College of Medicine
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4th stage

Rheumatic fever and Atherosclerosis

By

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Acute rheumatic fever (ARF)

Incidence and pathogenesis

- Usually affects children (most commonly between 5 and 15 years) or young adults.
- Represent the most common cause of acquired heart disease in childhood and adolescence.
- Triggered by an immune-mediated delayed response to infection with specific strains of group A streptococci
- Antibodies produced against the streptococcal antigens cause inflammation in the endocardium, myocardium and pericardium, as well as the joints and skin.
- Aschoff nodules are pathognomonic for ARF and occur only in the heart.

Clinical features:

- ARF is a multisystem disorder, usually presents with fever, anorexia, lethargy and joint pain, 2–3 weeks after an episode of streptococcal pharyngitis.

- Arthritis occurs in approximately 75% of patients.

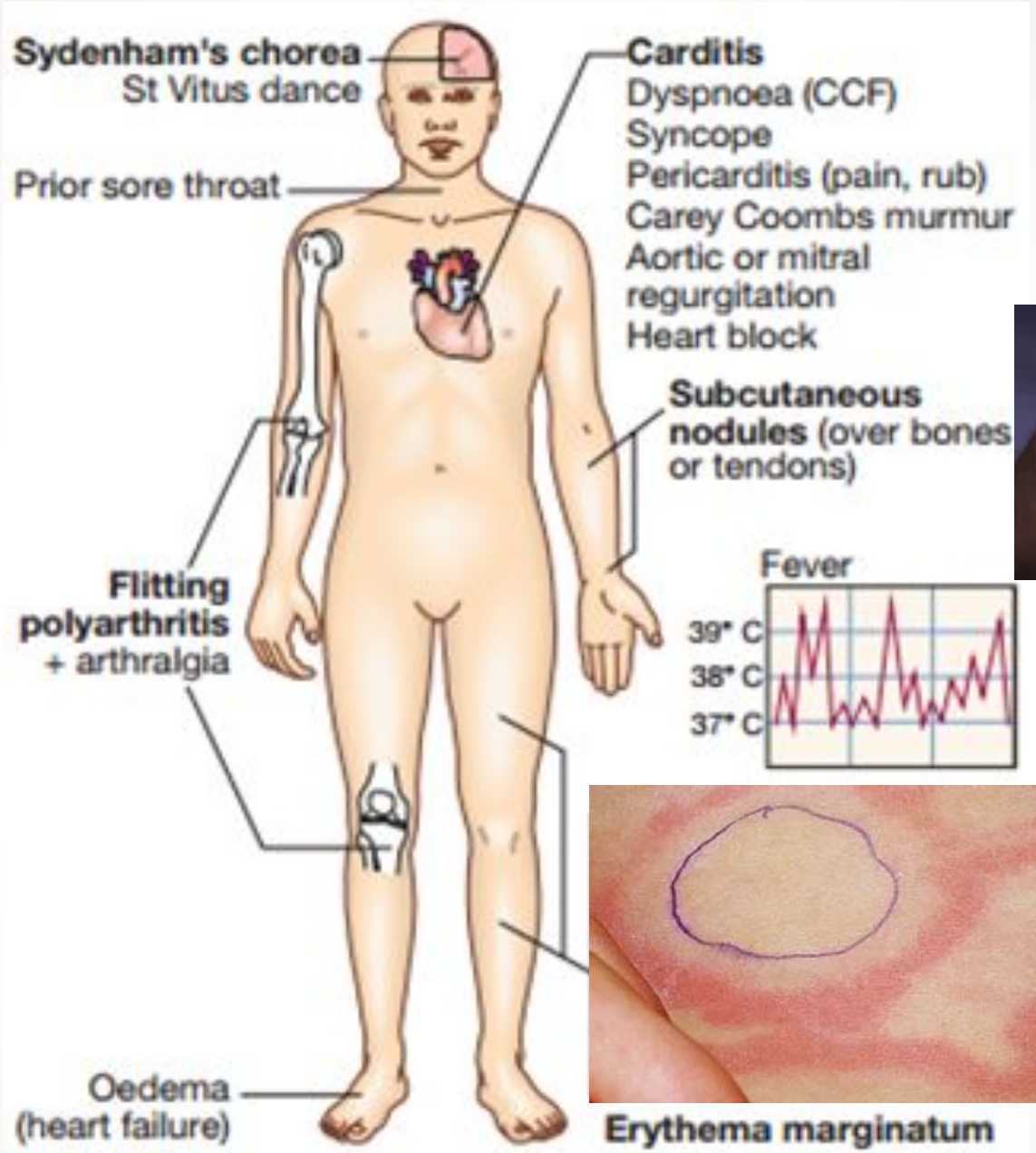
- Other features include rashes, carditis and neurological changes.

