CHAPTER 3
CLOTTING DISORDERS

Original authors: Edith A. Nutescu, Jessica B. Michaud, Joseph A. Caprini, Louis W. Biegler, and Robert R. McCormick
Abstracted by Kellie R. Brown

Introduction

The normal balance between clot formation and breakdown can be changed by the presence of certain genetic or acquired defects leading to abnormal clot formation. Reasons for the clot formation and breakdown processes to be unbalanced toward abnormal clot formation include blood vessel injury, venous stasis (lack of movement of the blood in the veins), and clotting disorders. These three factors make up Virchow’s triad. An alteration in any one of these three factors can lead to abnormal clotting. All risk factors for DVT or PE fall into one of these three categories. A venous thromboembolic event (VTE) is either a DVT or PE or both in the same patient.

Clotting disorders are present in the majority of patients who have a DVT. The typical story for a person with an inherited clotting disorder is a spontaneous DVT at an early age. Doctors now have a variety of tests that can be done to test for an inherited clotting disorder. There is controversy over which patients should get which tests and what positive results mean. This chapter reviews the most common clotting disorders.

What is a D-Dimer Level?

D-dimer is a by-product of clot breakdown. The D-dimer level is not really a risk factor for getting a DVT or PE, but it may be elevated when a DVT or PE is present. The D-dimer level is used to “rule out” (show it is not present) DVT when the suspicion for DVT is low. This is because if the level is normal, it is unlikely that a DVT exists. However, if the level is high, DVT may or may not be present. Elevated D-dimer levels can indicate the presence of abnormal clot, but levels can also be elevated from other causes such as recent surgery, bleeding, trauma, pregnancy, cancer or abnormal blood clot in an artery.

Clotting Disorders

There are 2 types of clotting disorders. The first is a hereditary disorder that is inherited from one or both parents. The second is an acquired disorder, which a person is not born with, but that develops later in life.

Hereditary Clotting Disorders

The hereditary clotting disorders come in 2 groups:

Group 1: A lack of anti-clotting factors in the blood
Group 2: An increased amount of pro-clotting factors in the blood

Provided by the American Venous Forum: veinforum.org
Group 1 disorders include anti-thrombin deficiency, protein C deficiency, and protein S deficiency. Group 2 disorders include activated protein C resistance (Factor V Leiden mutation), prothrombin G20210A mutation, and elevated levels of Factors VIII, IX, and XI. In general, the Group 1 disorders are less common but more likely to cause abnormal clotting than Group 2 disorders. Patients with Group 1 disorders usually have their first DVT at a young age, have a higher likelihood of recurrence, and are more likely to have a family history of DVT or PE than patients with a Group 2 disorder.

GROUP 1 DISORDERS:

A LACK OF ANTI-CLOTTING FACTORS IN THE BLOOD

Antithrombin Deficiency

Antithrombin is a natural blood thinner found in the body. It works to reduce clot formation. Over 100 gene mutations have been found that can lead to antithrombin deficiency. This disorder is inherited as an autosomal dominant trait, which means that if a person gets an abnormal gene from one parent and a normal gene from the other parent, they will have the disease.

How common is it?
Antithrombin deficiency is present in 0.07-0.2% of the general population and 0.5-8% of those with DVT.

How and when do you test for it?
The amount of antithrombin in the blood can be tested with a blood test.

Tests should be drawn 3 months after the VTE happens, and at least 5 days after any blood thinner has been stopped. This is because blood thinners affect the levels of antithrombin in the blood. Many other conditions can also affect the antithrombin levels, so test results should be interpreted with the patient’s entire medical history taken into account.

What is the risk of VTE in a person with antithrombin deficiency?
Antithrombin deficiency is a strong risk factor for DVT. The risk in most people with antithrombin deficiency is increased by 5 to 50 times. Most patients with this disorder will have had a DVT by age 30. Abnormal clotting in the arteries has been reported in people with this deficiency but it is uncommon and its association with the deficiency is not clear.

How do you treat antithrombin deficiency?
Patients with antithrombin deficiency are resistant to heparin therapy because heparin requires the presence of antithrombin to work. Heparin is a commonly used
intravenous blood thinner. Patients with antithrombin deficiency who need blood thinners should get another type of blood thinner that does not need antithrombin to work. Antithrombin itself can be given if necessary. After a VTE has occurred, lifelong oral anticoagulation is generally recommended.

**Protein C Deficiency**

Protein C is a natural anticoagulant that is made primarily in the liver. During the clotting process, protein C is activated, and along with protein S acts as a blood thinner to keep the clotting process in check. Deficiency in protein C results in decreased ability to keep the clotting process in check, leading to abnormal clot formation.

