Acquired & Iatrogenic Coagulation Deficiencies

Faizi Ali, MD

Definitions

- Acquired Deficiency

  Deficiency of coagulation proteins that occur in a previously normal individual in response to another disease process and are produced by a variety of mechanisms.

- Iatrogenic Deficiency

  Iatros (Physcian) genic (induced); Deficiency of coagualtion proteins that occur as a result of treatment process for a disease by a physician.

Acquired vs. Inherited Deficiencies

Acquired Deficiencies are

- Far more common than hereditary disorders
- More complicated because usually multiple factors defective
- Bleeding often simultaneously from more than one site
- Also involve deficiencies of naturally occurring Inhibitors

Acquired Disorders

- Disseminated Intravascular Coagulation
- Liver Disease
- Vitamin K deficiency
- Heparin Induced Thrombocytopenia
- Acquired Pathologic Inhibitors

DIC

- Syndrome, not a disease, secondary to a variety of disorders, caused by release of tissue factors, resulting in uncontrolled inappropriate Coagulation and Fibrinolysis.
- Acute DIC: (Uncompensated)

- Factors consumed faster than they are replenished.

- Chronic DIC: (Compensated)

- Factor consumption is compensated (or overcompensated) by replenishment of factors.

Etiology

- Infections: Bacterial,viral,fungal, protozoal…etc.
- Tissue Damage: Burn,Trauma, head injury, extensive surgery...etc
- Neoplasm (Malignant): Solid tumors (pancreatic, gastric, lung, breast, etc.)& Leukemias (e.g M3)
- Obstetric complications: Abruptio placentae, amniotic fluid embolism,septic abortion, retained placenta..etc
- Vascular Injury: Shock, Hypotension..etc
- Miscellaneous: Snake bite, Heat stroke, PNH, Any disease

DIC

- Incidence:
- Occurs in approx. 1 in 1000 hospital patients.
- Clinical Aspects
- About 20% cases asymptomatic and suspected only on the basis of lab data.
- Symptoms vary due to complex interaction and simultaneous activation of coagulation and fibrinolytic system factors, causing either Bleeding or thrombosis and resulting in shock.
- Mortality rate of DIC is 50-60%.

DIC

- Lab Data

- Thrombocytopenia, microangiopathic hemolytic anemia (e.g schistocytes), Decreased Fibrinogen and factor VIII

- Elevated PT, aPTT, TT, FSP/D-dimers
- Chronic DIC has normal platelets count, normal fibrinogen, PT,PTT, but elevated FSP/D-dimers
- Treatment: Eliminating the underlying cause and supportive.

Liver Disease

- Affects all haemostatic functions
- Most haemostatic proteins, involved in coagulation (all major factors except factor VIII), fibrinolysis as well as coagulation Inhibitors are synthesized in liver.
- Liver macrophages play a major role in removal of activated factors and products of activation such as fibrinopeptides, FDPs and plasminogen activator.
- Haemostatic functions are diminished when liver is diseased, but still preserved until 80% functional hepatic tissue lost.

Liver Disease

- Vitamin K deficiency may also be seen.
- DIC also seen due to defective clearance of activated clotting factors and fibrinolytic enzymes.
- All coag screening test including PT, PTT, TT are prolonged with N-Low fibrinogen levels. D-dimer may be normal thus differentiating from DIC.
- Acquired dysfibrinogenmia, & dys-prothrombinemia.

- Abnormal fibrinogen molecule with high sialic acid content may be synthesized, resulting in defective clot formation.

Liver Disease…

- Defective platelet function due to increased FDPs and circulating plasmin.
- Thrombocytopenia develops due to

