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Inherited and Secondary Thrombophilia: Clinician Update

Kevin P. Cohoon, D.O., M.Sc. and **John A. Heit, M.D.**
Divisions of Cardiovascular Diseases (KPC, JAH) and Hematology (JAH), Department of Internal Medicine; Mayo Clinic, Rochester, MN, USA

Keywords

Thrombosis; Venous thromboembolism; Hyperhomocysteinemia; Inherited type 1 antithrombin deficiency

Case 1

A healthy 19-year-old man presented with new chest pain and near syncope. CT pulmonary angiography showed a saddle pulmonary embolus. The patient denied recent travel, trauma, surgery, or hospitalization. His mother had two miscarriages at 10 weeks gestation, and his maternal grandfather had deep venous thrombosis at age 60 years.

Case 2

A healthy 45-year-old woman complained of new dyspnea and left calf pain. CT pulmonary angiography and compression venous duplex ultrasonography showed bilateral pulmonary emboli and acute left leg deep vein thrombosis, respectively. The patient denied exogenous hormone use, recent travel, trauma, surgery, or hospitalization. Her health maintenance was current, and she gave a family history of pernicious anemia, Grave's disease, and amyotrophic lateral sclerosis. Laboratory analyses showed reduced hemoglobin (11.4 g/dL; normal 12.0–15.5 g/dL), increased red cell distribution width (18.9 percent; normal 11.9–15.5 percent), and mild thrombocytopenia.

Neither patient had previous venous thromboembolism, and both were referred to the Mayo Clinic Thrombophilia Center for apparent idiopathic venous thromboembolism.

Introduction

Thrombophilia is defined as a predisposition (susceptibility) to thrombosis. Thrombophilia is not a disease per se, but may be associated with a disease (e.g., cancer), drug exposure (e.g., oral contraceptives) or condition (e.g., pregnancy or postpartum; "secondary thrombophilia"; Table 1), and thrombophilia may be inherited (Table 2).[1] This concept is important because disease susceptibility does not imply an absolute requirement for primary or secondary prevention, or for treatment. Most persons with a thrombophilia do not develop thrombosis. Thus, thrombophilia must be considered in the context of other risk factors for incident thrombosis, or predictors of recurrent thrombosis, when estimating the need for primary or secondary prophylaxis, respectively.

Address Correspondence to: John A. Heit, M.D., Stabile 6-Hematology Research, Mayo Clinic, 200 First Street, SW, Rochester, MN 55905, 507-284-4634 (voice), 507-266-9302 (fax), heit.john@mayo.edu.

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The role of special coagulation testing for an acquired or inherited thrombophilia is controversial. Thrombophilia testing should only be done if the results are likely to change medical management. There are no absolute indications for thrombophilia testing. Relative indications could include selected screening of asymptomatic or symptomatic family members of patients with a known inherited thrombophilia, populations at increased risk for thrombosis (e.g., prior to pregnancy, oral contraception or estrogen therapy, high-risk surgery, or chemotherapy with angiogenesis inhibitors), patients with an incident thrombotic event (e.g., incident venous thromboembolism; stillbirth or another complication of pregnancy; incident arterial thrombosis in a young person without other arterial disease), recurrent thrombosis, "idiopathic" thrombosis, thrombosis at a young age (e.g., ≤40–45 years for venous thrombosis, ≤50–55 years for arterial thrombosis), or thrombosis in unusual vascular territories (e.g., cerebral vein, portal vein, hepatic vein, mesenteric vein or artery, renal vein or artery, etc.). All of these potential indications are controversial and must be considered in the context of the clinical presentation.

Timing of Diagnostic Thrombophilia Testing: When should I test?

