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Acute Rheumatic Fever: A Public Health Concern in Resource-Poor Settings

Akut Romatizmal Ateş: Kaynakların Kısıtlı Olduğu Bölgelerde Bir Halk Sağlığı Sorunu

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ABSTRACT

Acute rheumatic fever remains a public health concern in developing countries as well as in poorer communities and among indigenous populations in some developed nations. It poses serious economic problem at individual, communal and national levels through direct and indirect health care costs. The objective of this article is to review acute rheumatic fever in the global context with some emphasis on the continuing burden of this disease in the developing settings. The review shows that acute rheumatic fever still occurs under conditions of impoverished overcrowding and poor sanitation and where access to healthcare services is limited. Since acute rheumatic fever is a preventable disease, improved housing and sanitation, access to effective healthcare services, early diagnosis, registration of cases and follow up remain the bedrock of the control of this disease

Key words: Acute rheumatic fever, rheumatic heart disease, developing countries.

ÖZET

Akut romatizmal ateş gelişmekte olan ülkelerde ve gelişmiş ülkelerinin bünyesindeki yoksul ve yerli topluluklarında önemli bir sağlık problemi olarak mevcudiyetini korumaktadır. Bu hastalık doğrudan ve dolaylı sağlık harcamalarına yol açmak suretiyle bireysel, topluluk ve millet bazında önemli ekonomik kayıplara neden olmaktadır. Bu çalışmanın amacı global düzeyde akut romatizmal ateş olgusunu, özellikle hastalığın topluma çıkardığı külfet eksenli olarak gözden geçirmektir. Bu çalışma; akut romatizmal ateşin yoksul, kalabalık, olumsuz sağlık koşullarına sahip ve sağlık hizmetlerine erişimin sınırlı olduğu topluluklarda varlığını sürdürdüğünü göstermektedir. Akut romatizmal ateş önlenebilir bir hastalık olmakla beraber bu hastalığın kontrolündeki temel öğeler; barınma

olanaklarının iyileştirilmesi, sağlıklı yaşam koşullarının oluşturulması, sağlık hizmetlerine erişimin kolaylaştırılması, erken tanı, olguların kayıt altına alınması ve takip edilmeleri gibi parametreleri içermektedir.
Anahtar kelimeler: Akut romatizmal ateş, romatizmal kalp hastalığı, gelişmekte olan ülkeler

Introduction

The introduction of antibiotics and improved sanitation have been associated with a rapid decline in the incidence of acute rheumatic fever (ARF) worldwide particularly in developed economies[1]. However, it remains a public health concern in sub-Saharan Africa, the Middle East, the Indian subcontinent and some parts of South America[2,3].

As many as 20 million new cases occur every year, most of them in the developing world[4,5]. The continuing high burden of ARF in Africa and Asia has been highlighted by an echocardiographic screening study which found that 2-3% of school-age children in Cambodia and Mozambique have rheumatic heart disease[6]. The economic effects of the morbidity and mortality caused by this disease are felt at individual, communal and at national levels through direct and indirect health care costs[7,8].

ARF has been known for many centuries. The first classic works on ARF were published by Bouillaud and Cheadle in 1836 and 1889 respectively. Much later in 1944, Jones formulated a set of clinical diagnostic criteria which was modified in 1992 and it is still in use today[9]. Although the term rheumatic tends to emphasize mainly the joints, it is the heart which bears the brunt: ARF licks the joints but bites the heart. In sub-Saharan Africa, although there have been sporadic studies on ARF and rheumatic heart disease (RHD), many countries do not have national registers for these diseases[7,10].

The objective of this article is to review ARF in the global context with some emphasis on the continuing burden of this disease in the developing settings.

Epidemiology

ARF occurs globally but disproportionately much more in the developing world. In the developed countries, it is more prevalent in poorer communities and among indigenous populations. It is common among American Samoans in Hawaii and in western Pennsylvania where 121 new cases were recorded between 1994 and 2003; in Aboriginal communities of

central and northern Australia and among the indigenous Maori and Pacific Island New Zealanders[11,14]. The annual incidence of ARF in developed countries is below 1.0 per 100,00015. In the developing world, incidence rate ranges from 1.0 per 100,000 school-aged children in Costa Rica, 72.2 per 100,000 in French Polynesia, 100 per 100,000 in Sudan, to 150 per 100,000 in China15,17. The mortality rate for RHD varies from 0.5 per 100,000 population in Denmark to 8.2 per 100,000 population in China, and the estimated annual deaths from RHD for year 2000 was 332,000 worldwide. An estimated 6.6 million disability-adjusted life years (DALY) are lost per year globally[15,18,19].

