Rheumatic Fever: A Never-Ending Story?

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Rheumatic fever was first described in the nineteenth century. Though potentially preventable, it continues to be a major health problem and is still a major cause of mortality from heart disease during the first 50 years of life.

The incidence of rheumatic fever in the western world began to decline long before the introduction of antibiotic treatment. In Denmark, for example, the incidence of the disease decreased from 250 per 100,000 population in 1862 to 100 per 100,000 in 1962 [1]. This trend was rapidly accelerated with the introduction of antibiotics, and the incidence reported in 1980 was less than 2 per 100,000.

In developing countries, however, the incidence is still high and is up to 13.4 per 100,000 hospitalized children [2]. According to current estimates, 10–20 million new cases per year are expected in these countries [3]. Nevertheless, the sudden reappearance of focal epidemics in the United States in the mid-1980s reminded us that the disease still poses a threat worldwide [4].

A better understanding of the pathogenesis of RF is needed to explain its changing incidence. Despite the expanding epidemiological and immunological evidence linking group A *Streptococcus* infection to RF, many unanswered questions remain. Studies have shown that not all group A streptococcal strains are rheumatogenic. It is known that pyoderma and soft tissue infections never cause rheumatic fever. Furthermore, even though the pharynx is the site of the antecedent rheumatic infection, not all group A streptococcal pharyngeal infections lead to RF.

Though opinions vary regarding the rheumatogenicity of certain streptococcal strains [3], several factors do support their existence, namely:

- Some of the 80 distinct streptococcal A serotypes, defined by their M protein molecule, have been associated with epidemics of RF.
- The *Streptococcus* A that causes RF is distinct from the one that causes glomerulonephritis.
- Certain M serotypes of group A streptococci, once so prevalent in RF epidemics, have made a recent reappearance.
- There is no association between RF and invasive streptococcal infections such as toxic shock syndrome.

The rheumatogenic strains are associated with certain characteristics [5]. They are highly contagious. They possess the M protein and large hyaluronate capsules, both responsible for the striking resistance to phagocytosis and virulence. Their most important property, however, is the inclusion in the large M protein molecules of epitopes that cross-react with cardiac and other host tissues.

Another important factor in the pathogenesis of RF is the site of the streptococcal infection in the pharynx, where the large repository of lymph tissue may be important in the initiation of the abnormal immune response [3].

The concept of a genetic predisposition to RF has long intrigued researchers [6]. Several studies have reported a genetic association with RF, some related to the major histocompatibility complex, others not. Patarroyo and colleagues [7] described a B cell alloantigen in several diverse populations with RF that was not MHC related. More recently, studies using monoclonal antibodies against B cells from patients with RF found that this B cell antigen is expressed in 100% of RF patients compared with only 10% of healthy individuals [8]. Thus, this antigen may serve as a marker of RF susceptibility. At the same time, other investigators have described an increased frequency of different HLA types in different populations with RF [9–11]. These conflicting results have led to the speculation that the reported association might be of genes located close to but not identical with the RF susceptibility gene, or that susceptibility to RF is polygenic.

Hence, RF represents an *autoimmune* response in *genetically* and *environmentally* predisposed individuals to an *untreated rheumatogenic strain* of group A streptococcal *pharyngitis*.

In this issue of *IMAJ*, Habib and colleagues [12] present important information about the incidence of RF during the last decade in the Nazareth area of Israel. They report a mean annual incidence of 5 per 100,000 population, with a peak in 1990 of 13.4 per 100,000. These numbers are astonishingly high compared to other developed countries.

RF = rheumatic fever

MHC = major histocompatibility complex

However, it should be emphasized, as the authors also noted, that they are representative only of a subpopulation living in Arab villages under very low socioeconomic conditions and cannot be extrapolated to all of Israel or to other areas of the country.

It is surprising that in Israel, where RF is relatively common, there are no accurate data regarding the extent of its morbidity. To the best of our knowledge, this is only the second published report on the incidence of RF in Israel. The first was conducted by Bitton and Joseph [13] and included 222 cases of RF in southern Israel from 1974 to 1983. This area is populated mainly by Jews from Arab countries and Bedouins and has a low socioeconomic rating. According to this study, the mean annual incidence of RF was 12–16 per 100,000, and it did not change significantly during the 10 year follow-up. In a third, unpublished, study of 144 cases of RF in central Israel from 1977 to 1987, a higher incidence of the disease was noted in Arabs than in Jews, with an overall decline in incidence from 6.5 per 100,000 in 1977 to 0.8 per 100,000 in 1987, and waves of higher incidence every 4–5 years (Z. Weissman, Rheumatic fever in two hospitals in central Israel, 1991). The figures of Habib and colleagues [12] fall between these two studies.

Regarding the clinical picture, Habib's team [12] noted that the arthritis was migratory in only half their cases. The term "migratory" is often used to describe the poly-arthritis of RF and is not meant to signify that inflammation necessarily disappears in one joint when it appears in another. Rather, the various locations usually overlap in time, and it is the onset that "migrates" from joint to joint [3].

The rate of carditis in the article (34%) was surprisingly low compared to other reports (65% to 91%) [14,15]. The reason for the discrepancy may lie in the authors' diagnosis of carditis on the basis of clinical and radiological findings, without echocardiographic screening of all their RF patients. This highlights the current debate regarding the use of echocardiography as the sole criterion of rheumatic carditis without accompanying auscultatory findings.

Finally, a few words about future treatment. The type-specific epitope of the purified M protein can now be completely separated from the molecular moieties cross-reacting with host tissue, enabling the development of vaccines free of such possibly dangerous antigens [16].

Recently, Dale and colleagues [17] developed a recombinant multivalent M protein vaccine, which evoked, in rabbits, bactericidal antibodies against all the serotypes presented. Most importantly, these antibodies did not cross-react with human tissues. Such a vaccine for human use is under trial. In the absence of an animal reservoir, effective multivalent M immunization focusing on heavily endemic areas or on susceptible hosts might ultimately eradicate the disease. Meanwhile, the best defense against rheumatic fever is a high level of awareness and prompt antibiotic treatment of streptococcal throat infection.

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