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Complications of physician misdiagnosis/treatment of rheumatic fever in the United States

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ABSTRACT

Rheumatic fever is an auto-immune disease caused by exposure to *Streptococcus pyogenes*. Over the last 50 years, reports of rheumatic fever within the United States have diminished. The decrease was attributed to the advent of penicillin in the treatment of streptococcus infections. We propose that current diagnostic and treatment methodologies may adversely increase the morbidity rate of rheumatic fever within the United States. Publication rates and interest in rheumatic fever has diminished over the last 30 years. Because of this decline, many physicians are only vaguely aware of the disorder. Additionally, the fear of antibiotic resistance has influenced the Center of Disease Control to suggest a significant decrease in the use of antibiotics by physicians. Although extremely valid for the future health and well-being of the population, such policies must be examined for each individual case carefully. The American Heart Association prescribes long-term antibiotic prophylaxis as the only current treatment; however literature reviews indicate that such therapy is rarely used. Therefore individuals diagnosed with rheumatic fever are not being treated. Additionally, because many physicians are not routinely testing for streptococcus or early signs of endocarditis, it is likely that cases of rheumatic fever will increase in the future, and many individuals may not be diagnosed until sever damage or morbidity occurs. Physician education and clear revised guide-lines are necessary to ensure adequate treatment of individuals with rheumatic fever. Misunderstandings of the disease and how it should be treated by first responders (*i.e.* primary care providers and pediatricians) are discussed.

Keywords: Physician Guidelines; Prophylaxis; Antibiotic Resistance; Penicillin; Rheumatic Heart Disease; Endocarditis

1. INTRODUCTION

Rheumatic fever (RF) is an auto-immune disease mediated by humoral and cellular auto-immune responses to *Streptococcus pyogenes* infections [1,2]. Initial RF episodes can produce either mild or severe symptoms and damage, however milder outcomes are more common with an initial presentation (e.g., endocarditis, heart valve damage, Sydenham's chorea, rheumatoid arthritis, and potentially depression and obsessive compulsive disorder) [3]. When diagnosed and treated early, most RF individuals have little to no life-altering symptomology. However, misdiagnosis and/or lack of prophylactic treatment lead to progressive damage, invasive interventions, decreased quality of life, and increased morbidity.

The following article is designed to increase the awareness of RF among physicians, explain reasonable guidelines for the detection of RF, and highlight treatment guidelines for health care providers.

2. METHODS

All data and subsequent treatment recommendations are derived from Pubmed, Medline, Center for Disease Control, and American Heart Association searches for articles containing rheumatic fever, rheumatic heart disease, endocarditis, and *Streptococcus pyogenes* from 2009-2012. Based on the relevancy of the article, 115 articles were selected for in-depth analysis. In addition, all seminal articles referenced in these papers were also examined and used for the current analysis.

3. RESULTS

3.1. Mechanism of Disease

Rheumatic Fever (RF) is an auto-immune disease mediated by humoral and cellular autoimmune responses to *Streptococcus pyogenes* infections [1]. In RF patients, antibody production to the streptococcal infection is cross-reactive with other cells or proteins within the host. Examples of cross-reactive proteins are: laminin, a protein in the extracellular matrix of the heart and heart valves; several cardiac myosin epitopes; vimentin; or lysoganglioside GM1 from neural cells [4,5]. In the acute

phase, the initial antibody response to the streptococcal infection can directly damage cellular tissue, mediate signal transduction, and trigger dopamine release in neural cells. Additional damage is mediated by antibody up-regulation of adhesion molecule VCAM-1 which leads to inflammation of one or more body regions and valve scaring [4-6].

Similarities of disease patterns between siblings and identical twins as well as HLA correlation studies [7,8] provide strong evidence for a genetic influence over RF susceptibility and potentially RF manifestation. Because the specific molecular components of the proteins targeted by the auto-immune response are genetically determined, and the different components of the immunological cascade are also genetically determined, a genetic predisposition for RF is not only plausible, but probable.

