Hypercoagulable States and Stroke: Fact or Fiction

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UPMC Stroke Update
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ARTERIAL THROMBOSIS
Differential Diagnosis (1)

1) Embolus
2) Paradoxical embolus
3) Atherosclerosis
4) Diabetes mellitus
5) Smoking
6) Hypertension
7) Obesity
8) Lupus anticoagulant
9) Vasculitis
ARTERIAL THROMBOSIS
Differential Diagnosis (2)

10) Heparin-induced thrombocytopenia
11) Homocysteinemia, MTHFR genes
12) Myeloproliferative disorders
13) Estrogens, OCP’s
14) Sickle Cell Disease
15) Prothrombin gene variant
16) Factor V Leiden
17) Cocaine
18) Protein Z
1) Individual markers for lipids show inconsistent results with recent prospective study of total cholesterol quintiles in women showing HR’s for ischemic stroke of 2.13 in highest vs. lowest quintiles and 1.68 for LDL after adjustment for other risk factors.

2) The INTERSTROKE study (2010) failed to show an association of ischemic stroke with total cholesterol.
SMOKING

1) Two-fold risk of ischemic stroke overall
   
   Goldstein LB et al., Circulation, 2006.

2) Two to fourfold risk of hemorrhagic stroke

3) Dose-response relationship in Framingham study of twice the risk of stroke in smokers of >40 cigarettes/day compared to smokers of <40/day

4) Damages vascular endothelium promoting atherosclerosis, increases fibrinogen, and enhances platelet aggregation (largely reversible with cessation
DIABETES

1) Linked to atherosclerosclerosis but DM shown to be independent risk factor for stroke

2) Honolulu Health study showed RR of ischemic stroke 3.45 in Japanese men with DM compared to 1.43 after 22 year f/u

3) California study showed that h/o DM elevated glucose levels >7.8 mmol/L after 12 yrs. raised stroke risk by RR of 1.8 for men and 2.2 for women
OBESITY

1) Elevated BMI and waist-to-hip (WHR) ratio are associated with an increased risk of stroke.

2) INTERSTROKE study comparing the highest tertile to lowest WHR showed an increased OR for stroke of 1.65.

3) Study of >20,000 male physicians showed those with BMI ≥ 30 doubled stroke risk compared to those with BMI ≤ 23 with a 4% increase in the adjusted RR for each unit increase.

4) Thrombosis may be enhanced by increasing pro-inflammatory and prothrombotic markers.
PHYSICAL INACTIVITY

1) Meta analysis of 23 studies showed that moderately intense physical activity reduced stroke risk in all stroke subtypes

2) Mechanism of thrombosis may be increased viscosity, platelet aggregation, and fibrinogen, and reduced fibrinolysis

Lee et al., Stroke, 2003.
## TRADITIONAL RISK FACTORS FOR ISCHEMIC STROKE

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>OR</th>
</tr>
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<tbody>
<tr>
<td>Hypertension</td>
<td>2.37</td>
</tr>
<tr>
<td>Current smoking</td>
<td>2.32</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>1.60</td>
</tr>
<tr>
<td>Obesity (WHR)</td>
<td>1.69</td>
</tr>
<tr>
<td>Regular physical activity</td>
<td>0.68</td>
</tr>
</tbody>
</table>

*O’Donnell et al., Lancet, 2010.*
CONGENITAL HYPERCOAGULABLE STATES

1) Antithrombin III deficiency
2) Protein C deficiency
3) Protein S deficiency
4) Heparin cofactor II deficiency
5) Factor XII deficiency
6) Dysfibrinogens
7) Plasminogen deficiency
8) Dysplasminogen
9) Plasminogen activator deficiency
10) Factor V Leiden mutation
11) Prothrombin variant
12) Homocysteinemia
13) Protein Z deficiency
RELATIVE FREQUENCY OF CONGENITAL THROMBOTIC DISORDERS

- Antithrombin III deficiency: 1:300,000
- Protein C deficiency: 1:16000
- Protein S deficiency: 1:16000
- Heparin cofactor II deficiency: <1:1,000,000
- Thrombotic dysfibrinogens: <1:1,000,000
- Plasminogen deficiency: <1:1,000,000
- Plasminogen activator deficiency: <1:1,000,000
- Factor V Leiden mutation: 1:17
- Prothrombin variant: 1:50-100
- MTHFR homozygotes: 1:50-100
# Testing Recommendations for Hypercoagulable States

<table>
<thead>
<tr>
<th>&lt; age 50</th>
<th>&gt; age 60</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Antithrombin III</td>
<td>1) Lupus anticoagulant</td>
</tr>
<tr>
<td>2) Protein C</td>
<td>2) APCr</td>
</tr>
<tr>
<td>3) Protein S</td>
<td>3) Prothrombin variant</td>
</tr>
<tr>
<td>4) APCr</td>
<td></td>
</tr>
<tr>
<td>5) Prothrombin variant</td>
<td></td>
</tr>
<tr>
<td>6) Lupus anticoagulant</td>
<td></td>
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</tbody>
</table>
Testing for Hypercoagulable States

Is it worth it?

