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LEARNING OBJECTIVES

- Review the diagnosis and pitfalls of testing for the most common genetic thrombophilic disorders
- Discuss the interaction between genetic risk factors and acquired risk factors associated with thrombophilic disorders
- Explain the treatment of patients with thrombophilic disorders

Genetic susceptibility to VTE: A primary care approach

After treatment of an acute thrombotic event, patients with genetic thrombophilia should be referred to a hematology specialist for long-term management.

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Approximately 30 conditions that increase the risk of venous thromboembolism (VTE), known as *thrombophilias*, have been identified. Some are relatively common and likely to be within the realm of primary care, whereas others are difficult to diagnose and require referral to a specialist. This variability and the risk involved with misdiagnosis demonstrate the need for primary care clinicians to be aware of these conditions as well as determine which patients should be referred to a hematologist.

This article reviews the diagnostic tests for the seven most common genetic thrombophilic conditions, the pitfalls of testing, and the follow-up for patients who test positive for one or more of the thrombophilias. A discussion of drug management is limited because of the complexity and individualization required when treating patients with thrombophilia. In addition, acquired causes of VTE are discussed only in their roles as aggravating factors in patients with thrombophilia.

CASE

A previously healthy 23-year-old woman began to notice pain behind her left knee in February 2007. She was an avid basketball player and frequently experienced trauma to her legs when playing, but she could not recall any specific injury to account for this pain. Further history disclosed that she was a nonsmoker, had a paternal grandmother who suffered a fatal pulmonary embolism (PE), and had recently started taking oral contraceptives. She had no other significant history. Physical examination revealed a Baker's cyst-like lesion in the left popliteal space. Venous Doppler ultrasound revealed a deep venous thrombosis (DVT) of the left popliteal vein.

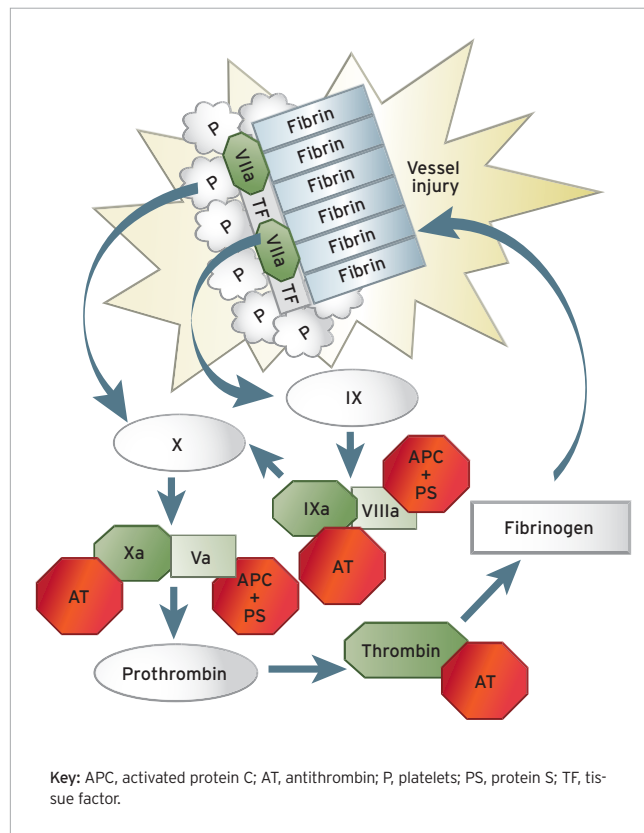


FIGURE 1. The interaction between platelets and the coagulation cascade at the site of vessel injury is shown. The red hexagons mark the site of action of the natural anticoagulants antithrombin, activated protein C, and protein S.

Note: Only the factors known to be essential for effective hemostasis are included.

CBC, prothrombin time (PT), and partial thromboplastin time (PTT) were within normal limits. She was prescribed low molecular weight heparin and warfarin (Coumadin, Jantoven, generics) for 8 days, followed by warfarin alone when the international normalized ratio (INR) became therapeutic. She was also placed on bed rest and told to discontinue oral contraceptives. The DVT resolved with treatment. Follow-up venous Doppler ultrasound 6 months later showed no abnormality. The warfarin was replaced with a daily dose of adult aspirin (325 mg).

