

## HYPERCOAGULABLE STATES : DIAGNOSTIC CHALLENGES

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**Abstract :** Patient with cerebral venous thrombosis or recurrent arterial strokes often have an underlying hypercoagulable state; this may be inherited or acquired. Knowledge of these diseases is required in order to guide treatment and prevent further thrombotic episodes. However, indiscriminate testing in all patients is warranted especially as some of these tests are expensive. Moreover, correct interpretation is also needed before labelling a patient as having a prothrombotic state. Our knowledge of these disorders is expanding but several lacunae still remain. In this review, we discuss various diseases associated with hypercoagulability and how to investigate these disorders.

Patients who develop deep venous thrombosis or pulmonary embolism are often labelled as having **hypercoagulable state**. It is important to realize that clots develop for many reasons; therefore, all that clots is not hypercoagulable. For someone to be labeled as having a hypercoagulable state, there are certain criteria that should be ascertained<sup>2</sup>. Hypercoagulable states are of acquired and inherited types<sup>5</sup>.

### INHERITED HYPERCOAGULABLE CONDITIONS INCLUDE

- Factor V Leiden (the most common)
- Prothrombin gene mutation
- Elevated levels of fibrinogen
- Deficiencies of natural proteins that prevent clotting (called anticoagulant proteins - such as antithrombin, protein C and protein S)
- “Sticky” platelets
- Abnormal fibrinolytic system, including hypoplasminogenemia, dysplasminogenemia, and elevation in levels of PAI-1
- Elevated levels of factor VIII (still being investigated as an inherited condition)<sup>6,11</sup>

### ACQUIRED HYPERCOAGULABLE CONDITIONS INCLUDE

- Cancer ● Recent trauma or surgery ● Pregnancy and exogenous estrogen use (including use of oral contraceptive pills)
- Hormone replacement therapy ● Prolonged bed rest or immobility (heart attack, stroke and other illnesses that lead to decreased activity) ● Heparin-induced thrombocytopenia ● Air travel ● Antiphospholipid antibody syndrome ● Previous deep vein thrombosis or pulmonary embolism ● Myeloproliferative disorders such as polycythemia vera or essential thrombocytosis

### HOW IS A HYPERCOAGULABLE STATE DIAGNOSED?

#### Careful medical history

Certain conditions increase a person's risk for developing blood clots, but do not necessarily indicate a genetic

hypercoagulable state<sup>1,3</sup>. Therefore, a careful evaluation of the patient's personal and family medical history is needed. Patients who should be screened for hypercoagulable states<sup>7</sup> include those who have:

- A family history of abnormal blood clotting
- Abnormal blood clotting at a young age (less than 50 years old)
- Thrombosis in unusual locations or sites: such as the portal (liver), mesenteric (intestinal) and cerebral (brain) veins
- Blood clots that occur without a clear cause (idiopathic)
- Blood clots that recur
- A history of frequent miscarriages
- Stroke at a young age

#### Unusual Venous Thromboembolic (VTE) Presentations of Hypercoagulable Conditions include :

Prothrombin G20210A, antithrombin deficiency, essential thrombocythemia, paroxysmal nocturnal hemoglobinuria, cerebral vein thrombosis in women using oral contraceptive pills, inferior vena cava, renal vein, mesenteric vein, portal and hepatic vein thrombosis, myeloproliferative syndromes, migratory superficial thrombophlebitis (Trousseau's syndrome), cancer (particularly adenocarcinoma of the gastrointestinal tract) recurrent superficial thrombophlebitis Factor V Leiden, polycythemia vera, deficiencies of natural anticoagulants, Protein C and protein S deficiencies, neonatal purpura fulminans unexplained fetal loss (three or more first-trimester miscarriages or one second- or third-trimester unexplained death of a morphologically normal fetus) Antiphospholipid antibodies

#### Laboratory testing

Laboratory tests (blood tests) should be performed only after clinical evaluation. These tests should be reserved for people who have one of the conditions listed previously. The tests should be performed in a specialized coagulation laboratory and interpreted by a pathologist or clinician with expertise in coagulation, vascular medicine or hematology. Testing is best performed when the patient is not having an acute clotting event<sup>8</sup>.

#### More common lab tests<sup>12</sup> include:

- **PT-INR:** Prothrombin time (PT or protime) test is used to calculate International Normalized Ratio (INR). The INR will help to determine how fast the blood is clotting and whether the medication dose needs to be changed. This

test is used to monitor the condition if the patient is taking Coumadin.

