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Overview of Pathogenesis Rheumatic Heart Disease and its Proper Management

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Abstract: **Rheumatic heart disease (RHD) is cardiac inflammation and scarring activated by an autoimmune response to infection with group A streptococci. In the intense phase, this condition consists of pancarditis, including inflammation of the myocardium, endocardium, and epicardium. Chronic disease is manifested by valvular fibrosis, leading to stenosis and/or insufficiency. This review provides an overview of the current evidence of pathogenesis of RHD, and we also intended to discuss the treatment approaches and prevention that can be taken in advances to avoid RHD. Very detailed search of the literature about Rheumatic heart disease was performed among following databases; PubMed/MIDLINE, and Embase for all relevant articles which were published until December, 2016. We specifically search for studies that are discussing the management and pathogenesis of RHD, we restricted our search for only English language publish articles with human subject. Cytokines play an essential role in inflammation and regulation of immune reaction in RF/RHD and IL-10 gene polymorphism might explain genetic predisposition in RHD patients. Specific medical treatment to manage or prevent heart damage and main prevention of RF continue to be evasive. Main prevention has to depend upon creating a vaccine to prevent GAS infection related suppurative as well as non-suppurative disease manifestations.**

Keywords: **Rheumatic heart disease.**

1. INTRODUCTION

Rheumatic heart disease (RHD) is cardiac inflammation and scarring activated by an autoimmune response to infection with group A streptococci. In the intense phase, this condition consists of pancarditis, including inflammation of the myocardium, endocardium, and epicardium. Chronic disease is manifested by valvular fibrosis, leading to stenosis and/or insufficiency (**Figure 1**) [(1)].

Rheumatic fever is rare prior to age 5 years and after age 25 years; it is most regularly observed in teenagers and children. The highest incidence is observed in children aged 5-15 years and in underdeveloped or developing nations where prescription antibiotics are not routinely given for pharyngitis and where compliance is low [(2)].

RHD is still a significant health issue in several countries due to the heart sores that follow a rheumatic fever (RF) episode in 30-45% of patients. The incidence of intense RF (ARF) in some developing countries surpasses 50 per 100,000 children. The worldwide prevalence of RHD is at least 15.6 million cases, and this disease is responsible for around 233,000 deaths/year [(3)]. RHD results from autoimmune responses activated by an unattended S. pyogenes throat infection causing extreme valvular damage in genetically prone people. Reoccurrences of ARF play a crucial role in the worsening of valvular lesions [(4,5)].

Rheumatic fever is a late inflammatory, nonsuppurative complication of pharyngitis that is triggered by group A-hemolytic streptococci [(6)]. Rheumatic fever results from cellular-mediated and humoral immune actions happening 1-3 weeks after the beginning of streptococcal pharyngitis. Streptococcal proteins display molecular mimicry acknowledged by the body immune system, specifically bacterial M-proteins and human cardiac antigens such as myosin [(6)] and valvular endothelium. Antimyosin antibody acknowledges laminin, an extracellular matrix alpha-helix coiled protein, which is part of the valve basement membrane structure [(4,6)].