In September 2007, however, the woman experienced another episode of seemingly unprovoked calf pain in her left leg. No history of trauma existed, nor had she resumed oral contraceptives. Her physical examination was unremarkable, including minimal difference in the circumference of her calves, normal pulses, and no calf or thigh tenderness. Nevertheless, a venous Doppler ultrasound revealed another DVT in the same popliteal vein. Because of the recurrence of seemingly unprovoked DVT, the woman was evaluated for hypercoagulability; she was found to be heterozygous for factor V Leiden and had protein S deficiency. Once again, she was treated with low molecular weight heparin and warfarin with the same target INR of 2.0 to 3.0. Furthermore, she was advised that she would need lifelong warfarin therapy to prevent DVT recurrences, was referred for genetic and prepregnancy counseling, and was given a follow-up appointment with a hematology specialist. A year later, the woman remains anticoagulated and thrombosis-free.

HEMOSTASIS AND VENOUS THROMBOSIS

The coagulation-antithrombotic system consists of a complex interaction of positive and negative feedback loops that work simultaneously to ensure equilibrium. The coagulation cascade is essential to complement primary hemostasis to prevent life-threatening bleeding following vessel damage (see Figure 1). The antithrombotic system simultaneously limits fibrin formation and abnormal clotting, or thrombosis. Thus, both prothrombotic and antithrombotic efforts must be intact to avoid hemorrhage or VTE.

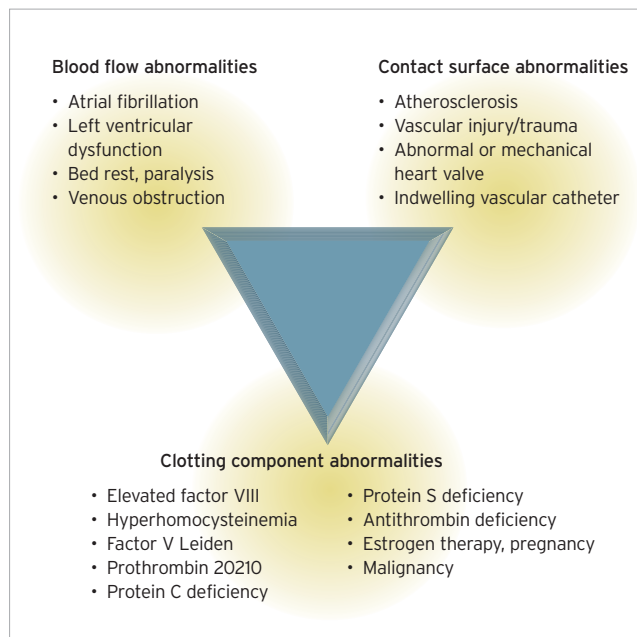


FIGURE 2. Virchow's triad

Incidence of VTE is approximately 1 per 1,000 adults per year. VTE is responsible for approximately 296,000 deaths per year in the United States.^{1,3} About two-thirds of patients present with DVT; and the rest present with PE.² Virchow's triad, first published in the late 1800s, illustrates the combination of blood flow stasis or turbulence; endothelial injury; and plasma alterations, referred to as *hypercoagulability*, that cause VTE (see Figure 2).

For unknown reasons, the incidence of DVT increases after age 50 years. Other acquired risk factors for VTE are well-established, including obesity, defined as body mass index higher than 30 kg/m²; surgery, especially orthopedic surgery; pregnancy; malignancy; trauma; use of oral contraceptives or hormone replacement therapy; immobility from bed rest or prolonged sitting; and conditions such as heart failure, myeloproliferative disorders, inflammatory bowel dis-