Many of the natural anticoagulant and procoagulant plasma proteins are acute phase reactants. Acute thrombosis can transiently reduce the levels of antithrombin and, occasionally, proteins C and S. Consequently, testing is usually not recommended during the acute phase of thrombosis or during pregnancy. A delay of at least six weeks after the acute thrombosis or childbirth allows sufficient time for acute phase reactant proteins to return to baseline. Heparin therapy can lower antithrombin activity and antigen levels and can impair interpretation of clot-based assays for a lupus anticoagulant. A delay of at least five days after heparin is stopped prior to testing is usually feasible. Warfarin therapy reduces the activity and antigen levels of the vitamin K-dependent factors, including proteins C and S. Rarely, warfarin may also increase antithrombin levels into the normal range in individuals with a hereditary deficiency. Novel oral anticoagulants may cause false-positive lupus anticoagulant (DRVVT) testing and falsely low antithrombin activity. Many authorities recommend delaying testing until the effects of warfarin or novel oral anticoagulant therapy have resolved. The effect of warfarin on protein S levels may not resolve for up to six weeks. Direct leukocyte genomic DNA testing for the factor V Leiden and prothrombin G20210A mutations is unaffected by anticoagulation therapy; such testing can be performed at any time.

Diagnostic Thrombophilia Testing: For what should I test?

Unfortunately, there is no single laboratory assay or simple set of assays that will identify all thrombophilias. Consequently, a battery of complex and potentially expensive assays is usually required. Many of these laboratory analytes are affected by other conditions such that the correct interpretation of the results can be complicated and require clinical correlation. The laboratory evaluation for individuals with thrombosis should be selective and based on the history and physical examination, and may include a complete blood count with peripheral smear, serum protein electrophoresis, serum chemistries for electrolytes and liver and renal function, serology, and urinalysis. Testing for inherited deficiency of antithrombin, protein C, and protein S should be considered in patients with thrombosis at a young age. Patients who develop arterial thrombosis should be considered for testing for antiphospholipid antibodies (e.g., lupus anticoagulant, anticardiolipin antibodies, anti-beta2 glycoprotein-1 antibodies), heparin-induced thrombocytopenia, myeloproliferative disorders, homocysteinuria, and hyperhomocysteinemia.

A young patient with organ or skin infarction in the absence of risk factors for atherosclerosis or cardioembolism should be carefully evaluated for "esoteric" or occult

arterial disease. An inherited thrombophilia is an unusual cause of stroke, myocardial infarction, or other organ or skin infarction. Detailed inquiry into constitutional or specific symptoms of vasculitis (primary or secondary), infection (systemic [e.g., endocarditis], local (e.g., infected aneurysm with artery-to-artery embolism) atheroembolism, trauma (accidental, thermal, or occupational), dissection, vasospasm, or vascular anomaly is required. In addition to a careful pulse examination (including an examination for aneurysmal disease), evidence of microcirculatory occlusive disease of the hand (e.g., livedo, skin or fingernail-bed infarction, or ulcer) should prompt a search for endocarditis (infectious and non-infectious), thoracic outlet syndrome, or other causes of repetitive arterial trauma (e.g., hypothenar hammer hand syndrome, “jackhammer” or “volleyball” hand), atheroembolism, and thermal injury. Such physical findings in the foot should include a similar search plus an evaluation for abdominal aortic or popliteal artery aneurysmal disease with athero- or thromboembolism.

How do I manage patients with thrombophilia?

Acute Therapy

In general, patients with an inherited or acquired thrombophilia and a first-lifetime venous thromboembolism should be managed in standard fashion with intravenous unfractionated heparin, low-molecular-weight heparin (LMWH), fondaparinux, or rivaroxaban.[2, 3] An acute treatment duration of six weeks to three months appears to be adequate for thrombosis related to transient risk factors, while patients with persistent risk factors require a longer duration of acute treatment.

Secondary Prophylaxis

Secondary prophylaxis may be recommended after completion of acute treatment for patients at high risk for VTE recurrence and acceptable risk for a bleeding complication. Recommendations of “life-long” or “indefinite’ secondary prophylaxis are inappropriate as the risks and benefits of such prophylaxis may change over time. In general, secondary prophylaxis is not recommended after a first-lifetime episode if the event was associated with a transient (e.g., surgery, hospitalization for acute medical illness, trauma, oral contraceptive use, pregnancy or the puerperium) clinical risk factor.