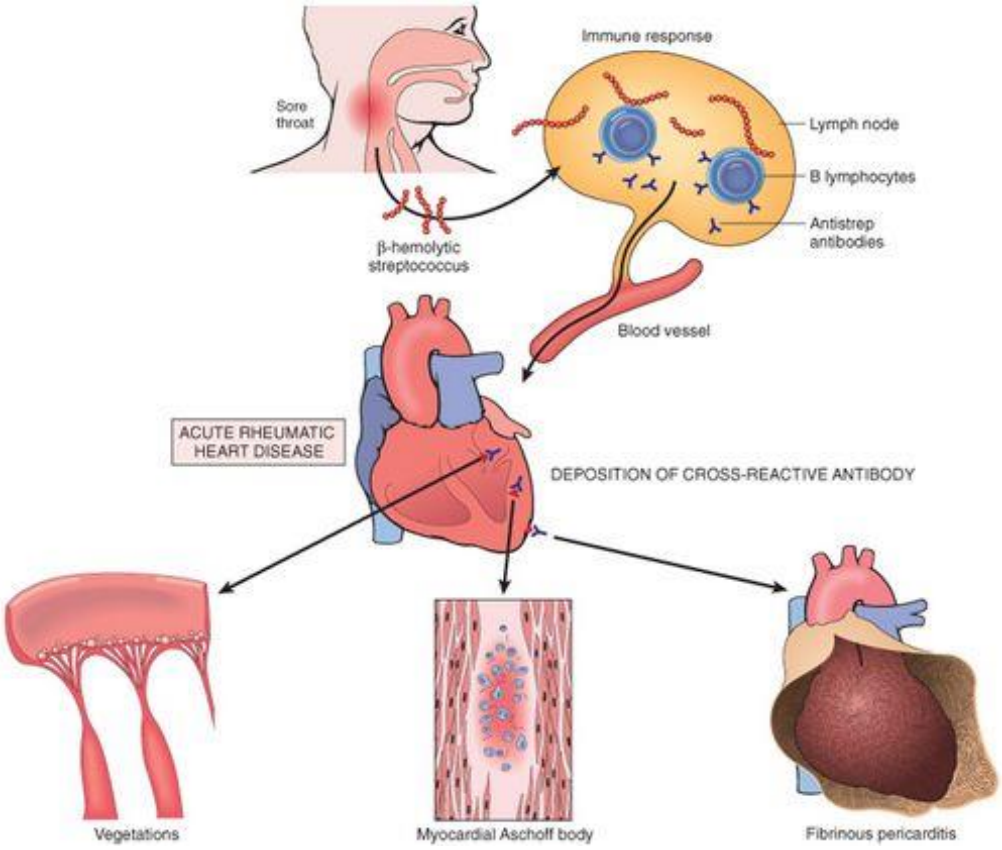

Figure 1: RHD process.

This review provides an overview of the current evidence of pathogenesis of RHD, and we also intended to discuss the treatment approaches and prevention that can be taken in advances to avoid RHD.

2. METHODOLOGY

Very detailed search of the literature about Rheumatic heart disease was performed among following databases; PubMed/MIDLINE, and Embase for all relevant articles which were published until December, 2016. We specifically search for studies that are discussing the management and pathogenesis of RHD, we restricted our search for only English language publish articles with human subject, and we used a following Mesh terms in our search: "Rheumatic heart disease" OR "RHD" combined with "pathogenesis", "prevention" and "treatment" OR "therapy".

3. RESULTS

- ***Pathogenesis of RHD***

The pathophysiology of RHD stays incompletely understood, with host, bacterial, environmental, and genetic factors all linked in its pathogenesis. Group A b-hemolytic Streptococcus (GAS) infection is undoubtedly included, the disease has strong heritability and significant variation in natural history and severity according to host factors and location. Classically, ARF usually occurs 2 to 6 weeks after an episode of unattended GAS pharyngitis in approximately 0.4% to 3.0% of patients [7,8]. In patients with an active episode of severe rheumatic fever (ARF), the throat culture might be unfavorable for GAS and antibody titers for streptococcal enzymes, such as streptolysin O and DNase, must be elevated. Rheumatic carditis is classically described as a pancarditis, including the myocardium, pericardium, and endocardium [9]. Histopathologically, rheumatic myocarditis is identified by the presence of focal perivascular inflammation, described Aschoff bodies [10,11]. The development of RHD takes place in some patients with ARF as a result of valvular damage from an immune-mediated procedure after one or duplicated infections. Among Brazilian children with ARF, 72% developed persistent valvular disease and 16% established serious mitral and/or aortic disease [12]. A dominating theory is that crossreactivity in between moieties in the GAS stress and cardiac antigens are accountable for immunologic activation and eventual tissue damage [7].

The streptococcal M protein and sarcomeric proteins, specifically specific "rheumatogenic" M types (1, 5, 6, 14, 18, and 24) are considered likely candidates due to their similarity with intramyocellular proteins [13]. Anti - group A carbohydrate antibodies have actually been implicated in the pathogenesis of valvulitis, with titer levels falling after surgical elimination of swollen valves [14]. Endothelial activation is likewise a needed element of this theory of pathogenesis, as the heart antigens are intracellular. Antibody-mediated endothelial damage leads ultimately to T-cell activation, scarring, and seepage [15,16]. Nevertheless, some scientists have actually noted that the M-protein cross-reactivity theory does not adequately explain the multisystem nature of the disease, or the particular pattern of cardiac participation with tendency for valvular tissue and sparing of the myocardium [17]. Although interstitial seepage and perivascular Aschoff blemishes are commonly seen, myocardial necrosis is hardly ever observed, with an absence of elevation of cardiac biomarkers [18,19]. An alternative mechanism for immune activation and molecular mimicry has actually been recommended, including collagen autoimmunity just like other collagen-mediated autoimmune disease (**Figure 2**) [17].