- **Activated partial thromboplastin time (aPTT):** measures the time it takes blood to clot; certain chemicals are added to the test. This test is used to monitor the condition if the patient is taking heparin.
- **Fibrinogen level**
- **Thrombin time:** measures the time it takes the blood to clot

Some of the tests listed previously help to detect the *antiphospholipid antibody syndrome* or *dysfibrinogenemias*, conditions which can be associated with hypercoagulable states.

**Tests used to help diagnose inherited hypercoagulable states :**

- Genetic tests include factor V Leiden (Activated protein C resistance) and Prothrombin gene mutation (G20210A)\*
- Antithrombin activity
- Protein C activity
- Protein S activity\*\*
- Fasting plasma homocysteine levels

*\*Factor V Leiden and prothrombin gene mutation (G20210A) are the more commonly identified genetic defects that increase a person's risk for blood clotting. Because of the very low prevalence of these disorders in Asian and African-American populations, it may be most appropriate to limit testing to Caucasian patients.*

*\*\*Additional lab tests, such as measurement of free (active) and total protein S antigen levels, may be required in order to validate protein S activity assay results.*

**Other tests used to help diagnose acquired hypercoagulable states include :**

- Anticardiolipin antibodies (ACA), part of the antiphospholipid antibody syndrome (APA)
- Lupus anticoagulant (LA), part of the antiphospholipid antibody syndrome
- Hyperhomocysteinemia
- Heparin antibodies

The presence of anticardiolipin antibodies (ACA) and a lupus anticoagulant (LA) is important when evaluating someone who has had recurrent miscarriages or arterial thrombosis.

Testing helps identify whether the patient is at risk for further clotting and helps determine an appropriate course and length of treatment to prevent future clots. Testing also may help to identify relatives who don't currently have symptoms but may be at risk.

There are no specific signs or symptoms associated with hypercoagulable states. The finding of *livedo reticularis* upon examination of the skin has been frequently associated with the presence of APA, but a true causality has not been established. The most common clinical manifestation of an underlying hypercoagulable state is lower-extremity deep

venous thrombosis<sup>10</sup> with or without pulmonary embolism. Because the clinical signs and symptoms associated with deep venous thrombosis and pulmonary embolism are insensitive and nonspecific; objective diagnostic confirmation by the use of an imaging method, such as contrast venography and duplex ultrasound, is mandatory

***Why Should a Patient Be Tested?***

Testing should be performed<sup>8</sup> if the results will affect management by guiding:

- Duration of anticoagulation therapy
- Choice of anticoagulant agent
- Intensity of anticoagulation therapy
- Therapeutic monitoring strategies
- Family screening
- Family planning
- Choice of concomitant medications

***When Should the Tests Be Performed?***

Ideally, testing should be performed in the outpatient setting at least 4 to 6 weeks after any acute thrombotic event. This is because acute illness states, including VTEs, can cause elevations of a number of acute-phase reactants, including factor VIII, C4b-binding protein, fibrinogen, and IgM anticardiolipin antibodies, all of which may interfere with testing and often lead to false-positive diagnoses. Heparins (unfractionated and low-molecular-weight) can interfere with antithrombin activity and with lupus anticoagulant assays, and warfarin predictably lowers protein C and S activity levels. Low activity levels of natural anticoagulants also occur as a result of liver disease, because protein C, protein S, and antithrombin are all synthesized in the liver. Antithrombin activity level may be reduced in nephrotic syndrome and active colitis, and protein S activity may also be reduced in the setting of HIV infection<sup>8</sup>.

***Pitfalls and cautions in investigation of prothrombotic disorders***

- Assays performed during acute illness or while patient is anticoagulated may be unreliable, leading to misdiagnosis. For example, anticoagulant therapy with warfarin may influence the levels of protein C and S and antithrombin, tests for lupus anticoagulants, and some tests for APC resistance, while heparin may influence the measurement of antithrombin. Recent thrombosis, inflammatory disease and pregnancy may also affect some of these tests. Normal levels in children may differ from those in adults.
- With the exception of oral contraceptives, hyperhomocysteinemia, and antiphospholipid antibodies, risk factors that predispose to VTE probably do not normally predispose to arterial thromboembolism. Other thrombophilic disorders should not be routinely tested for in this setting, although stroke in some young people may be an exception.
- Abnormal results for inherited prothrombotic disorders

should in general be confirmed by a second measurement obtained under ideal circumstances.

