Anti-A Antibody

Case Presentation

A recently immigrated 7 year old Filipino female, in her usual state of health, was referred for evaluation of an asymptomatic heart murmur. A previous history of rheumatic fever could not be elicited. Physical exam was significant only for a heart murmur consistent with mitral insufficiency. Laboratory values included: sodium 138; potassium 3.7; chloride 102; bicarbonate 28; hemoglobin 12.4; hematocrit 38.3; normal red blood cell indices; white blood count 8,600, with a normal differential; platelets 453,000; erythrocyte sedimentation rate 4 mm/hr; urinalysis: pH 6.0, specific gravity 1.008, trace hemoglobin, otherwise normal; anti-streptolysin 0 (ASO) titer 170 Todd units (normal < 170 Todd units). An anti-A antibody level was requested.

What is anti-A antibody?

The clinical differentiation between an acquired versus congenital isolated cardiac valve lesion is difficult. The most common cause of acquired cardiac valvular lesions is rheumatic heart disease, which follows acute rheumatic fever. In turn, acute rheumatic fever follows infection with group A streptococci. The diagnosis of rheumatic heart disease is important in that penicillin prophylaxis is instituted to prevent further attacks of acute rheumatic fever.

Many antibodies are produced in response to group A streptococcal infection. Antibodies to extracellular streptococcal products (e.g., anti-streptolysin 0, anti-hyaluronidase, anti-DNase B, anti-streptokinase, anti-NADase) are often measured to make the diagnosis of this infection (1-3). However, these extracellular streptococcal products are also produced by group C and group G streptococci (4), and are thus not unique markers for group A streptococcal infection.

Antibodies to intrinsic streptococcal cellular antigens have also been studied. This group of antibodies includes the anti-A antibody, which is directed against the group specific carbohydrate moiety of the group A streptococcus. As streptococcal grouping is based on serologic differences in the group specific carbohydrate, the anti-A antibody serves as a specific marker for group A streptococcal infection.

How is anti-A antibody measured?

The original method (6) for measuring levels of anti-A antibody employed $^{14}$C-labelled group A specific carbohydrate antigen ($^{14}$C-A-CHO) in a radioimmune precipitation assay. Group A streptococci were grown overnight in the presence of $^{14}$C-acetate. Cells were collected and cell walls isolated. The $^{14}$C-A-CHO was extracted from lyophilized cell walls by hot formamide, and dialyzed against distilled water. An aliquot of the patient's serum was then mixed with a known quantity of $^{14}$C-A-CHO. Antigen-antibody complexes were precipitated out of
solution by the addition of saturated ammonium sulfate, and radioactivity in the precipitate was measured by liquid scintillation counting. This immunoprecipitation could be blocked by the addition of N-acetyl-glucosamine, the carbohydrate moiety unique to group A streptococci (4).

Variations of this assay have utilized double diffusion gel precipitation (4), quantitative microagglutination (7), and enzyme-linked immunoassay (ELISA) (8) methodology.

**Significance of anti-A antibody:**

Group A streptococcal infections are associated with three serious clinical problems: rheumatic heart disease (RHD), acute post-streptococcal glomerulonephritis (APSGN), and Sydenham's chorea. The host immune response has been implicated in the development of each of these sequelae. In APSGN, the damage is thought to be caused either by deposition of antigen-antibody complexes on the glomerular basement membrane, or by an autoimmune response against the host kidney. In Sydenham's chorea, antibodies directed against the cytoplasm of caudate nuclei in the thalamic and subthalamic areas of the brain have correlated well with clinical course of the disease (9).

In RHD, autoantibodies against cardiac myofiber-smooth muscle antigen, heart valve fibroblast antigen, and heart valve structural glycoprotein have been identified. Immunologic cross-reactivity between group A streptococcal carbohydrate and heart valve structural glycoprotein was an interesting finding in one study (5), and was the impetus for theorizing a direct immune-mediated mechanism for heart valve damage following group A streptococcal infection. It should be emphasized that this study also observed similar immunologic cross-reactivity with structural glycoproteins of skin, cartilage, cornea and aorta.

