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Rheumatic Heart Disease

Objectives:

- To understand basis of rheumatic fever as an immunologically mediated late complication of Streptococcal infection.
- To know that autoimmunity results from production of cross reacting antibodies against Streptococcal antigens.
- To describe rheumatic heart disease as one of the several manifestations of rheumatic fever.
- To know the signs, symptoms, pathogenesis, treatment and prophylaxis of rheumatic heart disease.

Red: important notes.

Grey: extra information and explanation.

15-20 million new cases a year in developing countries

Epidemiology of Rheumatic Fever (RF)

~3% of persons with untreated group A streptococcal pharyngitis develop rheumatic fever

sk factors:

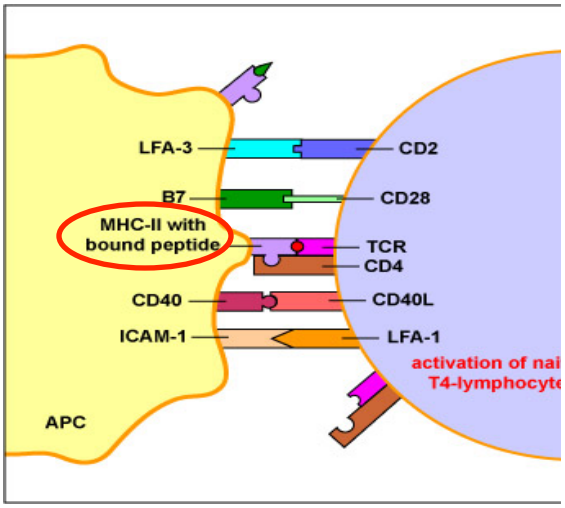
Crowding "in developing countries"

Low standard of living "due to immunodeficiency"

ndividual (HLA) susceptibility "Genetic factors"

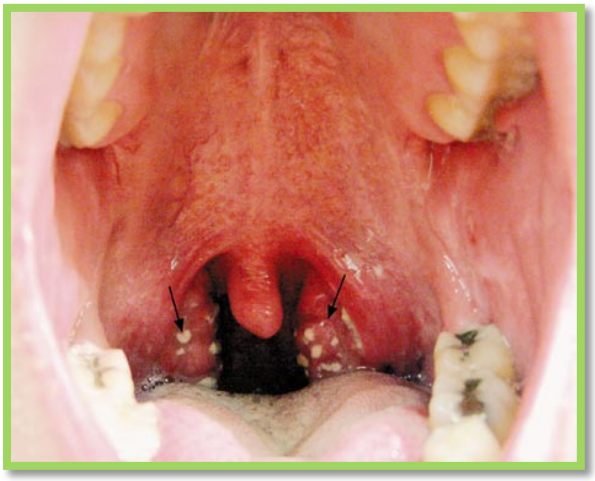
Antigen-presenting cells bearing the HLA-DR7 molecule from RHD patients preferentially recognize heart-tissue protein "those patients with HLA-DR7(HLA-DR7 is on the MHC class2) are more susceptible to develop heart disease "

We can also add 4) Environmental factors



Rheumatic fever

definition	age groupe	organs involved
• Rheumatic fever is an inflammatory disease which may develop after a Group A Streptococcal infection(group A β-hemolytic streptococcus) • Strep. throat infection or scarlet fever	• it commonly effects children between 5-15 years • however it can arise in adulthood	• heart • joints • skin • Brain



- **Caused by group A β-hemolytic streptococcus**
- **The onset of the clinical features is delayed about 3-4 weeks after the infection "LATENT PERIOD"**
- **All cases associated with recent infection (e.g. pharyngitis) or any upper tract**
- **Antibody and cellular immune response cross-reacts with human connective tissue**

This organism can also cause other diseases and activate other Hypersensitivity reactions :

Post streptococcal glomerulonephritis is caused by streptococcal antigen-antibody immune complexes (Type III hypersensitivity reaction). Post streptococcal glomerulonephritis is an auto-immune disease affects kidney

Virulence Factors: (that is secreted by Group A Streptococcal or part of its structure)

M proteins :	Attachment & interferes with host immune response (doctor said this protein stimulate immune response)
Hyaluronic acid capsule:	Camouflages the bacterium
Streptokinases:	Dissolves blood clots
Peptidases:	Degrades proteins involved in immune response
Pyrogenic toxins :	Stimulate fever, rash & shock
Streptolysins:	Lyse erythrocytes, leukocytes & platelets

