Rheumatic heart disease

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MED441
KING SAUD UNIVERSITY

Immunology
Team 441

Cardiovascular Block

Editing file

Objectives

1. To understand basis of rheumatic fever as an immunologically mediated **late complication** of Streptococcal infection

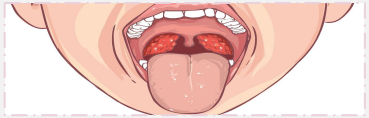
2. To know that autoimmunity results from production of cross reacting antibodies against Streptococcal antigens

3. To describe rheumatic heart diseases of the several manifestations of rheumatic fever

4. To know the signs,symptoms,pathogenesis, treatment and prophylaxis of rheumatic heart disease

Rheumatic Fever

Helpful video
"Ninja Nerd"



Definition

- Rheumatic fever is an acute, multisystem, autoimmune **inflammatory disease** which may develop **after a Group A Streptococcal** infection such as:
  - Streptococcal throat infection (Pharyngitis)
  - scarlet fever
- Can involve the **heart**, **joints**, **skin**, and **brain**

Epidemiology

- ~3%of persons with **untreated group A streptococcal pharyngitis** develop rheumatic fever
- 15-20 million new cases a year in developing countries
- It commonly appears in children ages **5 through 15**

Risk factors

- Low standard of living
- Crowding
- Individual **(HLA)** susceptibility
- The various HLA -typing methods
- Ways of grouping the cases
- Antigen-presenting cells bearing the **HLA-DR7** molecule from RHD patients preferentially recognize heart-tissue protein

HLA-DR7 (human leukocyte antigen HLA). This protein is a MHC class II molecule which has a role of increasing the possibility of developing rheumatic fever. ***#team439***

Organism

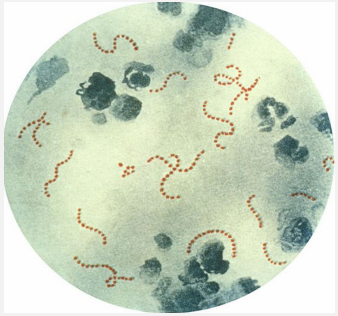
How does Rheumatic heart disease develop? Streptococcus Pharyngitis → Rheumatic fever → Rheumatic heart disease (RHD)

#439

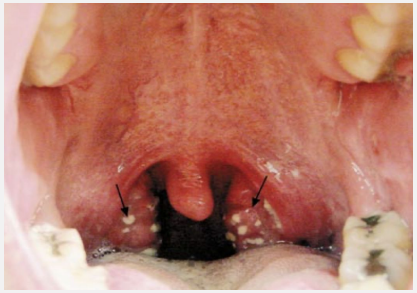
Caused by **group A** β-haemolytic **streptococcus**

Antibody and cellular immune response **cross reacts** with human connective tissue

There is a latent period of ~**3 weeks (**1–5 weeks) between the group A streptococcal infection and the appearance of the clinical features of Rheumatic fever (RF)

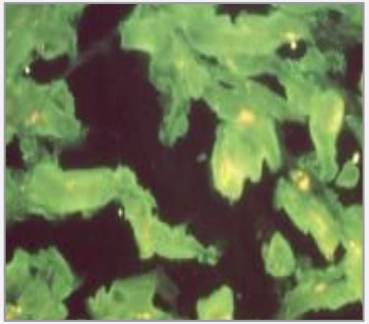


All cases associated with recent infection (e.g.pharyngitis)



Virulence factors of Group A streptococcus

M protein	Adherence of Streptococcus pyogenes to host cells & inhibiting the host immune response
Hyaluronic acid capsule	Camouflages the bacterium
Streptokinases	Dissolve blood clots
Peptidases	Degrades proteins involved in immune response
Pyrogenic toxins	Stimulate fever, rash & shock
Streptolysins	Lyse erythrocytes, leukocytes & platelets



Immunofluorescent staining of heart muscle with serum obtained from an acute rheumatic fever patients

Pathogenesis

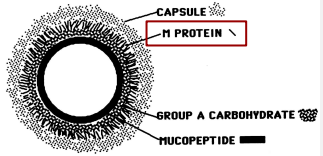
شرح

الأجسام المضادة الي ينتجها الجسم عشان تحارب البكتيريا صارت تحارب اعضاء الجسم الي تشبه البكتيريا في بروتيناتها والي غالبا تصيب المناطق بجوار الشرايين الصغيرة

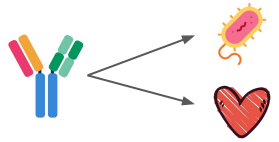
- Rheumatic fever affect the periarteriolar* connective tissue.
  *means adjust to Arteriole
- It is believed to be caused by **antibody cross-reactivity.**
- This cross-reactivity is a Type **II** hypersensitivity reaction and is termed molecular mimicry.