The first attack of ARF typically occurs between the ages of 5 and 15 years and rarely in persons younger than 3 years and older than 30 years[20]. There is no sex predilection for ARF. However, some of its clinical features may appear to be sex variable. For example, Sydenham chorea and mitral valve stenosis occur more often in females than in males[21].

Microbiology, Pathogenesis and Pathology

Although it has been established that ARF is a delayed autoimmune response to GABS pharyngitis, the precise mechanism has not been well defined[22]. There is considerable evidence that the severity of autoimmune response in an individual is determined by host genetic susceptibility, the virulence of the infecting strain and an appropriate environment[23]. Thus the pathogenesis of ARF is a complex interplay of host susceptibility, bacterial pathogenicity and environmental factors.

Host Susceptibility

There is strong evidence that ARF occurs in a susceptible host. Pedigree studies have suggested that the immune response to streptococcal antigens is genetically controlled with high responsiveness to the streptococcal antigens being expressed through a single recessive gene and low responsiveness through a single dominant gene[24]. The susceptibility gene may be present at, or close to, the HLA-DR locus in chromosome6. Ayoub et al[25] implicated HLA-DR2 and HLA-DR4 in blacks and caucasians respectively, other HLA alleles have also been reported to be associated with ARF[26,27]. HLA-DR7 has been the most frequently associated with ARF and RHD[28,31]. Although the exact mechanism by which certain genes can confer an increased susceptibility to ARF has not been clearly elucidated, there are theories about the roles they play. The HLA molecules support the molecular mimicry. Another protein that has been associated with ARF and RHD is the inflammatory cytokine, tumor necrotic factor-α

(TNF- α), which is also located on chromosome 6 near the HLA alleles. TNF-α may be up-regulated in patients with increased ARF susceptibility, leading to an increased inflammatory response and subsequent development of ARF[23]. The third factor, mannose-binding lectin (MBL), binds to various sugar molecules on the cell surface and helps to mark foreign cells for immune cells to eliminate[23].

Bacterial Virulence

M protein is the major determinant of streptococcal virulence. The ability of GABS to initiate disease is highly depends on M protein. It allows the organism to avoid infection by bacteriophage and ingestion by human leucocytes[32]. M protein has structural homology with cardiac tissues. It has been suggested that this homology is responsible for the pathological findings in acute rheumatic carditis. However, of the many M serotypes, only 3, 5, 18, 19 and 24 have been linked directly with ARF[33,34]. These serotypes are heavily encapsulated and have fimbriae coated with lipoteichoic acid that allows them to attach to the pharyngeal epithelial cells[32].

Host- Pathogen Interaction

Streptococcal infection occurs by the binding of the bacterial surface to specific receptors on the host cells. This is facilitated significantly by the streptococcal lipoteichoic acid and M protein[32]. The host response to streptococcal infection includes type-specific antibody production, opsonization and phagocytosis[5,32,34]. Kaplan et al demonstrated a cross-reactivity and molecular mimicry between human heart tissue and GABS and later anti-cardiac antibodies in patients with ARF[35,36]. The human heart tissue is the cardiac myosin and the component of GABS is the M protein. The cross reactivity induces T-cell mediated attack of the heart tissue and valves. Once the heart tissue is damaged and inflamed, the intracellular proteins are exposed to invading immune cells and lead to the development of more auto-antibodies directed at different components of valve tissues with further inflammation and scarring[23].

Environmental Factors

There is epidemiological association between ARF and environmental factors such as poor living conditions, overcrowding and lack of access to good health care services. There are also

seasonal variations in the incidence of ARF which closely mimic variations in streptococcal infections[37].

Pathology

ARF involves the heart, joints, central nervous system, skin, and subcutaneous tissues, together, in close succession or singly. It is characterized by an exudative and proliferative inflammatory lesion of the connective tissue, especially that of the heart, joints, blood vessels, and subcutaneous tissue[37]. The characteristic lesion of rheumatic carditis is the Aschoff nodules (AN) which are located perivascularly. The most characteristic component of AN is the Aschoff giant cells[32].

Clinical Features

ARF is a systemic disease and there may be a large variety of symptoms and signs. History of an antecedent sore throat 1-5 weeks prior to onset of ARF is present in about 70% of older children and young adults[9]. The diagnosis of ARF requires a high index of suspicion and is generally based on the revised Jones criteria. The Jones criteria for diagnosing ARF divide its clinical features into major and minor manifestations[9]. Because of concern that these criteria may not be sensitive enough in high-incidence populations, some authors have suggested that echocardiography should be performed in all patients with suspected ARF; that monoarthritis should be a major manifestation; that arthralgia be changed from a minor to a major criterion; and that the set point of fever of 38°C be lowered particularly in high incidence populations[5,36,39,40].