Does it make any difference?
LUPUS ANTICOAGULANTS
DEFINITION

1) Are a heterogeneous group of antiphospholipid antibodies
2) Found in a variety of clinical settings
3) Usually IgG or IgM
4) Prolong APTT and block coagulation factor activity \textit{in vitro}
5) Name is a misnomer since they are associated with thrombosis rather than bleeding
LUPUS ANTICOAGULANTS
MECHANISM OF THROMBOSIS

1) Remains poorly defined
LUPUS ANTICOAGULANTS
CLINICAL ASSOCIATIONS (1)

1) Seen in 2-4% of general population
2) May be asymptomatic in majority of patients
3) More frequent in elderly
4) Seen in 20-45% of patients with SLE, less often in other autoimmune disorders
5) Recurrent venous or arterial thromboses, antiphospholipid antibody antibody syndrome
6) Seen commonly in patients with AIDS
6) Recurrent miscarriages, especially 2nd trimester
7) Stroke, including Sneddon’s syndrome
8) Migraine
9) Myocardial infarction
10) Thrombocytopenia
11) Seen in association with many drugs
DRUGS ASSOCIATED WITH LUPUS ANTICOAGULANTS OR LUPUS-LIKE SYNDROMES (1)

1) Procainamide (Pronestyl)
2) Hydralazine (Apresoline)
3) Isoniazid (INH)
4) Diphenylhydantoin (Dilantin)
5) Primidone (Mysoline)
6) Ethosuximide (Zarontin)
7) Carbamazepine (Tegretol)
DRUGS ASSOCIATED WITH LUPUS ANTICOAGULANTS OR LUPUS-LIKE SYNDROMES (2)

8) Phenothiazines
9) Haloperidol (Haldol)
10) Sulfasalazine (Azulfidine)
11) Quinidine
12) $\alpha$-interferon
13) Antibiotics (In Children)
LUPUS ANTICOAGULANTS
LABORATORY ABNORMALITIES

1) Long APTT and mix
2) Long PT and mix
3) Dilute Russel Viper venom time ratio
4) Tissue thromboplastin inhibition index (TTI)
5) Hexagonal lipid neutralization
6) Interference with clotting factor assays
7) Anticardiolipin antibody
8) Antiphosphatidylserine antibody
9) $\beta_2$-glycoprotein I APAs
10) Platelet neutralization procedure
11) Thrombocytopenia
12) +ANA
13) +RPR
LUPUS ANTICOAGULANTS
RECOMMENDED TESTS

1) APTT and mix
3) Dilute Russel Viper venom time ratio
4) Tissue thromboplastin inhibition index (TTI)
5) Hexagonal lipid neutralization
7) Anticardiolipin antibody
9) $\beta_2$-glycoprotein I APAs
LUPUS ANTICOAGULANTS
TESTS NOT RECOMMENDED

1) Interference with clotting factor assays
2) Antiphospholipid antibody
3) Antiphosphatidylserine antibody
4) Platelet neutralization procedure
5) IgA antibodies
LUPUS ANTICOAGULANTS and THROMBOSIS

1) Most-associated with presence of a lupus anticoagulant rather than an IgG or IgM anticardiolipin or B2 GPI antiphospholipid antibody

2) Drug-induced LACs/APA Ab’s don’t appear to be associated with thrombosis
LUPUS ANTICOAGULANTS and STROKE

1) ACA associated with approx. 10% of stroke patients
2) IgG without IgM is usual finding

Hess et al., Neurology, 1991
Warfarin Aspirin and Recurrent Systemic Stroke

WARSS STUDY

Antiphospholipid Antibody and Systemic Stroke

APASS STUDY

WARFARIN vs. ASA and STROKE

1) Still no strong evidence that Coumadin is superior to antiplatelet agents for any stroke indication other than for atrial fibrillation

2) Warfarin and Recurrent Systemic Stroke (WARSS) study (N=2206) showed no evidence for benefit of Coumadin (INR 1.4-2.0) over 325 mg ASA

3) APASS study (N=1770) showed same for recurrent stroke prevention in patients with lupus anticoagulants (LACs)

