Familial Thrombophilia
Thrombophilia Screening
Management

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Familial thrombophilia

- Group of inherited disorders with a predisposition to venous thromboembolism is linked to defect or deficiency in natural anticoagulant mech.
### Table 31.3  Genetic risk factors for venous thromboembolism

<table>
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<th>Category</th>
<th>Factors</th>
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<td>Deficiency of anticoagulant</td>
<td>Antithrombin, Protein C, Protein S</td>
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<td>Abnormal protein</td>
<td>Factor V Leiden, Dysfibrinogen</td>
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<td>Increased procoagulant</td>
<td>Prothrombin, Factor VIII</td>
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<td>Abnormal metabolism</td>
<td>Homocystinuria</td>
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<td>Putative mechanisms</td>
<td>Thrombomodulin defects, Fibrinolytic defects</td>
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AntiThrombin Deficiency

- Egeberg 1965: Association between familial def. of antitrombin & venous thromboembolism
- Prevalence: 1 in 2000 to 1 in 40 000
- Seen in about 4% of pt who had venous thromboembolism < 45 yrs of age
- AT=Major plasma serine protease inhibitor not only of thrombin but also fac IXa, Xa, Xla, XIIa.
- Heparin, heparan sulphate: enhance inhibitory effect of AT.
- Inherited as autosomal dominant manner
Antithrombin Deficiency

Molecular Genetics and Classification

- AT molecule has 2 functional domain (heparin binding and thrombin binding domain)
- classify: (based on functional & immunological AT assay)
- Type I
  - overall ↓ in immunologically & functional level in plasma - majority (80-90%)
  - consequence of genetic mutation producing silent AT alleles
- 2) Type II
AntiThrombin Deficiency

Clinical features:

1) DVT of lower limbs \{recurrent, most
2) pulm embolism \{common
3) other ven: cerebral, mesenteric, portal, renal, vena cava

- Common precipitating factor: pregnancy, puerperium, immobilization, obesity.
- HMZ for type II: severe venous thrombosis + arterial thrombotic dz has been reported.

-for HTZ: strong association between risk of thrombosis and age.

Thaler & Lechner 1981: by age 55 yrs, thrombosis occurred in 85%, compares with 10% of affected children < 15 yrs
Protein C deficiency

- inheritance: Auto dominant trait.
- Epidemiology:
  - Present approximately 0.2% of general population
  - Subjects <45 yrs presenting with venous thromboembolism → 4% found to be Protein C def.
- Classified into:
  a) Type I (common) parallel reduction in both types of assay
Protein C deficiency

- Protein C
  - Vit K dependent glycoprotein with 9 γ-carboxyglutamic acid residues.
  - Synthesized in liver, circulates as covalently-linked 62 kDa dimer.
  - Following activation of thrombomodulin by thrombin, protein C combine with thrombomodulin to produce activated PC. It then binds to PS on surface of platelet (provide phospholipid to support clotting process).
Protein C deficiency

Clinical Features:

- Thrombotic manifestation for HTZ: DVT (commonest), splanchnic, cerebral venous vessel.

- 80% of deficient individual symptomatic < 40 yrs old

- Hemorrhagic infarction of skin when starting coumarin (warfarin induced skin necrosis) d/t rapid further reduction in protein C def on introduction of coumarin.

- HMZ protein C def. is rare, phenotypically variable

  range from purpura fulminans neonatalis (life
Protein S deficiency

- 1st describe in 1984.
- Autosomal dominant
- Account for 8% of venous thrombosis < 45 yrs old.
- Protein S:
  - 70 kDa glycoprotein, single chain protein with 11 γ-carboxylated residues; vit K dependent.
  - unbound Protein S is functionally active
Protein S deficiency

- **Clinical features:**
  - indistinguish from HTZ protein C def
  - propensity for warfarin-induced skin necrosis

- **Classification:**
  a) Type I def- reduce amount of free and bound forms. Function: N.
  a) Type II-defective protein S, amount is normal
  b) Type III- low amount of free PS, overall normal total PS
Factor V Leiden

• Dahlback:

  Study a family of dominant thrombophilia but no evidence of def of AT, protein C, protein S nor any dysfunctional fibrinogen or defective fibrinolysis.

