

Immuno-prophylaxis against development of cardiac valvular complications in patients with rheumatic fever: A proposed method

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Abstract

Rheumatic heart disease (RHD) is a serious medical condition recognized as an immunologically mediated complication of rheumatic fever with an autoimmune component due to molecular mimicry between the bacterial antigens and certain body tissues. In view of the prevalence and seriousness of the disorder, its prophylaxis assumes high significance and serious concern. The current attempts at the prevention of RHD do not appear very promising and effective. This brief paper postulates an immunomodulated prophylactic measure aimed to decrease the magnitude and intensity of the antigenic stimulation by the beta-hemolytic group A streptococcus and body tissues which share heterophilic antigenicity between themselves in a hope to minimize heart damage and also prevent or delay the progression of the disease itself.

Introduction

RHD is believed to be the most common cause of heart disease in children in developing countries and is also considered as a major cause of morbidity and mortality in adults. Prevalence is believed to be around 2.2-2.3/1000 but some researchers claim it could be as high as 21.5- 30.4/1000 as studied by echocardiography (1).

Rheumatic fever is an acute multisystem inflammatory disease possessing an autoimmune pathogenesis (2-19) in which M protein of β hemolytic group A streptococcus shows molecular mimicry with cardiac cytoskeletal myosin protein and some other tissue proteins like vimentin, LMM (light meromyosin), laminin, GlcNAc (N-acetyl- β D-glucosamine and HMM (heavy meromyosin) (20-32). Since myosin is not present in valvular tissue of the heart, it is believed that cross reaction of laminin, (which is recognized by anti-myosin, anti-M protein T cells) and N-acetylglucosamine of group A streptococcal carbohydrate with antibodies against valvular tissue together account for the valvular damage. It is characterized by a constellation of findings that are

grouped into major and minor criteria (Jones criteria) (33).

Severe RHD is mediated by T lymphocytes, which participate in a delayed type hypersensitivity inflammation and thus damage and autoimmune aggression leading to damage (34-36). Damage in the patients of rheumatic heart disease has been found to be due to the infiltrating T and B cells (antibody mediated) (15, 37-39). It has been found that peptides like M5(81-96) peptide a major immunodominant antigen and others like M5(83-103), M5(163-177), M5(11-25), M5(62-82) are responsible for the molecular mimicry and hence contribute to the pathogenesis of RHD (40-41). T cells sensitized in the periphery by M5 protein during streptococcal infection, in particular the M5(81-96) peptide in HLA DR 7+ DR53+ RHD patients, migrate to the heart and initiate heart tissue damage after reactivation due to cross-reactive recognition of relevant heart antigen(s). The identification of several M5(81-96) peptide reactive T-cell clones that recognize valve fraction of 90-150 kDa and 30-65kDa further indicates cross reactivity between streptococcal and valvular proteins in the pathogenesis of RHD (41). The fact that some patients also exhibited T cell reactivity in the periphery against streptococcal M peptides and heart tissue-derived proteins support the idea that streptococci-primed T cells migrate from the periphery to the heart, triggering valvular damage (4, 9). It is also believed that antibodies directed against the M protein of certain strains of the streptococcus, cross-react with glycoprotein antigen in heart, joints, skin and brain (42-49). Some studies describe the ability of cross-reactive antibodies to bind to the endothelial surface leading to inflammation, cellular infiltration and valve scarring (2, 3, 27).

The current prophylactic measure against development of RHD consisting of long-term administration of antibiotics particularly penicillin does not appear very effective and promising. Although secondary prophylaxis can prevent the development of lesions due to new ARF episodes there is a general consensus among clinicians that this form of prophylaxis is more cost-effective to prevent new rheumatic fever episodes (50). Therefore our proposed technique may assume greater significance.

Thus this brief article is intended to postulate an immunomodulated technique with a hope to provide a highly effective mode of prophylaxis for RHD.

Physiological basis of the hypothesis

When T cells are activated by antigens and co-stimulators, they secrete locally acting proteins called cytokines under the influence of a cytokine IL-2, which causes other T cells to proliferate, thus generating a large number of antigen specific lymphocytes. Some of these cells differentiate into effector cells, which perform the function of eliminating the antigen that initiated the response. Other activated cells differentiate into memory cells, which are long lived and are poised to respond rapidly to repeated encounters with the antigen. TH1 subset synthesizes and secretes IL-2 and γ -IFN whereas TH2 cells-IL4, 5, 13. TH1 subset is involved in facilitating delayed hypersensitivity, macrophage activation and synthesis of opsonins and complement fixing antibodies. TH2 subset aids in synthesis of other classes of antibodies notably IgE. CD8+ T cells function mainly as cytotoxic cells but like to CD4+ T cells, they can also secrete cytokines, primarily of TH1 type (51).

In rheumatic fever, antigenic entities that are coated with immunoglobulin (i.e. opsonized) are recognized by phagocyte Fc receptors resulting in phagocytosis (52) or cellular lysis without phagocytosis (ADCC) (53) or an inflammatory state leading to release of injurious substances such as enzymes and reactive oxygen intermediates causing tissue destruction and ultimately to the hypersensitivity state (54-55). Circulating antibodies present against the bacteria, which are involved in the type II hypersensitivity, react with bacterial M protein via its Fab part and with mononuclear and polymorphonuclear cells via its Fc part (56) to initiate the immunological reaction (57-58) that may provoke hypersensitivity. Therefore an antigenic entity opsonized with an incomplete antibody, which is devoid of Fc fragment, is likely to escape the above destructive process.

