Hypercoagulability — Primary and Secondary Causes

In Hypercoagulability disorder, the risk of thrombus formation in the body is raised. The number of procoagulants is increased that promote clot formations in the vessels of the body. The primary cause is genetic and cannot be cured, but therapies are given to reduce the level of procoagulants. The secondary cause involves diseases or conditions producing a hypercoagulable state of the blood. For those, it is necessary to control the underlying disease or condition. Hypercoagulability needs an active and thorough treatment plus monitoring as it can lead to harmful consequences.

Definition of Hypercoagulability

Hypercoagulability, in other terms, is known as thrombophilia. Thrombophilia is an abnormal tendency of clot formation. The propensity of blood clotting is increased many times the normal state. Frequent blood clots are formed, which is called thrombosis.

Any of the vessels of the body's vascular system like coronary vessels, mesenteric vessels, brain vessels, pulmonary vessels, portal, and the hepatic circulatory system can get partially or completely occluded as a result of thrombosis and lead to serious consequences. There are two main causes of Hypercoagulability: primary, which basically includes the genetic mutations, and the secondary causes.
Pathophysiology of Hypercoagulability

Homeostasis is maintained through an effective regulatory mechanism in the body. A balance is kept between the procoagulant and the anticoagulant activity in the blood. Hypercoagulability occurs when the procoagulant factors are in excess and remain unchecked. The specific pathophysiology varies with each subtype of the Hypercoagulability disorder.

Primary Causes of Hypercoagulability

A positive family history, along with signs and symptoms in a child, is a strong clue of an inherited hypercoagulability disorder. The important genetic causes are discussed one by one.

Factor V Leiden

This is the most common type of Inherited thrombophilia disorder. People having this type have a mutant form of factor V. This makes it resistant to the inactivating effects of Activated Protein C (APC). The APC is necessary to down-regulate clotting factors like V and VIII. It is estimated that 20 - 60% of people have a Hypercoagulability disorder due to Factor V Leiden. On chromosome 1, point mutations in the genes of factor V occur. Glutamic acid and the cleavage site replaces arginine leading to an alteration that makes it resistant to the effects of APC.

Prothrombin 20210A

It is also called as the Factor II mutation. Prothrombin is an important protein in the coagulation pathway, which makes clots. A genetic mutation occurs which leads to an excess formation of Prothrombin. This, in result, leads to more production of the clots. Guanine gets replaced with Adenine in the non-coding region of factor II genes.

Deficiencies of Protein C and S

These two proteins are synthesized in the liver. Vitamin K is important for the functioning of both these proteins. The genes for protein C are located on chromosome number 2 and for protein S on chromosome number 3. The deficiencies are mostly autosomal dominant but can also, rarely, be recessive. These two proteins are the natural
anticoagulants that prevent excessive clot formations. The deficiency results in an increase in the coagulant activity.

**Antithrombin deficiency**

Antithrombin is a protein that acts on the final pathway of the conversion of fibrinogen into fibrin. The protein is transmitted to the offspring in an autosomal dominant pattern of inheritance. Deficiency or the inheritance of dysfunctional protein can lead to **unrestricted procoagulant activity and clot formation**. When the deficiency of antithrombin (AT) occurs, the clotting factors X and activated thrombin cannot be neutralized.

**Hyperhomocysteinemia**

*High levels of homocysteine produce many effects like:*

- Peroxidation injuries
- The proliferation of blood vessels
- Increased monocyctic chemotaxis
- Promote cytotoxicity
- Enhanced clotting
- Inhibition of the anticoagulants
- Activation of the platelet aggregation

The levels of homocysteine are closely linked to the vitamin B in the body. Low quantities of vitamin B are associated with an elevated concentration of Vitamin B.

**Secondary causes of Hypercoagulability**

There are many secondary causes that are listed as follows:

The secondary causes of hypercoagulability can be derived from Virchow's triad. The presence of any of the risk factors leads to a hypercoagulable state and clot formation.

**Venous stasis results from events such as:**

- Immobility due to factors such as major surgery requiring bed rest and trauma
- Long flights
- Recent casting of a limb fracture

**Endothelial damage results from occurrences such as:**

- Malignancies
- Venous Instrumentation
- Thromboangitis Obliterans
- HIV vasculitis

**Physiological or pathological hypercoagulability states include:**

- Antiphospholipid antibody syndrome
- Nephrotic syndrome
- HIT (heparin-induced thrombocytopenia)
- Paroxysmal nocturnal hemoglobinuria
- Inflammatory bowel disease
- Bechet’s syndrome
Clinical Presentation of Hypercoagulability

There are no definitive clinical signs and symptoms. A set of various investigations is needed to detect a hypercoagulable state. Some of the clinical manifestations that can be a clue to an underlying ongoing process of thrombosis include:

- Sudden onset of a severe headache
- Chest pain
- Back pain
- Pain and swelling in the legs
- Warm and tender skin in areas of clots.
- Shortness of breath
- Coughing
- Lightheadedness
- Fainting
- Dizziness

Diagnosis of Hypercoagulability

The diagnosis of Thrombophilia is based on clinical judgment and the initial evaluation of the patient. All the tests are not required in a single person. The decision to undertake a certain investigation is based on physical examination findings and clinical scoring of the patient for the pretest probability of having the disease.

The scoring systems include:

- The modified Wells score
- The revised Geneva score

The tests to consider include:

- Fibrin D dimer levels
- Coagulation panel
Thrombodynamics test
Reptilase time
Lupus anticoagulant
Anti-cardiolipin antibody
Anti-β2 glycoprotein-1 antibody
Protein C resistance
Fibrinogen Tests
Prothrombin mutations
Factor V Leiden
Homocysteine levels

Treatment of Hypercoagulability

The treatment depends on the underlying cause. In primary cases, it is usually the maintenance therapy as there is no cure for it. In the secondary causes, such as nephrotic syndrome, surgery or traumas, correction of the underlying cause relieves the hypercoagulability state.

Supportive management is focused on avoiding the formation of a clot and its dislodgement to vital organs. This is achieved by making blood thinner and more difficult to clot which is done by the administration of various types of anticoagulant drugs:

- **Heparin** injections are given for immediate action in emergency cases. They can be given as infusions or subcutaneous injections thus, they are more suitable for use in the in-patient set-up. However, these patients need long term therapy and therefore cannot rely on heparin alone as an infusion. Newer subcutaneous agents are considered for outpatient use.

- **Warfarin** tablets are mostly given as a maintenance therapy since it is administered orally and has a predictable dose-response. It must be bridged with heparin for 3-5 days because:
  - Warfarin takes some time to initiate its action as it works by inhibiting the synthesis of vitamin K dependent factors that require some time to be
depleted in circulation.
- It has an initial prothrombotic effect that must be controlled by administration of heparin.
- A test known as INR (International Normalized Ratio) is done regularly for patients on warfarin. For people who are on warfarin, the targeted limit is 2 – 3. It is important, as the excessive levels of anticoagulants in the blood can lead to a severe bleeding episode.

**New oral anticoagulant agents (NOAC)** such as rivaroxaban and apixaban are now the drugs of choice due to their ease in administration and a well-predicted dose-response thus do not require monitoring as compared to other drugs above.

**References**


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