Review Article

Pathophysiology and Pathogenesis of Rheumatic Fever (RF) and Group A Beta - Hemolytic Streptococcal Pharyngitis in Causing Rheumatic Heart Disease (RHD)

Dr. Donozio Tumwebaze*

***Corresponding Author: Dr. Donozio Tumwebaze** MBChB, School of Health Sciences, Kampala International University, Western Campus, Uganda.

Received Date: April 11, 2021
Publication Date: May 01, 2021

Description

Rheumatic Fever (RF) is an immunologically mediated, multi-system inflammatory disease that occurs a few weeks (usually 2 to 3 weeks) following an episode of Group A (Beta-hemolytic) Streptococcal (GAS) Pharyngeal infection.

It is common in children between the age of 5 and 15 years. An estimated 20% of the first-time attack occurs in adults. There is no significant sex or racial predisposition to infection with Streptococci leading to Rheumatic Fever. The rate of development of Rheumatic Fever in individuals with untreated Streptococcal Pharyngitis is estimated to be 3%.

The recurrence of Rheumatic Fever is relatively common in the absence of maintenance of low dose antibiotics, especially during the first 3 to 5 years after the initial episode of the disease. Heart complications may be long-term and severe if the valves are involved.

Survivors of Rheumatic Fever often have to take antibiotics (preferably Penicillins) to prevent Streptococcal infections which could lead to other subsequent episodes of Rheumatic Fever that could prove fatal.

Rheumatic Fever (RF) may progress to Chronic Rheumatic Heart Disease (RHD). This is a stage that involves the heart. In this case, the heart muscle, the myocardium is affected and this may result in symptoms like Shortness of breath, Congestive Heart Failure (CHF) symptoms, Pericarditis causing Pericardial Rub, and Chronic Valvular deformities, characterized by deforming fibrotic Valvular diseases

most often the mitral Valves leading to Mitral valve stenosis.

It should however be noted that Rheumatic Fever does not follow Streptococcal infections at other sites of the body such as skin.

Pathogenesis of Rheumatic Fever

Rheumatic Fever (RF) occurs as a result of antibody cross-reactivity that can involve the heart, Joints, Skin, Subcutaneous tissue, and Brain. Hypersensitivity reaction induced by Group A Beta-hemolytic Streptococci occurs and this is type II hypersensitivity reaction (antigen-antibody interaction/reaction)

The activation of B cells to become plasma cells and subsequent production of antibodies against the cell wall of Streptococci occurs. The antibodies may also react against the Myocardium and joints producing symptoms. Involvement of Joints, Skin, Subcutaneous tissue, Heart, and brain lead to the development of Rheumatic Fever symptoms.

