخر المريض في أخذ المشورة الطبية. ولذلك فمتابعة

المرضى في العيادات العامة. وإحالتهم إلى طبيب الأطفال وتخصصات متعددة في وقت مبكر يساعد أخصائي القلب لتحديد المشكلة، علمًا بأن بنسلين بنزاثاين Benzathine لا يزال أفضل خيار علاجى للعلاج والوقاية الثانوية لفعاليته وانخفاض تكلفته.