Diagnosis:

✔ By using the revised Jones criteria:

- ≥ 2 major manifestations or
- one major plus ≥ 2 minor criteria along with evidence of preceding streptococcal infection.

✔ Only about 25% of patients will have a positive culture for group A streptococcus at the time of diagnosis



Clinical features of rheumatic fever. Bold labels indicate Jones major criteria (CCF = congestive cardiac failure)

Jones criteria for diagnosis of rheumatic fever

Major manifestations

- Carditis
- Polyarthritis
- Chorea
- Erythema marginatum
- Subcutaneous nodules

Minor manifestations

- Fever
- Arthralgia
- Previous rheumatic fever
- Raised ESR or CRP
- Leucocytosis
- First-degree AV block

Plus

- Supporting evidence of preceding streptococcal infection: recent scarlet fever, raised antistreptolysin O or other streptococcal antibody titre, positive throat culture

N.B. Evidence of recent streptococcal infection is particularly important if there is only one major manifestation.

- ✔ A presumptive diagnosis of ARF can be made without evidence of preceding streptococcal infection in cases of *isolated chorea or pancarditis*, if other causes for these have been excluded.

- ✔ In cases of established rheumatic heart disease or prior rheumatic fever, a diagnosis of ARF can be made based only on the presence of multiple minor criteria and evidence of preceding group A streptococcal pharyngitis.

Carditis: A 'pancarditis' involves the endocardium, myocardium and pericardium to varying degrees,

- Incidence declines with increasing age.
- May manifest as breathlessness (due to heart failure or pericardial effusion), palpitations or chest pain (usually due to pericarditis or pancarditis).

Endocarditis:

Carey Coombs murmur or Coombs murmur occurs in patients with mitral valvulitis due to ARF (short mid-diastolic rumble best heard at the apex, which disappears as the valvulitis improves). It is often associated with an S_3 gallop rhythm, and can be distinguished from the diastolic murmur of MS by the absence of an opening snap before the murmur.

Pericarditis:

- May cause chest pain, a pericardial friction rub and precordial tenderness.
- Cardiac failure may be due to myocardial dysfunction or valvular regurgitation.
- ECG changes commonly include ST and T wave changes.
- Conduction defects (heart block) sometimes occur and may cause syncope.

Arthritis:

- The most common major manifestation and occurs early when streptococcal antibody titers are *high*.
- An acute painful asymmetric and migratory inflammation of the large joints typically affects the knees, ankles, elbows and wrists.
- The joints are involved in quick succession and are usually red, swollen and tender for between a day and 4 weeks.
- The pain characteristically responds to aspirin; if not, the diagnosis is in doubt

Skin lesions:

Erythema marginatum

- occurs in less than 5% of patients.
- start as red macules that fade in the center but remain red at the edges, and occur mainly on the trunk and proximal extremities but *not the face*.

