Thrombophilia – Diagnosis and Evaluation

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Disclosure Slide

I have nothing to disclose related to the content of this presentation
Doctor, I think I have “Thrombophilia”

“Alrighty, let’s Google those symptoms and see what we come up with?”
ESSENTIAL THROMBOPHILIA
REPORT OF FIVE CASES

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Fellow in Surgery, the Mayo Foundation
AND
GEORGE E. BROWN, M.D.*

SUMMARY

Five cases are presented in detail, in all of which there was thrombosis of the larger arteries and veins, not only of the extremities but also of other regions of the body. This thrombosing disease shows a tendency toward relapse, with recurrence of thrombosis. The thrombosis is initiated without evidence of antecedent disease or of existing disease or any known predisposing factors. The pathologic changes in the vessels are those of a nonreacting type of thrombosis without evidence of disease in the intima or other coats of the vessel. There is an associated hypercoagulability of the plasma during these episodes. It is believed that this condition represents a separate disease entity, and to it has been given the name essential thrombophilia.
What is Thrombophilia?

*International Consensus Statement*

- Term used to describe an increased risk for venous and occasionally arterial thromboembolism due to *hematological abnormalities*.
- Can be multifactorial where *inherited* defects of anticoagulant or procoagulant factors combine with *acquired hematological* abnormalities.
- Consider in patients with an unexplained thrombotic episode or a positive family history.
Causes of Thrombophilia

- Deficiency of naturally occurring coagulation inhibitors
  - Antithrombin, protein C and S deficiencies
- Abnormal functions of naturally occurring coagulants
  - Resistance to activated protein C (Factor V Leiden)
  - Prothrombin mutation G20210A
- Hyperhomocysteinemia (>100 μmol/L)
- Antiphospholipid Syndrome
- Elevated levels of naturally occurring coagulation factors (VIII, IX, XI, fibrinogen)

“The Hypercoagulable State”

Patients unusually predisposed to *thrombosis*

Generally not the result of one defect, but “*multiple factors*”
Pathophysiology of the Hypercoagulable State

Abnormal Vessel Wall
(endothelial dysfunction/damage, contact pathway activation, tissue factor release)

Virchow’s Triad

Abnormal Blood Flow
(venous obstruction/stasis, atrial fibrillation, aortic stenosis, mechanical valves)

Abnormal Blood Constituents
(abnormalities in platelet/coagulation and fibrinolytic pathways)
(Other cellular components/microparticles)

“Thrombophilia”
Thrombosis – Hypercoagulable State

**Is it Venous?**
- Deep vein thrombosis
- Pulmonary embolism
- Superficial thrombophlebitis
- Cerebral vein thrombosis
- Mesenteric vein thrombosis
- Portal, hepatic vein thrombosis
- Gonad vein thrombosis
- Renal vein thrombosis

**Is it Arterial?**
- Stroke
- Myocardial infarction
- Mesenteric ischemia
- Arm or Leg ischemia

or a combination of **Venous and Arterial Thrombosis?**
Venous Thrombosis

- Is it Inherited?
- Is it Acquired or Environmental?

Most are a Combination of Factors
Features of Inherited Venous Thrombosis

- Family history
- Thrombosis at a young age
- Thrombosis in unusual locations
- Recurrent thrombosis
- Resistance to anticoagulation
- Purpura fulminans
- Skin necrosis on warfarin
- Stroke or MI at a young age

Resistance:
- Antithrombin
- Pregnancy
- Elevated FVIII
- Cancer
- HIT
Acquired Causes of Venous Thrombosis

Some of the most prevalent preexisting medical characteristics associated with increased risk for VTE

- 48 or more hours of immobility in preceding month
- Current hospitalization
- Hospital admission - past three months
- Surgery - past three months
- Infection - past three months
Acquired Causes of Venous Thrombosis

- Cancer and chemotherapy
- Surgery
- Trauma
- HRT use
- OCP’s
- Pregnancy

Cancer and chemotherapy, surgery, trauma, HRT, OCP’s, pregnancy
Acquired Causes of Venous Thrombosis

Thoracic outlet syndrome, pacemaker wires, CVP catheters
Acquired Causes of Venous Thrombosis

- Pneumonia
- Old age
- Hospitalization
- Varicose veins
- Obesity

Infection, hospitalization, old age, obesity, varicose veins, systemic diseases
Acquired Causes of Venous Thrombosis

*Inferior Vena Cava Filters*

Up to a 20% risk for a **DVT** if the filter is not removed and/or patient not on anticoagulation
Acquired Causes of Venous Thrombosis

May-Thurner and Popliteal Entrapment Syndromes
Additional Causes of Venous Thrombosis

An Association between Atherosclerosis and Venous Thrombosis

Paolo Prandoni, M.D., Ph.D., Franca Bilora, M.D., Antonio Marchiori, M.D., Enrico Bernardi, M.D., Francesco Petrobelli, M.D., Anthonie W.A. Lensing, M.D., Ph.D., Martin H. Prins, M.D., Ph.D., and Antonio Girolami, M.D.
# Prevalence of Inherited Thrombophilia and Associated Relative Risk for VTE