KEY POINTS

- The antithrombotic system simultaneously limits fibrin formation and abnormal clotting, or thrombosis. Thus, both prothrombotic and antithrombotic efforts must be intact to avoid hemorrhage or venous thromboembolism (VTE).
- A number of genetic disorders called thrombophilias predispose patients to VTE. Thrombophilias significantly increase the risk of VTE when combined with an acquired risk factor. Not only does the prevalence of the thrombophilias vary among ethnic groups, but so do the acquired risk factors.
- A complete history and physical examination are essential for identifying a person with a thrombophilic disorder. Indeed, history is the more important component and should include a three-generation pedigree or family tree. Some of the factors to look for include a family history of VTE, a VTE developing in an unusual location or shortly after starting oral contraceptives, and an MI in a female smoker younger than 50 years.
- Diagnostic testing for thrombophilia is generally deferred during the acute phase of VTE management because test results have no impact on patient management at this stage. The management of VTE is the same regardless of the presence of a genetic thrombophilia; therefore, laboratory testing or evaluation by a specialist is not cause to delay treatment of the acute thrombotic event. Long-term management of thrombophilia disorders is complicated and needs to be individualized, so referral to specialists is necessary.

TABLE 1. Most commonly occurring congenital thrombophilias

Genetic disorder	Prevalence in general population	Diagnostic laboratory test	Acquired causes that mimic a genetic condition and will cause abnormal test results
Antithrombin deficiency	0.02%	Plasma activity assay (sodium citrate)	<ul style="list-style-type: none"> Disseminated intravascular coagulation Heparin therapy Liver disease Nephrotic syndrome Recent thrombosis
Elevated factor VIII	11%	Plasma activity assay (sodium citrate)	<ul style="list-style-type: none"> Hormone replacement therapy Illness Pregnancy Recent thrombosis Stress Surgery
Factor V Leiden	5% (US whites)	Screen with APC resistance assay (sodium citrate)	None
Hyperhomocysteinemia	5%	Fasting plasma level (EDTA)	<ul style="list-style-type: none"> Acute phase reaction Vitamin B₆, B₁₂, or folate deficiency
Protein C deficiency	0.3%	Plasma activity level (sodium citrate)	<ul style="list-style-type: none"> Liver disease Thrombosis Vitamin K deficiency Warfarin therapy
Protein S deficiency	Unknown	Plasma activity level (sodium citrate)	<ul style="list-style-type: none"> Acute phase reaction Liver disease Pregnancy Thrombosis Use of hormone replacement therapy Use of oral contraceptives Vitamin K deficiency Warfarin
Prothrombin 20210/20210A mutation	2% (US whites)	DNA assay (EDTA)	None

Key: APC, activated protein C; EDTA, ethylenediaminetetraacetic acid.
Data from Rosendaal FR.⁶

ease, nephrotic syndrome, hyperviscosity syndrome, multiple myeloma, and sickle cell anemia.^{4,5} In addition, a number of genetic thrombophilias predispose patients to VTE⁶ (see Table 1). Thrombophilias significantly increase the risk of VTE when combined with an acquired risk factor. Not only does the prevalence of the thrombophilias vary among ethnic groups, but so do the acquired risk factors.⁴ Thrombophilias may not be suspected until a VTE develops in association with an acquired risk factor.⁷

VTE caused by thrombophilias is no different than that associated with acquired risk factors. Therefore, a complete personal and family history and physical examination are essential for identifying a person with a thrombophilic disorder. Indeed, history is the more important component and should include a three-generation pedigree or family tree.

Some of the factors to look for include a family history of VTE, a VTE developing in an unusual location or shortly after starting oral contraceptives, and an MI in a female smoker younger than 50 years. Table 2 is a complete list of the factors to keep in mind when taking a patient's history. Doppler ultrasonography is the test of choice to confirm the diagnosis.

INHERITED THROMBOPHILIAS

Increased factor VIII levels Factor VIII is a key component of the coagulation cascade. A patient with a deficiency of factor VIII develops a condition called *hemophilia A*. Conversely, factor VIII activity above 150% (150 IU/dL) is common and some studies have linked persistently elevated levels to a 500% increase in risk of VTE formation.⁸ The cause of the higher level is unknown but likely to be genetic.

The diagnostic test for elevated factor VIII activity is a functional assay applied to a plasma specimen collected in tubes containing sodium citrate as an anticoagulant. Factor VIII normally increases during an acute phase reaction, such as VTE; therefore, testing must be delayed until several months after recovery from any thrombotic event is achieved.