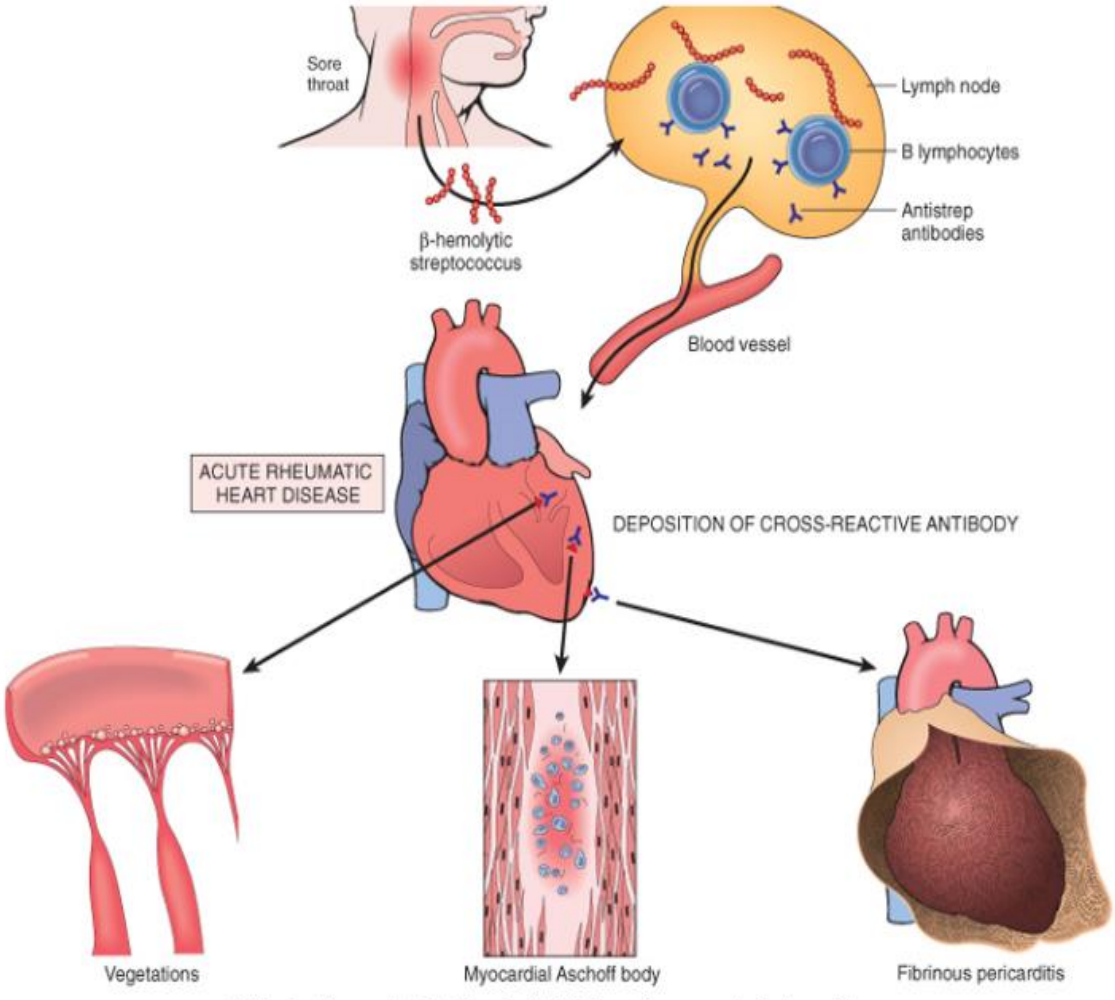


Figure 1

Diagnostic Criteria of Rheumatic Fever

Rheumatic Fever (RF) is diagnosed using ***Modified Jones Criteria.***

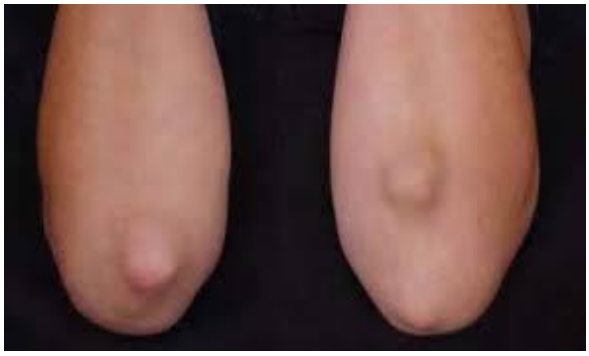
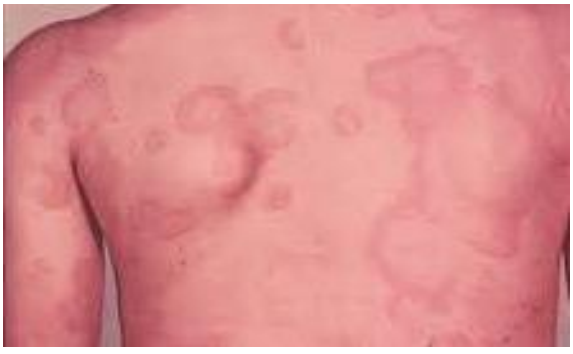
Modified Jones Criteria was first published in 1944 by ***T. Duckett Jones, MD***. It has been periodically reviewed by the American Heart Association (AHA) in collaboration with other groups.