How common is it? Protein C deficiency is present in up to 0.4% of the population and may be present in about 4% of patients with DVT or PE.

How and when do you test for it? The amount of protein C in the blood can be tested for with a blood test. The test should be done 2-4 weeks after any warfarin therapy is stopped. Many things can cause protein C to be low, such as new clot formation, low Vitamin K, liver disease, severe infections (sepsis), kidney failure, post-operative state, breast cancer patients after certain chemotherapies, and massive bleeding. A normal protein C level after a new clot has occurred rules out the disease, but a low level in this situation would need to be re-checked after therapy for the new clot is completed before the diagnosis could be made.

What is the risk of VTE in a person with protein C deficiency? People with protein C deficiency are about 3 times more likely to experience a DVT or PE than the general population. By age 40, about 50% of those with protein C deficiency will have had a DVT or PE. There is not a significantly increased risk of artery clot in these patients.

How do you treat protein C deficiency? If a person has protein C deficiency, and they have never had a VTE, then no medication is required. They need to have blood thinners given to prevent VTE prior to surgery or during other situations where they would be at increased risk of VTE. If a person who has protein C deficiency has a VTE, they will need to have blood thinners. It is important for patients with protein C deficiency to have a fast-acting blood thinner such as heparin started before starting warfarin (an oral blood thinner). Warfarin alone may initially make the patient more likely to clot than less, until the appropriate levels have been reached. Therefore, a fast acting anticoagulant is used first and then stopped once the warfarin level is adequate.

**Protein S Deficiency**

Protein S acts with protein C to keep the body’s natural clotting process controlled. A low protein S level has similar effects as a low level of protein C.

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How common is it?
About 0.2% of the general population has protein S deficiency. In patients with DVT or PE, up to 5% have protein S deficiency.

How and when do you test for it?
The level of protein S can be tested from a blood sample. However, diagnosis of this condition can be challenging because many things can affect the protein S level. Conditions associated with decreased protein S include use of warfarin (an oral blood thinner) and contraceptive use, pregnancy, liver disease, nephrotic syndrome, and severe clot formation.
As with protein C and antithrombin, a normal test at the time of a new clot rules out the disease, but an abnormal test must be repeated after warfarin has been stopped for 2-4 weeks. If it is still abnormal on re-check, then the diagnosis can be made.

What is the risk of VTE in a person with protein S deficiency?
Varying rates of DVT or PE have been reported with protein S deficiency. It is difficult to study given that it is so uncommon. The risk of VTE in protein S deficiency has been reported from 0 to 11.5 times over that of patients without deficiency. There is no proven increase in artery clot with protein S deficiency.

How do you treat a person with protein S deficiency?
As with protein C deficiency, patients with protein S deficiency who have never had a VTE don’t need any specific treatment, but if they are to be in any situation that would put them at risk for VTE, they should have preventative blood thinners.

A person who has an episode of VTE should have a fast-acting blood thinner such as heparin started prior to starting a longer term blood thinner such as warfarin.

GROUP 2 DISORDERS:
AN INCREASED AMOUNT OF PRO-CLOTTING FACTORS IN THE BLOOD

Activated Protein C Resistance/Factor V Leiden Mutation

Activated Protein C (APC) resistance refers to the resistance of Factor V (one of the proteins in the blood that helps to regulate clot formation) to the activated protein C in the clotting reaction. Since activated protein C works on Factor V to slow down the clotting reaction, resistance to this causes increased risk of clotting. The majority of APC resistance is due to the Factor V Leiden mutation, which is a mutation in the gene that codes for Factor V.

How common is it?
Factor V Leiden is the most common inherited blood clotting disorder, with an especially high occurrence in people of Caucasian or European descent. It occurs in about 5% of Caucasians, 1.2% of African Americans, 2.2% of Hispanic Americans, 1.2%
of Native Americans, and 0.45% of Asian Americans. In patients with VTE, 10-20% have this gene mutation.

**How and when do you test for it?**
There is a test that looks at whether the Factor V is resistant to the APC, and there is a genetic test for the Factor V Leiden mutation. Either test can diagnose the condition.

**What is the risk of VTE with APC resistance?**
APC resistance is a relatively weak risk factor for abnormal clot formation. People with one abnormal gene for Factor V have a 3 to 7 fold increased risk of clot, and people with both genes abnormal have a 50 to 100 fold increase in risk. The lifetime probability of a symptomatic DVT or PE in patients with one abnormal gene for Factor V is about 10%, thus the vast majority of patients with this condition will never have a DVT or PE.