4) There is evidence to use heparin or LMWH rather than Coumadin for stroke pts with dissecting stroke, carotid stenosis, or with decreased mobility/paralyzed limb
Plasminogen

Plasminogen Activator

PAI*

Protein C

Protein S

Activated Protein C

Antithrombin III

Heparin Cofactor II

Plasmin

α₂ Anti-plasmin

↔ = Inhibitory
→ = Activating
* Plasminogen Activator Inhibitor
APC RESISTANCE ASSAY

1) Recommended for patients with thrombotic history and normal APTT
2) APC ratio is developed where:

\[
\text{APC RATIO} = \frac{\text{APC-APTT}}{\text{APTT}}
\]

3) Low APC ratios (APC resistant) are associated with a thrombotic tendency
4) 80% of low APC ratios are associated with the factor V Leiden mutation
FACTOR V LEIDEN MUTATION

1) Remains the most common congenital thrombotic disorder described – 6% incidence in U.S.

2) Eliminates the protein C cleavage site on Factor V

3) Caused by mutation of guanine to adenine (G→A) in the factor V gene

4) Results in replacement of arginine by glutamine (Arg→Gln) in the factor V amino acid sequence
FACTOR V LEIDEN MUTATION

1) Best evidence is that it clearly primarily promotes venous thrombosis (Ridker)

2) But some flaws in study and some question about homozygotes causing arterial
## FACTOR V LEIDEN MUTATION
### Thrombotic Events in 114 Pts

<table>
<thead>
<tr>
<th>Events</th>
<th>No. (%)</th>
</tr>
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<tbody>
<tr>
<td>DVT</td>
<td>75 (66%)</td>
</tr>
<tr>
<td>PE</td>
<td>31 (31%)</td>
</tr>
<tr>
<td>CVA/TIA</td>
<td>11 (10%)</td>
</tr>
<tr>
<td>SVT</td>
<td>9 (8%)</td>
</tr>
<tr>
<td>RVO</td>
<td>8 (7%)</td>
</tr>
<tr>
<td>MI</td>
<td>8 (7%)</td>
</tr>
<tr>
<td>Mes. Vasc. Occ.</td>
<td>5 (4%)</td>
</tr>
<tr>
<td>Other</td>
<td>7 (6%)</td>
</tr>
</tbody>
</table>

Plasminogen → Protein C → Protein S → Activated Protein C → Antithrombin III → α₂ Anti-plasmin → Fibrin

* Plasminogen Activator Inhibitor

→ = Inhibitory

= Activating
PROTHROMBIN VARIANT
Factor II Mutation

1) Variant form of factor II
2) Found in 1-2% of the U.S. population
3) Caused by a point mutation on chromosome 11
4) Probably leads to increased circulating level of normal factor II molecule
5) Found in 5% of new patients of new pts with venous thrombosis
## PROTHROMBIN VARIANT

**Factor II Mutation**

**Thrombotic Risks**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Relative Risk</th>
</tr>
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<tbody>
<tr>
<td>Venous thrombosis in heterozygotes</td>
<td>2.3:1</td>
</tr>
<tr>
<td>MI in young female smokers</td>
<td>4-6:1</td>
</tr>
<tr>
<td>Arterial stroke</td>
<td>5:1</td>
</tr>
<tr>
<td>MI in diabetics</td>
<td>7:1</td>
</tr>
<tr>
<td>Miscarriage</td>
<td>9.5:1</td>
</tr>
<tr>
<td>Cerebral VT in heterozygotes</td>
<td>10:1</td>
</tr>
<tr>
<td>Cerebral VT in heterozygotes on OCP’s</td>
<td>149:1</td>
</tr>
</tbody>
</table>
PROTHROMBIN VARIANT
Factor II Mutation
Thrombotic Risks

1) Controversial
2) Meta-analysis of 19 studies suggests small arterial risk
3) Also may be significant risk in young pts with very low arterial thrombotic risk
(Fibrinogen)

II

(Prothrombin-Thrombin)
Plasminogen

Plasminogen Activator

PAI*

Plasminogen

Plasmin

$\alpha_2$ Anti-plasmin

\[ \rightarrow = \text{Inhibitory} \]
\[ \leftarrow = \text{Activating} \]

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Natural Anticoagulants Causing Exclusively Venous Thrombosis

1) Antithrombin (III)
2) Protein C
3) Protein S
Plasminogen

Plasminogen Activator

PAI*

Plasminogen

Plasmin

α₂ Anti-plasmin

Antithrombin III

Fibrin

* Plasminogen Activator Inhibitor

↔ = Inhibitory

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ANTITHROMBIN (III) DEFICIENCY