According to ***Modified/Revised Jones Criteria***, the diagnosis of Rheumatic Fever is made when: **2 of the Major Criteria, or 1 Major Criterion plus 2 Minor Criteria are present**, along with evidence of Streptococcal Pharyngeal infection.

The exception to this rule is ***Chorea*** and ***Indolent Carditis,*** each of which by itself could be suggestive of Rheumatic Fever

Major Criteria:

1. ***Migratory Polyarthritis:*** A temporary migrating inflammation of the large joints, usually beginning with the joints of the legs and migrating upwards.
2. ***Carditis:*** Inflammation of the heart muscle which can manifest as Congestive Heart Failure (CHF) with Shortness of breath, Pericarditis with a Rub, or a new Heart Murmur.
3. ***Subcutaneous nodules:*** This involves Painless, firm collections of collagen fibers over bones and/or tendons. They commonly appear on the back of the wrist, the outside of the elbow, and the front of the knees.
4. ***Erythema Magnatum:*** A long-lasting rash that begins on the trunk or arms as macules and spreads outwards to form a snake-like ring while clearing in the middle. The rash never starts on the face and is made worse with heat.
5. ***Sydenham's Chorea (St. Vitus Dance):*** A characteristic series of rapid purposeless movements of the face and arms. This commonly occurs later in the disease process.

A  **B** 

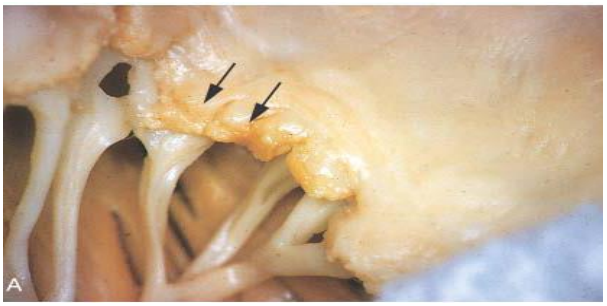


Figure 2: A: Subcutaneous Nodules, **B**: Erythema Magnatum, **C**: Valvular Deformities (stenosis) as seen in Carditis.

Minor Criteria:

1. ***Fever***
2. ***Arthralgia:*** Joint pains without swelling
3. ***Raised Erythrocyte Sedimentation Rate*** or C reactive protein
4. ***Leucocytosis***
5. ***ECG showing features of heart block*** such as prolonged PR interval
6. ***Supporting evidence of Streptococcal infection;*** elevated or rising Antistreptolysin O titer or DNAase
7. ***Previous episode of Rheumatic Fever or inactive Heart Disease***.

From the above Criteria, diagnosis can be made when: 2 Major criteria or 1 Major Criterion plus 2 Minor Criteria are present in a patient.

Morphological Changes in Rheumatic Fever

1. ***Characteristic Aschoff bodies:*** Composed of swollen eosinophilic collagen surrounded by Lymphocytes, occasional plasma cells, and plump macrophages called Anistschkow cells (pathognomonic for Rheumatic Fever). The larger macrophages become multinucleated to form Aschoff giant cells
2. ***Pancarditis:*** Diffuse inflammation and Aschoff bodies may be found in Pericardium, Myocardium, or Endocardium.
3. ***Bread-and-butter Pericarditis:*** The inflammation is accompanied by a fibrinous and a sero-fibrinous Pericardial exudate.
4. ***Myocarditis:*** This takes the form of Aschoff bodies within the interstitial connective tissues, often perivascular.
5. ***Concomitant involvement of the Endocardium*** and the left-sided heart valves by inflammatory foci results in fibrinoid necrosis within the cusps or along with the tendinous cords on which sit its

small *vegetations verrucae* (1 to 2 mm) along the line of closure.