Pathogenesis Steps :

1 Group A streptococcus pyogenes has a cell wall composed of branched polymers which sometimes contain **M proteins** that are highly antigenic



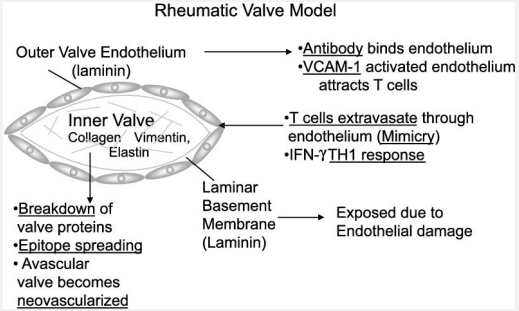
2 The antibodies which the immune system generates against the **M proteins** may cross react with cardiac myofiber protein myosin and smooth muscle cells of arteries, inducing cytokine release and tissue destruction

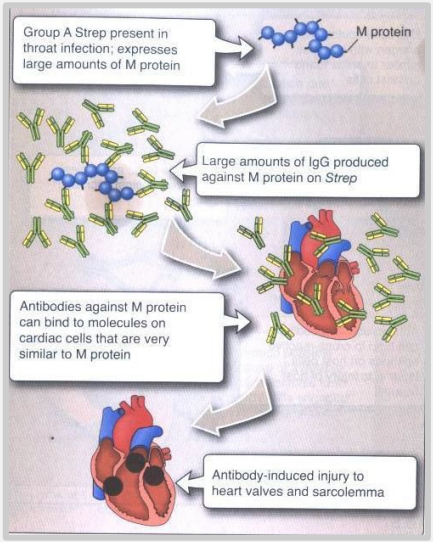


3 This inflammation occurs through direct attachment of complement and Fc receptor-mediated recruitment of neutrophils and macrophages

Pathogenesis

Diagram illustrating the process of initial **mimicry** which leads to **granuloma formation**, gamma interferon production and scarring in the valve. After the initial process has developed **inflammation** in the valve, other proteins in the valve may then be recognized by the immune system leading potentially to **epitope spreading** and responses against other valve proteins such as vimentin and collagen.





1. Immune system becomes sensitive two some violence factors of streptococcus such as M protein
2. Antigen presenting cells present the antigen (M protein) to the helper T cell
3. T cells will activate B cells to produce antibodies against the cell wall of Streptococcus
4. Antibodies will cross react with whatever mimics the M protein (myocardium, valvular tissue and joints) producing the symptoms of RF
5. Tissue will be destructed (endothelium) making the inner structure of the valve exposed
6. A granuloma will be formed, gamma interferon produced and the valves will be scarred
7. The granuloma will be chronic
8. The immune system will produce antibodies against proteins inside the inner valve leading to an epitope spread

