جامعة الملك سعود
King Saud University

Rheumatic Heart Disease

Color code:
Important in red
Extra in blue

Immunology
MED438

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Editing file

Objectives

- To understand the 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

Rheumatic Fever

An acute, multisystemic, autoimmune inflammatory disease that develops after a Group A Strept infection (e.g. Pharyngitis, scarlet fever).

It commonly appears in children aged 5-15, and risk factors include:

- Low living standards
- Crowding
- Individual HLA susceptibility (APC's bearing HLA-DR7 preferentially recognize heart tissue proteins)

Group A Streptococcus

Virulence Factors	
M Protein	Adherence of the bacteria to host cells & Inhibiting the immune response
Hyaluronic Acid Capsule	Camouflage
Streptokinases	Dissolving blood clots
Peptidases	Degrade proteins involved in the immune response
Pyrogenic Toxins	Stimulate fever, rash, & shock
Streptolysins	Lyse erythrocytes, leukocytes, & platelets

Pathogenesis

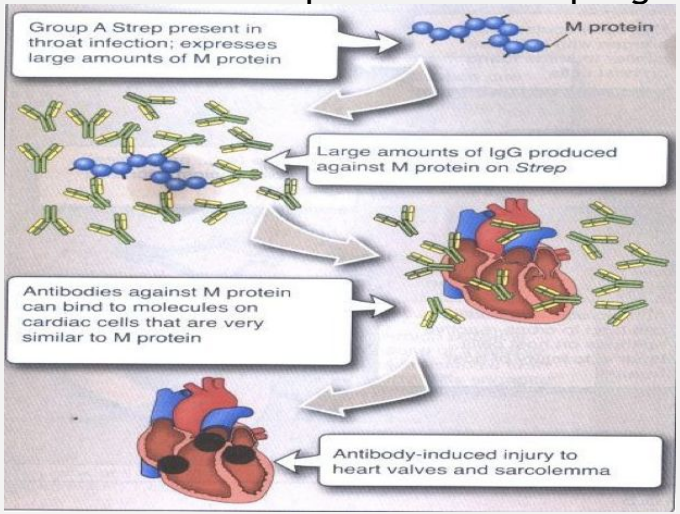
Rheumatic fever affects the peri-arteriolar connective tissue. It is Believed to be caused by antigen-antibody cross reactivity (Type II hypersensitivity Molecular Mimicry)

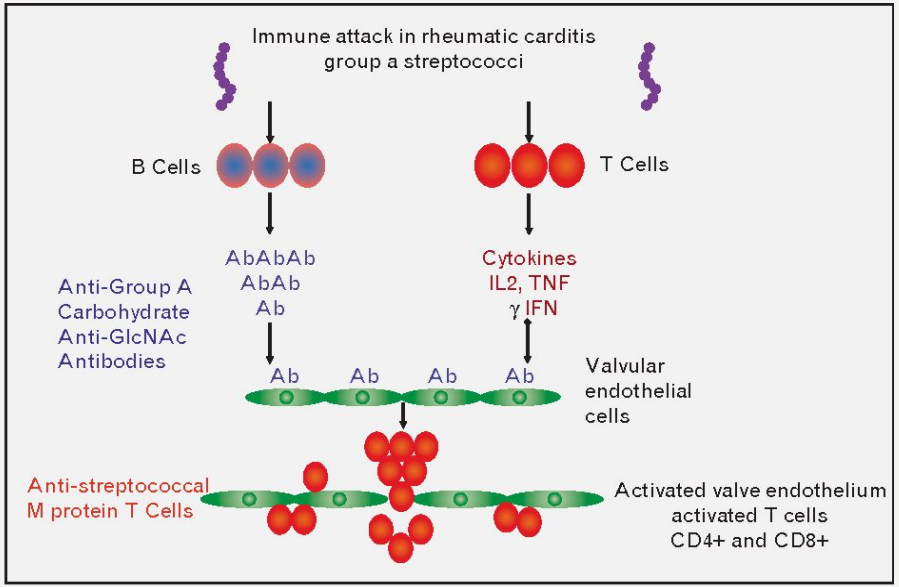
- M proteins located on the cell wall of GAS are highly antigenic
- They resemble (mimic) the cardiac myofiber protein (myosin) and smooth muscle cells of arteries.