Most RF patients have distinct but limited cells and organs with proteins that are cross-reactive to antibodies that attack streptococcal bacterium (mimic cells), and are thus affected by RF. Such genetic variability is likely to contribute to the vast differences in RF damage and symptomology. In all cases, the mimic cells are permanently susceptible to RF damage. Therefore with each repeated streptococcal infection, the previous damage is perpetuated and expanded.

3.2. Environmental Factors

The proclivity for streptococcal infection increases in several populations of individuals regardless of societal local. Group settings such as day-cares, schools, hospitals, and military facilities are specifically prone to the spread of streptococcus throughout a population. Day-care facilities and schools are predominantly prone to such infections due to the lack of sanitary precautions by young children (e.g., hand-washing and covering their mouths when sneezing). Although numerous studies have determined a higher incidence of RF in school-aged children, in-depth analysis of these individuals over time has not been performed.

3.3. Environment-Location

Deaths associated with RF in the developing world are not dramatically different than reports of RF pre-antibiotic discovery (20-51/100,000 people), while deaths in the developed world are much more rare (0.2-1.9/100,000 people) [4]. This disparity has caused several investigators to assume a socio-economic proclivity for RF among disparate populations. Populations with lower socio-economic status have less access to health care, antibiotics, and less knowledge about simple ways to fight disease perpetuation such as hand washing. Therefore populations within the developing world have a high risk of being infected multiple times. Because each incidence of infection increases damage, these individuals have a high risk of mortality from RF.

Closer examination of cases within the United States over the last several years show an increase in RF infection rate (Utah 1986: 11.8/100,000 people) [9]. Although socioeconomic factors may play a role in RF formation within the United States, in the study above 56% of the patient families had attended or completed college and were above the poverty line [9]. Deaths associated with these cases are less common within the United States, and are likely to be mitigated by access to health care and adherence to treatment regimens.

3.4. Current Clinical Guidelines

Global guidelines by the Center for Disease Control recommend no antibiotic treatment unless a diagnosis of streptococcal infection is confirmed by a laboratory test [10-12]. These guides are meant to decrease unnecessary antibiotic use throughout the United States. RF directed guidelines were published by the American Heart Association in 2009. They indicate a treatment of continuous antibiotic prophylaxis for 10 years or age 40 for RF patients with persistent valvular disease, 10 years or age 21 for RF patients with RF and no valvular disease, and 5 years or age 21 for RF patients without carditis. Individuals with evidence of valvular damage or those at high risk of recurrence (e.g., children, military recruits, students, teachers, physicians, and health care workers) are recommended to continue prophylactic treatment permanently, or until the risk of infection is reduced [13]. This guideline proposes antibiotic prophylactic treatment during any stage of life in which the likelihood of streptococcal infection is high to prevent recurrence of infection and subsequent physical damage.

4. DISCUSSION

4.1. Decrease of RF in States

Reports of RF within the United States have dramatically decreased. These findings are based on population-based surveys and state surveillance systems. State surveillance for most states ceased during the mid 1980s [9]. Therefore accurate counts of RF within the States have been lacking for numerous years. It is possible that the RF infection rate has decreased due to differences in streptococcal strains in the last 50 years, however it is also probable that many RF cases are not diagnosed due to lack of physician knowledge and testing for the disease. Analysis of accurate trends within the United States will require physician training in RF diagnosis as well as additional surveys or re-instated state surveillance systems.

4.2. Misconceptions

4.2.1. Age Misconceptions

Numerous reports indicate that RF is a childhood-ado-

lescent disease. These statements are based on larger percentages of younger patients than older patients worldwide. This is a widely held misconception. RF has been shown to be induced by proteins on mimic cells that are targeted by the body's immune response to streptococcus. Over a life-time, the genetics of an RF individual do not change. Therefore a 65-year-old individual would be just as susceptible to recurrent RF episodes as a 13-year-old. The decrease in RF in older populations is resultant from a decrease in the risk of streptococcal contact for the older population. Older populations in environments prone to streptococcal exposure should be considered at high risk for repeated streptococcal infection, repeated RF damage, and at a high risk for severe damage and mortality.