The Jones criteria were subsequently reviewed and modified by World Health Organization (WHO) in 2001 to provide additional guidelines on how it should be applied in primary and recurrent episodes[15]. In Australia, because the Jones and WHO criteria appear too restrictive for diagnosing ARF in indigenous populations, a new set of criteria have been determined for use in high- and low-risk populations[41].

Carditis

Carditis is the most serious and second most common feature of ARF which occurs in about 40-50%. The suspicion of a primary episode of rheumatic carditis is established by the presence of one or more of the following: sinus tachycardia that may be out of proportion with the fever; significant new or changing murmur of mitral and/ or aortic regurgitation; an S3 gallop; a

pericardial friction rub; and cardiomegaly42. Mitral valve is the most commonly involved and commoner in females while aortic disease is more in males43. Congestive heart failure (CHF) may develop secondary to severe valve insufficiency or myocarditis. Physical findings associated with heart failure include tachypnea, orthopnea, jugular venous distention, rales, hepatomegaly, a gallop rhythm, and peripheral swelling and edema.

Arthritis

Arthritis is the most common feature and is frequently the earliest manifestation of acute rheumatic fever. It occurs in about 70-75% of cases[38]. Typically, it is polyarticular and migratory affecting large joints such as knees, ankles, wrists and elbows. Characteristically, the arthritis begins in the large joints of the lower extremities (i.e., knees, ankles) and migrates to other large joints in the lower or upper extremities (i.e., elbows, wrists. The arthritis persists for 2-6 days (rarely more than 4 wk) at each site and is migratory not additive[38]. Rarely, monoarticular involvement can also occur, small joints may be principally affected or the arthritis may not be migratory[43,44]. The arthritis usually heals completely without joint deformity. However, deformity may occur as it is the case in Jaccoud's arthritis (JA), a very rare variant of ARF arthropathy common in young adults[45,46].

Sydenham's Chorea

It is a central nervous disorder which occurs in 5-10% of cases. Chorea is rapid purposeless movements of the face and upper extremities. It often manifests much later and very difficult to detect at the onset with a long latency period between GABS pharyngitis and chorea of 1-6 months. It is a diagnosis of exclusion and may be the only feature of the disease. Sydenham's chorea is more common in females and tends to be associated with emotional lability[47].

Erythema Marginatum

It occurs in about 5% of cases of ARF. It is a serpiginous looking macular rash with central pallor and rounded borders usually found over the trunk and extremities. The rash occurs early in the course of the disease and remains long past the resolution of other features[9].

Subcutaneous Nodules

Subcutaneous nodules are an infrequent feature of ARF. Before it used to occur in about 10% but has declined considerably in the past several years. They are pea-sized, firm, painless

nodules on the extensor surfaces of the joints such wrists, elbows, knees, ankles, knuckles, scalp, and spinous processes of the lumbar and thoracic vertebrae[9, 43].

Investigations

There is no single specific confirmatory laboratory investigation for ARF. However, some investigations are required to support clinical diagnosis and to monitor both the disease and the treatment[48].

Routine investigations such as complete blood counts (CBC) and erythrocyte sedimentation rate (ESR) are measures of inflammatory markers. Leucocytosis is common in ARF, and elevated ESR and serum C reactive protein support diagnosis[49]. Throat culture is the gold standard for confirmation of GABS pharyngitis but often fails to grow the organism by the time ARF develops[49]. Streptococcal serology tests do not have conclusive diagnostic significance and have varying sensitivity and specificity. Anti-streptolysin O is the most frequently tested. Others are anti-deoxyribonuclease B or anti-hyaluronidase antibodies. The rising titers are of more diagnostic significance than the absolute values[48,49.] Synovial fluid analysis is rarely done and not necessary for diagnosis[49].

Other investigations that are more related to detection of carditis are highlighted below:

Electrocardiography

It may reveal a prolonged P-R interval, sinus tachycardia or sinus bradycardia..Prolongation of P-R interval is present in about 25% of all cases and is neither specific for nor diagnostic of ARF[49].

Chest Radiography

This may show cardiomegaly and other features of congestive heart failure. Normal chest radiography does not exclude carditis[49].