1) Found ~25 patients in 50 yrs. with true congenital deficiency at ITxM lab

2) Scattered reports of antithrombin deficiency associated with stroke can be found but there is little to suggest a significant risk of arterial stroke

3) Acquired deficiency is very common ~5/day at ITxM lab = ~2500:1 ratio of acquired to congenital
ANTITHROMBIN III (2)

5) Decreased in:
   a) Acute thrombosis
   b) Liver disease
   c) DIC
   d) Heparin therapy
   e) Sepsis
   f) Nephrotic syndrome
   g) Post-operative state
   h) Newborns
   i) ECMO
   j) HELLP syndrome
Plasminogen

**Plasminogen Activator**

PAI*

→ = → = → = → =

Inhibitory

Activating

* Plasminogen Activator Inhibitor

Plasminogen

Protein C

Activated Protein C

Protein S

Activated Protein C

Fibrin

α₂ Anti-plasmin

* → = Inhibitory

* → = Activating
PROTEIN C DEFICIENCY

1) Found 40-50 patients in 30 yrs. with true congenital deficiency at ITxM lab

2) Scattered reports of protein C deficiency associated with stroke can be found but there is little to suggest a significant risk of arterial stroke

3) Acquired deficiency is very common ~3/day at ITxM lab = ~700:1 ratio of acquired to congenital
PROTEIN C (2)

10) Decreased in:
   a) Acute thrombosis
   b) Liver disease
   c) Vitamin K deficiency
   d) Coumadin therapy
   e) DIC
   f) Adult RDS
   g) Post-operative state
   h) Newborns
Plasminogen

Plasminogen Activator

PAI*

Protein C

Activated Protein C

Protein S

Activated Protein C

Plasmin

α₂ Anti-plasmin

Fibrin

→ = Inhibitory

→ = Activating

* Plasminogen Activator Inhibitor
1) Found 40-50 patients in ~25 yrs. with true congenital deficiency at ITxM lab
2) Scattered reports of protein C deficiency associated with stroke can be found but there is little to suggest a significant risk of arterial stroke
3) Acquired deficiency is very common ~4/day at ITxM lab = ~500:1 ratio of acquired to congenital
PROTEIN S (2)

6) Decreased in:
   a) Acute thrombosis
   b) Coumadin therapy
   c) Vitamin K deficiency
   d) Liver disease
   e) Pregnancy
   f) Women taking OCP’s, estrogens
   g) Conditions elevating C4b protein
Plasminogen

Plasminogen Activator

PAI*

Plasminogen

Plasmin

α2 Anti-plasmin

Protein Z

Fibrin

→ = Inhibitory

→ = Activating

* Plasminogen Activator Inhibitor
PROTEIN Z

1) 3rd vitamin K dependent natural anticoagulant
2) Deficiency associated with thrombotic stroke and miscarriage
HYPERHOMOCYSTEINEMIA

Controversies

1) Mechanism of thrombosis unclear
2) Elevated plasma homocysteine levels may only reflect folate intake
3) Elevated plasma homocysteine levels or certain MTHFR pattern mildly increase thrombosis risk
4) Many RCT show that folate, B6, and B12 do not lower thrombotic risk
5) Recommend against homocysteine and MTHFR testing
SICKLE CELL DISEASE and STROKE

With SSD: 11% at 20 yrs.
15% at 30 yrs.
24% at 45 yrs.

HEPARIN-INDUCED THROMBOCYTOPENIA and STROKE

1) Causes venous and less commonly arterial thrombosis, including stroke

2) 30/960 (3.1%) of HIT pts found to have stroke

Lamonte et al., Critical Care Medicine, 2004.
1) Polycythemia vera has greater incidence of stroke than essential thrombocytosis

2) The use of the somatic mutations JAK2 for p. vera and CALR for ET has significantly improved diagnostic capability and may be future targets for therapy
MALIGNANCY and STROKE

1) In 4 yr. period from 1997-2001, 96 pts at MSKCC were found with stroke; 61.5% were men.

2) Carcinoma of the lung (30%) was the most common primary tumor followed by brain (9%) and prostate (9%).

3) Strokes were embolic 52 (54%) and non-embolic 44 (46%) 3 had definite dx of marantic endocarditis.

4) 25% of pts died within 30 days; treatment had no impact on survival.

_Cestari, et al., Neurology, 2004._
PFO and STROKE

1) 14-20% of pts have PFO
2) Opens up the venous prothrombotic markers to cause a stroke, making the full w/u more reasonable
3) Also in pts with strong FH of thrombosis may be worth it.