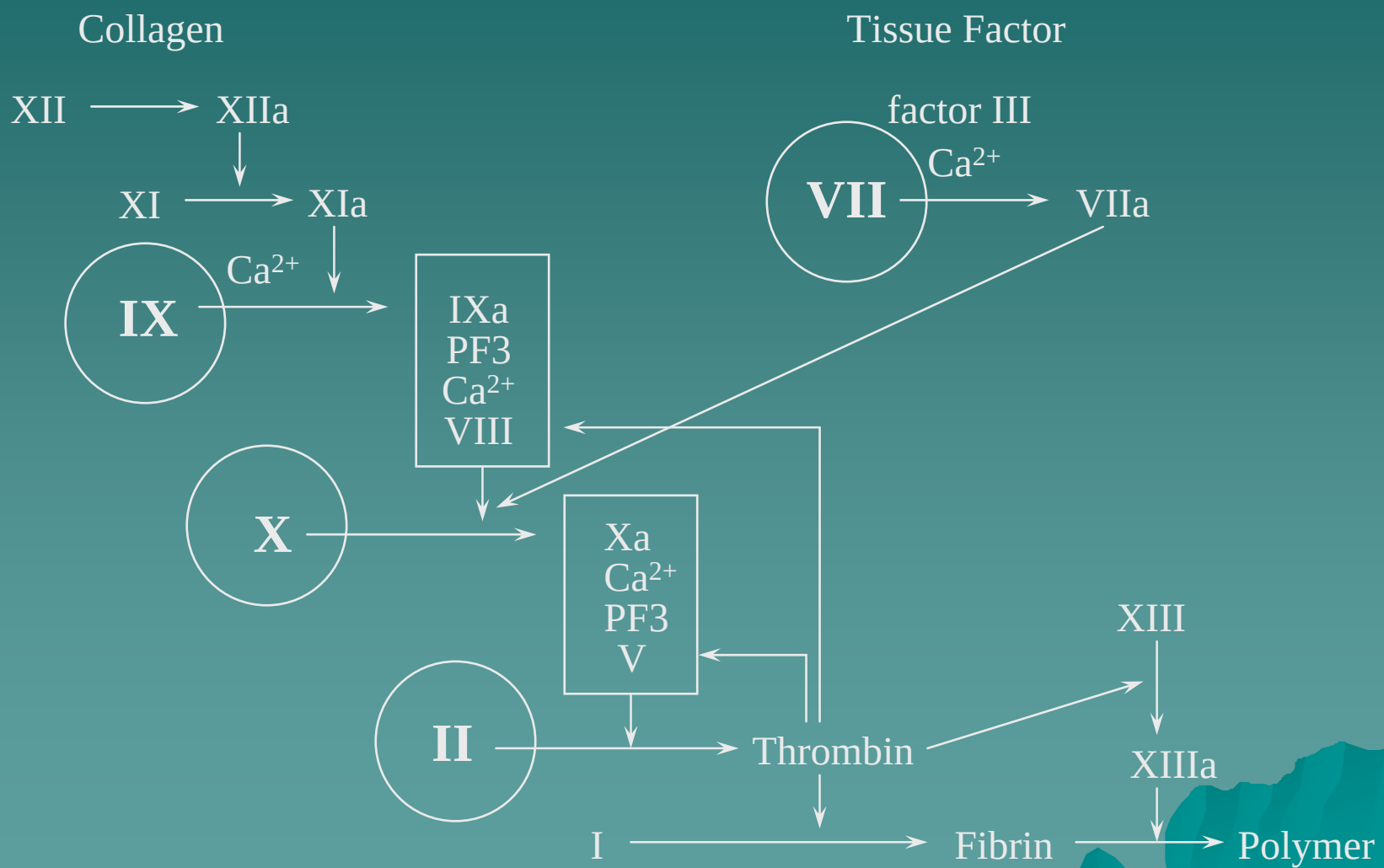
- Hypersplenism: sequestration of platelets in the spleen due to portal hypertension.
- Decreased thrombopoeitin synthesis.
- Alcohol toxicity of the bone marrow
- Platelet consumption in DIC

Liver Disease…

- Ecchymoses and epistaxis may occur but bleeding from local GI lesions is common.
- Available treatments are sub-optimal, treatment is difficult

- FFP: has volume constraints, possible viral infection vector
- Platelets: offer temporary support but don’t reverse pathophysiology of portal hypertension
- Cryoprecipitate: has fibrinogen, can’t reverse consumptive coagulopathy

Vitamin K dependent factors



Vitamin K dependent factors

- II, VII, IX, X, protein C , & S.
- Liver needs Vitamin K to add gamma-carboxy glutamic acid residues to these proteins, required for Ca2+ linking of factor to phospholipid surface
- Sources of Vitamin K are green leafy vegetables in diet and/ synthesized by GI microorganisms, and absorbed from GI tract with bile salts
- Very long PT, long PTT, normal TT

