Rheumatic Fever Licks at the Joints, but Bites at the Heart

Konstantinos Dean Boudoulas^a Antonios Pitsis^b Harisios Boudoulas^{a, c}

^aDepartment of Medicine, Division of Cardiovascular Medicine, The Ohio State University, Columbus, OH, USA;

^bDepartment of Cardiothoracic Surgery, St. Luke's Hospital, Thessaloniki, Greece; ^cBiomedical Research Foundation, Academy of Athens, Athens, Greece

Rheumatic fever is the result of an abnormal autoimmune response to group A streptococcal pharyngeal infection in a susceptible host. However, in approximately one-third of cases a history of pharyngeal infection is not elucidated prior to the development of rheumatic fever. In certain individuals, which is not uncommon, streptococcal pharyngeal infection does not result in rheumatic fever. As a general rule, rheumatic fever affects young individuals (6–15 years old), but can occur in adulthood. The clinical manifestations of rheumatic fever include migratory arthritis, fever, erythema marginatum (non-pruritic rash with sharp erythematous borders), subcutaneous nodules, chorea, and carditis [1–3].

During the acute phase of the disease, typically the left sided cardiac valves appear edematous and inflamed. Tiny verrucae (1–2 mm in diameter), consisting of platelets and fibrin, are seen along the lines of valve closure. These findings can be detected with current imaging techniques, especially echocardiography. Inflammation involving the connective tissue of the valves can also be seen in the mitral annulus and the chordae tendineae. Mitral regurgitation is the most common clinical presentation of acute valvulitis, ranging from mild to severe [1].

In this issue of *Cardiology*, Narang et al. [4] report the clinical presentation of 126 children with acute rheumat-

ic fever who were treated in a tertiary medical center (60 patients had a previous history of rheumatic fever). Joint symptoms were present in 29% and fever in only 25% of the patients; 2.4% of the patients had subcutaneous nodules and there were no patients with erythema marginatum or chorea. Tachycardia and heart failure were present in 53 and 21% of the patients, respectively. Echocardiogram demonstrated mitral leaflet thickening in 77%, small nodules on the tip of the mitral leaflets in 43%, thickening of the aortic valve in 27%, and nodules in the aortic cusps in 8% of the patients. Mitral regurgitation ranging from mild to severe was present in 95%, mitral stenosis in 16%, aortic regurgitation in 44%, and tricuspid regurgitation in 56% of the patients. Of interest, mitral valve prolapse (MVP) was seen in 29% and flail leaflet was seen in 5% of the patients. The most recent modified Jones criteria (2015) for the diagnosis of acute rheumatic fever were present in only 32% of the patients [5].

Natural History of Rheumatic Valvulitis

After a long latent period, varying from 10 to 40 years, symptoms related to the underlying valvular disease occurs. It should be noted that approximately 50% of pa-

Fig. 1. a Frequency of symptoms/events in patients with mitral stenosis with and without a history of rheumatic fever. Note the similarity between the two groups. **b** Time intervals from the initiation of symptoms to severe symptoms in patients with mitral stenosis are shown (from Boudoulas and Grvanis [1] and Boudoulas et al. [6]). FC, functional class.

tients with rheumatic valve disease have no history of rheumatic fever; interestingly, after the beginning of symptoms the “natural history” of rheumatic valve disease is the same in patients with no history of rheumatic fever as compared to those with a history of rheumatic fever. In a previous study, 176 patients with mitral stenosis hospitalized in the A’ Medical Department of the Aristotle University of Thessaloniki, AHEPA Hospital, Greece, from 1962 to 1972 were analyzed. The average age of symptom onset in patients with a history of rheumatic fever ($n = 93$) was similar to those without a history of rheumatic fever ($n = 83$): 36.5 ± 14 versus 36.7 ± 13 years, respectively; however, there was a wide distribution in age at symptom onset in both groups. The frequency of major symptoms was also similar in both groups (Fig. 1a). The time interval from the initiation of symptoms (functional class II) to severe symptoms (functional class IV) was approximately 10 years and was similar in both groups (Fig. 1b). These patients represent the natural history of mitral stenosis in an era where mitral valve surgery was not widely available in Greece and in which valvuloplasty was yet to be introduced into clinical practice; patients were treated only with digitalis and diuretics. The onset of symptoms and

the natural course of the disease is similar with other valvular heart disease of rheumatic etiology regardless of a history of rheumatic fever. Mitral stenosis is presented here as it is considered entirely due to rheumatic etiology, if congenital causes are excluded [1, 6].

