Acute rheumatic fever and its consequences: A persistent threat to developing nations in the 21st century

Jennifer L. Lee, Stanley M. Naguwa, Gurtej S. Cheema, M. Eric Gershwin *

Division of Rheumatology, Allergy and Clinical Immunology, University of California at Davis School of Medicine, 451 Health Sciences Drive, Suite 6510, Davis, CA 95616, United States

A B S T R A C T

Acute rheumatic fever (ARF) is an autoimmune, multi-system response secondary to molecular mimicry following Lancefield group A streptococcus (GAS) pharyngitis; it is now most commonly found in the pediatric populations of developing nations. The major source of morbidity and mortality of ARF stems from rheumatic heart disease (RHD), although the cardinal symptoms of the disease also include polyarthritis, Sydenham's chorea, subcutaneous nodules, and erythema marginatum. Therapy is aimed towards treating the initial GAS infection, using anti-inflammatory medications for acute symptoms and surgery to correct RHD. Secondary prevention is crucial, given the high risk of recurrence, and includes long-term antibiotic prophylaxis. However, vaccination towards GAS may soon be on the horizon, which may assist in both decreasing the risk of initial infection in naïve patients and helping to lower the risk of recurrence.

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* Corresponding author. Tel.: +1 530 752 2884; fax: +1 530 752 4669.
  E-mail address: megershwin@ucdavis.edu (M.E. Gershwin).

1. Introduction

Acute rheumatic fever (ARF) is a constellation of symptoms that stems from a nonsuppurative, auto-inflammatory multi-system response following infection by group A streptococcus (GAS), or *Streptococcus pyogenes*. Particularly because of its chronic effects on cardiac valves, termed rheumatic heart disease (RHD), ARF continues to contribute a significant amount to global morbidity and mortality. In many developing countries, RHD is the most common source of acquired heart disease in children and young adults. The recognition of symptoms comprising the syndrome of ARF dates back centuries ago, with Poynton and Paine initially reporting the potential link between streptococcal pharyngitis and rheumatic fever in 1900. Diagnosis is now centered around the 1992 updated Jones' criteria, which includes carditis, polyarthritis, erythema marginatum, Sydenham's chorea, and subcutaneous nodules, in the setting of a preceding GAS infection.

2. Epidemiology

The prevalence of ARF now appears to be much higher in less developed countries, particularly in indigenous and less affluent areas, and varies significantly from one region to the next (See Table 1). In 2005, it was estimated that the incidence of ARF was more than 471,000 cases per year, with 336,000 cases in those 5–14 years of age. The prevalence of RHD is estimated to range from 15.6 to 19.6 million cases worldwide, with 282,000 newly diagnosed with over 233,000 deaths attributed to RHD each year. Unfortunately, given the disease's predilection for children, over 2.4 million of these cases were in patients aged 5–14 years old [1]. A higher incidence has been reported among the aborigines of Australia, the Maoris of New Zealand, and populations in sub-Saharan Africa [2]. However, given the limitations of reports related to limited resources in many of these endemic areas,

it is likely that numerous cases, and therefore the prevalence and incidence, of ARF and RHD are largely underestimated.

A systematic review of 10 population-based studies published from 1967 to 1996 describes the worldwide incidence of ARF [3]. The highest reported annual incidence rate was 51 per 100,000 per year by a study conducted in northern India, with the mean incidence of all studies at 19 per 100,000 per year. The lowest incidence rates were found in American and Western European nations, while higher rates are found in Eastern Europe, Asia, Australasia, and the Middle East. Of note, information from Africa is not available for this study, though it is widely known that African nations have a high predominance of pediatric patients with RHD.

The first episode of ARF most commonly strikes children and young adolescents, usually from ages 5–14 years old, though younger and middle-aged adults are also affected at a lower frequency. It is rare for patients to experience their initial RF episode younger than 2 years or greater than 35 years of age [2]. In a study of 541 pediatric patients with ARF at the University of Utah by Tani et al., it was found that 5% of these patients were younger than 5 years old at diagnosis [4].

In the United States, the number of ARF cases has fallen dramatically over the last half century. A national study conducted in 2000 detailing the characteristics of American pediatric patients hospitalized with ARF found that the incidence was 14.8 cases per 100,000 hospitalized children (though the true national incidence of ARF cases is <1 case per 100,000 population), with the greatest number of hospitalizations for ARF occurring in Utah, Hawaii, Pennsylvania, and New York [5]. Patients of Asian or Pacific Island descent with ARF were also more likely to be hospitalized than those who were Caucasian.

Concern in the 1980s had arisen over several outbreaks in several states including Tennessee, Ohio, and Pennsylvania. However, cases have since decreased and are now mainly limited to Salt Lake City, Utah. The overall decline is believed to be due to improvements in aspects of primary prevention, including access to health care and crowding and use of antibiotics. It has also been postulated that evolving differences in the streptococcal M protein type, the main bacterial virulence factor to which host antibodies bind to confer protective immunity, has also played a role in the number of diminishing cases [6]. However, it still remains unclear why the trend has moved away from rheumatogenic strains of GAS to those that do not commonly lead to the development of RF.

3. Pathogenesis and association with group A streptococcal pharyngitis

ARF is believed to be a consequence of molecular mimicry, an autoimmune phenomenon that occurs after host infection with GAS and involves both humoral and cellular immune responses. The concept of molecular mimicry is well described elsewhere. Anti-streptococcal antibodies are produced by B cell lymphocytes that cross-react with host tissue epitopes, causing inflammation in various organ systems. In addition, bacterial peptide fragments, many of which are similar to host proteins, are presented to T cell lymphocytes (with a prominent role by CD4+ T cells in rheumatic valvular lesions) via major histocompatibility complex (MHC) molecules, inducing an immune response [7]. Shared epitopes are located on the M protein of GAS and human cardiac (especially myosin), synovial, and neuronal tissues. In Sydenham's chorea, antibodies are directed against neuronal cells of the basal ganglia. Other similarities have been found between hyaluronidate located in the capsule of GAS and hyaluronic acid found in human synovium, as well as between N-acetylglucosamine in the streptococcal cell wall/capsule and in human cardiac valves [7,8].

The development of RF is likely due to contributions from both genetic and environmental influences. An association with MHC Class II antigens, which help to present extracellular antigens to the T cell

Table 1
Collective summary of the characteristics and treatment of rheumatic fever.

At-risk populations	Clinical signs/ symptoms 1	Diagnosis (updated Jones' Criteria [12])	Treatment
Ethnic sub-groups	Non-specific	Major criteria	Antibiotics
Maori (New Zealand)	Fever	Carditis	Penicillin
Aborigines (Australia)	⇧ ESR, CRP	Polyarthritis	Anti-inflammatories
Pacific Islanders	Anemia	Sydenham's chorea	Salicylates
Sub-Saharan Africa	Cardiac	Erythema marginatum	Corticosteroids
Age groups	Pancarditis	Subcutaneous nodules	Surgery
Ages 5 to 15	Pericarditis	Minor criteria	Valve repair
Risk Factors	Myocarditis	Arthralgias	
Low socioeconomic status	Arthritis	Fever	
Overcrowding	Polyarticular	Elevated inflammatory markers	
Limited access to medical care	Migratory	Prolonged P–R interval	
History of rheumatic fever (for recurrences)	Large joints	Preceding Streptococcal infection	
	Neuropsychiatric	Positive throat cultures	
	Sydenham's chorea	Elevated or rising ASO titers	
	OCD/ADHD		
	Tic disorders		
	Cutaneous		
	Erythema marginatum		
	Subcutaneous nodules		