Antecedent Streptococcal Infection in Acute Rheumatic Fever

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(See the article by McDonald et al. on pages 683–9)

One of the most intriguing pathogenetic puzzles of the many illnesses with unsolved origins—even in this age of molecular biology—is rheumatic fever. Despite a half-century of intensive and productive, basic, epidemiological, and clinical research, the precise mechanism(s) remain unknown. Of equal importance is the opportunity to employ research findings to benefit potentially affected patients and populations is extremely limited.

In this issue of Clinical Infectious Diseases, McDonald et al. [1] report epidemiologic and microbiologic data from their household studies of cases of streptococcal infection among Aboriginal people in northern Australia, a population group that experiences an extraordinarily high incidence of acute rheumatic fever (ARF). On the basis of their observations, the authors raise critical questions regarding the nature of the antecedent streptococcal infections that give rise to ARF.

For many years, it has been established dogma that ARF only follows upper respiratory tract infection with group A streptococci (GAS), in contrast to post-streptococcal acute glomerulonephritis (AGN), which may follow GAS infection of either the throat or skin. This dogma is based on an accumulated body of epidemiologic evidence relating to both primary and recurrent episodes of rheumatic fever. Among such evidence are observations from both civilian and military populations in which ARF followed epidemics of pharyngitis and/or scarlet fever caused by strains of a limited number of “rheumatogenic” GAS M protein types. Moreover, ARF incidence has not been found to increase during epidemics of pyoderma-associated AGN.

McDonald et al. [1] report low rates of sore throat and GAS pharyngeal colonization, but in contrast, they report high rates of pyoderma in the 3 communities they examined in northern Australia. The authors present a novel hypothesis to explain their findings; namely, that “recurrent skin infections immunize against throat colonization and infection” [1, p. 688]. However, they do not specify what the mechanism(s) for such immunization might be, nor do they provide any evidence for its existence. Acquired protective immunity to GAS throat infection is believed to be mediated primarily by anti-M protein opsonic antibodies that are both type-specific and long-lasting. Despite the frequency with which pyoderma, cellulitis, and erysipelas recur in individual patients, however, sufficient information about the role, if any, of acquired cutaneous protective immunity to prevent subsequent skin infection (much less, throat infection) is lacking. Although opsonic antibodies are detectable in some pyoderma patients [2, 3], such antibodies were not protective in an animal model of streptococcal soft-tissue infection [4]. Thus, the authors’ proposal must be considered highly speculative.

McDonald et al. [1] further contend that in the population they studied, ARF does not invariably follow symptomatic GAS throat infection. Therefore, the implication, although not explicitly stated, is that in Aboriginal people in Australia, streptococcal pyoderma, per se, gives rise to ARF. This intriguing and iconoclastic contention deserves careful scrutiny. The major thrust of the argument is that, with a seeming paucity of recovered upper respiratory tract streptococcal isolates, and with a seeming paucity of documented sore throats, infection of the skin cannot be ignored. With due respect, however, we believe that the presented data are insufficient to support this contention. There are too few observations. Calculation of the presented data indicates that two-thirds of the subjects enrolled were seen for culture “consultations” <5 times during the entire period of observation, either in the community where studies were carried out for 2 years or in the 2 communities where enrolled subjects...
were followed up for only 1 year. Can so few observations be representative either of the incidence of symptomatic pharyngitis or of colonization of the upper respiratory tract or be truly representative of the M types of GAS (or of the epidemiology of groups C or G streptococci) and their epidemiology in the participating communities? Previous studies have emphasized the rapidity with which streptococcal strains enter and leave populations [5, 6]. With relatively few observations in the presented data, it is possible that such an epidemiological event could have occurred and not have been detected either in individuals or in the population.

McDonald et al. [1] compare the low incidence of sore throat and symptomatic GAS pharyngitis that they observed in Aboriginal persons with much higher rates reported previously in another population in Melbourne, in the south of Australia. The Melbourne study [7], however, was conducted among stable family groups with children 3–12 years old. In contrast to the studies in northern Australia, the observed Melbourne families maintained a health diary and reported to their general practitioner whenever a case of pharyngitis occurred in any family member. Clearly, the incidence rates in the 2 epidemiologic groups are in no way comparable.

Other investigators have studied populations in which ARF and high prevalences of GAS pyoderma coexist. For example, in Memphis, Tennessee, a temporal disparity was found between the occurrence of ARF and AGN among patients admitted to the public hospital [8]. Despite the frequent isolation of “pyoderma strains” from the throat, ARF did not appear during the peak of the pyoderma season. It was concluded that pyoderma strains of GAS were unlikely to be associated with ARF in that epidemiologic setting. Potter et al. [9] studied the relationship of ARF to AGN in a population in Trinidad in which epidemics of pyoderma-associated AGN occurred with some frequency. They found that the GAS strains isolated from patients and families with ARF generally differed from those found in patients and families with AGN. Moreover, only 22% of family members with ARF had skin infections, in contrast to 61% of family members with AGN [10]. Berrios et al. [11] studied the epidemiology and bacteriology of ARF and AGN in Santiago, Chile. Pharyngeal isolation rates were significantly lower among patients with ARF and their household contacts (7.8%) than among patients with AGN and their contacts. Nevertheless, isolates of M-type 5, a classic pharyngeal “rheumatogenic” type, were obtained from several patients with ARF. Following up on this lead, the investigators identified M5-type–specific antibodies in serum samples of 32% of the patients with ARF but in only 3% of the matched controls [12]. These observations suggest that, despite the well known and often-reported difficulty of isolating GAS from throat specimens from patients with ARF, pharyngeal strains of rheumatogenic streptococci may persist in the community and give rise to the disease. Thus, these previous studies have failed to implicate a pathogenetic role for skin infections, even though the investigations were conducted in pyodermic endemic communities. The investigations mentioned above were all conducted in the Western Hemisphere. Strains associated with ARF may well be quite different elsewhere [13]. Nevertheless, it is difficult to ignore the conclusions of these carefully conducted studies.

The epidemiologic data provided by McDonald et al. [1] are provocative. The question remains, however, of how to either confirm or disprove the authors’ hypothesis. This is a thorny, practical issue, given the remote geographical living areas and the somewhat mobile lifestyle of the study population. Outbreaks of AGN have been, on occasion, clearly related to 1 or a few predominant pyoderma streptococcal strains, perhaps most notably in the classic studies of M49 in Red Lake, Minnesota [14–16]. ARF epidemics caused by rheumatogenic pharyngeal strains, (e.g., the recent epidemic in Salt Lake City, Utah, caused by M-18 [17]) have provided definitive evidence of causality. Might intensified individual subject and population surveillance uncover a similar situation among Australian Aboriginal persons? Lacking an experiment of nature, such as a discrete ARF epidemic caused by 1 or a few readily identifiable strains, and in the absence of a universally accepted animal model for the study of rheumatic fever and rheumatic heart disease, unusually intensive prospective, epidemiological studies are required in tropical Australia and elsewhere and should be augmented by the laboratory tools of molecular biology to clarify this pathogenetic puzzle. Until then, a degree of skepticism is warranted.

Acknowledgments


Reference

8. Bisno AL, Pearce IA, Wall HP, Moody MD, Stollerman GH. Contrasting epidemiology of acute rheumatic fever and acute glomerulone-