Haemophilia

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Blood and Immunology Module

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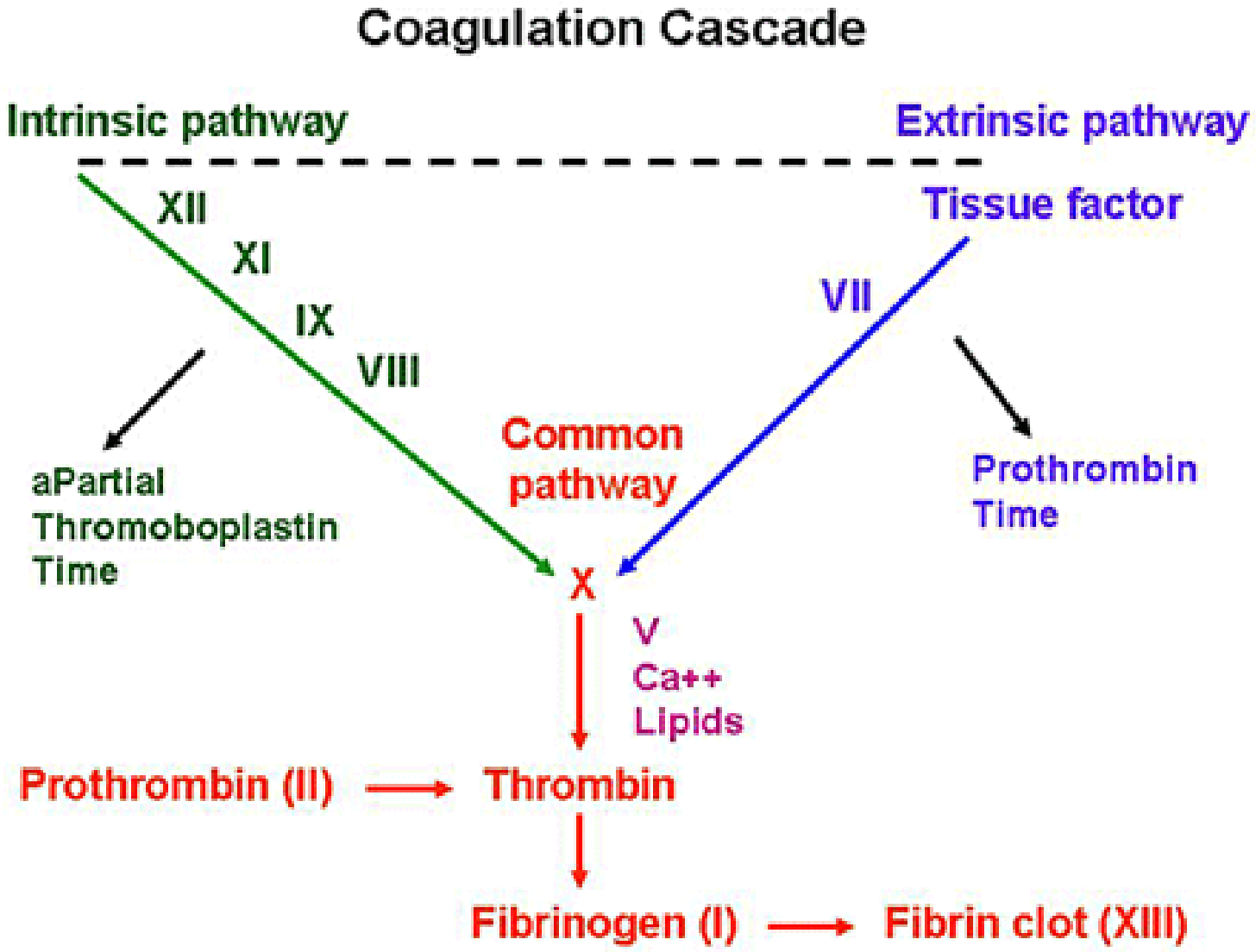
Introduction

- Haemophilia is the most common congenital coagulation defect/ bleeding disorder

- Two types
  - Haemophilia A – Factor VII deficiency (Most common)
  - Haemophilia B – Factor IX deficiency