Hyperhomocysteinemia This condition is a risk factor for venous and arterial thrombosis⁹ and is the result of a combination of genetic and acquired conditions, such as vitamin B₆, B₁₂, and folate deficiencies; older age; chronic renal failure; and use of antifolate drugs.¹⁰ Genetically determined polymorphisms in the methylenetetrahydrofolate reductase and cystathionine β-synthase enzymes involved in homocysteine intracellular metabolism can lead to hyperhomocysteinemia. However, the reliability of this genetic defect as a risk factor for VTE is questionable.¹⁰

Hyperhomocysteinemia occurs in 5% to 10% of the general population, and approximately 10% of young patients with VTEs have elevated homocysteine levels.¹⁰ Diagnosis is made by determining a fasting homocysteine level. Although available, genetic testing is not clinically reliable for evaluating risk for VTE. Hyperhomocysteinemia is a risk factor for VTE development, however, treatment of mildly elevated levels of homocysteine with multivitamins has not been shown to decrease the risk of VTE recurrence.¹¹

Factor V Leiden and activated protein C resistance Factor V Leiden is an autosomal dominant disorder that results from a mutation in coagulation factor V, a key protein of the coagulation cascade required for normal thrombus formation. Activated protein C (APC) and protein S inactivate factor V under normal circumstances. When factor V Leiden is present, the abnormal protein resists APC and protein S breakdown, leading to an increased risk of VTE. Presence of factor V Leiden is a common genetic thrombophilic disorder of variable prevalence among ethnic groups, including 5% in US whites, 2% in Hispanics and Native Americans, 1% in African-Americans, and rare in Asians.^{1,12} Prevalence of factor V Leiden disorder in patients with recurrent pregnancy loss is estimated to be 34%, compared with 11% or less in control subjects.^{1,13} Persons with the heterozygous form of factor V Leiden mutation are believed to have a 10% lifetime risk of developing VTE; the lifetime risk for persons with the homozygous form is 80%.^{10,12}

Testing for factor V Leiden should start with a modified APC resistance assay. If findings are not normal, a DNA test is needed to confirm the diagnosis and determine if the patient is heterozygous or homozygous for the disorder. APC resistance should be part of a standard thrombophilia workup. In some cases, genetic counseling and testing for the condition should also be offered to relatives of patients with factor V Leiden.¹⁴

Prothrombin 20210 or 20210A mutation Another thrombophilia that results from a single mutation in a coagulation factor is the prothrombin 20210 or 20210A mutation. The mechanism of increased risk of VTE is not known in all cases, but some patients demonstrate an increase in prothrombin activity. The disorder is inherited as an autosomal

TABLE 2. Indications for thrombophilia

Family history of VTE
History of multiple miscarriages or stillbirths
MI in female smoker <50 y
Recurrent VTE
VTE before age 50 y
VTE during pregnancy, postpartum, or while using oral contraceptives
VTE in an unusual location (not in a lower extremity)
VTE with no known environmental risk factors
Key: VTE, venous thromboembolism.

TABLE 3. Counseling points for patients with thrombophilia

Avoidance of estrogen-containing medications
Benefits and side effects of anticoagulation
Education to recognize and report early signs of thrombosis
Genetic screening of family members
Implications for pregnancy
Implications of potential health and supplemental insurance exclusions and premiums
Lifestyle changes, including smoking cessation, weight control, hypertension management, avoidance of high-risk physical activities
Lipid control
Potential for psychological problems in patient and/or family upon identification of a genetic condition

dominant mutation, and 2% of US whites and 0.4% of African-Americans have the mutation.¹ Four percent to 8% of young persons with VTE are believed to harbor the condition. Nearly a 300% increase in risk of VTE is thought to occur in heterozygous individuals; the level of risk for homozygotes has yet to be established. Prevalence in women with recurrent spontaneous abortion ranges from 2% to 10%. The disorder is diagnosed by DNA analysis.^{1,10,13}