Secondary prophylaxis may be recommended for idiopathic, recurrent, or life-threatening venous thromboembolism (e.g., pulmonary embolism, especially in association with persistently reduced cardiopulmonary functional reserve due to chronic cardiopulmonary disease; phlegmasia with threatened venous gangrene; or purpura fulminans), persistent clinical risk factors (e.g., active cancer, chronic neurological disease with leg paresis, or other persistent secondary causes of thrombophilia), a persistent lupus anticoagulant and/or high-titer anticardiolipin or anti-beta2 glycoprotein-1 antibody, antithrombin, protein C or protein S deficiency, increased basal factor VIII activity or hyperhomocysteinemia, combined heterozygous carriers for more than one familial thrombophilia (e.g., heterozygous for the factor V Leiden and prothrombin G20210A mutations, etc.), or homozygous carriers (Table 3), a persistently increased plasma fibrin D-dimer, and possibly residual vein thrombosis. The risk of recurrence among isolated heterozygous carriers for either the factor V Leiden or prothrombin G20201A mutations is relatively low and insufficient to warrant secondary prophylaxis. A family history of venous thromboembolism is not a predictor of venous thromboembolism recurrence and should not influence the decision regarding secondary prophylaxis. Because of the high risk of recurrent venous thromboembolism among active cancer patients due to warfarin failure, LMWH is recommended over warfarin as secondary prophylaxis as long as the cancer remains active. The risk of venous thromboembolism recurrence decreases with time following the incident

event, and the risk of anticoagulant-related bleeding also may vary over time. Consequently, the benefits and risks of secondary prophylaxis must be continually re-evaluated.

Case Resolution

Case 1: Special coagulation testing for an inherited or acquired thrombophilia showed reduced plasma antithrombin activity (46%; normal 80–130%) and antigen (41%; normal 80–130%). *SERPINC1* (antithrombin gene) sequencing revealed a heterozygous cytosine to thymine transition at nucleotide 9839 in exon 6 resulting in a premature stop codon at arginine 359, consistent with a novel inherited type I antithrombin deficiency. Secondary prophylaxis was recommended after acute treatment was completed.

Case 2: A sensitive thyroid stimulating hormone (TSH) was increased (6.6 mIU/L; normal 0.3–5.5 mIU/L) as were thyroid peroxidase (TPO) antibodies (469 mIU/mL; normal < 9 mIU/ml), consistent with incipient hypothyroidism from Hashimoto's thyroiditis. Special coagulation testing for thrombophilia was normal except for an increased plasma homocysteine (99 umol/L; normal ≤ 13 umol/L). The methylmalonic acid was increased (19 nmol/mL; normal ≤ 0.4 nmol/mL) as were anti-parietal cell antibodies (84.4 U, normal < 20 U), consistent with vitamin B12 deficiency due to pernicious anemia. Repeat plasma homocysteine and TSH were normal after treatment with B12 and thyroid replacement, and no secondary prophylaxis was recommended after acute treatment was completed.

Conclusions

Homocysteinuria is associated with childhood features of mental retardation, ectopia lentis, marfanoid habitus, premature atherosclerosis and venous thromboembolism. As opposed to “normal” fasting plasma homocysteine levels of 13–15 μmol/L, homocystinurics have levels in the range of 100–400 μmol/L. Hyperhomocysteinemia is a weak risk factor for incident and recurrent VTE.[4–7] In one study, VTE patients with plasma homocysteine above the 90th percentile (20.1 μmol/L) had a 1.8-fold increased risk for VTE recurrence.[8] Finally, in one study, Hashimoto’s thyroiditis and pernicious anemia were associated with 5.3- and 3.9-fold increased risk for VTE.[9] For both of these cases, thrombophilia testing identified treatable and acquired important risk factors for VTE and guided recommendations for secondary prophylaxis.