Subcutaneous nodules

- occur in 5–7% of patients.
- firm and painless, and best felt over extensor surfaces of bone or tendons.
- typically appear more than 3 weeks after the onset of other manifestations

Sydenham's chorea (St, saint Vitus dance)

- ✔ late neurological manifestation that appears at least 3 months after episode, when all the other signs may have disappeared.
- ✔ occurs in up to one-third of cases and is more common in females.
- ✔ emotional lability may be the first feature and is typically followed by purposeless, involuntary, choreiform movements of the hands, feet or face.
- ✔ speech may be explosive and halting.
- ✔ spontaneous recovery usually occurs within a few months.

Other systemic manifestations are rare but include pleurisy, pleural effusion and pneumonia.

Investigations:

A. Evidence of systemic illness

Leucocytosis, elevated ESR and CRP (for monitoring progress of the disease).

B. Evidence of preceding streptococal infection

- ✔ Positive throat swab cultures (only 10–25% of cases), also from family member
- ✔ ASO titres are normal in one-fifth of adult cases and most cases of chorea. (>200 U in adult , >300 U in childiren)

C. Evidence of carditis

- ✔ CXR: (cardiomegally, pulmonary congestion)
- ✔ ECG: first and rarely second degree HB, features of pericarditis, T wave inversion, reduction in QRS complex
- ✔ Echocardiography: typically shows MR, dilatation of the mitral annulus, prolapse of the anterior mitral leaflet and may also show AR, pericardial effusion and cardiac dilatation.

Management of the acute attack

1. A single dose of benzyl penicillin (1.2 million U IM) or oral phenoxymethylpenicillin (250 mg 4 times daily for 10 days), in case of penicillin-allergic, erythromycin or a cephalosporin can be used.

2. Bed rest and supportive therapy is important, it lessens joint pain and reduces cardiac workload. The duration guided by symptoms, along with temperature, leucocyte count and ESR. Patients can then return to normal physical activity but avoid heavy exercise in those who have had carditis.

3. Heart failure should be treated as necessary. Some patients (in early adolescence) develop a fulminant form of HF with severe MR and sometimes concomitant AR, not response to medical treatment, valve replacement may be necessary. Pacemaker insertion rarely needed in state of heart block.

4. Aspirin: relieves the symptoms of arthritis rapidly and a response within 24 hours helps confirm the diagnosis. A starting dose is 60 mg/kg/day, divided into six doses. In adults, 100 mg/kg per day may be needed up to the limits of tolerance or a maximum of 8 g per day.

Mild toxicity includes nausea, tinnitus and deafness; vomiting, tachypnoea and acidosis are more serious. Aspirin should be continued until the ESR has fallen, and then gradually tailed off.

5. Corticosteroids: produce more rapid symptomatic relief than aspirin and are indicated in cases with *carditis or severe arthritis*. Prednisolone (1.0–2.0 mg/kg per day in divided doses) should be continued until the ESR is normal, and then tailed off.

Secondary prevention of rheumatic fever

- ✔ Patients are susceptible to further attacks of rheumatic fever if another streptococcal infection occurs, and long-term prophylaxis with penicillin should be given as benzathine penicillin (1.2 million U IM monthly), or oral phenoxymethylpenicillin (250 mg twice daily), if compliance is in doubt.
- ✔ Sulfadiazine or erythromycin may be used if the patient is allergic to penicillin.

- ✔ Further attacks are unusual after the age of 21. However, it should be extended if an attack has occurred in the last 5 years, or if the patient lives in an area of high prevalence or has an occupation (e.g. teaching) with high exposure to streptococcal infection.

- ✔ In those with residual heart disease, prophylaxis should continue until 10 years after the last episode or 40 years of age.

Atherosclerosis

Pathogenesis

- ✔ progressive inflammatory disorder of the arterial wall with focal lipid rich deposits of atheroma that remain clinically silent until they become large enough to impair tissue perfusion, or until ulceration and disruption result in thrombotic occlusion or distal embolization of the vessel.