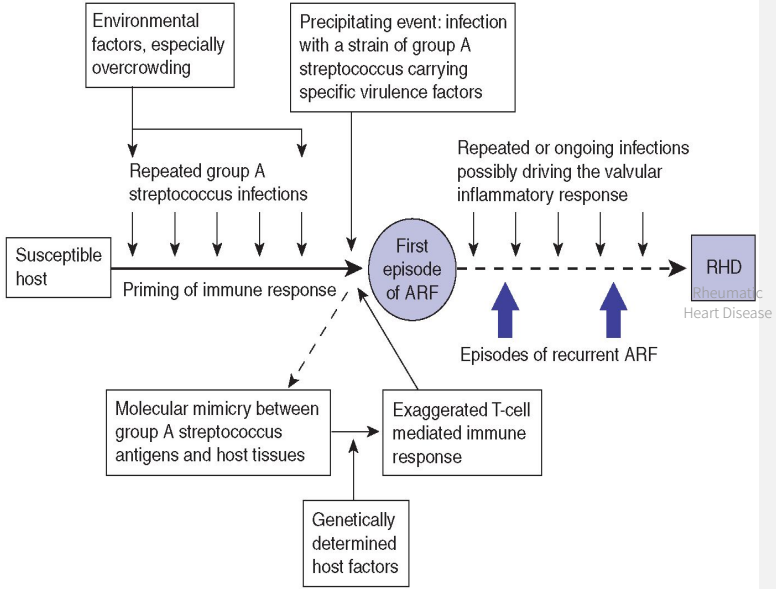
Thank you #team435 - #team439

Pathophysiology

1. During a Streptococcus infection, activated **antigen presenting cells** (APCs) such as macrophages present the bacterial antigen to helper T cells

2. **Helper T cells** subsequently **activate self reactive B cells** and induce the production of antibodies against the cell wall of Streptococcus

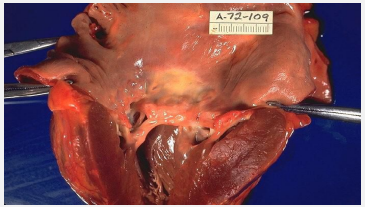
3. However the antibodies may also react against the myocardium and joints, producing the symptoms of rheumatic fever



Clinical Presentations

Heart

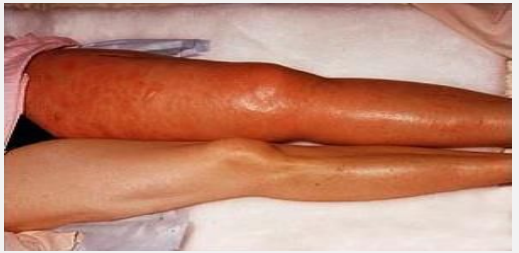
- Up to 60% of patients with ARF progress to Rheumatic Heart Disease **(RHD)**
- The heart is the only manifestation of ARF (acute rheumatic fever) with significant potential to cause long-term disability and/or death
- The endocardium, pericardium, or myocardium may be affected **(pancarditis)**
- Valvular Damage is the hallmark of rheumatic carditis. The **mitral valve** is almost affected



Left ventricle has been cut open to display characteristic severe thickening of mitral valve, thickened chordae tendineae, and hypertrophied left ventricular

Joints (arthritis)

- This is usually polyarthritis, sometimes **flitting** from joint to joint (**migratory**), affecting the **larger joints more** than the smaller ones.
- Swelling, redness and tenderness are the common findings and occasionally joint effusions.



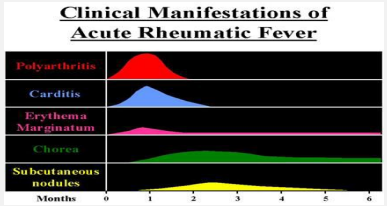
Inflamed knee Joint

Clinical Presentations

Central Nervous System

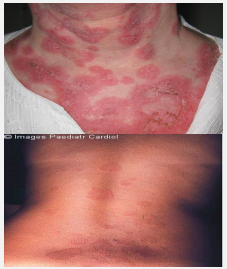
Sydenham's chorea

- Occurs in **children**, rare in adults
- The choreiform movements affect particularly the **head** and the **upper limbs**
- They may be generalized or restricted to one side of the body (hemichorea) (=either right or left)
- Chorea eventually resolves completely, usually within 6 weeks
- likely due to **molecular mimicry**, with **autoantibodies reacting with brain ganglioside**



Skin

Erythema Marginatum (Skin lesions)
The classical **erythema marginatum** lesions with prominent margins slightly raised لها زي الحواف او الحدود المرتفعة شوي

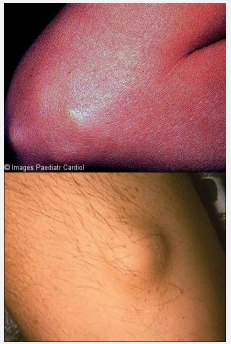


Subcutaneous nodules

-These are **painless, round, firm lumps** over laid by normal looking skin

-They range from a few millimeters to 1.5 cm in diameter

- They are normally localized over **bony prominences** like the elbow, shin and spine, they sometimes last longer than a month