- **Rheumatic fever affect the peri-arteriolar connective tissue**
- **It is believed to be caused by antibody cross-reactivity**

Type II hypersensitivity reaction (molecular mimicry)

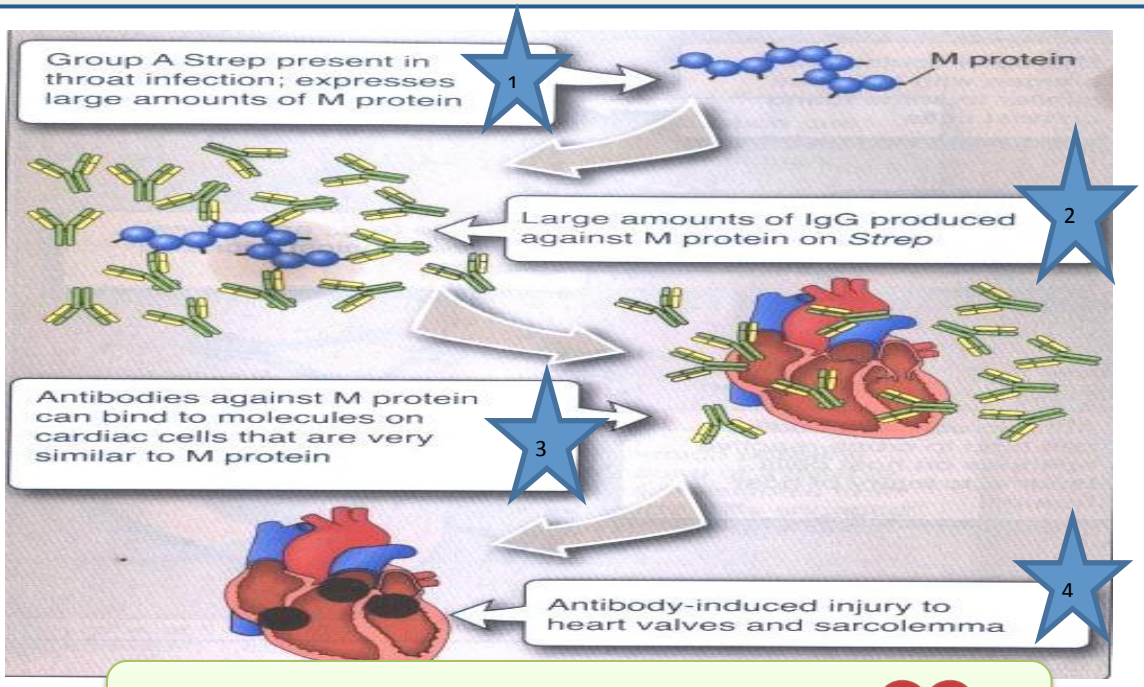
To differentiate between hypersensitivity type 2 and type 3 you should know that type 2 when antigen is attached to tissues like in Rheumatic Fever, but type 3 the antigen is free like in Post streptococcal glomerulonephritis

PATHOGENESIS

Group A streptococcus cell wall composed of branched polymers which sometimes contain **"M proteins"** that are highly antigenic

Immune system generates **antibodies against the "*M proteins*"**
may cross react with cardiac myofiber protein myosin and smooth muscle cells of arteries. inducing cytokine release and tissue destruction

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



Note: The issue is in the presence of IgG which attack the

1\ Molecular Mimicry is when a structure of an antigen is similar to a structure in the human body making the immune system mistakenly attack the similar structure in the body.
2\ The complement system is a part of the immune system that helps or complements the ability of antibodies and phagocytic cells to clear pathogens from an organism

3\Fc receptors bind to antibodies that are attached to infected cells or invading pathogens. Their activity stimulates phagocytic or cytotoxic cells to destroy microbes