  Plasma was resistant to prolongation of APTT by activated Protein C (APC)

• 1994: Bertina et al in Leiden showed the basis of APCR d/t mutant Fac V molecule with N procoagulant properties but resistance to proteolysis by APC.
Fac V Leiden

- **Mech of action:**
  
  Phenomenon called APCR where a genetic mutation in fac V gene making it resistant to inactivation by protein C.(refer picture)

  This result in fac V Leiden is inactivated by activated protein C at a much slower rate leading to thrombophilic state by increase activity of fac V in blood.
Fac V Leiden

- More common in northern Europe
- 4-7% is HTZ; 0.06-025% HMZ
- Uncommon in Asia, Africa, North America
- A/w primarily with venous thrombosis
- Mutation: single G to A base change resulting in replacement of an arginine with glutamine in the protein., destroying a cleavage site and thereby limiting fac V degradation by APC.
Factor V Leiden

- Thrombosis risk is ↑ 7-fold in HTZ and 80-fold in HMZ compared with normal people. The risk is higher when environmental risk condition occur eg: pregnancy, OCP, surgery, immobilization.
Other causes:

• **Elevated Fac VIII** - Most common in early onset venous thrombosis after APCR/fac V Leiden.

• **Dysfibrinogenaemia**
  - extremely uncommon cause of thrombophilia.
  - incidental finding: prolong thrombin clotting time
  - 30% a/w bleeding tendency, poor wound
• Prothrombin Gene mutation G20210A

- prothrombin is the precursor to thrombin in coagulation cascade
- exact mech on it result in thrombophilic state: unclear
- common in Caucasian, 1-2% of population is HTZ
Homocystinuria

- inborn error of metabolism
- Deficiency of:
  1) cystathione synthetase (required to convert homocysteine to cysteine) result in homocysteine level to rise
  2) Methylenetetrahydrofolate reductase (MTHFR), methionine synthetase (MS) require to convert homocysteine to methionine
- autosomal recessive
Homocystinuria

- C/features:
  - venous thromboembolism, may manifest in infancy
  - premature arterial occlusion → tissue infarction
  - skeletal abN: Marfan-like habitus, MR, ectopia lentis
- aggravating factor: folate def or inherited defects (thermolabile variant of methylene tetrahydrofolate reductase)
Screening for Thrombophilia

• Indication:
  1. Develop venous thrombosis
  2. Strong family history
  3. Thrombosis at unusual site
  4. Recurrent episodes of thromboembolism
  5. Recurrent miscarriage >3x
<table>
<thead>
<tr>
<th>First-line tests (APTT, PT, TT, and platelet count)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Clotting times shorter than normal, platelet count raised</td>
</tr>
<tr>
<td>To confirm or elucidate, measure: fibrinogen, VIII:C and vWF, fibrinolytic potential; inhibitors, platelet hyperreactivity</td>
</tr>
<tr>
<td>2. Clotting times normal, platelet count normal</td>
</tr>
<tr>
<td>Acquired thrombotic tendency</td>
</tr>
<tr>
<td>Investigate as under 1.</td>
</tr>
<tr>
<td>Or:</td>
</tr>
<tr>
<td>Congenital thrombophilia</td>
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<tr>
<td>Measure: plasma inhibitors and inactivators, plasminogen</td>
</tr>
<tr>
<td>3. APTT prolonged, PT normal or long, with an inhibitor pattern of behaviour</td>
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<tr>
<td>Lupus anticoagulant</td>
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<tr>
<td>4. TT prolonged</td>
</tr>
<tr>
<td>Dysfibrinogaemia</td>
</tr>
<tr>
<td>5. All clotting tests slightly prolonged, platelets low, normal or high</td>
</tr>
<tr>
<td>Measure: FDP and D-dimer; platelet hyperreactivity; inhibitors</td>
</tr>
<tr>
<td>Aetiology</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Acute phase reaction</td>
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<tr>
<td>Malignancy</td>
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<tr>
<td>Myeloproliferative diseases</td>
</tr>
<tr>
<td>Oestrogen-containing pill</td>
</tr>
<tr>
<td>Lupus anticoagulant</td>
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<tr>
<td>Nephrotic syndrome</td>
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<tr>
<td>Vasculitic diseases and arthropathies, including Behcet's syndrome</td>
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<tr>
<td>ARDS*</td>
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<tr>
<td>Paroxysmal nocturnal hemoglobinuria</td>
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</tbody>
</table>
Diagnostic approach: APLA

• **1. Ix for presence of lupus anticoagulant**
  - detection of La should not preclude further Ix eg; coexistent PS, PC, ATIII def.