4.2.2. Treatment Misconceptions

Common guidelines for both RF and non-RF patients have been guided primarily by the fear of the development of antibiotic resistance. Such arguments are valid for maintaining the overall health and safety of the general population. However caution should be taken when applying this principle to all patients. Treatment of existing streptococcal infections may decrease the overall damage from that episode, but it will not eliminate damage from the initial infection. In the Utah study, 53% of patients who received antibiotic treatment for a streptococcal infection were subsequently diagnosed with heart damage associated with RF [9]. Therefore treatment of each streptococcal infection will not stop the progression of the RF damage associated with those infections. Second, at least one third of episodes of acute RF result from non-symptomatic streptococcal infections [13]. If physicians only treat symptomatic infections, a large percentage of infections would go un-noticed and un-treated. Therefore, broad application of the CDC guidelines would deny treatment and health to RF patients.

4.3. Initial Diagnosis

The symptoms of streptococcal infections are similar to those of the common cold as well as viral infections such as the flu (e.g., sore throat, pain when swallowing, fever 101 or above, swollen tonsils, petechiae on soft or hard palate, headache, and nausea) [10]. Current CDC guidelines indicate that antibiotic treatment should not be implemented until after streptococcal laboratory diagnosis. Because physicians routinely test for streptococcus only when an infected individual does not recover after 10 days (the time necessary for viral infections to cease), the first acute RF episode in children is likely to be more severe. To alleviate this possibility, two vital diagnostic tools should be utilized by physicians. First, for each sore throat, a throat swab should be performed to determine whether the infection is caused by streptococcus. The test is inexpensive, fast, and easy to perform. This fast diagnosis will lead to faster treatment, shorter infection times, and less sever RF immunological reactivity. Second, physicians should become more aware of the cardiac health of their patients. Although heart auscultations are standard, endocarditis is commonly not audible in RF patients. Therefore echocardiograms should be added to the standard physician repertoire in patients with a familial history of RF. This added vigilance would assist with early detection of RF damage. Because RF damage is cumulative, early diagnosis and treatment would improve the future health and wellness of the patient.

4.4. Patient Physician Interaction in Treatment

Once diagnosed, physicians should initiate open and informed discussions of the costs, benefits, and life events for each patient to identify the prophylactic treatment that is best suited for an RF patient. As indicated by the AHA, individuals at high risk for streptococcal infection should seriously consider antibiotic prophylactic treatment until they are no longer in a streptococcal prone environment. Individuals not in high-risk environments should continue to be monitored for potential relapses at intervals agreed upon by the physician and patient throughout life. These informed discussions will contribute to patient physician confidence and places some of the patient's health decisions back into the patient's hands. This may potentially alleviate legal complications from advancing RF damage if it occurs in the future.

Insufficient physician/patient interaction, physician inattention, or physician misunderstanding of the disease may lead to denial of monitoring and necessary prophylactic treatment for RF patients. Once RF is diagnosed, denial of treatment will leave the physician liable for subsequent RF damage from streptococcal infections in those patients. Although litigation should not be a factor in treatment, it is a common occurrence within the United States, and physicians should be aware of their responsibilities and potential liability in these cases.

5. CONCLUSION

RF is a misunderstood disease that affects numerous people around the world. Catastrophic damage associated with RF damage is easily prevented through adequate physician monitoring and prophylactic treatment. Because the morbidity rate for RF has decreased within the United States, knowledge of RF within the physician population has waned. As a result, it is likely that fewer patients are being tested, diagnosed, and treated for RF. Therefore we predict that the incidence of RF with severe symptomology will increase within the United States. To prevent this possibility, physicians should be aware of the disease and the progressive nature of RF

damage to be able to adequately communicate treatment options and treat RF patients.

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