Review Article

Rheumatic Fever and Antibody Response to Group A Streptococcal Infections

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INTRODUCTION

Rheumatic fever is non-suppurative sequel of group A streptococcal infection. It is a multifocal inflammatory disease, affecting primarily the heart, joints, skin and central nervous system occurring in 0.1% to 3% after untreated pharyngitis. It was a major cause of death and a common cause of chronic structural heart disease in children until 1960. It has declined in developed countries due to advent of penicillin and improved social conditions. Rheumatic fever is very common disease among children in developing countries till date. Rheumatic fever and its clinically significant sequel, rheumatic heart disease, continue to be a major health problem in developing countries like Nepal. Rheumatic fever is still a major cause of death and heart disease.1

- It is caused by beta hemolytic streptococcus Lancefield group A. however, there are number of other types with M antigen which can cause the disease.
- It affects joints, skin and heart. Immune response of individual is important for disease production and about 5-6% of people have genetic relationship.
- Hypersensitivity reaction caused by cross reacting antibodies is responsible for the features of the disease.
- In 30-70% of first attacks there is cardiac involvement but subsequent attack raise this figure to 75-90%.

This review mainly focuses on pathogenesis and immune response in rheumatic fever.

Pathogenesis

Although the observation of pharyngitis preceding rheumatic fever was described by Poynton and Pame 2 as early as 1900, the exact pathogenesis and immune mechanisms are still largely unknown.

- Host susceptibility, virulence of the bactrerial agent and the environment combine to determine the clinical manifestation and severity of the disease.
- There is a combined humoral and cell mediated immune response which through molecular mimicry, cross reacts with the tissues of human host. Upon infection, host immune antibody response directed against antigens of the streptococci cross react with the epitopes of host tissues. It is apparent that various extracellular and somatic components of group A streptococci share common epitopes, or molecular similarities with human tissues, which are believed to initiate an autoimmune response.
- Numerous studies have shown cross reaction between M proteins of group A streptococci and human cardiac tissues including myosin as well as joint and neuronal tissues. Other examples include capsule of streptococcus including hyluronidate which has similar structure to hyluronic acid, a component of most human joint tissue. N-acetylglucosamine, a component abundant in the group A carbohydrate moiety of the cell wall is found in high concentration in human heart valves.
- More recent studies have also shown similarities in structure between virulence factors of group A streptococci and human neuronal components, establishing a possible mechanism in the pathogenesis of Sydenham chorea.
- Only certain strains of streptococcus have been associated with rheumatic fever. To date, over 100 different M proteins have been identified among group A streptococci. It is particularly linked to the M antigem (M types 1, 3, 5, 6, 18, 19, 24, 3, 12). However, it has been discovered in communities where other serotypes have been associated.

Immune response to group A streptococci

- The human host mounts specific antiobody responses to both cellular and extracellular antigenic components of the organism in response to infection with group nA streptococci. The extracellular antigens related by streptococci include streptolysin O (SLO) and S, which act as hemolysin, the deoxyribonuclease (DNase) isoenzymes A, B, C and D as well as streptokinase and hyluronidase.
- Since group C and G beta – hemolytic streptococci also produce many of these enzymes, antiobodies to these are considered nonspecific markers of group A streptococcal infection but they are useful to define previous streptococcal infection.
- Cellular components which elicit specific antibody response include M-Protein, an antiphagocytic surface constituent, streptococcal C5a peptidase, a highly specific surface endopeptidase that cleaves C5a; and group a carbohydrate, a cell wall component.

NONSPECIFIC ANTIGENS

SLO

Although SLO and S both are distinct cytolytic toxins affecting numerous cell types, only SLO is antigenic eliciting naturally occurring antibodies. The antibody produced against SLO, antistreptolysin O (ASO), has been well characterized, and its detection is widely used in the serodiagnosis of a precending streptococcal infection. In patient with group A streptococcal pharyngitis, more than 80% have and elevated level antibody response to SLO. ASO rises 1 week to 10 days after initial infection and reaches a peak 3 to 6 weeks later and

begins to decline after 6 to 8 weeks in most patients but may remain elevated in some individuals. Although the ASO titer is relatively short-lived in case of umcomplicated pharyngitis, it may remain elevated in patients with rheumatic fever.

DNase-B

Among 4 DNases, the most consistent immune response is directed against DNase-B which is produced by the majority of group A streptococcal serotypes. Antibody concentration against it begins to rise within 1 to 2 week of the initial pharyngitis, with high titer suggestive of current infection. The peak antibody response time is 6 to 8 weeks, hence peaking later than ASO titers. antiDNase – B antibodies show longer persistence (2,3 months) than ASO making it more reliable to diagnose previous infection in patients suspected of having Sydenam Chorea.

SPECIFIC ANTIGENS

Group A streptococcal C5a peptidase (SCPA)

Group A SCPA of group A streptococci is a virulence factor which helps to evade the inflammatory response. It is a surface protein that cleaves the complement derived chemotaxin C5a, which is important for leukocyte activation and chemotaxix. SCPA is conserved in many serotypes of group A streptococci making it a component for vaccine development.