  - 1st line test:
    - TT normal, APTT ↑ (not corrected by plasma mixing)
    - PT N/↑

  - samples of plasma tested must be free of platelet
    (double centrifuge/ microfilter)
-at least 2 of these test must be performed when confirming LA:

1. Kaolin clotting time
2. Dilute Russell’s viper venom (dRVVT)
3. Platelet neutralization test (PNT)
• *dRVVT (LA Screen & LA confirm)*
  - RVV activate fac X in the presence of phospholipid + Ca^{2+}
  - LA prolongs clotting time by binding to phospholipid & prevent action of RVV.
  - If ratio (Screen/Confirm) > 1.3 suggest LA or abn fac II, V, X
• **Platelet neutralization test**
  
  - quenching of anticoagulant effect by suspension of freeze-thawed, washed platelet is demonstrated

2. **Anticardiolipin Assay**

  - antibodies detected using an immunoassay on microtitre plate to test for IgG and IgM antibodies.

  • Advisable to test after discontinuation of anticoagulants if possible.

  • APLA may arise transiently (after infection, tissue injury) thus a **single POS test esp weak POS** is open to
Ix of suspected familial thrombophilia

1. Protein C activity assay
2. Protein S activity assay
3. Antithrombin activity assay
4. Activated protein C impedance test
5. Prothrombin gene mutation + fac V Leiden – PCR
6. Homocysteine level
• Other Ix:
  - TT
  - fibrinogen level
  - D dimer
  - fac VIII:C assay
  - fac XII assay
• Limitation of thrombophilia testing:
  - most test are affected by post thrombotic phase, should be performed a few months after acute episode.
  - specifically AT level are reduced by heparin
  - must ensure warfarin was off 2-3 weeks before testing as PC, PS are vit K dependent proteins → production decreased by warfarin
Management

- Patient on warfarin, goal is to keep PT at INR 2-3.0 (best risk-benefit ratio)

- Pt with identifiable hypercoagulable state, should be anticoagulated indefinitely.

- Pt without identifiable protein def, therapy is more empiric:
  - 1\textsuperscript{st} DVT: anticoagulated 6 months
  - 2\textsuperscript{nd} episode: indefinitely anticoagulation
  - thrombosis at unusual place: indefinite anticoagulation
Mx - familial thrombophilia

- Pt with PC, PS def should never be anticoagulated with warfarin unless fully anticoagulated with heparin. (reason: Both protein are vit K dependent, initiation of warfarin led to further decline the level, manifest as warfarin skin necrosis of buttocks or breast)

- Following DVT, reasonable to continue with oral anticoagulant 3-6 months (longer if pulm emboli)

- Prophylactic sc heparin strongly recommended prior to elective surgery, prolong immobilization.
• Management of Fac V Leiden

a) HMZ with or without hx of thrombosis, receive preventive therapy during at risk situation and extended anticoagulant Tx after thrombotic event

b) HTZ with hx of thrombosis treated like PC, PS, AT def

c) Counselling about secondary risk situation, offer relative for screening
Mx of APLA

- major venous & arterial thrombosis require anticoagulant
- avoidance: OCP, smoking
- immunosuppression should't play a role in therapy of thrombotic APLA (exception: catastrophic APLA)
- anticoagulation with INR 3.0-3.5 effective
Mx of other acquired thrombophilia

- **Cancer**
  - Cancer related thrombosis require anticoagulation.
  - Warfarin: reasonable choice for initial therapy
  - Pt with evidence of DIVC or those with pancreatic tumours require long term heparin

- **Myeloproliferative dz**
  - Venous thrombosis: warfarin; arterial dz: aspirin
• Pregnancy with DVT
  -LMWH (enoxaparin 1mg/kg bd or dalteparin 100u bd throughout pregnancy)
  -warfarin best avoided d/t ↑risk of fetal malformation
  -LMWH stop at delivery, cont afterward followed by warfarin 10mg daily x 6 months

prophylaxis:
• **Acute myocardial infarction**

- aspirin 160-325 mg initially then 75-150mg/d
- thrombolytic therapy: streptokinase/ anistreplase
- Following pt should receive heparin /LMWH and then warfarin for 1-3 months:
  1) Severe LV dysfx
  2) CCF
  3) Hx of PE/ systemic embo
• DVT prophylaxis in Surgery

b) Med risk pt ( > 40 yrs, > 30 min procedure)
- low dose heparin, compression stocking, LMWH

c) High risk pt (Hx of thrombosis, pelvic / abd / lower limb ortho surgery)
- LMWH, warfarin

• hyperhomocysteinemia
THANK YOU