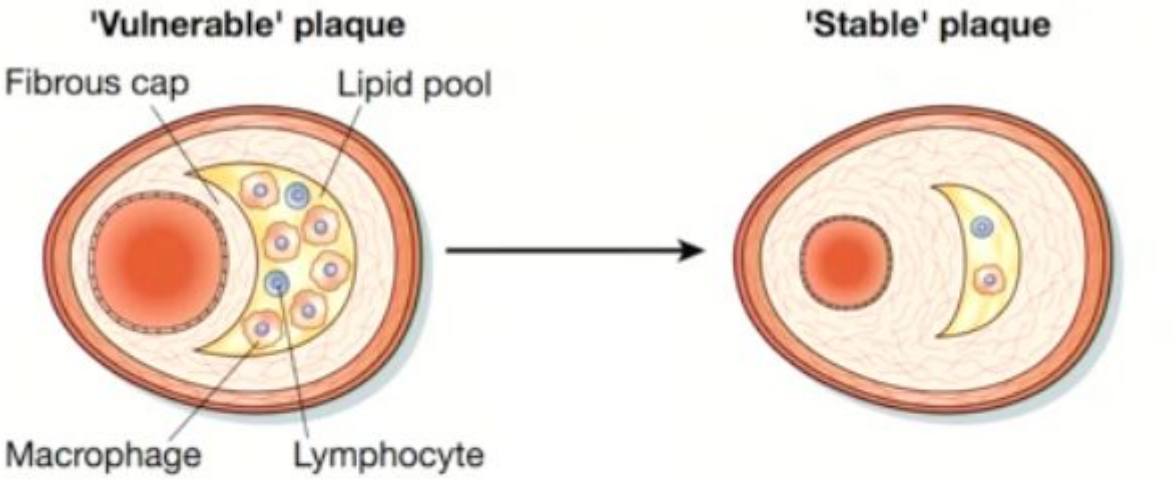
- ✔ begins early in life (childhood) which tend to occur at sites of altered arterial shear stress, such as bifurcations. Macrophages that infiltrate into vascular wall and pick up lipids, forming foam cells --> create fatty streaks

- ✔ The number and complexity of arterial plaques increase with
  - age and risk factors

- ✔ *Vulnerable plaques* are characterized by a lipid-rich core, a thin fibrocellular cap, speckled calcification and an increase in inflammatory cells that release specific enzymes to degrade matrix proteins.

- ✔ In contrast, *stable plaques* are typified by a small lipid pool, a thick fibrous cap, heavy calcification and plentiful collagenous cross-links.

- ✔ Atherosclerosis may induce complex changes in the media that lead to arterial remodeling. Some arterial segments may slowly constrict (negative remodeling), while others may gradually enlarge (positive remodeling).



Risk factors

1. Age and sex

- Age is the most powerful independent risk factor for atherosclerosis.
- Pre-menopausal women have lower rates of disease than men, although the gender difference disappears after the menopause.
- Hormone replacement therapy (HRT) is not effective in the prevention of CAD, and HRT in post-menopausal women is associated with an increased risk of cardiovascular events.

2. Genetics

Atherosclerotic CAD often runs in families and a positive family history is common in patients with early-onset disease (age < 50 in men and < 55 in women).

3. Smoking: There is a strong relationship between cigarette smoking and CAD, especially in younger (< 70 years) individuals, and this is probably the most important modifiable risk factor.

4. Hypertension

The incidence of atherosclerosis increases as BP rises, and this is related to systolic, diastolic BP and pulse pressure.

5. Hypercholesterolaemia

The risk of atherosclerosis and CVD is proportionate with serum cholesterol concentrations.

6. Diabetes mellitus

Potent risk factor for all forms of atherosclerosis, especially type 2 DM. It is often associated with diffuse disease that is difficult to treat.