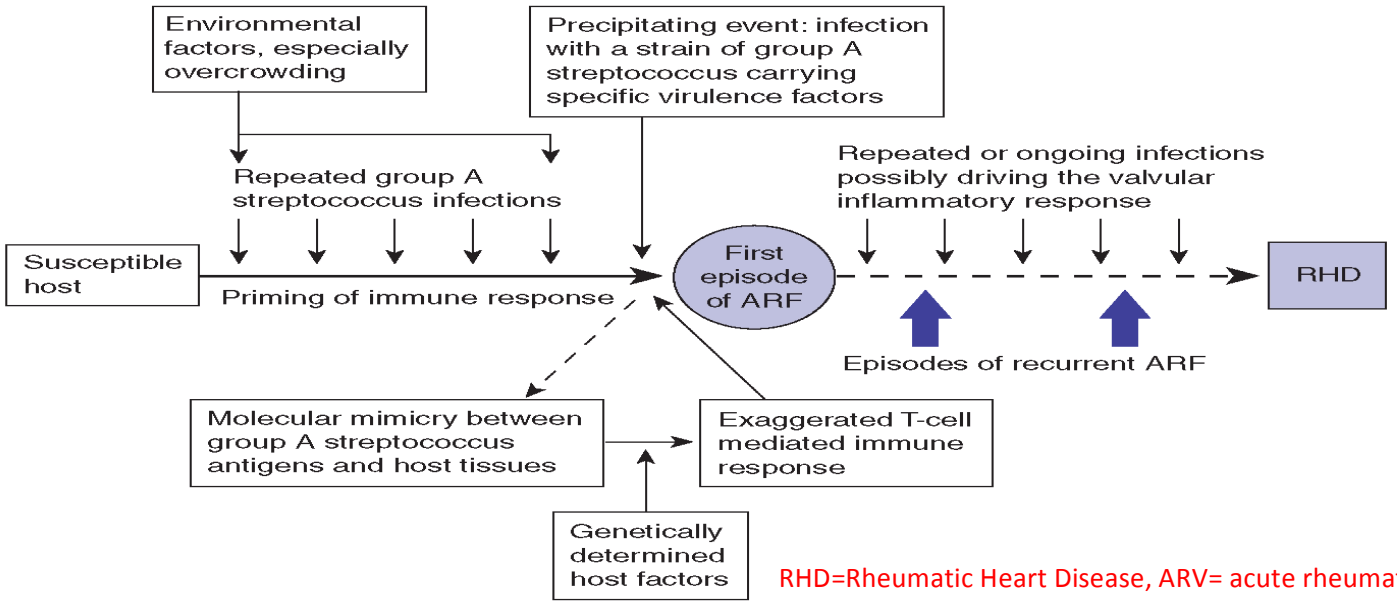
Pathophysiology:

During a Strep. Infection:

- activated antigen presenting cells such as macrophages present the bacterial antigen to helper T cells

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

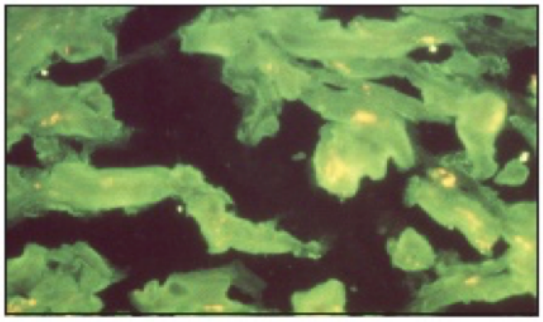
- antibodies may also react against the myocardium and joints, producing the



