Hypercoagulation

CP Conference 11/14/2006
Overview

- Hypercoagulation: poorly understood phenomena
- No definite cause is identified in > 40% of cases
- Three major factors in thrombus formation (Rudolf Virchow, 1845): decreased blood flow; changes in the circulating blood (coagulation factors & inhibitors); changes in the vessel wall
Overview (cont'd)

- Review is restricted to changes in circulating blood
- Identification of the etiology is critical for: specific treatment (LA in pregnancy); long-term treatment; counseling of family members (inherited disorders)
- Approach to diagnosis: clinical history, family history, laboratory tests
Hypercoagulation Disorders

- **Well established:**
  - Factor V Leiden (12-40% of hypercoagulation cases), V
  - Prothrombin gene mutation (6-18%), V
  - Protein C deficiency (6-10%), V
  - Protein S deficiency (5-10%), V
  - Antithrombin III (AT III) deficiency (5-10%), V
  - Lupus anticoagulant (LA) (10-20%), A+V
  - Anticardiolipin antibodies (ACA) (5-10%), A+V
  - Heparin-induced thrombocytopenia, A+V
  - Hyperhomocysteinemia (10-20%) +/- secondary to Methylenetetrahydrofolate reductase mutation, A+V

- **Legends:** A (arterial thrombosis), V (venous thrombosis)
Factor V Leiden

- Described by Dahlback in 1993: single base pair substitution at nucleotide location 1691 in chromosome 1, guanine-> adenine (G1691A), resulting in arginine -> glutamine at location 506 (R506Q). This results in poor inhibition of factor V by activated protein C (APC)-> venous thrombosis; normal F V activity
- Autosomal dominant. In 3-5% of Caucasian population; risk increased 3-6 fold (heterozygote), 80 fold (homozygote)
- 20-60% of hypercoagulation cases. Tx: heparin, coumadin
- Laboratory: APC resistance ratio=( PTT with APC/ PTT without APC) < 2.2 -> positive; interference (false pos): lupus anticoagulant, heparin, hirudin, argatroban. Confirmatory: PCR testing (positive in 90% of APC resistance cases)
Prothrombin Gene Mutation

- Single base pair substitution at nucleotide position 20210 in chromosome 11, guanine-> adenine (G20210A). This results in relatively high prothrombin level with increased risk for venous thrombosis (132% vs 105% of normal)
- Autosomal dominant. 1-3% of Caucasion population; risk increased 3 fold (heterozygote)
- 5-18% of hypercoagulation cases. Tx: heparin, coumadin
- Laboratory: Factor II assay, PCR testing for G20210A
Protein C Deficiency

- Protein C: a vitamin K-dependent coagulation inhibitor; synthesized in the liver; inactivating F Va and F VIIIa
- Protein C deficiency: autosomal dominant; 0.14-0.5% of population; risk increased 6.5-8 fold; 6-10% of hypercoagulation cases
- Clinical manifestation: recurrent deep vein thrombosis, pulmonary embolism, neonatal purpura fulminans (in homozygote). Tx: heparin, Coumadin
- Laboratory: immunological, functional assays, no mutation testing (>160 mutations)
Protein S Deficiency

- Protein S: a vitamin K-dependent protein; synthesized in the liver and megakaryocytes; cofactor of protein C
- Protein S deficiency: autosomal dominant; 0.7% of population; risk increased 1.6-11.5 fold; 5-10% of hypercoagulation cases
- Clinical manifestation: recurrent deep vein thrombosis, pulmonary embolism, neonatal purpura fulminans. Tx: heparin, coumadin
- Laboratory: immunological assay, functional assay, no mutation testing (>70 mutations)
AT III Deficiency

- AT III: inactivates thrombin and other factors (Xa, IXa, Xla, XIIa, kallikrein); accelerated by heparin
- AT III deficiency: autosomal dominant; 0.17% of population; risk increased 5-8.1 fold; 5-10% of hypercoagulation cases
- Clinical manifestation: recurrent deep vein thrombosis, pulmonary embolism. Tx: AT III, coumadin
- Laboratory: functional assay (chromogenic), immunologic assay, no mutation testing (>250 mutations)
Lupus Anticoagulant