Insulin resistance (normal glucose homeostasis with high levels of insulin) is associated with obesity and physical inactivity, and is also a risk factor for CAD.

7. Haemostatic factors

Platelet activation and high plasma fibrinogen concentrations are associated with an increased risk of coronary thrombosis, whereas antiphospholipid antibodies are associated with recurrent arterial thrombosis.

8. Physical activity

Regular exercise (brisk walking, cycling or swimming for 20 minutes two or three times a week) has a protective effect, whereas inactivity roughly doubles the risk of CAD and is a major risk factor for stroke.

9. Obesity

Particularly if central or truncal, is an independent risk factor for atherosclerosis, although it is often associated with other adverse factors such as hypertension, DM and physical inactivity.

10. Alcohol Excess

Alcohol consumption is associated with hypertension and CVD

11. Diet

- ✔ Diets deficient in fresh fruit, vegetables and polyunsaturated fatty acids are associated with an increased risk of CVD.
- ✔ The introduction of a mediterranean-style diet reduces cardiovascular events.
- ✔ However, dietary supplements, such as vitamins C and E, beta-carotene, folate and fish oils, do not reduce cardiovascular events.

12. Personality

Certain personality traits are associated with an increased risk of CAD

13. Social deprivation

- Strongly related to CVD
- Partly due to associations with lifestyle risk factors, such as smoking and alcohol excess, which are more common in socially deprived individuals.

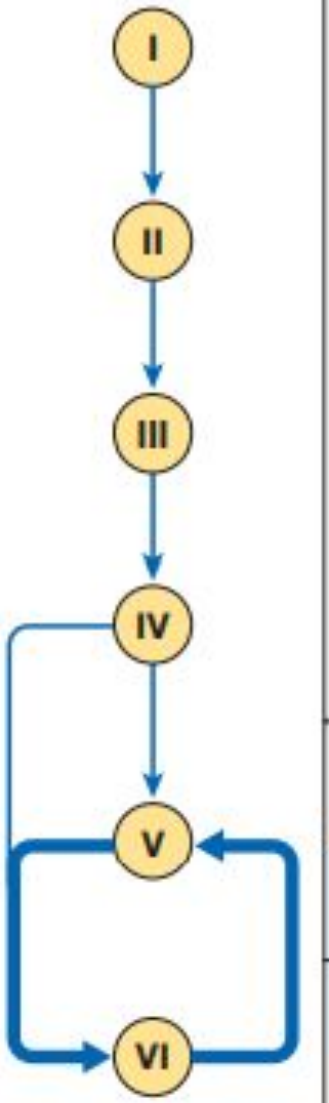
Management

Primary prevention

- Do not smoke
- Take regular exercise (minimum of 20 mins, three times per week)
- Maintain an ‘ideal’ body weight
- Eat a mixed diet rich in fresh fruit and vegetables
- Aim to get no more than 10% of energy intake from saturated fat

Secondary prevention

This involves targeting interventions at individuals who already have evidence of CVD with specific treatment

Nomenclature and main histology	Sequences in progression	Main growth mechanism	Earliest onset	Clinical correlation
Type I (initial) lesion Isolated macrophage foam cells 		Growth mainly by lipid accumulation	From first decade	Clinically silent
Type II (fatty streak) lesion Mainly intracellular lipid accumulation 				
Type III (intermediate) lesion Type II changes and small extracellular lipid pools 			From third decade	
Type IV (atheroma) lesion Type II changes and core of extracellular lipid 				Clinically silent or overt
Type V (fibroatheroma) lesion Lipid core and fibrotic layer, or multiple lipid cores and fibrotic layers, or mainly calcific, or mainly fibrotic 		Accelerated smooth muscle and collagen increase	From fourth decade	
Type VI (complicated) lesion Surface defect, haematoma-haemorrhage, thrombus 		Thrombosis, haematoma		

The six stages of atherosclerosis. **(Stary classification)**


THANK YOU