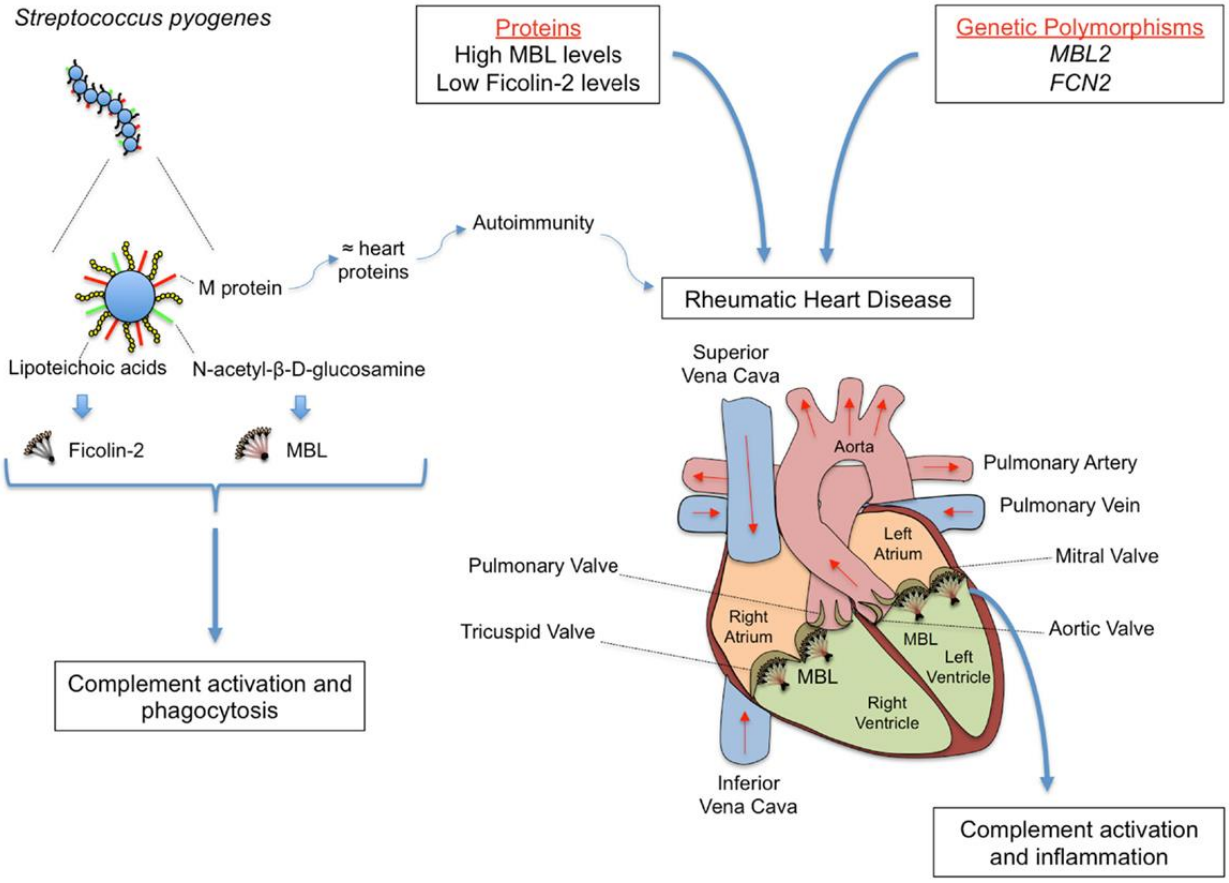

Figure 2: Rheumatic fever (RF) and its most severe sequel chronic rheumatic heart disease (RHD) are chronic inflammations that follow oropharynx infection by Streptococcus pyogenes.

Roles of Cytokines in pathogenesis of RHD:

Cytokines seem to play a critical function in the activation of inflammatory and immunological reactions in RF. It has been shown that peripheral blood mononuclear cells (PBMC) from children with RF produce more TNF-α than healthy controls [20]. Moreover, interleukin-6 (IL-6) and TNF-α are considered inducers of the intense phase of RF and are highly correlated with C-reactive protein [21,22]. TNF-α is a proinflammatory cytokine that has actually been related to the seriousness of various autoimmune and inflammatory diseases. The gene that encodes this cytokine is located within the MHC region on chromosome 6p21.3. This area is extremely polymorphic, and the TNF-alpha gene also includes a large number of polymorphisms [23]. A few of these were investigated in RF/RHD patients in various countries. An SNP in the promoter region of TNF-alpha (-308 A) was connected with vulnerability to RHD in Mexico, Turkey, Brazil, and Egypt [21,22,23]. The TNF-alpha -238 G allele was also connected with RHD in Brazilian and mexican patients [24,25]. The TNF-alpha gene has a proinflammatory effect and is most likely related to the exacerbation of the inflammatory reaction in RF/RHD patients who provide with high serum TNF-α levels [20,22,26] and large numbers of TNF-α-producing cells in the throat and valves [4].