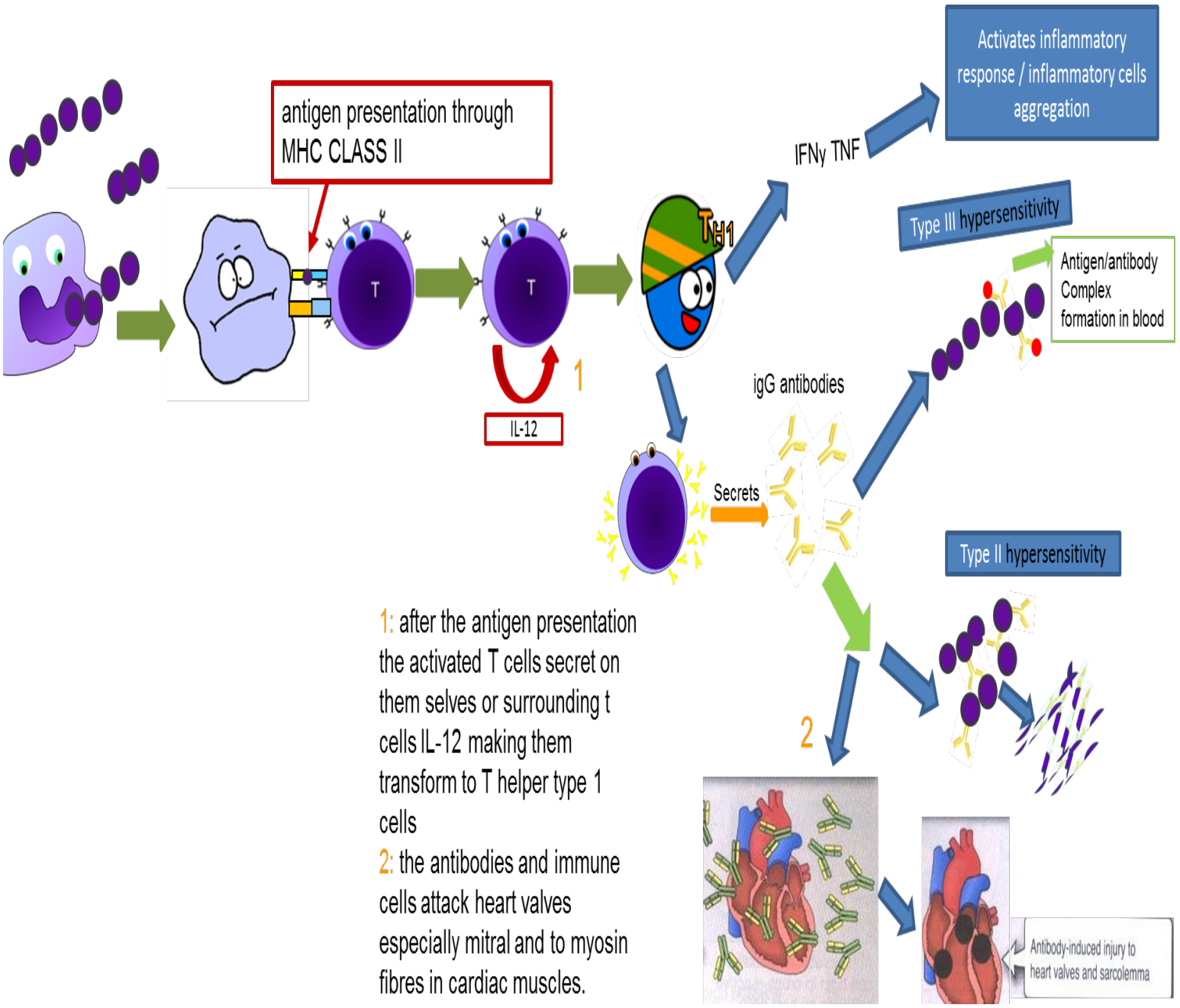
RHD=Rheumatic Heart Disease, ARV= acute rheumatic fever

Doctor explained this diagram "patient with any risk factor would have ARF then repeated or ongoing ARF would cause RHD"

ARF affects many organs as we mentioned before, but RHD affects just the heart

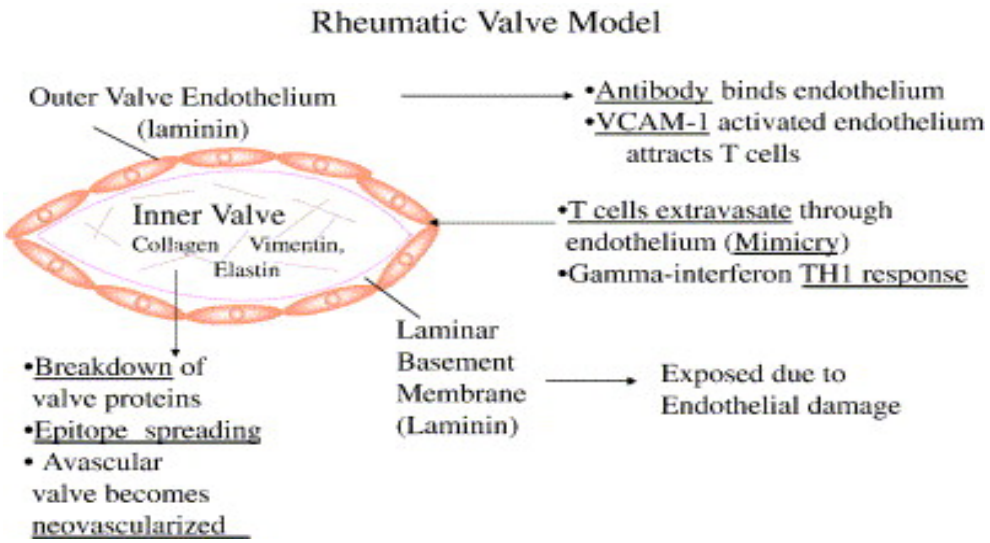


Immunofluorescent staining of heart muscle with serum obtained from an acute rheumatic fever patients



1: after the antigen presentation the activated T cells secret on them selves or surrounding t cells IL-12 making them transform to T helper type 1 cells

2: the antibodies and immune cells attack heart valves especially mitral and to myosin fibres in cardiac muscles.