However, when a person with APC resistance has another risk factor for clot, such as oral contraceptive use, hormone replacement therapy or pregnancy, they have increased risk for abnormal clot formation. APC resistance may increase the risk of recurrent pregnancy loss and obstetric complications. It is also associated with poorer outcomes in kidney transplant recipients. Whether this condition is associated with abnormal clot in the arteries is unknown.

**Prothrombin Defects; Prothrombin Gene 20210A Mutation**

The prothrombin G20210A mutation is an inherited defect of the gene for prothrombin. Prothrombin is a protein in the blood that helps clot to form. A person with this condition has high levels of prothrombin, which increases the risk of abnormal clot formation.

**How common is it?**
This disorder is the second most common inherited clotting disorder. It is present in 2% of Caucasians, 3% in people of southern European descent, and rare in Native Americans, Asian-Americans or African-Americans. Between 5 to 10% of patients with VTE have this disorder.

**How and when do you test for it?**
There is a blood test that can find the defect in the gene. This test can be accurately performed at any time before, during or after a clot has formed.

**What is the risk of VTE with this disorder?**
The risk of abnormal clotting is relatively low, with a 2 to 3 times increased risk of VTE. Most patients with this prothrombin gene mutation will not have had an episode of VTE by age 50. Half of clotting episodes in patients with this disorder occur around surgery, trauma, prolonged immobilization, pregnancy or estrogen therapy. This disorder doesn’t appear to increased the risk of abnormal clot in an artery.
**Factor Elevations (Elevations in the levels of different proteins in the blood that participate in the clotting process.)**

The elevation of coagulation Factors V, VII, VIII, IX, X, and XI can occur. The association of these with increased risk of clotting is unclear, but persistently high factor levels are more common in patients with a history of VTE.

**How and when do you test for elevated factor levels?**

There are blood tests available for all of the factor levels. Knowing what the results mean is more difficult. Many things can affect the factor levels. This makes diagnosis of an ongoing elevation of one of these factors challenging. Conditions that can affect factor levels include Vitamin K deficiency, malnutrition, liver disease, biliary disease, oral contraceptive use, pregnancy, abnormal cholesterol, obesity, aging, stress, chronic inflammation, recent aerobic exercise, and blood type. Therefore, interpreting the levels of these factors is difficult, as is making the diagnosis of persistent elevated factor levels.

**What is the risk of VTE with this condition?**

Elevated levels of Factors V and VII have not been clearly associated with abnormal vein clot formation, but may be associated with abnormal artery clot formation. In contrast, elevation of Factors VIII, IX, and XI likely increase the risk of VTE slightly. Factor VIII elevation has the strongest association with VTE with the risk of VTE increasing as the level of Factor VIII increases.

**Hyperhomocysteinemia**

Hyperhomocysteinemia refers to an acquired or inherited elevation of the level of the amino acid homocysteine. Amino acids are the building blocks that make up proteins in the body. Homocysteine is one of several types of amino acids. Acquired hyperhomocysteinemia can occur with certain medical conditions, such as kidney failure, hypothyroidism, folate deficiency or Vitamin B6 or B12 deficiency. Inherited hyperhomocysteinemia results from mutations in the genes coding for enzymes that break down homocysteine. These enzymes are methylene-tetrahydrofolate reductase (MTHFR), cystathione B synthase (CBS), or methionine synthase. Defects in these enzymes may or may not lead to hyperhomocysteinemia, depending on their severity. Hyperhomocysteinemia is associated with both artery and vein clotting problems. How hyperhomocysteinemia affects blood clotting is not fully known.

**How common is it?**

Up to 50% of the general population may have one mutation affecting the metabolism of homocysteine. This doesn’t result in high homocysteine levels in every case.
How and when do you test for this condition?
The diagnosis of **hyperhomocysteinemia** is based on the blood level of **homocysteine**. Levels of **homocysteine** may be elevated for several months after a new **VTE** event, so testing must be done several months after the **VTE** is discovered in order to be accurate.

What is the risk of VTE in a person with hyperhomocysteinemia?
**Hyperhomocysteinemia** is associated with both abnormal artery and vein clotting, although it is not clear whether **hyperhomocysteinemia** is just a sign of the clotting, or a cause of the clotting. The **homocysteine** level can be lowered with medication, but this doesn’t change the risk of **VTE**, therefore the value of testing for this condition is unclear.

How do you treat Hyperhomocysteinemia?
High **homocysteine** levels can be decreased with folic acid, vitamin B6 and vitamin B12 therapy. However, the value of lowering the **homocysteine** level is in question.

Other Inherited Clotting Disorders

There are likely other **inherited clotting disorders** that are not yet fully known. As more of these disorders are figured out, many of the people who now get a **DVT** or **PE** for “unknown” reasons will likely be found to have an inherited condition that increases **VTE** risk.