The Fall of Rheumatic Fever

The incidence of rheumatic fever and rheumatic valve disease has declined dramatically in the USA and other economically developed countries over the last 7–8 decades. Rheumatic fever, however, still remains a major cause of morbidity and mortality in low-income countries and persists in immigrants in economically developed countries. Factors responsible for this decline include socioeconomic improvements in many parts of the world, improvement in medical care, and use of antibiotics. The decline in the incidence of rheumatic fever, however, was noted well before the use of antibiotics [7, 8] (Fig. 2). Changes in the virulence of the microorganisms involved, host susceptibility, or both may account for this phenomenon. Evidence suggests that the incidence of streptococ-

Fig. 2. Unadjusted rates of death due to rheumatic fever in the USA, 1910–1977 (from Gordis [7]).

cal infection and its virulence have decreased over time. Furthermore, cofactors that may operate in concert with streptococcal infection to facilitate the development of the disease (e.g., viral infections) may have also changed. Better living conditions may also have resulted in an increased resistance to streptococcal infection by the host [7]. Genetic factors related to the host obviously cannot be changed in such a short period of time. It remains unknown, however, why only “some people, some of the time” with streptococcal infection develop rheumatic fever [2]. Better understanding of the mechanisms related to host susceptibility would provide insights into the pathogenesis and possible prevention of the disease.

Genetic Susceptibility to Rheumatic Fever

There is a genetic susceptibility to rheumatic fever, but the magnitude of genetic factors remains mostly unknown. In a study of 435 twins (175 monozygotic, 260 heterozygotic), it was found that the risk of acute rheumatic fever in monozygotic twins with a history of rheumatic fever was increased 6-fold compared to heterozygotic twins [9]. The search for genetic markers and susceptibility of rheumatic fever has revealed association patterns with HLA antigens (chromosome 6; 6p21.3) [1, 2]. Other studies also suggest that certain single nucleotide polymorphisms of transforming growth factor- β 1 (TGF- β 1) increase susceptibility for the development

acute rheumatic fever [10]. Of interest, TGF pathways are also related to the pathophysiologic mechanisms of floppy mitral valve (FMV)/MVP [11].

In a study by our group, characteristics of mitral valves in 17 normal (autopsy), 27 mitral stenosis (surgery), and 13 FMV/MVP (surgery) individuals were evaluated. Values that were 2 standard deviations above the normal mean of mitral annular circumference, mitral annular area, and mitral leaflet area were considered abnormal. All measurements were abnormally large in FMV/MVP patients, which is mostly considered a heritable disease. In mitral stenosis, there was also an increase in mitral annular circumference, mitral annular area, and mitral leaflet area by 37, 48, and 52% of the cases, respectively [12]. The data suggest that certain patients with mitral stenosis have dimensional characteristics that resemble FMV. Fibrosis, which is the dominant pathologic change in chronic rheumatic mitral stenosis, would not be expected to result in an increase in valvular dimensions. Thus, rheumatic mitral stenosis may more often occur in patients with underlying FMV/MVP.

Concluding Remarks

The only significant sequela of rheumatic fever is rheumatic valve disease, while arthritis, erythema, and subcutaneous lesions are transient events. Thus, cardiac in-

volvement should be the main (if not the only) focus in patients with rheumatic fever and diagnostic criteria should be based mostly on echocardiography. However, since approximately half of the patients with rheumatic valve disease have no history of rheumatic fever, no matter what diagnostic criteria are used, the diagnosis of the acute episode could be missed in a large proportion of patients. It follows that attempts should be made to identify high-risk individuals prone to disease and to provide preventive measures in these highly susceptible individuals [2, 7, 9, 10]. Genome-wide association studies may

help to achieve this goal. Prophylactic measures in this high-risk group, including use of antibiotics and vaccination (when a vaccine is available), will result in a decrease in the incidence and may result in the eradication of rheumatic fever worldwide in the years to come.

Disclosure Statement

The authors declare that they have no conflicts of interest to disclose.

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