Th2 cells activated by APCs produce antibodies against the M protein, which will cross react with the cardiac molecules and induce an inflammatory reaction by activating the complement system (classical pathway)

- This immune process includes both adaptive and humoral immunities (more details next slide)
- It includes Fc receptor-mediated recruitment of neutrophils and macrophages + cytokine release

Because this process takes about 3 weeks (1-5), there is a latent period between the moment of infection and the appearance of symptoms



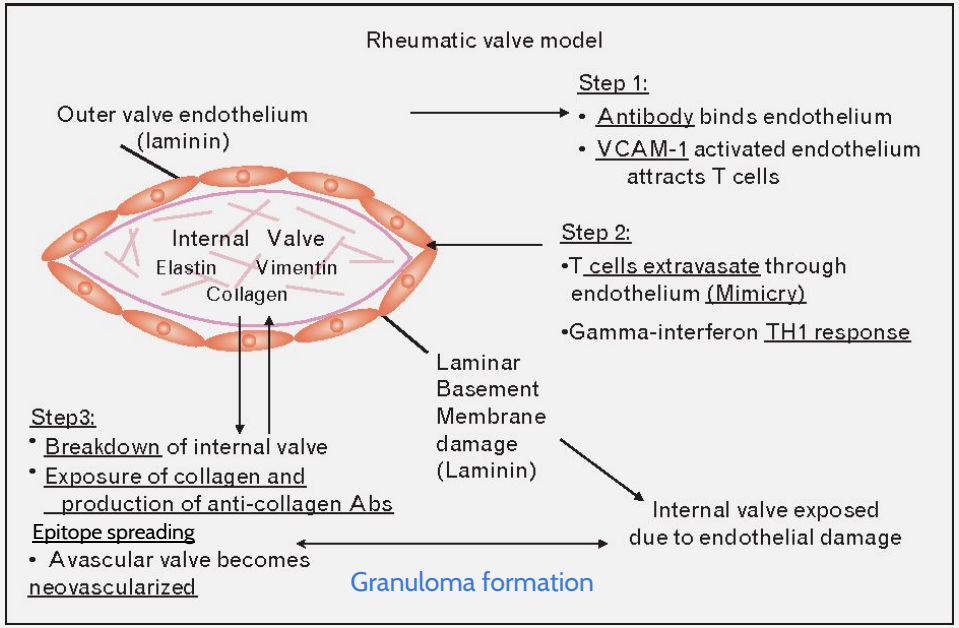


The figure on the left is known as the "two hit theory", expressing humoral (left) and adaptive (right) immunities.

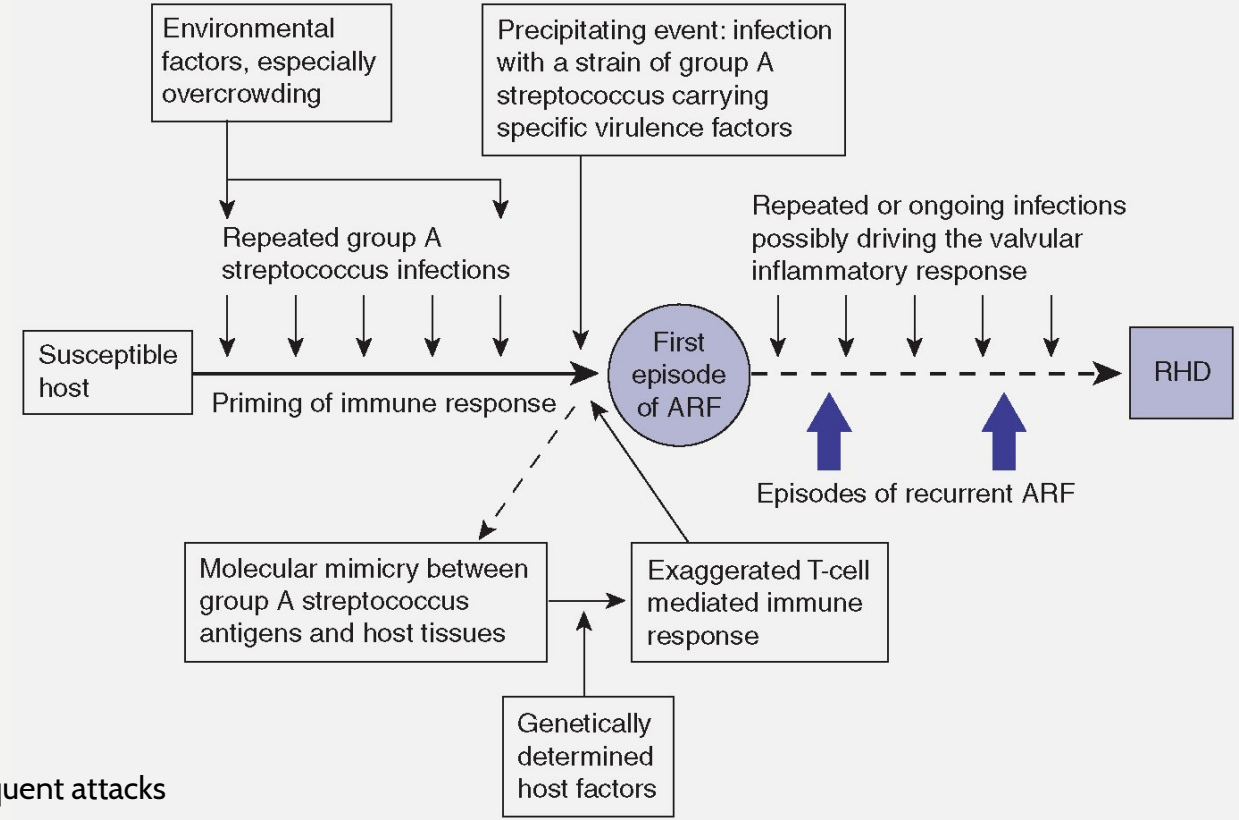
The figure at the bottom is known as the rheumatic valve model, which further clarifies how the valves become damaged