Role of Interleukin-10 in pathogenesis of RHD:

Interleukin-10 (IL-10) is an essential immunoregulatory cytokine which helps in managing immune actions through its pleiotropic effects [27]. Gene encoding IL-10 is located on chromosome 1 and includes 5 exons [28]. IL-10 has actually been examined by many researchers and it is found that promoter area of IL-10 gene is extremely polymorphic and is associated with reduced or increased expression of cytokine [29]. IL-10 is produced by monocytes, NK cells, B cells, T cells [30,31] and CD4+ Foxp3+ CD25+ regulatory T cells (Treg) [32], however lymphocytes relatively produce low levels of this cytokine. In the recent past, it has actually been observed that T-regulatory type 1 (Tr1) cells, which is a subset of Tregs, produces considerably high levels of IL-10 in humans and rodents [33]. It is anti-inflammatory in nature and prevents production of pro-inflammatory Th1 cytokines (IL-12 and IFN-c) which in turn results in reduced leucocyte maturation and recruitment of cells during inflammation. Other important functions of IL-10 are regulation of immune cells (T cells, B cells, mast cells and antigen presenting cells) and tolerance to self-antigens [33]. IL-10 likewise plays a crucial role in regulation of antigen discussion and it serves as an immunosuppressive cytokine by hindering MHC II expression and consequently modifying activity of antigen presenting cells [34]. High levels of IL-10 prevent CD28 co-receptor activity present on T-cells and act as an immunosuppressive representative throughout unhealthy condition [35]. Conceivably, these immunomodulatory functions of IL-10 as displayed in (Figure 2), account for its function in pathogenesis of various contagious and autoimmune diseases. It has been shown that inflammatory cytokines might play a pathogenic role in RF/RHD [36]. Cytokine profiles and many other genetic markers have been studied by many scientists to develop an association in between polymorphism of these genes and increased susceptibility towards RF/RHD. Pathogenesis of RHD is not totally understood however the majority of the investigations recommended that molecular mimicry in between Streptococcus pyogenes antigens (M protein and group A carb antigen N-acetylb-d-glucosamine) and human proteins results in autoimmune response which contributes to the pathogenesis of RHD [37].