Vitamin K deficiency

- GI malabsorption syndrome, e.g sprue
- Liver disease
  - Malabsorption due to obstruction of biliary tract, (Vit. K is a fat soluble vitamin)
  - Deficiency of I, V, XIII, AT, II, VII, IX, X
  - Dysfibrinogenemia (increased sialic acid)
- Antibiotics: inhibition of g-carboxylation
  - cephalosporins and b-lactams
  - cefamandole, cefoperazone
  - moxalactam

Vitamin K deficiency

- ICU Syndrome
  - Starvation
  - Tube feedings without supplementation
  - Sterilization of GI tract
  - Decreased GI transit time
  - Nasogastric suctioning
- Hypolipidemics (bile acid sequestration)
  - Colestid, Questran

Treatment

- Correct underlying defect
- Administer Vitamin K
  - subcutaneous, intramuscular, intravenous
  - oral
- Fresh frozen plasma administration

Heparin Induced Thrombocytopenia(HIT)

- Complication of Heparin therapy
- More common with unfractionated heparin than low molecular weight heparin- 8 fold greater risk.
- 2 types
- Type 1: Non-immune platelet activating mechanisms, and not associated with Abs, Mild thrombocytopenia (>100K), develops several days after starting on heparin, Pt. asymptomatic, resolves w/o discontinuing heparin

HIT…..

- Type 2:
- Immune mediated
- starts 5-15 days after start of heparin therapy, unless there has been prior sensitization event
- Pathogenesis: Upon exposure to exogenous heparin, multimolecular complexes composed of PF4 and heparin are formed

  Heparin + PF4 → Multimolecular complexes

  Formation of these multimolecular complexes results in conformational change in PF4, exposing a neoepitope which elicits an immune response usually IgG type of antibody.

HIT

- IgG binding to PF4/heparin complex triggers platelet activation and aggregation through transmembrane signaling.
- Platelet activation leads to release of phospholipids microparticles from cell membranes which initiates coagulation cascade leading to thrombosis.
- PF4/heparin immune complex bind to endothelium, leading to endothelial injury which can lead to a “thrombosis storm” associated with this syndrome.
- Moderately severe thrombocytopenia (<100K)

HIT

- Heparin must be immediately stopped, and alternative anticoagulant be used (Danaparoid, Lepirudin, Argatoban)
- Lab often called to

- Confirm diagnosis of HIT
- Justify continued use of alternate anticoagulant
- Guide future exposure to heparin

- Lab Methods: 1: Functional assay
  2: Antigenic assay

HIT…

- Functional assay: Based on the ability of Pt. immunoglobulin (Abs) to activate normal platelets in the presence of heparin.
- Source of Pt. Abs either serum or plasma.
- Detection of platelet activation may be based on

  1: Platelet aggregation

  2: Release of granular contents (e.g serotonin)

  3: Change in membrane properties (flow cytometry)

HIT…

- Antigenic Assay:

- Measures presence of Abs capable of binding to PF4-heparin complex.
- Detection system can be modified to detect IgG, IgM or IgA antibodies.
- Assay usually performed in ELISA format and is more sensitive than functional assay.

Acquired Pathologic Inhibitors

- Antiphospholipid syndrome
  - Lupus anticoagulant
  - Anticardiolipin antibodies
- Not specific for single factor, bind to phospholipid in vitro, inhibiting assay
- Not associated with increased risk of bleeding
- Associated with risk of thrombosis

Prolongation of PTT

- Antibodies to factors
  - factor VIII most common target
  - factor V antibodies similar to “lupus anticoagulants”
  - others rare

Iatrogenic defects

- Surgical
  - Operations
  - Biopsies
  - Intravenous and intra-arterial catheters
- Medical
  - Starvation
  - Medications

Case History:

- 22 year old newly wed
- Presents with uncontrolled nosebleed, extensive ecchymoses, PT 42 seconds
- Normal platelet count, hemoglobin 12.2 g/dL
- Denies trauma, drug ingestion
- Physical exam otherwise unremarkable

Case History, continued:

- Married six days ago, Caribbean cruise for honeymoon
- Developed nausea, vomiting and diarrhea on cruise
- Nose bleed cut cruise short
- Admitted to Beaumont as inpatient

Case History conclusion:

- Factor deficiency due to starvation
  - dieting prior to wedding
  - nausea, vomiting, diarrhea, anorexia during cruise
- Rapid response to food and oral vitamin K with cessation of bleeding and correction of PT