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Table 1

Secondary Thrombophilia

Active cancer (including myeloproliferative and myelodysplastic disorders)
Antiphospholipid antibodies (lupus anticoagulant, anticardiolipin antibody, anti-beta-2 glycoprotein-1 antibody)
Autoimmune disorders (e.g., Behçet's syndrome, celiac disease, inflammatory bowel disease, ITP, multiple sclerosis, myasthenia gravis, pernicious anemia, polymyalgia rheumatica, rheumatoid arthritis, systemic lupus erythematosus, thromboangiitis obliterans [Buerger's disease], systemic sclerosis, thyroiditis, TTP, vasculitis, Wegener's granulomatosus, etc.)
Chemotherapy (L-asparaginase, anti-angiogenesis therapy, aromatase inhibitors, cytotoxic and immunosuppressive therapy, growth factor therapy [e.g., erythropoietin], immunomodulatory therapy)
Estrogen
Tamoxifen and raloxifene (selective estrogen receptor modulator [**SERM**])
Dehydration
Dyslipidemia
Heparin-induced thrombocytopenia (**HIT**)
Hyperhomocysteinemia
Infection (HIV, sepsis, urinary tract infection)
Intravascular coagulation and fibrinolysis/disseminated intravascular coagulation (**ICF/DIC**)
Microalbuminuria, nephrotic syndrome and possibly chronic kidney disease
Obesity
Paroxysmal nocturnal hemoglobinuria (**PNH**)
Progestin
Pregnancy/post partum state

Table 2

Inherited Thrombophilia

Antithrombin deficiency (*SERPINC1*)
Protein C deficiency (*PROC*)
Protein S deficiency (*PROS*)
Factor V Leiden (*F5* rs6025; activated protein C resistance)
Prothrombin G20210A (*F2* rs1799963)
ABO blood group non-O (*ABO* rs8176719)
Fibrinogen gamma (*FGG* rs2066865)
Factor XI (*F11* rs2036914)
Homocystinuria
Increased plasma factors I (fibrinogen), II (prothrombin), VIII, IX, XI
Dysfibrinogenemia
Sickle cell disease
Weakly Supportive Data
Hypofibrinolysis
Hypoplasminogenemia and dysplasminogenemia
Reduced tissue plasminogen activator (tPA)
Increased plasminogen activator inhibitor (PAI-1)
Reduced protein Z and Z-dependent protease inhibitor [ZPI]
Reduced tissue factor pathway inhibitor (TFPI)
Factor XIII polymorphisms
Increased thrombin-activatable fibrinolysis inhibitor (TAFI)

Table 3

Inherited or Secondary Thrombophilia: Estimated Prevalence by Population, and Incidence and Relative Risk of Incident or Recurrent Venous Thromboembolism by Thrombophilia

Thrombophilia	Prevalence (Whites, %)			Incident VTE		Recurrent VTE	
	Normal	Incident VTE	Recurrent VTE	Incidence* (95% CI)	Relative Risk (95% CI)	Incidence* (95% CI)	Relative Risk (95% CI)
Antithrombin deficiency	0.02–0.04	1–2	2–5	500 (320, 730)	17.5 (9.1, 33.8)	10,500 (3800, 23000)	2.5
Protein C deficiency	0.02–0.05	2–5	5–10	310 (530–930)	11.3 (5.7, 22.3)	5,100 (2500, 9400)	2.5
Protein S deficiency	0.01–1	1–3	5–10	710 (530, 930)	32.4 (16.7, 62.9)	6,500 (2800, 11800)	2.5
Factor V Leiden†	3–7	12–20	50–50	150 (80, 260)	4.3‡ (1.9, 9.7)	3,500 (1900, 6100)	1.3 (1.0, 3.3)
Prothrombin G20210A†	1–3	3–8	15–20	350	1.9 (0.9, 4.1)		1.4 (0.9, 2.0)
Combined	-	-	-	840 (560, 1220)	32.4 (16.7, 62.9)	5,000 (2000, 10300)	-
Hyperhomocysteinemia	-	-	-	-	-	-	2.5
Antiphospholipid Ab	-	-	-	-	-	-	2.5
Factor VIII (>200 IU/dL)	-	-	-	-	-	-	1.8 (1.0, 3.3)

*per 100,000 person-years

†Heterozygous carriers

‡Homozygous carriers relative risk~80