- Clinical features and presentation are identical

Pathophysiology



Epidemiology and Genetics

- Incidence 1:5000
- Haemophila A – 85%; Haemophila B – 15%
- Found in all ethnic groups

- Genes for Facto VIII and IX are found in the X chromosome
- X-linked

Clinical Features

- Variable onset – In utero (factor VII and IX does not cross the placenta) to childhood
- Spontaneous bleeding or bleeding following minor trauma
  - Easy bruising
  - Muscle Haematomas
  - Haemarthroses
  - Intracranial bleeding (rare <2%)
- Bleeding following medical interventions
  - Circumcision
  - Vaccination (i.m. injections)
  - Dental extraction

Haemarthroses

- Hallmark of hemophilic bleeding
- Following minor trauma or spontaneous
- Ankle, Knee and Elbow commonly affected
- Very young children
  - major swelling and fluid accumulation in the joint space
- Older kids
  - warm, tingling sensation in the joint before obvious swelling

Target joints

- Repeated bleeding episodes into the same joint lead to “target” joint
- Recurrent bleeding may then become spontaneous because of the underlying pathologic changes in the joint.

Muscle Haematomas

- Most of the time – obvious
  - Localized pain, swelling and discolouration
- Exception – iliopsoas haematoma
  - Minimal pain – may be referred to hips
  - Can bleed large volumes without signs
  - Hip movements

    Flexed, internally rotated position (due to iliopsoas spasms)

    Inability to extend
  - Diagnosis – US scan/ CT Scan

Life-threatening Haemorrhages

- CNS bleeding
- Upper airway bleeding
- External trauma
- Gastrointestinal haemorrhage
- Iliopsoas haemorrhage

Laboratory findings

- APTT – prolonged
- Platelet count, BT, PT/INR, TT – normal
- Mixing of normal plasma + patient plasma – corrects APTT
- Factor VIII or Factor IX assay – Factor levels <50% Confirms diagnosis

Classification

- Based on level of factor
- 1 IU of each factor is defined as that amount in 1 mL of normal plasma.
- Thus normal level is 100 IU/dL (100% activity)

Severity Classification	Factor Level	Bleeding
Severe	<1%	Spontaneous
Moderate	1-5%	Mild trauma
Mild	5-50%	Severe trauma

Classification

- In the newborn, factor VIII values may be artificially elevated because of the acute-phase response
- In contrast, factor IX levels are physiologically low in the newborn

- Female carriers of Haemophila A and B
  - reduction of factor VIII or factor IX
  - to result in mild bleeding
  - due to Lyonization

Treatment

- Early appropriate therapy is crucial
- Elevate factor levels in situations of bleeding
  - Mild-moderate bleed – elevate to 35%-50%
  - Life threatening bleeds – elevate to 100%

- Recombinant Factor VIII and IX

- Calculate doses

rFVIII IU = % desired (rise in FVIII) X Wt (kg) X 0.5

rFIX IU = % desired (rise in FIX) X Wt (kg) X 1.4


RECOMBINATE
Baxter

Treatment of Specific Bleeds – Haemophila A

Type of bleed	Treatment
Haemarthrosis	50-60 IU/kg factor VIII on day 1; then 20-30 IU/kg on days 2, 3, 5 until joint function is back to baseline
Muscle haematoma	50IU/kg factor VIII on day 1; Then 20 IU/kg EOD until resolved
Tooth extraction	20 IU/kg factor VIII; Antifibrinolytic therapy
Major surgery/ Life-threatening haemorrhage	50-75 IU/kg factor VIII, then 25 IU/kg 8-12h for 5-7 days, then 50 IU/kg q24h for 7 days

Desmopressin acetate

- Release of patient's endogenously produced factor VIII
- Only in mild Haemophilia A (Factor levels are too low in mod-severe haemophila for desmopressin to act)
- Not effective in Haemophilia B
- Intranasal
- Dose is
  - 150 µg (1 puff) for children weighing <50 kg
  - 300 µg (2 puffs) for children weighing >50 kg.

