NOTES
HYPERCOAGULABLE DISORDERS

GENERALLY, WHAT ARE THEY?

PATHOLOGY & CAUSES

- Unregulated activation of coagulation cascade → vascular thrombosis

CAUSES

- Inherited/acquired
- Secondary to liver disease, autoimmune systemic disorders, renal failure, acute thrombosis, exposure to toxins, anticoagulation therapy

COMPLICATIONS

- Venous, arterial thrombosis, obstetric

SIGNS & SYMPTOMS

- Deep vein thrombosis (DVT) → pulmonary embolism (PE)

DIAGNOSIS

- Family history of thrombophilia, thrombosis under age of 50 years, thrombosis in unusual location (e.g. portal veins), recurrent thromboembolic episodes

LAB RESULTS

- Assays for specific proteins/factors, antibodies
- Genetic testing

TREATMENT

MEDICATIONS

- Anticoagulants/thrombolysis
  - If symptomatic
- Prophylactic anticoagulation when high risk for thrombosis
  - E.g. perioperatively/in postpartum period
  - If asymptomatic

ANTIPHOSPHOLIPID SYNDROME (APS)

osms.it/antiphospholipid-syndrome

PATHOLOGY & CAUSES

- Acquired autoimmune multisystem disorder; associated underlying disorders, systemic lupus erythematosus (SLE)
- AKA lupus anticoagulant syndrome
  - May be idiopathic; may appear after exposure drugs/infectious agents
- Antiphospholipid antibodies (aPL) bind to targets → induce hypercoagulable state
- Pathways
  - Thromboembolic episodes/pregnancy morbidity
  - Increase in atherosclerosis, fetal loss, neurological damage; aPL-associated increase in vascular tone
- Catastrophic APS (rare)
  - Widespread thrombosis → multiorgan failure

COMPLICATIONS

Pregnancy complications

- Spontaneous abortions; fetal death
- Premature birth due to preeclampsia/placental insufficiency

Cutaneous complications

- Livedo reticularis (most common)
  - Obstruction of microvasculature → net-like purplish discolouration of skin
- Cutaneous ulcers

Ocular complications

- Retinal venous/arterial circulation occlusion; anterior ischemic optic neuropathy

SIGNS & SYMPTOMS

- Recurrent venous thromboses
  - DVT → PE → pulmonary hypertension
  - Superficial thrombophlebitis
  - Hepatic/portal vein thrombosis → Budd-Chiari syndrome, hepatic infarction, portal hypertension, cirrhosis
  - Adrenal vein thrombosis → hemorrhagic infarction
- Recurrent arterial thromboses (less common)
  - Stroke/transient ischemic attack
  - Myocardial infarction
  - Bowel infarction
  - Multiple capillary, arterial thromboses → renal microangiopathy → renovascular hypertension

DIAGNOSIS

LAB RESULTS

- ≥ one antiphospholipid antibodies
  - Lupus anticoagulant, AKA lupus antibody
  - Anticardiolipin antibody
  - Anti-beta$_2$ glycoprotein I
- ≥ one clinical feature
  - Vascular thrombosis/pregnancy morbidity
- Moderate thrombocytopenia
- Prolonged PT, aPTT
  - Not corrected by plasma transfusions
- False positive in venereal disease lab test, rapid plasma reagin test for syphilis
  - Cardiolipin phospholipid as major reagent

TREATMENT

MEDICATIONS

- Aspirin/anticoagulants (e.g. warfarin)
  - To stabilize coagulation pathways
  - Lifelong systemic therapy with antiplatelet medications

ANTITHROMBIN III DEFICIENCY

osms.it/antithrombin-III-deficiency

PATHOLOGY & CAUSES

- Endogenous serine protease inhibitor in coagulation cascade; inactivates thrombin (factor IIa), factor Xa.

CAUSES

- Inherited
  - Autosomal dominant gene mutation; variable penetrance
- Acquired
  - Defective synthesis; liver disease, therapy with vitamin K antagonists (e.g. warfarin)
  - Loss in urine; renal failure/nephrotic syndrome
  - Depletion in acute thrombosis/ disseminated intravascular disease (DIC)

COMPLICATIONS

- Venous thromboembolism
- Heparin resistance

SIGNS & SYMPTOMS

- Deep vein thrombosis → pulmonary embolism

DIAGNOSIS

LAB RESULTS

Genetic testing

Functional assay

- Reduced plasma antithrombin III activity
- PT/aPTT/thrombin time
  - No change + aPTT → diminished increase following heparin