<table>
<thead>
<tr>
<th>Inherited thrombophilia</th>
<th>Prevalence (%) in general population</th>
<th>Prevalence (%) in patients with VTE</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>AT deficiency</td>
<td>0.07 - 0.16</td>
<td>1 - 3</td>
<td>20</td>
</tr>
<tr>
<td>PC deficiency</td>
<td>0.2 - 0.4</td>
<td>3 - 5</td>
<td>10</td>
</tr>
<tr>
<td>PS deficiency</td>
<td>0.03 - 0.13</td>
<td>1.5</td>
<td>10</td>
</tr>
<tr>
<td>FV Leiden mutation</td>
<td>3 - 15</td>
<td>20</td>
<td>5</td>
</tr>
<tr>
<td>Prothrombin mutation</td>
<td>1 - 2</td>
<td>4 - 7</td>
<td>2-3</td>
</tr>
<tr>
<td>Hyperhomocysteinemia</td>
<td>5</td>
<td>10</td>
<td>2.5</td>
</tr>
<tr>
<td>Elevated factor VIII</td>
<td>11</td>
<td>25</td>
<td>5</td>
</tr>
</tbody>
</table>
Incidence of DVT Is Correlated With the Number of Risk Factors

Arterial Thrombosis

Is it Inherited (Rare)?
- Factor V Leiden
- Prothrombin gene mutation
- Antithrombin deficiency
- Protein C deficiency
- Protein S deficiency
- Antiphospholipid syndrome
- Homocystinuria

Is it Acquired?
- Advancing age
- Male gender
- Hyperlipidemia, Diabetes mellitus
- Atherosclerosis
- Smoking
- Cocaine use
- Meds: UFH, LMWH, antiplatelet agents, OCP’s, HRT, chemotherapy agents
- TTP
- Cancer
- Antiphospholipid syndrome
- Myeloproliferative disorders
- PFO (Paradoxical embolism)

“The literature contains no solid evidence to support an important relationship between thrombophilic defects (other than APS and homocysteine) and arterial thrombosis.”

Semin Thromb and Hemostas 2007;6:588-596
Traditional Risk Factors for Arterial Thrombosis
Causes of Combined Arterial and Venous Thrombosis

- Heparin induced thrombocytopenia (HIT)
- Disseminated intravascular coagulation (DIC)
- Antiphospholipid syndrome
- Elevated levels of Homocysteine
- Oral contraceptives
- Hormone replacement therapy
- Pregnancy
- Malignancy
- Myeloproliferative disorders

- Vasculitis
- Cocaine use
- Paradoxical embolism
- Hyperviscosity syndromes (Sickle cell, Multiple myeloma, Waldenstrom’s macroglobulinemia)
- Paroxysmal nocturnal hemoglobinuria
- Inflammatory bowel disease
- Popliteal artery entrapment syndrome
- Behcet’s disease
Evaluating the Patient with Thrombosis

- History of Present Illness (thrombosis)
- Past Medical History
- Medications
- Family history
- Social history
- Review of systems
- Physical examination

- Thrombosis (venous, arterial, or combination)
- Previous thrombosis? Was it inherited or acquired?
- Obesity, diabetes? hyperlipidemia? cancer?
- Additional risk factors?
Evaluating the Patient with Thrombosis

- History of Present Illness (thrombosis)
- Past Medical History
- Medications ✓
- Family history
- Social history
- Review of systems
- Physical examination
Medications that can cause Thrombosis

- Heparin or Low molecular weight heparin, Fondaparinux
- Warfarin
- Oral contraceptives, HRT
- Infertility therapy
- Chemotherapy
- Antiplatelet medications
Medications – Heparin or LMWH

Heparin-induced thrombocytopenia (HIT)

- Develops 5 to 14 days after starting UFH, LMWH
- Thrombocytopenia (not always present)
- Venous and or arterial thrombosis
Medications – Warfarin

Coumadin skin necrosis

- Develops 3 to 5 days after starting warfarin
- More common in obese women
- Breasts, buttocks, thighs most often involved
- Some patients have Protein C deficiency
Medications: Heparin and Warfarin

Venous Limb Gangrene + Skin Necrosis in Patients with HIT

Patients with HIT whose:
- Platelet counts have not recovered from acute HIT when starting warfarin
- Often have a supratherapeutic INR
Medications - OCP’s, HRT, Chemotherapy

• Venous and/or arterial thrombosis
  (MI, stroke, DVT, PE, limb ischemia)
Medications - Clopidogrel

Thrombotic thrombocytopenia purpura (TTP)

Platelet count

Admission
Before PCI
Following PCI
Evaluating the Patient with Thrombosis

- History of Present Illness (thrombosis)
- Past Medical History
- Medications
- **Family history ✓**
- Social history
- Review of systems
- Physical examination

- Family history of venous or arterial thrombosis?
- Especially first degree relatives?
- Thrombosis at a young age?
Family History
First-Degree Family History of Venous Thrombosis