Echocardiography

Doppler echocardiography (DE) is more sensitive than standard auscultation in detecting valvular regurgitation which is the hallmark for diagnosis of carditis[49-52]. However, there has been controversy over the use of Doppler echocardiography in the diagnosis of ARF[49,50]. Many argue that echocardiography can help to diagnosis subclinical RHD, especially among high-

risk populations[3,15,42,55]. However, since it is not known how much valvular regurgitation is "normal", there is concern for over diagnosis of carditis by relying on DE[53]. The current American Heart Association guidelines recommend the use of DE as a supplement to diagnosis, but evidence of valvular regurgitation should not be used as a major or minor criterion.

Endomyocardial Biopsy

The value of endomyocardial biopsy has been investigated for the diagnosis of rheumatic carditis since myocarditis is an obligatory component of cardiac involvement in ARF. However, this is an invasive procedure and it is not necessary for routine diagnosis[56].

Treatment

With very few exceptions, all patients with definite or possible ARF should be admitted to hospital. There are two major treatment goals: eradication of GABS with antibiotic therapy and treatment of clinical features of the disease[57,58].

Eradication of Group A Beta-haemolytic Streptococcal Infection

Antistreptococcal antibiotic treatment should be given to all patients with ARF regardless of organism detection[32]. Penicillin still remains the drug of choice in patients who are not at risk of allergic reaction. Erythromycin and first-generation cephalosporins are alternatives in those who are allergic to penicillin, but as many as 5% may also be allergic to cephalosporins. Fluoroquinolones, tetracyclines, and sulfonamides are not recommended to treat GABS pharyngitis[59, 60].

Treatment of Acute Rheumatic Fever

The arthritis of ARF responds very well to non-steroidal anti-inflammatory drugs (NSAIDS). In fact, it can be a useful diagnostic feature as arthritis which continues unabated for more than three days after starting NSAIDS is not likely to be due to ARF Therefore, salicylates or NSAIDS should be withheld until the diagnosis is confirmed. Salicylates are effective and have remained the mainstay of treatment. However, high doses are often required usually for 4-6 week, and other NSAIDS such as naproxen has been used in those who cannot tolerate salicylates[61-63]. Some authors recommend the use of corticosteroids in severe carditis with heart failure[15,41]. Conventional measures in heart failure are also required[64]. If the medical

treatment fails, cardiac surgery may be needed to replace or repair damaged valves [65]. This can be done even in acute heart failure. There is no conclusive evidence that NSAIDS, corticosteroids or immunoglobulins reduce the risk of heart valve lesions[66]. Bed rest is important, but complete bed rest may be inappropriate, except in cases of persistent active carditis or severe heart failure. Chorea disappears with sleep, and thus adequate sedation provides a lot of relieve. Mild chorea responds to benzodiazepines, particularly diazepam. However, haloperidol has been found to be useful in ARF with severe chorea[67].

Prophylaxis

ARF is a preventable disease. Apart from eradicating poverty and overcrowding and improving access to healthcare services among disadvantaged people in poor communities and developing countries, prevention of ARF is divided into primary and secondary prophylaxis[68,69].

Primary prophylaxis of rheumatic fever requires adequate treatment for GABS pharyngitis. In selecting a treatment regimen, certain factors should be considered: bacteriologic and clinical effectiveness of the drug, ease of adherence to the recommended regimen, cost, spectrum of activity of the selected drug, and potential adverse effects[69]. Intramuscular PGB, oral penicillin V potassium, and oral amoxicillin are the recommended antimicrobial agents for the treatment of GABS pharyngitis in persons without penicillin allergy. Individuals allergic to or intolerant of penicillin should use macrolides such as oral azithromycin, oral clarithromycin and narrow spectrum cephalosporins like cephalexin and cefadroxil[69].

Secondary prophylaxis is prevention of GABS pharyngitis in individuals with a previous attack of ARF. Recurrent ARF is associated with the development of RHD. Prevention of recurrent GABS pharyngitis is the most effective method of preventing severe RHD. This strategy has been proven in randomized controlled trials to prevent GABS pharyngitis and recurrent ARF and to reduce the severity of and mortality from RHD[41,70]. Therefore, prevention of recurrent ARF requires continuous antimicrobial prophylaxis rather than recognition and treatment of acute episodes of GABS pharyngitis. Continuous prophylaxis is recommended in patients with well-documented histories of ARF and in those with evidence of RHD.