TREATMENT

MEDICATIONS

- Treat deep vein thrombosis / pulmonary embolism
  - Anticoagulants with vitamin K antagonists/direct oral anticoagulants (DOACS)
- If ≥ two thromboembolic events occur → lifelong anticoagulant therapy (e.g. vitamin K antagonists/ DOACs)
- Prophylactic antithrombin replacement
  - High-risk thrombophilic situations (e.g. surgery/pregnancy)

FACTOR V LEIDEN (FVL)

osms.it/factor-v-leiden

PATHOLOGY & CAUSES

- Inherited thrombophilia
- Mutant form of coagulation factor V, lacks Arg506 cleavage site

CAUSES

- FVL → resistance to degradation by activated protein C (aPC) → unregulated activation of coagulation cascade → hypercoagulable state → venous thromboembolism (VTE)

RISK FACTORS

- FVL homozygosity
- Coinheritance with other thrombophilia disorders
- Pregnancy (physiologic hypercoagulability)
- Oral hormonal contraceptives

SIGNS & SYMPTOMS

- VTE
- DVT/thrombosis in superficial veins of lower extremities/cerebral, portal, hepatic veins
- Possible fetal loss

DIAGNOSIS

LAB RESULTS

- Genetic testing
  - FVL mutation (direct analysis of genomic DNA)
  - Functional aPC resistance assay (individual's plasma mixed with factor V-deficient plasma)

OTHER DIAGNOSTICS

- Family history of thrombophilia
- VTE at young age/in unusual location

TREATMENT

MEDICATIONS

- Anticoagulants/thrombolysis
  - Treat for DVT/PE
  - If ≥ two thromboembolic events → lifelong anticoagulant therapy
- Prophylactic anticoagulation
  - High risk thrombophilic situations (e.g. surgery, pregnancy)

PROTEIN C DEFICIENCY

osms.it/protein-c-deficiency

PATHOLOGY & CAUSES

- Protein C deficiency → familial thrombophilia
- Protein C
  - Vitamin K-dependent inhibitor of factors V, VIII
  - Protein C deficiency → unregulated activation of coagulation cascade → increased thrombotic risk

TYPES

- Type I
  - Reduced protein C levels
- Type II
  - Normal protein C levels, reduced function

CAUSES

- Autosomal dominant inherited disorder
- Acute thrombosis, disseminated intravascular coagulation, liver disease, vitamin K antagonist anticoagulants

COMPLICATIONS

- Due to treatment
  - Warfarin-induced thrombotic skin necrosis

SIGNS & SYMPTOMS

- Venous thromboembolism (VTE)
- In homozygotes, neonatal purpura fulminans

DIAGNOSIS

LAB RESULTS

Functional assay

- Reduced protein C

OTHER DIAGNOSTICS

- Monitor if recurrent VTE, family history of VTE, thrombosis in unusual location/at young age

TREATMENT

MEDICATIONS

- Anticoagulants/thrombolysis
  - Treat deep vein thrombosis/VTE
- Prophylactic protein C concentrate
  - Asymptomatic individuals (e.g. perioperatively/in postpartum period)

Warfarin-induced skin necrosis

- Stop warfarin; start vitamin K, heparin, protein C concentrate/fresh frozen plasma administration

MNEMONIC

Proteins C & S

C and **S** inhibit coagulation: they are **C**lot **S**toppers

PROTEIN S DEFICIENCY

osms.it/protein-s-deficiency

PATHOLOGY & CAUSES

- Deficiency of protein S → familial thrombophilia
- Protein S
  - Cofactor of protein C
  - Protein S deficiency → decreased protein C activity → enhanced activity of coagulation cascade → increased thrombotic risk

TYPES

- Type I (classic)
  - Reduced total protein S, free protein S, protein S function
- Type II (rare)
  - Normal total, free protein S, reduced function
- Type III
  - Reduced free protein S, protein S function; normal total protein S

CAUSES

- Autosomal dominant inherited condition
  - Most individuals heterozygous for *PROS1* gene mutation
- Pregnancy, oral hormonal contraceptive, disseminated intravascular coagulation (DIC), acute thrombosis, HIV infection, nephrotic syndrome, liver disease

SIGNS & SYMPTOMS

- VTE
- In homozygotes, neonatal purpura fulminans

DIAGNOSIS

- Monitor if recurrent venous thromboembolism (VTE), family history of VTE, thrombosis at young age/in unusual location

LAB RESULTS

- Protein S assay

TREATMENT

MEDICATIONS

- Anticoagulants/thrombolysis
  - Treat deep vein thrombosis
- If asymptomatic, avoid drugs that predispose to thrombosis (e.g. oral contraceptives)
- Prophylactic anticoagulation (e.g. preoperatively/in postpartum period)