Protein C and protein S deficiency In normal circumstances, activated factors V and VIII are inactivated by APC and free protein S. A deficiency in either of these proteins leads to an increased risk of VTE formation. These deficiencies are inherited as autosomal dominant disorders, but prevalence is quite low in the general population.^{10,15} Only heterozygous persons are seen in clinical practice because the homozygous form is fatal, resulting in severe spontaneous thrombosis at or before birth.^{10,16} These deficiencies, along with antithrombin deficiency, are detected in 5% to 15% of young persons with VTE.¹⁰ The deficiencies have also been

found in women who have had recurrent spontaneous abortions, but the increased risk is negligible compared with that of the controls.^{1,17} Timing is important when evaluating for protein C and protein S deficiencies, and plasma activity levels should be measured first, followed by a confirmatory antigen level if the activity is decreased. The combination of activity and antigen levels is used to classify the type of deficiency into types I and II for protein C or types I, II, or III for protein S. In view of the low prevalence of these disorders and the complexity of a full evaluation, further discussion is beyond the scope of this article. However, all clinicians must be aware that a number of acquired and transient conditions affect the levels of these proteins and that test results must be interpreted in light of the patient's condition.

Antithrombin deficiency Thrombin, also known as *activated factor II*, is the primary enzyme in the clotting cascade. A deficiency in antithrombin, the principal thrombin inhibitor, increases the risk of VTE.⁷ Antithrombin is also responsible for inhibiting several other steps in the clotting cascade, including inactivation of factors IX and X. This deficiency is inherited as an autosomal dominant disorder and is lethal in its homozygous form. Thus, only heterozygous persons are seen in the general population.^{1,10} Whereas the prevalence of this disorder is quite low, recent studies revealed the presence of the deficiency in 2% to 6% of young persons with VTE.^{10,18} Antithrombin activity level can be measured during a standard thrombophilia workup, although acquired causes that mimic genetic conditions must be ruled out before a diagnosis of antithrombin deficiency can be established.¹⁹ If a decrease in antithrombin activity is confirmed and no secondary causes are identified, a plasma antigen level will help determine the type of deficiency present. Anticoagulant properties of heparin are mediated by antithrombin; therefore, a lack of response to the drug suggests an antithrombin deficiency that requires further laboratory evaluation and consultation with a hematologist.

When to order laboratory tests Diagnostic testing for thrombophilia is generally deferred during the acute phase of VTE management because test results have no impact on patient management at this stage.⁴ A notable exception is lupus anticoagulant, an antiphospholipid antibody, which is

an acquired risk factor for VTE. If a lupus anticoagulant is present, the antibody may cause prolongation of the PTT and preclude this test from being used to monitor heparin therapy. An INR of 2.5 to 3.5 should be maintained during warfarin therapy in patients with antiphospholipid syndrome, so the presence of lupus anticoagulant impacts VTE therapy.²⁰ None of the genetic causes of thrombophilia impacts diagnosis and treatment of an acute VTE, so there is no need to test for them at diagnosis. The timing of future testing is important, however, because several tests are affected by drugs used in VTE therapy. At the appropriate time, a workup for factor V Leiden; prothrombin 20210/20210A mutation; antithrombin; factor VIII; protein C and protein S activities; fasting homocysteine; and antiphospholipid antibodies, such as lupus anticoagulant and anticardiolipin antibodies; PT; and PTT⁴ will be necessary to determine the presence of the various disorders. A positive result in any of these tests should prompt a referral to a hematology specialist and genetic counseling.

TREATMENT OF THROMBOPHILIC DISORDERS

Some individuals with thrombophilic disorders will never develop VTE; however, some physicians believe that the presence of any thrombotic disorder produces a 1% to 10% lifetime increase in risk of VTE.¹⁰ The risk is higher for persons with a combination of genetic disorders, and it is also higher if a genetic disorder is superimposed on an acquired risk factor.¹ When oral contraceptive use precipitates the thrombosis, such as in the case presented in this article, significant lifestyle changes are necessary, including the use of an alternative contraceptive method.