- Immunoglobulins that prolong in-vitro phospholipid-dependent clotting times
- Found in various conditions; 30% of patients have thrombosis; 10-20% of hypercoagulation cases
- Antiphospholipid antibodies (lupus anticoagulant, anticardiolipin antibody, antiphosphatidyl serine, anti Beta 2 Glycoprotein I, etc): 1-2% of population, 50% of SLE patients
- Clinical manifestation: variety of thrombotic diseases. Tx: Heparin, Coumadin, Aspirin & prednisone (to prevent fetal demise)
- Laboratory: aPTT, dilute Russell Viper venom time (dRVVT), Hexagonal Phospholipid Neutralization
Anticardiolipin Antibodies

- ACA: IgG, IGM, IgA
- Found in various conditions; thrombotic manifestations known as antiphospholipid syndrome; in 5-10% of hypercoagulation cases.
- Tx: not well worked out, including Heparin, coumadin, and steroid
- Laboratory: ACA by ELISA; high levels are associated with high risks of thrombosis
## Anticardiolipin Antibodies (cont’d)

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<tr>
<th></th>
<th>Normal range</th>
<th>Clinically insignificant</th>
<th>Moderate risk</th>
<th>High risk</th>
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<tbody>
<tr>
<td>IgG</td>
<td>&lt; 15 GPL</td>
<td>15-20</td>
<td>20-80</td>
<td>&gt; 80</td>
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<tr>
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<td>IgA</td>
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Methylenetetrahydrofolate reductase (MTHFR) mutation

- MTHFR is an enzyme in the folate-dependent homocysteine remethylation, catalyzing the reduction of 5,10 methylenetetrahydrofolate -> 5 methyltetrahydrofolate
- Single base pair substitution at nucleotide location 677 in chromosome 1, Cytosine->Thymine (C677T). This results in Alanine-> Valine at location 223 (A223V), decreased MTHFR, causing hyperhomocysteinemia and subsequent thrombophilia (mechanism: blood vessel injury, coagulation activation, fibrinolysis inhibition, platelet activation)
- Autosomal recessive. 11% of Caucasian population (homozygote); increased risk 3 fold (homozygote). Tx: folate with or without vitamin B6 (pyridoxine) and vitamin B12
- Laboratory: homocysteine assay; PCR testing (currently not fully accepted as part of the routine battery)
MTHFR Deficiency

↑ homocysteine ➔ Methylcobalamin (B12) ➔ methionine ➔ protein

5,10 methylene THF ➔ 5 methyl THF (folate)
Methylenetetrahydrofolate reductase (MTHFR) mutation (cont’d)

- Other causes of hyperhomocysteinemia:
  - B12, folate, B6 deficiency
  - Renal failure
  - Hypothyroidism
  - Meds: methotrexate, phenytoin, theophylline
  - Malignancy
  - SLE
- Rare homozygous genetic disease:
  Cystathionine β-synthase (CβS) deficiency -> homocysteinuria
Cystathionine β-synthase (CβS) deficiency -

\[ \text{Cys} \xrightarrow{\text{CβS, B6}} \text{CysH} \xrightarrow{\text{Methylcobalamin (B12)}} \text{Met} \xrightarrow{\text{Protein}} \text{THF} \]

\[ \text{5,10 methylene THF} \xrightarrow{\text{MTHFR}} \text{5 methyl THF (folate)} \]
Genetic and Environmental Factors

- “Double-hit” hypothesis: genetic abnormality + environment factor (trauma, surgery, immobility, pregnancy, oral contraceptive, etc.)
- Combination of abnormalities: a genetic abnormality + another genetic or acquired abnormality (Common genetic abnormalities: FV Leiden, Prothrombin gene mutation, MTHFR mutation)

- Example: Factor V Leiden heterozygote (risk 3-6 fold) + Prothrombin gene mutation heterozygote (risk 3 fold) -> risk 25 fold