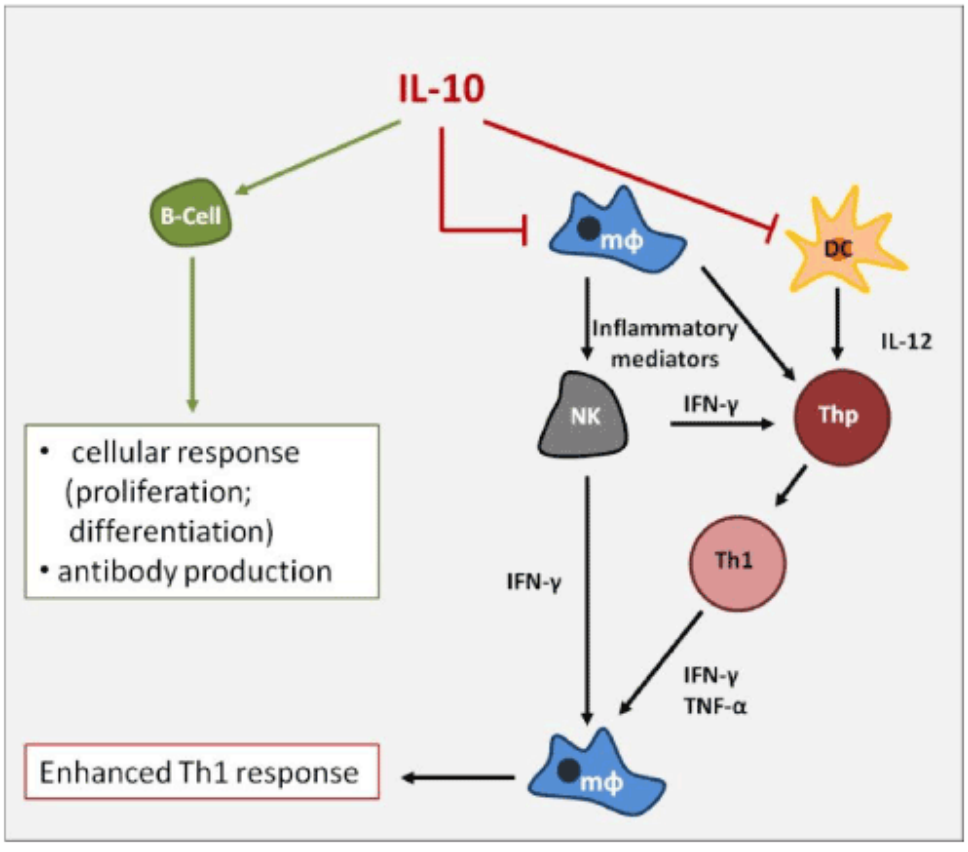

Figure 2. IL-10 is able to modulate the immune reactivity activating the cellular response via B-Cells and inhibiting the IFN-γ- mediated Th1 response.

Management and Prevention of RHD:

Management approaches count on a combined of preventive and restorative strategies. Preventive efforts can avoid the initial GAS infection (primordial prevention), hinder progression from GAS infection or ARF to valvular disease (primary

prevention), or impede intensifying of valvular disease among those with existing RHD (secondary avoidance). Patients with symptomatic chronic valvular disease have limited restorative alternatives with medical therapy, but if required can take advantage of lifesaving surgery or percutaneous interventions. Primary and primordial Prevention Primordial avoidance broadly describes social enhancements in living, sanitation, and hygiene conditions that avoid the transmission of GAS infection. Such environmental change needs significant facilities investment at the country level, however is the most efficient way to modify the trajectory of the disease at the population level [38,39]. In fact, degrading living standards following the economic decrease within the previous Soviet Union has actually led to a boost in RHD occurrence [40]. Primary avoidances with early antimicrobial treatment of streptococcal pharyngitis must avoid the waterfall of immunologic activation that results in ARF. Primary avoidance needs access to penicillin, and ideally to diagnostic tests such as rapid streptococcal testing and microbiology laboratory services. Such gain access to at a population level depends on a well-functioning decentralized health system free of physical and monetary barriers to care, experienced health care workers, and an all set supply of good-quality penicillin, which are typically lacking in endemic regions [41]. The use of clinical choice rules to selectively treat patients with pharyngitis without throat culture can be cost-effective at lowering RHD problem [42]. Secondary prevention refers to the prevention of persistent attacks of ARF through the administration of long-term suppressive antibiotics, therefore halting or delaying the development of valvular disease [42].

Rheumatic valvular stenosis or regurgitation might progress with time. Although mitral regurgitation is the most common type of RHD amongst the young, [43,44] the most typical reason for mitral stenosis globally is RHD [45]. Rheumatic aortic valve disease is usually comorbid with mitral disease, although separated aortic regurgitation can occur [46]. RHD of the tricuspid and lung valves is unusual in isolation, and is usually in addition to mitral disease [47]. The subsequent hemodynamic problems might eventually lead to symptomatic heart failure with ventricular improvement and dilation, progression to valvular cardiomyopathy, and end-stage cardiac arrest. Although, in general, valvular cardiomyopathy is considered a surgical disease, there is some evidence that medical therapy might be useful. A number of studies have actually demonstrated the benefits for left ventricular improvement with angiotensinconverting enzyme inhibitors (ACEIs). For example, in a placebo-controlled study of 47 patients with very little or moderate symptoms and moderate to serious mitral regurgitation from either RHD or mitral valve prolapse, treatment with enalapril was associated with a significant decrease in left ventricular diastolic diameter (by 0.3 cm) and 25% reduction in mitral regurgitation volume after 12 months [48]. Another study using enalapril and nicoradil was connected with a substantial decrease in left ventricular end-systolic index and enhancement in ejection portion at 6 months compared with baseline [49]. In addition, low-dose ACEIs might have advantage in severe rheumatic mitral stenosiswas approved by the very same study.

4. CONCLUSION

Molecular involved in pathogenesis of RF/RHD are still under investigation. Cytokines play an essential role in inflammation and regulation of immune reaction in RF/RHD and IL-10 gene polymorphism might explain genetic predisposition in RHD patients. Specific medical treatment to manage or prevent heart damage and main prevention of RF continue to be evasive. Main prevention has to depend upon creating a vaccine to prevent GAS infection related suppurative as well as non-suppurative disease manifestations.

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