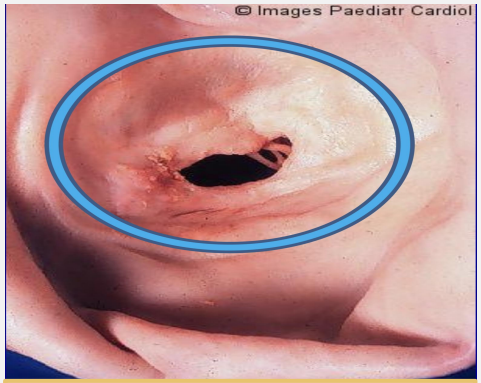


Clinical Presentations

Subsequent attacks

- Increased vulnerability to **reactivation of disease** with subsequent streptococcal infections
- **Same** symptoms with each attack
- Carditis worsens with each attack
- Heart valves (mitral) are frequently **deformed**
- Heart failure **develops** after decades
- Can be **Acute**, **recurring**, **chronic**
- **Chronic** disease can lead to **fibrosis** (chordae tendineae + valve cusps) which makes the valves stiff and unable to move the blood in proper way

Opened stenotic mitral valve



Stenotic mitral valve seen from left atrium

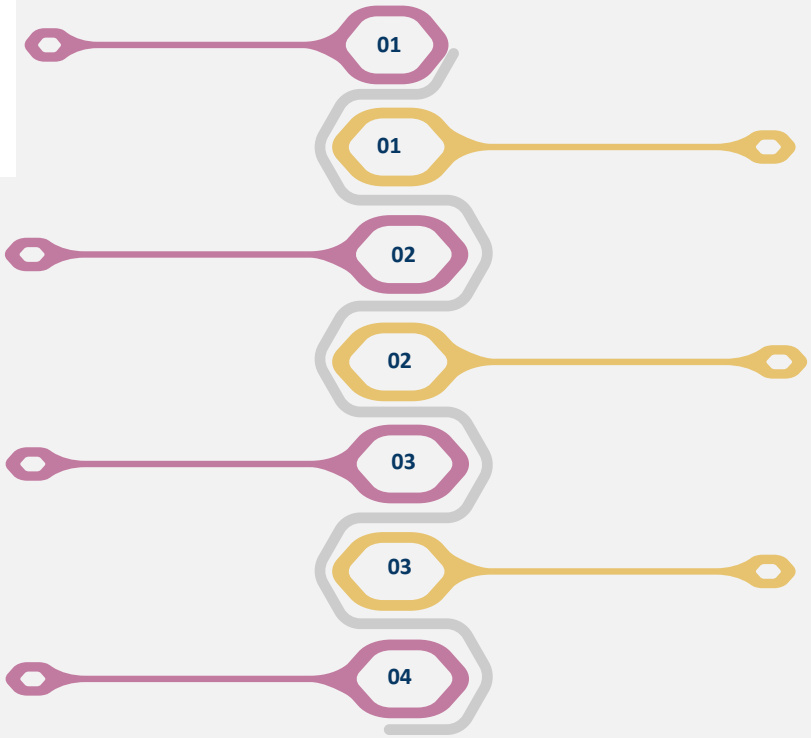
Investigation of Rheumatic Fever

Antistreptolysin O (ASO) titer
– At least 80% of patients with ARF have an **elevated antistreptolysin O** titer at presentation
(Rising titer is more convincing)

Anti-DNAse B

Anti-hyaluronidase test

Throat culture for group A streptococci (2 - 3 cultures)
(gold standard)



Treatment of Rheumatic Fever

Treat first strep throat infection with penicillin

Treat other manifestations symptomatically

Prophylactic long term anti-strep therapy given to anyone who has had rheumatic fever

Take home messages

FOR THE LECTURE SUMMARY
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For questions done by Q Bank team
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1. Rheumatic Heart Disease Results From Cross Reacting antibodies binding the heart valves.
2. Repeated attacks of Streptococcal throat infection over the years damage heart valves resulting in either stenotic or incompetent heart valves.
3. Treatment Involves Surgical Replacement of the damaged heart valves.
4. In patients with Rheumatic Fever long term administration of penicillin is recommended for prevention of future infections by group A Streptococcus.

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★ Special thanks and gratitude to Immunology Team (439)

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