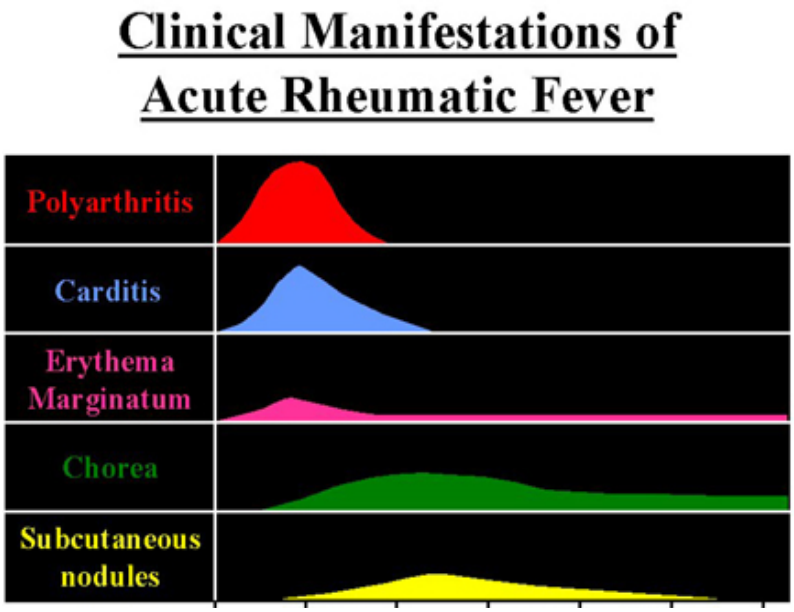


In rheumatic fever the antibodies bind to the endothelium and activates it which in return activates the VCAM-1 which increase the space between the cells (diapedesis). These antibodies causes type II hypersensitivity, these two cause the endothelium destruction making the inner structure exposed "laminar basement membrane" . The exposed area is damaged due to the inflammatory response.

The inflammatory hypersensitivity type 2 response that is happing causes:

1. **breakdown of valve proteins.**
2. **Epitope spreading: epitope is the surface portion of an antigen capable of eliciting an immune response which more immunological response- poor heart valves.**
3. **Avascular valve became neovascularized, meaning that your valves which have no blood going through them are now have blood going through them. "THIS IS JUST TO EXPLAIN THE PICTURE. HONESTLY,WE DO NOT KNOW IF IT IS EXTRA OR YOU SHOULD STUDY IT "**

Clinical Presentations:



This picture mean:

Polyarthritis (severe) , carditis (severe and irreversible) and Erythema Marginatum occur in the beginning

.. Chorea (reversible) and subcutaneous nodules occur after the developing of Rheumatic fever

1)Heart:

Up to 60% of patients with ARF "Rheumatic Fever" progress to Rheumatic Heart Disease (RHD)

- **The endocardium, pericardium, or myocardium may be affected (pancarditis)**

1.Endocarditis: including valves (valvulitis) and chordae tendineae. **2.Pericarditis**: fibrinous or serofibrinous deposits between visceral and parietal layers of the pericardium.

3.Myocarditis: Can cause sudden death.

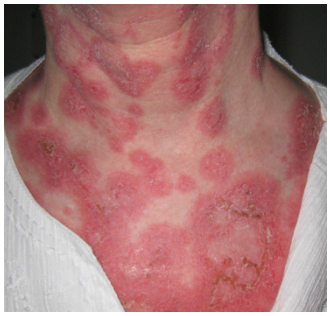
- **Valvular damage is the hallmark of rheumatic carditis. (The mitral valve is almost always affected)**

2) Joint (arthritis)