**AntiPhospholipid antibody Syndrome (APS)**

**Antiphospholipid antibodies** are a family of antibodies that are directed against proteins in the blood that are important for coagulation. These antibodies include the lupus anticoagulants and the anticardiolipin antibodies. **Primary APS** includes patients who have **APS** but do not have lupus or other autoimmune diseases. **Secondary APS** includes those patients with **APS** and systemic lupus erythematosus (SLE).

How common is it?
This condition is reported in only 2% of healthy individuals, but is found in up to 20% of patients with **VTE**.

How and when do you test for this?
Diagnosis of this condition is based on both clinical and laboratory tests. In order to be diagnosed with this condition a person must have elevated antibody levels on two tests at least 6 weeks apart, and they must have had an abnormal clotting event or have had pregnancy related complications.
What is the risk of VTE in people with APS?
The risk of VTE in people with APS is relatively high. Approximately 1/3 of people with APS have had an abnormal clotting event. Usually this event is a DVT. People with APS who do not have lupus have an 11-fold increase in risk of VTE over those who do not have APS. They also have an increased risk of artery clot formation. Patients with lupus are at increased risk of abnormal clot formation even if they don’t have the antibodies.

How do you treat APS?
People with APS who have a first VTE are usually treated with a short acting blood thinner such as heparin, and then change over to warfarin therapy after 5 days. The length of time to continue the blood thinners after the first abnormal clotting event is somewhat controversial and can range from 12 months to lifelong. In patients with APS who have not had a VTE event, daily aspirin therapy is recommended, but if other additional risk factors exist, warfarin or heparin therapy should be considered.

Heparin Induced Thrombocytopenia

Heparin induced thrombocytopenia (HIT) is a severe side effect of heparin therapy that can cause abnormal clotting. This condition occurs when a person’s body makes an antibody against the heparin, and that antibody also targets their platelets. The antibody binding to the platelets causes them to clump up, which forms a clot.

How common is HIT?
Although heparin-induced antibodies form in 10-20% of people who get heparin, most of these patients do not develop HIT. Only 1-3% of people who use heparin for 5 days get HIT. This can go up to 6% after 14 days of continuous use. Low-molecular weight heparin (a more purified form of heparin) has a lower risk of HIT, but is harder to reverse and is more expensive.

How and when do you test for HIT?
A person who develops a new clot while on heparin is suspicious for HIT. A falling platelet count in the blood is another sign of HIT. In HIT, platelet counts fall starting 5-10 days after the start of heparin therapy, and reach a low by 7-14 days. This is known as “typical-onset” HIT. “Delayed-onset” HIT occurs when the platelet count falls later (up to 20 days after heparin starts) and can even occur after a patient has stopped the heparin. “Rapid-onset” HIT can occur within 24 hours of starting heparin. This can occur in patients who have had heparin before. A drop in the number of platelets by 50%, or a fall to below 100,000 is considered suspicious for HIT. To make the diagnosis of HIT, a lab test needs to be done. There are several available tests, some that look at platelet function, and one that looks for the antibodies themselves. If a patient is suspected of having HIT, the heparin should be stopped immediately while testing is done.
What is the risk of VTE in a person with HIT?
The most common complication of HIT is abnormal clot formation. About 50% of patients with HIT will develop a clot or die within 30 days if not treated. The risk of abnormal clot formation is increased 30 times in HIT patients. The most common clotting event is DVT. PE is also common in these people. Abnormal artery clotting is less common. Abnormal skin lesions can form in patients with HIT about 20% of the time.

How do you treat HIT?
The first thing to do is to stop all sources of heparin. Also, a different blood thinner should be started to help prevent the abnormal clot formation. Other blood thinners that could be used include lepirudin, argatroban and bivalirudin. Low-molecular weight heparin is still a heparin, and should not be used. Once the platelet count has come back up to normal, warfarin can be started, but should overlap with the other blood thinner by 5 days.

A person who has had HIT should not get heparin again in their life, unless under rare and very special circumstances.

Cancer

VTE is a major cause of complications in cancer patients. PE is the cause of death in one of seven hospitalized cancer patients who dies. The risk of VTE is much higher in cancer patients than in non-cancer patients, and most of the clots occur without another risk factor being present. Surgery, chemotherapy, central venous line placement, and immobility all further increase the risk of clotting in cancer patients. Treatment of VTE in cancer patients should continue until the cancer is in remission and no further chemotherapy is planned.

CONCLUSION

There are many different factors that can increase the risk of VTE. Some of these increase the risk more than others. These conditions should be looked for in any person who has a VTE, unless the cause is already known.