It would be of great significance to check the auto reactivity process early by decreasing the active antigenic sites because once an autoimmune disease has been initiated, it tends to be progressive, sometimes with sporadic relapses and remissions and the damage becomes inexorable due to epitope spreading (59) and the progression and chronicity of which may be maintained by continued recruitment of auto reactive T cells that recognize normally cryptic self-determinants (59-61). During acute episodes,

even the decreased number of expansion of auto-reactive T cells is sufficient to sustain heart damage (62). Peripheral blood mononuclear cells (PBMC) from RF-RHD patients display a vigorous recall response to previous streptococcal infection (63).

Incomplete antibody (blocking antibody): An incomplete antibody is one which coats an antigen but which according to the lattice theory does not have a second receptor for attachment to another molecule of the antigen. In the case of Rh +ve erythrocytes, an anti-Rh incomplete antibody may coat the erythrocytes but not cause them to agglutinate (Coomb's test) (64). An incomplete antibody is prepared either directly by using papain, bromelain etc. enzymes, which fragments complete circulating antibodies into 2 Fab and 1 Fc portions due to cleavage of an immunoglobulin between CH1 and CH2 regions (the hinge region of the immunoglobulin) or indirectly through an intermediate F(ab')₂ (65-76) and these immunoglobulin fragments are associated with the greater advantages over the intact immunoglobulin (69, 77). Lastly, by virtue of its nature, the chances of hypersensitivity due to the incomplete antibody itself are also very less.

Identification of causal antigens

It has been shown that oligoclonal T-cell expansions are more frequently observed in the heart lesions than in the PBMC of patients with severe RHD. Researchers have identified five immunodominant M5 peptides contained in the N-terminal M5 protein regions that are not only preferentially recognized by PBMC from patients with severe or mild RHD but also by intralesional and peripheral T cell clones (63). Thus for producing complete (27, 78) and then incomplete antibodies in vitro, there is need to first identify the particular antigen(s) in the patient which had led to the cross-reactivity. For this purpose, PBMC would be derived from peripheral blood sample of the patient and also intralesional T cells possibly from heart tissue sample(s). These would be used for the identification of the peptides responsible for the disease (36, 40). Complete and then incomplete antibodies are formed by using these peptides for the immunotherapy for the patient(s) by the two methods of hybridoma technique available for the production of monoclonal antibodies.

THE HYPOTHESIS

Aim:

The postulated hypothesis is aimed to use incomplete antibodies to prevent participation of body tissues (heart, joints, brain and skin) in the antigen-antibody reaction of delayed type hypersensitivity owing to their property of heterophilic antigenicity with the bacterial antigen(s). This will be achieved by administration of incomplete antibodies where they will cover maximum antigenic sites of the body tissues and block further antigenic stimulation by the bacterial antigens also. This technique is exemplified by suggested use of omalizumab in asthmatic patients, post traumatic therapeutic vaccination, immunotherapy in hemolytic disease of new born in the pregnant mother and as a diagnostic test in brucellosis (79-85).

The postulation:

It is proposed that the administration of incomplete antibody which is associated with lowered steric hindrance and possesses greater affinity for antigens as compared to complete antibody leads to the covering of the heterophilic antigenic sites in heart, joints, brain and skin (corresponding incomplete antibodies), and at the same time the active sites of M protein of streptococcus also, if present. Thus, the antigen will be prevented from exposure to circulating antibodies, T cells and antigen presenting cells which will lead to reduction or cessation of the progression of antigenic-stimulation which in turn would decrease immunoglobulin production and sensitized T cells (59, 61) resulting in subsidence of the hypersensitivity reaction and gradual suppression of memory cells (60). The subsidence of the hypersensitivity reaction can be assumed to be accelerated and enhanced by the cessation of interaction of incomplete antibodies with inflammatory cells owing to the absence of Fc portion in the incomplete antibodies (54-55). The amount of the incomplete antibody can be decided on the basis of existing antibody and sensitized T cells in accordance with the available titer in the patients which can result in greater precision as the incomplete antibodies will be blocking corresponding M proteins and heart tissues owing to their similar antigenic structure thus blocking overall antigenic stimulation. This prophylactic measure taken against the development of rheumatic heart disease may be instrumental in improving the quality of life and its expectancy even in patients who have already developed RHD and in whom the damage is still going on.

Significance of the hypothesis:

1. Delay in the rate or even prevention of progression of the disease.

2. Possibility of development of resistance and side effects against the proposed therapy is very less as compared to the current prophylactic measure (penicillin, corticosteroid).

3. The significance of the hypothesized immunomodulated technique can be enhanced by its combination with conventional therapy.

4. It may prove better than the proposed vaccination therapy as the latter could be less significant after the initiation of the autoimmune aggression (59, 63, 86) as their main target is to prevent bacterial growth. In vitro, clinically it is a difficult task to refer all the patients of pharyngitis for preliminary streptococcal tests in the developing countries for diagnosis and access to vaccination schedules (86-87).

5. Finally, the hypothesized concept can also be applied in other autoimmune diseases such as diabetes mellitus type I, systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis, post-streptococcal glomerulonephritis etc. (88).

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