A number of studies have investigated this theory. Dudding and Ayoub (6) were able to demonstrate elevated anti-A antibody levels in patients with acute rheumatic fever and chronic RHD. The anti-A antibody levels remained persistently elevated for at least 3 years in patients with RHD, whereas levels declined within 1 year to control levels in patients with APSGN or Sydenham's chorea. The ASO and anti-DNase B levels, although elevated at the time of rheumatic fever, returned to normal values within 1 year in all patients. It was suggested that the persistence of anti-A antibody levels was important in the pathogenesis of rheumatic valvulitis.

Subsequent studies have had mixed results. In support of Dudding and Ayoub, three studies (10-12) were also able to document persistently elevated levels of anti-A antibody in patients with RHD. One study chose to analyze all patients with mitral valve disease (12), and were able to show that in patients with documented rheumatic fever and subsequent RHD, elevated anti-A antibody levels with concomitant normal ASO and anti-DNase B titers were consistent findings. They also studied a group of patients with mitral valve disease of unknown origin, and were able to define a subset of patients with elevated anti-A antibody levels in the face of normal ASO and anti-DNase B levels. It was postulated that this subset had mitral valve disease of rheumatic origin, and was suggested that unrecognized
rheumatic valvulitis (as opposed to congenital mitral valve lesions) could be identified by this pattern of laboratory test values.

In direct contrast to these findings, Zimmerman et al. (4) measured anti-A antibody levels in children and adults who had had at least one attack of rheumatic fever, and who were on chronic anti-streptococcal prophylaxis. They demonstrated that patients without RHD had higher anti-A antibody levels than those patients with RHD. In addition, they and Kaplan et al. (13) noted that anti-A antibody levels increased with age alone, and that peak levels were reached during the late teens. This finding was remarkable for the fact that streptococcal infections are more common in childhood and that the peak incidence in rheumatic fever occurs at a much earlier age than the peak rise in anti-A antibody levels. On the basis of these results, the authors questioned the causal role of anti-A antibody in RHD.

Kaplan (14) reviewed his experience with measuring anti-A antibody levels to conclude that such measurements did not correlate well with clinical presentation. Two-thirds of the population he studied were between the ages of 8 and 15 years old, and interpretation of anti-A antibody levels was difficult either because of recent streptococcal infection, or because of elevated levels in patients without clinical evidence of valvular disease. In addition, although epidemiology data demonstrated that RHD followed streptococcal pharyngitis (as opposed to streptococcal pyoderma), elevated anti-A antibody levels were also detectable in patients with streptococcal pyoderma.

Further characterization of the anti-A antibody by Shulman and Ayoub (15) demonstrated lower association constants in patients with acute rheumatic fever than in those with APSGN or Sydenham's chorea. The significance of these low affinity antibodies was unclear.

Many factors contribute to the development of rheumatic heart disease. It is well documented that multiple bouts of group A streptococcal pharyngitis are necessary, as well as an exaggerated and protracted rise in anti-streptococcal antibody titers. In addition, genetic factors may influence susceptibility, as evidenced by the fact that the incidence of rheumatic fever remains constant in the face of epidemics of streptococcal infection, or in populations with endemic streptococcal infections.

In summary, the current ambiguity in the literature regarding the interpretation of this test suggests that there is no clinical usefulness of measuring anti-A antibody levels to make the diagnosis of rheumatic heart disease. Elevated levels are well demonstrated in any type of streptococcal infection as well as with increasing age alone. Repeated values at yearly intervals for at least three years would be necessary to document a persistence of anti-A antibody, provided the patient was free from streptococcal infection during that period. In the case presented, the confusion is complicated by a borderline elevated ASO titer, which suggests a recent streptococcal infection, and makes interpretation of an anti-A antibody level impossible.
References