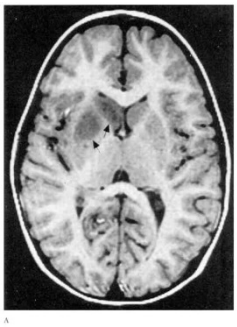
- **usually polyarthritis, sometimes flitting from joint to joint (migratory), affecting the larger joints more than the smaller ones.**
- **Swelling, redness and tenderness are the common findings and occasionally joint effusions.**

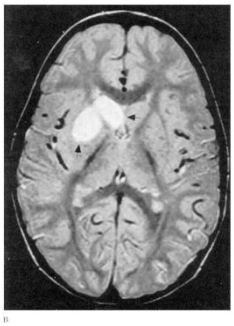
3) Skin (Erythema Marginatum):

- **The classical erythema marginatum—lesions with prominent margins (demarcated) slightly raised**



4) Central nervous system (chorea):



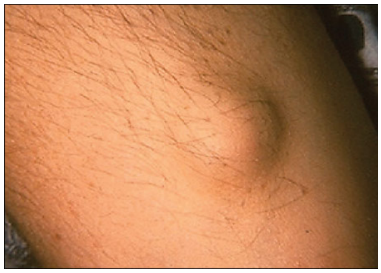


- Also known as Sydenham's chorea (chorea related to rheumatic fever)

- The choreiform movements affect particularly the head and the upper limbs
- They may be generalized or restricted to one side of the body (hemi-chorea)
- Chorea eventually resolves completely, usually within 6 weeks

5) Subcutaneous nodules

- Subcutaneous nodules : These are painless, round, firm lumps overlaid by normal looking skin
- They range from a few millimeters to 1.5 cm in diameter, and are localized over bony prominences like the elbow, shin and spine. They sometimes last longer than a month



Investigation of Rheumatic Fever

- Anti-streptolysin O (ASO) titer : a blood test to measure antibodies against streptolysin O, (a substance produced by group A Streptococcus bacteria).
- At least 80% of patients with ARF have an elevated anti-streptolysin O titer at presentation
    - Rising titer is more convincing

  – Anti-DNAse B & Anti-hyaluronidase test is performed to determine a previous infection of a specific type of *Streptococcus*, group A beta-hemolytic *Streptococcus*
- Throat culture for group A streptococci (obtain 2 or 3 cultures)

Clinical Course of Rheumatic Fever :

- Subsequent attacks :
  - Increased vulnerability to reactivation of disease with subsequent strep infections
  - Same symptoms with each attack → i.e. (rheumatic Heart disease, arthritis, Erythema Marginatum, chorea and Subcutaneous nodules)
  - Carditis worsens with each attack
  - Heart valves are frequently deformed (mitral e.g. Stenosis[1] of mitral valve)
  - HearT failure develops after decades

Acute, recurring, chronic rheumatic fever :

- Symptoms prone[2] to recur with subsequent Strep. infections
- Chronic disease leads to fibrosis (chordae of heart valves + valve cusps)

[1] Stenosis: a narrowing of a passage or vessel
[2] Prone: having a natural tendency to something

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

IMPORTSANT NOTS:

-Not everyone who has HLA-DR7 on the MHC class II has to have Rheumautic fever or rheumatic heart disease.

-The Sterptococcus infection to the throat is what causes the problems if not treated or with recurrent attacks, the soar is not important and becomes a problem to us if he or she have developed the rheumatoid fever or heart disease , and if he or she develops the rheumatic fever or heart disease , they become our problem NOW!! not the soar throat

- The hyaluronic acid "virulent factor of the S.coccus" function is to camouflages (HIDES) the bacteria

-Post streptococcal glomerulonephritis effects the kidney , causing a RENAL DISEASE

ARF is a wide broad spectrum

Rheumatic Heart Disease *(Summary)*

Rheumatic Heart disease is one of the many complications of *Rheumatic Fever*, which is an inflammatory condition occurring as a result of a Group A β-haemolytic Streptococcal infection (Throat infection).

Both branches of the Adaptive immune response (Antibody + Cellular Mediated Immunity) are responsible for the manifestations of Rheumatic fever.

Caused by an **Antibody cross reactivity**, which is a **Type II Hypersensitivity** called **Molecular Mimicry**.

Pathogenisis:

Group A strep. Pyogens have cell walls that might contain M proteins, which is also found in lots of places in the body, including the cardiac muscles. Antigen presenting cells present bacterial antigens to T Cells, which activates the B Cells. B Cells release Antibodies (Mostly IgG) against the M protein. The antibodies might **cross react** with the M Protein in other areas in the body, resulting in an inflammatory response. Recurrent or untreated *rheumatic fever* leads to the destruction of the valves of the heart, a condition known as *Rheumatic Heart Disease*.