<table>
<thead>
<tr>
<th>Family History</th>
<th>Patients with Venous Thrombosis (n=1605)</th>
<th>Control Subjects (n=2159)</th>
<th>Odds Ratio (95% Confidence Intervals)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>1100 (68.5)</td>
<td>1786 (82.7)</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Positive FH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- any relative</td>
<td>505 (31.5)</td>
<td>373 (17.3)</td>
<td>2.2 (1.9-2.6)</td>
</tr>
<tr>
<td>- relative &lt; 50 y</td>
<td>240 (15.0)</td>
<td>144 (6.7)</td>
<td>2.7 (2.2-3.4)</td>
</tr>
<tr>
<td>- &gt;1 Relative</td>
<td>97 (6.0)</td>
<td>40 (1.9)</td>
<td>3.9 (2.7-5.7)</td>
</tr>
</tbody>
</table>

In clinical practice, family history may be more useful for risk assessment than thrombophilia tests.

Arch Intern Med 2009; 169: 610-615
Evaluating the Patient with Thrombosis
Social History

- Smoking
- Cocaine
- IV drug abuse
- Doping substances
  - Stimulants
    - Amphetamines
    - Methamphetamines
  - Anabolic Steroids
    - Testosterone
    - Stanozolol
Evaluating the Patient with Thrombosis

Review of Systems ✓

• **General:** fever, night sweats, weight loss?
• **CNS:** amaurosis fugax, arm or leg weakness, difficulty with speech or balance?
• **Cardiac:** chest pain-crushing or pleuritic or radiating, palpitations, valvular heart disease?
• **Pulmonary:** shortness of breath, cough, hemoptysis?
• **GI:** abdominal pain, diarrhea or constipation, change in bowel habits, melena, weight loss?
• **GU:** hematuria or flank pain?
• **Musculoskeletal:** swelling or leg pain?
• **Cancer screening up to date? ✓**
Evaluating the Patient with Thrombosis
Physical Examination √
Diagnosis - What Tests Do I Order?

Routine Studies:
- CBC with platelets
- Blood smear
- Chemistry profile
- Urinalysis
- PT + APTT
## What Tests Do I Order to Identify a Thrombophilia Condition?

### Inherited
- Activated protein C (APC) resistance ratio
- DNA-based assay for
  - Prothrombin gene mutation 20210A
  - Factor V Leiden (if APC ratio abnormal)
- Fasting plasma homocysteine
- Antithrombin, protein C, free and total protein S
- Factor VIII

### Acquired
- Lupus anticoagulant, anticardiolipin antibodies, beta$_2$ glycoproteins
- Assays for DIC (fibrinogen, d-dimer)
- Anti-PF4 antibodies or SRA for HIT
- PNH (CD55/59)
- JAK 2 mutation
- Drug testing

Tests I do not order routinely:
- Factor IX, XI
- MTHFR
- PAI-1
- Plasminogen
Who Should be Tested?

- Strong family history of thrombosis
- Thrombosis at a young age
- Thrombosis at unusual anatomic locations
- Resistance to anticoagulation
- Recurrent thrombosis or miscarriages
- Unexplained MI, CVA or arterial thrombosis at a young age
- Purpura fulminans or skin necrosis on warfarin

Routine Screening of the population at large-NOT RECOMMENDED
Who Should be Tested?

- VTE at any age with a strong family history of thrombotic disease (i.e., several affected relatives or relatives with VTE < 50 years of age)
- Women suffering VTE in association with pregnancy or immediate postpartum period
Why Should I Test?

There are no absolute indications

- If it will influence duration of treatment
- If it will influence choice of an anticoagulant
- If it will identify a patient at risk for recurrence or (asymptomatic) relatives at risk who might use OCP’s, HRT or become pregnant
- If it alleviate the fear of an occult cancer
Why Should I Test?

Non medical Reasons

- Patients and families expect it
- Referring doctors expect it
- Peers expect it
- Workup considered incomplete without it

Slide courtesy of Sam Goldhaber
Semin Thromb and Hemostasis 2009; 35: 695-710
Why Not Test?

- Insurance/genetic discrimination
- Anxiety and family issues
- Risk of overtreatment
- Expensive
- Usually does not change management
- High chance of false positives
How Do the Test Results Affect My Management?
Little evidence to suggest identifying an inherited thrombophilia will influence the duration of anticoagulation

No randomized controlled trials that have assessed the benefits of testing for thrombophilia on the risk of recurrent VTE
Thrombophilia Testing does not help to predict or reduce the incidence of thrombosis recurrence

- Presence of most risk factors including factor V Leiden are at best only weak predictors of recurrence
- Thus knowledge of the thrombophilia status of affected patients fails to substantially help clinicians in practice to prevent recurrence of VTE in those patients
- Exception – Antiphospholipid syndrome
- Clinical setting- a more useful predictor of recurrence than inherited thrombophilia
Considerations for the physician and patient when deciding whether thrombophilia testing is appropriate.
Thrombophilia Testing for Prevention of Recurrent Venous Thromboembolism
The Cochrane Collaboration 2013

There is currently no information available from RCT or CCT on the benefits of thrombophilia testing to reduce the risk of recurrent VTE