Intramuscular BPG is superior to oral penicillin. There is a lot of debate on the 3- or 4-weekly delivery of BPG. Some studies have shown that the 3-weekly delivery of BPG appears to be more effective than 4-weekly delivery in some studies[71,74]. However the 4-weekly BPG remains the treatment of choice, except in patients with severe carditis or a history of valve surgery

who show good adherence to less frequent injections, and those who have confirmed breakthrough ARF despite full adherence to a 4-weekly BPG regimen, in whom 3-weekly administration is recommended[41].

Although the duration of secondary prophylaxis is controversial, the bottom line is that it must be individualized depending on factors such as presence of carditis and its severity, level of risk of having further GABS pharyngitis, age of the patient and potential harm from recurrent ARF[24, 68 70].

Infective Endocarditis

Infective endocarditis (IE) is a dangerous complication of RHD and a common adverse event after prosthetic valve replacement. AHA guidelines support the use of antibiotic prophylaxis in people with established RHD or prosthetic valves before undergoing procedures expected to produce bacteraemia[68]. However, it no longer recommends prophylaxis for IE in most patients with RHD. The exceptions are patients with prosthetic valves or valves repaired with prosthetic material, patients with previous endocarditis or specific forms of congenital heart disease, and cardiac transplant recipients who develop cardiac valvulopathy[68]. In these patients, an agent other than penicillin should be used to prevent IE, because alpha-hemolytic streptococci have likely developed resistance to penicillin[68].

Prognosis

Cardiac involvement is the major cause of long term morbidity. Caparetis et al (2005) pointed that 50-60% of all ARF cases develop into RHD. [33] Sydenham's chorea may continue in a relenting fashion for years. There is a need for long term follow up of the cardiac condition. The WHO Exper Consultation on Rheumatic Fever and Rheumatic Heart Disease states that in 2000, the global mortality was 5.5 per 100,000 population with the lowest of 1.8 per 100,000 population in the Americas and the highest of 7.6 per 100,000 population in South-East Asia[19,74,19].

Table 1: 2002-2003 WHO criteria for the diagnosis of rheumatic fever and rheumatic heart disease (based on the revised Jones criteria) [37]

Diagnostic categories	Criteria
Primary episode of RF[a]	Two major* or one major and two minor** criteria plus evidence of a preceding GABS infection***
Recurrent attack of RF in a patient without established RHD[b]	Two major or one major and two minors criteria plus evidence of a preceding GABS infection
Recurrent attack of RF in a patient with established RHD	Two minor criteria plus evidence of GABS infection[c]
Rheumatic chorea	Other major manifestations or evidence of GABS not required
Insidious onset rheumatic carditis[b]	Other major manifestations or evidence of GABS not required
Chronic valve lesion of RHD (patients presenting for the first time with pure mitral stenosis or mixed mitral valve disease and/or aortic valve disease)[d]	Do not require any other criteria to be diagnosed as having rheumatic heart disease
*Major criteria	• Carditis; • polyarthritis; • chorea; • erythema marginatum; • subcutaneous nodules
**Minor criteria	• clinical: fever, polyarthralgia • laboratory: elevated acute phase reactants (erythrocyte sedimentation rate or leucocyte count) • electrocardiogram: prolonged P-R interval • elevated or rising antistreptolysin-O or other streptococcal antibody, or other streptococcal antibody, or • a positive throat culture, or • rapid antigen test for group A streptococci, or • recent scarlet fever
***Supporting evidence of a preceding streptococcal infection within the last 45 days	

[a]Patients may present with polyarthritis (or with polyarthralgia or monoarthritis) and with several (3 or more) other minor criteria, together with evidence of recent group A streptococcal infection. Some of these cases may later turn out to be rheumatic fever. It is prudent to consider them as cases of ''probable rheumatic fever'' (once other diagnoses are excluded) and advise regular secondary prophylaxis. Such patients require close follow up and regular examination of the heart. This cautious approach is particularly suitable for patients in vulnerable age groups in high incidence settings.

[b]Infective endocarditis should be excluded

[c]Some patients with recurrent attacks may not fulfill these criteria

[d]Congenital heart disease should be excluded

Conclusion

The review shows that though the incidence of ARF has declined globally, it remains a public health concern in settings of impoverished overcrowding and poor sanitation and where access to healthcare services is limited. These settings are found in developing countries and in disadvantaged and marginalized communities in developed economies. ARF is a preventable disease. Most cases of ARF can be prevented with antibiotic treatment of GABS pharyngitis Improved housing and sanitation, access to effective healthcare services, early diagnosis, registration of cases and follow up remain the bedrock of the control of this disease. High index of suspicion of and capacity building for healthcare workers, and scale up of public education on infection control are other pivotal ways to combat this disease.

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