The cross reaction of the Anti-Group A carbohydrate antibodies with the valve endothelium will up-regulate VCAM-1 (Vascular Cell Adhesion Molecule)

This will cause Anti M-protein T cells to adhere to VCAM-1 on the valvular endothelium and penetrate into the valve, causing damage through Th1 response



Pathogenesis Summary

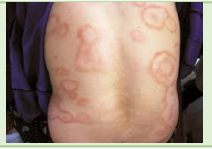
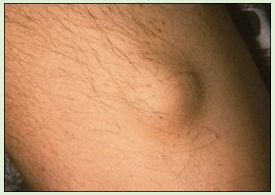


Clinical course: Subsequent attacks

- Increased vulnerability to reactivation with subsequent infections
- Same symptoms with each attack
- Can be acute, recurrent, or chronic (leads to fibrosis of cusps and choardae)
- Carditis worsens with each attack
- Heart valves are frequently deformed (mitral)
- Heart failure develops decades later

Clinical Presentations

5 Major criteria of jones index

Heart (Rheumatic Heart Disease)	• Pancarditis (all 3 cardiac layers may be affected) + the most common among the five (60%) • Valvular damage is the hallmark of rheumatic carditis (mitral valve is most commonly affected) • The only manifestation of ARF with significant potential to cause long-term disability and/or death • Clinical manifestation: highest after the first month and lasts for 2 months
Joints (arthitis)	• Migratory polyarthritis (larger joints affected more) • Swelling, redness, tenderness, and occasional joint effusions • Clinical manifestation: highest after the first month and lasts for 2 and a half months
Skin	• Erythema Marginatum (lesions with prominent margins slightly raised) • Clinical manifestation: highest during the first month and lasts for 6+ months 
CNS	• Sydenham's chorea (rare in adults and may resolve within 6 weeks) • likely due to molecular mimicry with autoantibodies reacting with brain ganglioside • The involuntary rapid movements affect particularly the head and the upper limbs and may be restricted to one side of the body (hemi-chorea) • Clinical manifestation: highest after 1-4 months and lasts for 6+ months
Subcutaneous	• Subcutaneous nodules (painless, round, firm lumps overlaid by normal skin) • Range from a few millimeters to 1.5 cm in diameter • localized over bony prominences (elbow, shin and spine) • Clinical manifestation: highest after 2-3 months and lasts for 5 months 

Investigations

- Anti-Streptolysin O titer (at least 80% have elevated ASO titer)
- Anti-hyaluronidase test
- Anti-DNAse B
- Throat culture (2-3 cultures) gold standard

Treatment

- Treat the strept throat infection with penicillin
- Other manifestations are to be treated according to the symptoms
- Treat with surgery/valve replacement in case of chronic (fibrotic) cases
- For patients who previously had rheumatic fever, they should receive long-term prophylactic anti-strept therapy

Take Home Message

- Rheumatic heart disease results from cross reacting antibodies binding the heart valves
- Repeated attacks of Streptococcal throat infection over the years damage heart valves resulting in either stenotic or incompetent heart valves
- Treatment involves surgical replacement of the damaged heart valves

  In patients with rheumatic fever long term administration of penicillin is recommended for prevention of future infections by group A Streptococcus

Quiz:

1. Which of the following is the target for the antibodies in rheumatic fever

a) Streptolysin O
b) Bacterial Nucleic acid
c) M protein
d) Hyaluronic acid capsule

2. After five days of GAS infection, which of the following RF clinical manifestation should be observed?

a) Pancarditis
b) Fever
c) Migratory polyarthritis
d) None of the above

3. Which of the following facilitates extravasation of T cells into the valve

a) M protein
b) VCAM-1
c) Anti-group A carbohydrate antibodies
d) Th2

4. Which of the following happens after T cells extravasate into the valve?

a) Antibodies bind to the endothelium
b) Epitope spreading
c) VCAM-1 attracts B cells
d) None of the above

5. Which of the following is the most severe clinical presentation of RF?

a) Pancarditis
b) Syndenham's chorea
c) Erythema marginatum
d) Subcutaneous nodules

6. Which valve is most commonly affected in RHD?

a) Aortic
b) Pulmonary
c) Mitral
d) Tricuspid

1.C 2.D 3.B 4.B 5.A 6.C

Done by: Ibrahim Aldakhil

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