- Confirmation of the presence of a familial abnormality in first degree relatives of patients with functional test abnormalities is desirable.
- Comprehensive testing is recommended. Subjects with VTE often have more than one abnormality.
- The significance of anticardiolipin antibodies in subjects with VTE is currently controversial

The issue of screening for thrombophilic defects is controversial<sup>9</sup>. The laboratory evaluation is expensive, and the short-term treatment of venous thromboembolism is the same in all patients, regardless of cause; therefore, it is unclear which patients warrant screening. In addition, there is little evidence to show that testing would influence the intensity or duration of long-term anticoagulation, except in the antiphospholipid syndrome

Although certain tests can be performed at the time of the initial event, heparin interferes with clotting-based assays for APC resistance, the lupus anticoagulant, and factor VIII levels. Protein C, protein S, and antithrombin functional and antigenic tests should be performed only in strongly thrombophilic patients: those with a venous thromboembolism prior to age 50, with recurrent venous thromboembolism, or with an extensive family history of thrombus. In addition, testing for protein C, protein S, and antithrombin cannot be reliably performed during an acute event or while the patient is taking anticoagulants, because the levels fluctuate during active thrombosis and are suppressed by warfarin therapy. If indicated, testing for antithrombin, protein C, and protein S can be performed 3 weeks after anticoagulant therapy has been discontinued. In contrast, there are many compelling arguments to test *appropriate* patients for inherited thrombophilia. Testing advances the knowledge base of the pathophysiology of venous thromboembolism, although data on specific recommendations for length and intensity of anticoagulant therapy are lacking. More importantly, identifying patients at risk for thrombosis carries significant implications in *family counselling* and high-risk situations. The affected family members of individuals with an identified hypercoagulable defect are also at increased risk of thrombosis.

When venous thromboembolism occurs in a woman taking

*oral contraceptives*, testing may be warranted in order to provide adequate counseling about continued oral contraceptive use and the risks of thromboembolism in pregnancy. Similarly, testing for factor V Leiden may be warranted when venous thromboembolism occurs in breast cancer patients taking tamoxifen (Nolvadex), because of an increased risk of thrombosis in this group.

*Venous thromboembolism* is a common disease that causes significant morbidity and mortality<sup>4</sup>. In recent years, the ability to diagnose inherited genetic defects and common acquired conditions predisposing to thrombosis has greatly increased. Venous thromboembolism is now understood to be a complex interaction of genetic and environmental factors leading to thrombosis. Integrating the various factors to individually assess thrombotic risk still poses a challenging clinical problem that will likely become easier as more data accumulate. As the ability to accurately assess risk increases, the data can then be translated into tailored treatment regimens. Until then, only general guidelines regarding evaluation and management are available. In the future, it is likely that other prothrombotic conditions will be elucidated, adding to the pool of data

## RECOMMENDED READING

1. Bauer KA, Goodnight SH, Ridker PM. Hypercoagulable states—translation of risk factors to clinical practice. *American Society of Hematology education session, Dec 1998*:255-73
2. Bauer KA. *The hypercoagulable state: evaluation and management. Update on thrombophilia. American Society of Hematology education session, 1999*:231-5
3. Bauer KA. *The thrombophilias: well-defined risk factors with uncertain therapeutic implications. Ann Intern Med 135*:367-373, 2001.
4. Bick RL. Preface. *Semin Thromb Hemost 1999*;25(3):251-3
5. Bick RL, Kaplan H. *Syndromes of thrombosis and hypercoagulability: congenital and acquired causes of thrombosis. Med Clin North Am 1998*;82(3):409-58
6. De Stefano D. *Inherited thrombophilia and life-time risk of venous thromboembolism: is the burden reducible? J Thromb Haemost 2*:1522-1525, 2004.
7. Laffan M, Tuddenham E. *Science, medicine, and the future: assessing thrombotic risk. BMJ 1998*;317(7157):520-3
8. Moerloose P, Bounameaux HR, Mannucci PM. *Screening tests for thrombophilic patients: which tests, for which patient, by whom, when, and why? Sem Thromb Hemostas 24*:321-32
9. Nachman RL, Silverstein R. *Hypercoagulable states. Ann Intern Med 1993*;119(8):819-27
10. Rosendaal FR. *Venous thrombosis: a multicausal disease. Lancet 1999*;353(9159):1167-73
11. Seligsohn U, Lubetsky A. *Genetic susceptibility to venous thrombosis. N Engl J Med 344*:1222-1232, 2001.
12. Van Cott EM, Laposata M. *Laboratory evaluation of hypercoagulable states. Hematol Oncol Clin North Am 1998*;12(6):1141-66

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