Tranexaemic acid

- Anti-fibrinolytic agent
- Indicated in
  - Bleeding after dental extraction
- Contraindicated in
  - Haematuria

Supportive care

- Anticipatory guidance, use of car seats, seatbelts, and bike helmets
- Older boys should be counseled to avoid violent contact sports
- Early psychosocial intervention
- Avoid aspirin and other NSAIDs
- Hepatitis B vaccination

Gene therapy

- Using adeno-associated virus vector containing the factor IX gene
- Preliminary trials underway
- Encouraging results

Prophylaxis

- Aims
  - Prevent spontaneous bleeding
  - Prevent joint deformities
- In severe haemophila
- Primary prophylaxis – before target joints
- Secondary prophylaxis – after target joints
- Initiated usually with the first joint hemorrhage
- Central venous line/ peripheral line
- Every 2-3 days to maintain a measurable plasma trough level of clotting factor (1-2%)
- Life-long

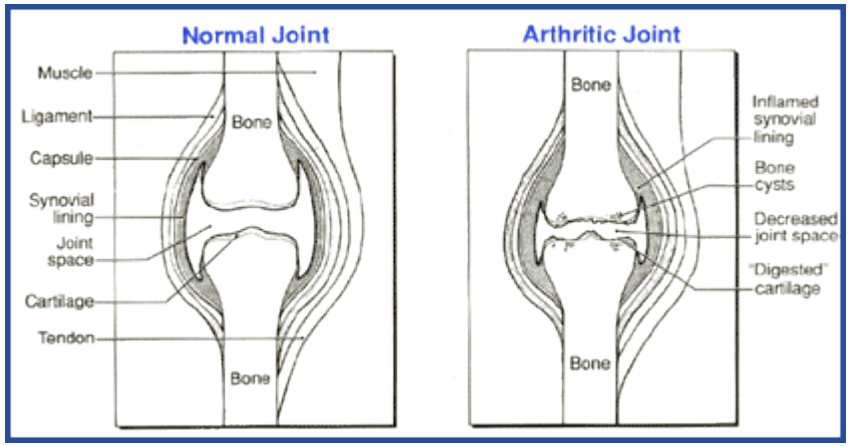
Complications

- Chronic arthropathy
- Development of Inhibitors to Factor VII and IX
- Transfusion-transmitted infectious

Chronic arthropathy

- Recurrent hemorrhages into specific joints
- After joint hemorrhage
  - proteolytic enzymes released into the joint (by WBC)
  - heme iron induces macrophage proliferation
  - leading to inflammation of the synovium
  - synovium thickens
  - develops frond like projections susceptible bleeding
  - cartilaginous surface eroded exposing raw bone
  - articular fusion
- Prevented by giving prophylaxis

Chronic arthropathy



Development of Inhibitors

- Replacement of factor VIII or IX may initiate an immune response in patients with haemophilia
- Inhibitors - antibodies against factor VIII or IX
- Block the coagulation activity
- Develop in 25-35% of patients with haemophila A

- First sign - Failure to respond to factor replacement
- Confirm by - Bethesda assay for inhibitors
  - measures the antibody titer

Management of inhibitors

- Several options to remove inhibitors

1. Continued regular infusion of factor concentrates
   - Many patients loose inhibitors with time
2. Desensitization / immune tolerance induction
   - Patients are given very high doses of Factor VIII/IX
   - To saturate the antibody and body to develop tolerance
3. Rituximab
4. Prednisolone, cyclophosphamide, cyclosporin

Management of inhibitors

- If patients continue to have inhibitors
  - Prophylactic use of factor VIII/IX is discontinued

- Bleeding episodes are treated with
  - very high-doses of factor VIII
  - recombinant factor VIIa
  - activated prothrombin complex concentrates

Transfusion transmitted infections

- Past
  - plasma-derived factor products were used
  - transmitted hepatitis B and C and HIV
- Currently
  - recombinant factor products are used
  - Minimal risk of infection

Multidisciplinary care

- Should be managed in specialized haemophilia centers
  - Pediatricians / physicians
  - Orthopedic surgeons
  - Nurses
  - Physiotherapists
  - Psychologists
  - Social workers