Morphological changes in Chronic RHD

1. Organisation of the acute inflammation and subsequent fibrosis.
2. Valvular leaflets become thickened and retracted, causing permanent deformity, commissural fusion and shortening.
3. Thickening and shortening of the tendinous cords/chordate tendinae of the heart (mitral or tricuspid).
4. Microscopically, there is diffuse fibrosis and often neovascularisation that obliterate the originally layered and avascular leaflet architecture.
5. Aschoff bodies are replaced by a fibrous scar.
6. Rheumatic Heart Disease (RHD) is the most frequent cause of Mitral valve stenosis (about 99% of cases).

Mitral valve involvement alone accounts for about 65 to 70% of cases. Both Mitral valve and Aortic valve involvement account for about 25% of cases.

7.Fibrous bridging across the Valvular commissures and calcification creates *fish mouth* or *buttonhole* stenoses.

8. With tight Mitral stenosis, the atrium progressively dilates and may harbor *mural thrombus* either in the appendage or along the walls.
9. Long-standing Congestive changes in the lungs may induce pulmonary vascular and parenchymal changes and with time this could lead to right ventricular hypertrophy.

Management of Rheumatic Fever

1. Use of antibiotics (Penicillins are specifically indicated and of better choice in the treatment of Rheumatic Fever. An example is Benzyl Penicillin 0.6 -1.2g I.M or Penicillin V 250 - 500mg 12hourly or 8hourly orally for 10days. Give Erythromycin or Azithromycin for 10days in case of patients who are allergic to Penicillins.
2. Give analgesics and anti-inflammatory drugs for Carditis and arthritis. Aspirin is the drug of choice in the treatment of Rheumatic Fever. Give aspirin 100mg/kg/d in divided doses for 2days, then 70mg/kg/d for 6weeks. Monitor salicylate level. Toxicity causes Tinnitus, hyperventilation, and metabolic acidosis.
3. Immobilise the joints in severe arthritis.
4. Give Haloperidol (0.5mg/8hourly orally) or Diazepam if Chorea symptoms are present.
5. In case of heart failure, treat appropriately.
6. Bed rest is prescribed for at least 2 weeks to 3 months depending on the severity.

Prognosis

About 60% of cases with Carditis develop Chronic Rheumatic Heart Disease. This correlates with the severity of the Carditis. Acute attacks last an average of 3 months. Recurrence may be precipitated by further Streptococcal infections, pregnancy, or use of a pill.

Cardiac sequelae affect Mitral (70%), aortic (40%), tricuspid (10%), and pulmonary (2%) valves. Incompetent lesions develop during the attack, stenoses occur years later.

Secondary Prophylaxis

Prevention of recurrence is achieved by eradicating the acute infection and prophylaxis with antibiotics. The American Heart Association (AHA) recommends daily or monthly prophylaxis, long-term prophylaxis and perhaps for life.

Use Penicillin V 250 - 500mg 12hourly orally. Alternatives are Sulfadiazine 1g daily (0.5g if <30kg), or Erythromycin 250mg 12hourly (if allergic to Penicillins). Duration: If Carditis and Persistent Valvular disease are present, continue at least until the age of 40 (sometimes lifelong). If Carditis but no Valvular disease, continue for 10years. If there is no Carditis, 5years of prophylaxis (until age 21) is sufficient.

References

1. Muir's Textbook of Pathology, Thirteenth Edition, Chapter 12.

2. Robbin's and Cotran: Pathologic Basis of Disease, Seventh Edition, Chapter 12.

3. Murray Longmore, Ian B. Wilkinson, Edward H. Davidson, Alexander Foulkes, Ahmad R. Mafi: Oxford handbook of Clinical Medicine, Eighth Edition, Chapter Three, Page 136.

4. Stephen Chapman, Grace Robinson, John Stradling, Sophie West, John Wrightson: Oxford Handbook of Respiratory Medicine, Third Edition, Chapter 39, Page 398, 399.

5. Uganda Clinical Guidelines, 2016 Edition.

Volume 2 Issue 4 May 2021

©All rights reserved by Dr. Donozio Tumwebaze