Clinical presentation of Rheumatic Fever:

1) Heart: Rheumatic Heart Disease. (Most important) (ACUTE)
2) Joints: Arthritis, affecting large joints and migrating from one joint to another. (ACUTE)
3) Skin: Erythema Marginatum (Redness) (ACUTE + CHRONIC)
4) Central Nervous System: Sydenham's chorea. (CHRONIC)
5) Subcutaneous Nodules. (CHRONIC)

Investigations for Rheumatic Fever

A) Anti-Streptolysin O (ASO) titer B) Throat Culture : for group A Strep.

-With each recurrent Streptococcal infection, the symptoms reappear and the Cardiac inflammation gets worse in addition to the deformity of the heart valves (Stenosis or incompetence of valves).

-Chronic Rheumatic Fever can result in Heart Failure, and most importantly, Fibrosis of the valves.

Treatment:

1) Penicillin : for Strep throat infection, and as a prophylactic therapy for patients with previous rheumatic fever
2) Treating each manifestation symptomatically.
3) For damaged valves: surgical replacement.

PATHOGENISIS " simpler way to memorize"

Strep. Infection → M Proteins → APC presents antigens to T Cells → Activates → B Cells, which release antibodies (IgG) against M Proteins → Cross Reaction → with M Proteins in body leading to → Inflammatory Response.

Recurrent or untreated *Rheumatic Fever* leads to the destruction of the valves of the heart, a condition known as *Rheumatic Heart Disease*.

1-Rheumatic fever is an inflammatory disease which may develop after :

A)Group A Streptococcal

B)Staphylococcus aureus

C)M. catarallis

2-rheumatic fever is commonly seen in patients from:

A)30 to 45 yrs

B)5 to 15 yrs

C)over 60 yrs

3-rheumatic fever is mediated my which of the following:

A)cell mediated immune response

B)antibody mediated immune response

C)both A and B

4-Post streptococcal glomerulonephritis is caused by:

A)type I hypersensitivity

B)type II hypersensitivity

C)type III hypersensitivity

5-rheumatic fever is caused by:

A)type II hypersensitivity

B)type III hypersensitivity

C)type IV hypersensitivity

6-the valve that is almost always affected in rheumatic heart disease:

A)aortic valve

B)mitral valve

C)tricuspid valve

7-pateints with acute rheumatic fever will have:

A)increased anti-streptolysin O titer

B)decreased anti-streptolysin O titer

C)normal anti-streptolysin O titer

8-treatment of damaged heart valve:

A)penicillin

B)surgery

C)no treatment

9-What is a CNS presentation in ARF?

A)Sydenham's chorea

B)erythema marginatum

C)Polyarthritis

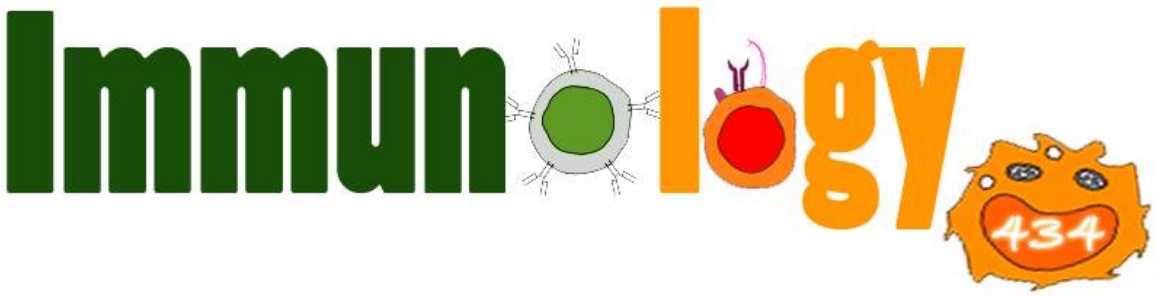
10- Which of the following virulent factors of the S.coccus virus dissolves blood clots?

A)Peptidases

B)Streptokinase

C)Streptolysins

1)A, 2)B , 3)C, 4)C, 5)A .6)B, 7)A, 8)B, 9)A, 10)B.



We tried to make it easy

Best Wishes ☺ ☺ ☺

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