Acute Rheumatic Fever (ARF)

Background

Acute rheumatic fever (ARF) is a sequela of streptococcal infection—typically following two to three weeks after group A streptococcal pharyngitis—that occurs most commonly in children and has rheumatologic, cardiac, and neurologic manifestations. The incidence of ARF has declined in most developed countries, and many physicians have little or no practical experience with the diagnosis and management of this condition. Occasional outbreaks in the United States make complacency a threat to public health.

Diagnosis rests on a combination of clinical manifestations that can develop in relation to group A streptococcal pharyngitis. These include chorea, carditis, subcutaneous nodules, erythema marginatum, and migratory polyarthritis. Because the inciting infection is completely treatable, attention has been refocused on prevention. See the image below.

Clinical manifestations and time course of acute rheumatic fever.

Pathophysiology

Although the inciting bacterial agent is well known, susceptibility factors remain unclear. The location of the streptococcal infection seems to play an important role. The clinical syndrome typically follows a streptococcal pharyngitis, but streptococcal cellulitis has never been implicated.

The earliest and most common feature is a painful migratory arthritis, which is present in approximately 80% of patients. Large joints such as knees, ankles, elbows, or shoulders are typically affected. Sydenham chorea was once a common late-onset clinical manifestation but is now rare.[1]Carditis (with progressive congestive heart failure, a new murmur, or pericarditis) may be the presenting sign of unrecognized past episodes and is the most lethal manifestation.

Genetics may contribute, as evidenced by an increase in family incidence. No significant association with class-I human leukocyte antigens (HLAs) has been found, but an increase in class-II HLA antigens DR2 and DR4 has been found in black and white patients, respectively. Evidence suggests that elevated immune-complex levels in blood samples from patients with ARF are associated with HLA-B5.[2]

In a study of 15 patients with rheumatic heart disease and a control group of 10 patients who had been exposed to group A streptococci but did not develop either acute rheumatic fever or rheumatic heart disease, 13 genes were differentially expressed in the same direction (predominantly decreased) between the two groups. Seven of those were immune response genes involved in cytotoxicity, chemotaxis, and apoptosis. The researchers concluded that the high proportion of differentially expressed apoptotic and immune response genes supports a model of autoimmune and cytokine dysregulation in ARF.[3]

Etiology

Although the mechanism by which streptococcal organisms cause disease is not entirely clear, overwhelming epidemiologic evidence suggests that ARF is caused by streptococcal infection, and recurrences can be prevented with prophylaxis.

Strains of group A streptococci that are heavily encapsulated and rich in M protein (signifying virulence in streptococcal strains) seem to be most likely to result in infection.

[Group A Streptococcus](http://emedicine.medscape.com/article/228936-overview) is thought to cause the myriad of clinical diseases in which the host's immunologic response to bacterial antigens cross-react with various target organs in the body, resulting in molecular mimicry. In fact, autoantibodies reactive against the heart have been found in patients with rheumatic carditis. The antibody can cross-react with brain and cardiac antigens, and immune complexes are present in the serum. The problem has been the uncertainty of whether these antibodies are the cause or result of myocardial tissue injury.

Epidemiology

**United States**

The incidence of an acute rheumatic episode following streptococcal pharyngitis is 0.5-3%. The peak age is 6-20 years. Although the incidence of ARF has steadily declined, the mortality rate has declined even more steeply. Credit can be attributed to improved sanitation and antibiotic therapy. Several sporadic outbreaks in the United States could not be blamed directly on poor living conditions. New virulent strains are the best explanation.

In Hawaii, the incidence of ARF has remained several times higher than in the continental United States, particularly among ethnic Polynesians. Unusual group A streptococci emm types that are uncommon in the continental United States appear to play a significant role in the epidemiology of ARF in Hawaii.[4]

**International**

Most major outbreaks occur under conditions of impoverished overcrowding where access to antibiotics is limited. Rheumatic heart disease accounts for 25-50% of all cardiac admissions internationally. Regions of major public health concern include the Middle East, the Indian subcontinent, and some areas of Africa and South America.

As many as 20 million new cases occur each year. The introduction of antibiotics has been associated with a rapid worldwide decline in the incidence of ARF. Now, the incidence is 0.23-1.88 patients per 100,000 population. From 1862-1962, the incidence declined from 250 patients to 100 patients per 100,000 population, primarily in teenagers.

Notably, natives of Polynesian ancestry in Hawaiian and Maori populations are an exception. For example, in a study from a New Zealand district, the ethnicity of ARF patients was 85% Maori and 10% Pacific. Although the annual incidence of ARF was 3.1 per 100,000 population, in with Maori children aged 5-14 years the incidence was 46.1 per 100,000 population. Almost three-quarters of all patients lived in severely socioeconomically deprived areas.[5]

Mortality/Morbidity

Mortality rates are steadily improving because of better sanitation and health care. The current pattern of morbidity is difficult to measure because the first attack of rheumatic fever follows an unpredictable course. As many as 90% of episodes are clinically contained within 3 months.

Carditis causes the most severe clinical manifestation because heart valves can be permanently damaged. The disorder also can involve the pericardium, myocardium, and the free borders of valve cusps. Death or total disability may occur years after the initial presentation of carditis.

**Racial, Sexual, and Age-related Demographics**

An association between certain class-II HLA antigens (DR2 in blacks and DR4 in whites) and ARF has been reported.

No general clear-cut sex predilection for ARF has been reported, but certain of its manifestations seem to be sex variable. For example, chorea and tight mitral stenosis occur predominantly in females, while aortic stenosis develops more often in males.

The initial attack of ARF occurs most frequently in persons aged 6-20 years and rarely occurs in persons older than 30 years. The disease may cluster in families. In some countries, a shift into older groups may be a trend.