Long-term decisions regarding thrombophilia are complex and outside the realm of primary care providers. However, the initial treatment of VTE when a thrombophilic disorder is suspected is the same as when no disorder is suspected and is within the scope of primary care. Combination of a standard low molecular weight heparin and warfarin plus bed rest should be used. PAs should consult the American Academy of Family Physicians Anticoagulation Worksheet for a detailed treatment protocol.²¹ As a general rule, an INR of 2.0 to 3.0 should be maintained.²² The decision regarding long-term anticoagulant therapy should be made with a hematology specialist and is based on several factors, including whether the patient has acquired or reversible risk factors versus genetic or irreversible ones.^{23,24}

RISKS FOR RECURRENCE

Multiple studies have examined the risk of VTE recurrence for the thrombophilias in order to determine the need for long-term or lifelong anticoagulation. One recent study followed approximately 300 patients with VTE and an underlying thrombophilic disorder and approximately 200 patients with VTE who do not have thrombophilia for several years. The overall results revealed that although the risk of VTE recurrence was slightly higher for patients with thrombophilia, the difference was not significant.²⁵ Furthermore, the

Key genetic terms

Autosomal dominant condition: A condition that requires only one mutated copy of a gene pair to express the symptoms of a disorder

Heterozygote: A person with one normal copy of a gene pair and one mutated copy

Homozygote: A person with mutated copies of both genes in a gene pair

Polymorphism: A common genetic variant found in at least 1% of a particular population

risk of VTE recurrence was not significantly increased for patients with factor V Leiden or prothrombin 20210/20210A mutation; risk was only slightly increased in patients with protein C, protein S, and antithrombin deficiencies; and risk was not significantly increased in patients with elevated factor VIII or hyperhomocysteinemia.²⁵ Risk for recurrence was slightly increased for patients with more than one genetic disorder. As a result of these findings, researchers concluded that a complex interaction between acquired or environmental factors and intrinsic or genetic factors is responsible for any increased propensity toward thrombosis formation and recurrence.²⁵

The evidence presented in this review suggests that persons with a single known thrombophilia are better suited to simply avoiding conditions and/or medications that are known to increase the risk of thrombosis (ie, smoking, use of oral contraceptives or hormone replacement therapy, etc) rather than embark on long-term anticoagulation therapy. On the other hand, persons with multiple thrombophilias will probably benefit from long-term anticoagulation therapy, similar to that prescribed for the case patient. Her hematologist recommended that she remain on lifelong warfarin therapy, refrain from smoking, and avoid all medications containing estrogen. In the event that she becomes pregnant, she will be switched to low molecular weight heparin to avoid the teratogenic effects of warfarin.

REFERRALS FOR PATIENTS WITH THROMBOPHILIA

Patients with thrombophilic disorders require long-term follow-up by a hematologist, and women of reproductive age should be counseled by a maternal/fetal medicine specialist or perinatologist regarding the risks of pregnancy, anticoagulation therapy, miscarriage, stillbirth, intrauterine growth retardation, preeclampsia, and placental abruption. Table 3 (page 23) lists aspects of patient counseling for persons with thrombophilia. Genetic counseling concerning the long-term consequences of the disorder and the need for other family members and future offspring to be tested is also recommended. Local resources and physicians familiar with the implications of thrombophilia are generally available and should be consulted for the proper management of these patients.

SUMMARY

Genetic thrombophilic disorders are variably common and primary care clinicians must be aware of them because of the increased risk of VTE. A physical examination will not be able to determine if a given VTE resulted from a genetic predisposition or not. In some instances, a patient's personal and family history will alert a clinician to the existence of a thrombophilic disorder, but diagnosis of the specific thrombophilia will require laboratory evaluation and referral to a specialist. The acute management of VTE is the same regardless of the presence of a genetic thrombophilia; therefore, laboratory testing or evaluation by a specialist is not cause to delay treatment of the acute thrombotic event. After the initial treatment and stabilization of the patient, ample

time exists to perform a thrombophilia workup. Long-term management of thrombophilia disorders is complicated and needs to be individualized, so referral to specialists is necessary. Primary care clinicians need to keep abreast of the studies being conducted on thrombophilia because numerous families continue to be plagued by VTEs without a recognizable cause. Undoubtedly, new causes of inherited thrombophilias are yet to be unveiled. **JAAPA**

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