Inherited thrombophilia: Diagnostic approach

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Abstract:
Hemostatic abnormalities include both bleeding and thrombosis disorders. Adherence to most common guidelines for the diagnosis of thrombophilia is recommended especially in some developing countries. High level of orientation to thrombophilic disorders needs wide spectrum of knowledge about the causes, primary or secondary, investigations to most common risk factors, selecting candidates to investigations, in addition to covering the possibility of multifactorial background of disease. Limited data are available that focus on the thrombophilic disorders with imperfect diagnostic cooperation between clinical and laboratory aspects to reach the full picture of these hemostatic abnormalities. In this short review of literature, we considered the most important publications that assessed the inherited thrombophilia at levels of presentation, diagnosis, and management with focus on the practical side. The aim of this review is to summarize the most important aspects of the thrombophilia presentation, inherited causes, indications for testing, and investigations required for thrombophilic patients.

Keywords:
Inherited thrombophilia, laboratory investigations of thrombophilia, thromboembolism

Introduction

Thrombophilia refers to predispositions to thromboembolism, and in practice, the term is used to describe patients who are at significantly increased long-term risk of venous and arterial thromboembolism. The predisposing factors may be genetically determined, acquired, or both. Moreover, the coagulation cascade was considered to have two different starting points, the extrinsic and intrinsic pathways. By the time, it has become obvious that these pathways do not function as independent systems. It has been established that the tissue factor/activated Factor VII (TF/FVIIa) complex of the extrinsic pathway activates both systems, implying a correlation among them. This newer model identified the importance of the TF/FVIIa complex in the activation phase of the system and considered that coagulation process has four phases; initiation, amplification, propagation, and termination.

We collect many articles that deal with thrombophilia, inherited and acquired and select the available and specialist articles in field of hematology, then filtered according to causes, presentation, and diagnostic tools of inherited thrombophilia, and summarized to give a general review on this important field of hematology.

Clinical Manifestation of Thrombophilia

- Superficial or deep vein thrombosis and pulmonary embolism
- Possible arterial thrombosis (stroke and acute myocardial infarction)
- Possible pregnancy complications (intrauterine growth restriction, stillbirth, severe preeclampsia, abruptio placentae, and recurrent fetal loss)
- Thrombosis of unusual venous circulation

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(e.g., cerebral, hepatic, renal, arm, portal, ovarian, and retinal veins)
- Warfarin-induced skin necrosis
- Purpura fulminans (neonatal or adult).

**Causes of Thrombophilia**

Thrombophilia causes can be divided into two types: acquired (secondary) and hereditary (primary) causes.

**Acquired or secondary thrombophilia**

*Strongly supportive data*

Strongly supportive data are active cancer and chemotherapy (L-asparaginase, thalidomide, anti-angiogenesis therapy), heparin-induced thrombocytopenia, myeloproliferative disorders, disseminated intravascular coagulation (DIC), thrombotic thrombocytopenic purpura (TTP), sickle cell disease, antiphospholipid antibodies, paroxysmal nocturnal hemoglobinuria (PNH), pregnancy/postpartum state, estrogen therapy, oral contraceptive pills, and tamoxifen drug.

*Supportive data*

Supportive data are inflammatory bowel disease, inflammatory states (e.g., thromboangiitis obliterans, Behcet syndrome, and systemic lupus erythematosus), progesterone therapy, infertility therapy, dehydration, HIV infection, and hyperhomocysteinemia.

**Hereditary or primary thrombophilia**

This type of thrombophilia is divided into three types of data:

*Strongly supportive data*

Strongly supportive data are antithrombin (AT) deficiency, protein C deficiency, protein S (PS) deficiency, prothrombin G20210A, homocystinuria, activated protein C resistance (APC-R), and Factor V Leiden (FVL).

*Supportive data*

Supportive data are increased plasma Factor I, II, VIII, IX, and XI, Factor XII deficiency, Factor XIII polymorphism, hyperhomocysteinemia, dysfibrinogenemia, and reduced TF pathway inhibitor.

*Weakly supportive data*

Weakly supportive data are reduced protein Z and Z-dependent protease inhibitor (ZPI), tissue plasminogen activator (tPA) deficiency, increased plasminogen activator inhibitor (PAI-1), increased thrombin-activatable fibrinolysis inhibitor, hypoplasmogenemia and dysplasminogenemia, and hypofibrinolysis.

**Hereditary thrombophilia**

*Antithrombin deficiency*

AT is the primary inhibitor of thrombin and other factors such as XIIa, XIa, Xa, and IXa. AT deficiency inherited as an autosomal dominant trait. The majority of cases are heterozygous, and the homozygous AT deficiency is incompatible with life and possibly lethal to the embryo. The different types of AT deficiency are:

- Type I: It results from the synthesis of biologically normal AT molecules. In this type, both antigenic and functional activity of AT decreased.
- Type II: It results from distinct molecular defect in the protein itself. The immunologic activity of AT is still normal, but the functional activity extensively reduced.
- Type III: In this type of AT deficiency, there is a normal functional and antigenic level in plasma, but AT fails to interact with heparin. A number of abnormal AT molecules are recognized to have a defect in heparin-binding site, such defect leads to decrease in heparin cofactor activity reaches to 50% but with normal activity of AT.

*Protein C deficiency*

It is a very rare disorder and its inheritance pattern is not obvious as AT deficiency, but in general, it is an autosomal dominant inheritance of incomplete penetrance. It may cause severe thrombosis and have two types:

- Type I: It is more common than Type II, characterized by decreased PC concentration into 50% of normal in its immunologic and functional assays.
- Type II: It is characterized by a normal antigenic level of protein C but reduction in its functional activity.

In general, in protein C deficiency, there is a reduction in the capacity to downregulate thrombin generation that propagated by the action of the activated Cofactors V and VIII.

*Protein S deficiency*

It is a homozygous or compound heterozygous rare disorder. Most cases are heterozygous with autosomal dominant inheritance pattern, and on the bases of total PS antigen concentration, free PS concentration, and PS functional activity, there are three subtypes:

- Type I: It is characterized by a reduction in the total PS antigen that may reach to 50% than normal in addition to sever reductions in free PS concentration and PS functional activity, it is known as the classic type.
- Type II: It is characterized by normal total PS antigen and normal free PS concentration but a reduction in PS functional activity.
- Type III: It is characterized by normal total PS antigen concentration but a reduction to 40% than normal in both free PS concentration and PS functional activity.
**Prothrombin G20210A gene mutation**

It is a mutation located in the 3'-untranslated region of the prothrombin gene, at position 20210 in which nucleotide altered from a guanosine to an adenosine causes no amino acid change, but increasing the protein expression which leads to high plasma prothrombin levels.\[^{15}\] The plasma prothrombin was elevated to 30% in heterozygous carriers and in homozygous reaches to 70%; this disorder inherited as an autosomal dominant trait and is frequently observed in Caucasian peoples.\[^{10}\]

**Hyperhomocysteinemia and homocystinuria**

Homocysteine, amino acid, metabolizes by two pathways; remethylation and transsulfuration pathways. In remethylation pathway, the homocysteine is removed and converted it to methionine by the action of enzyme methionine synthase on S-methyltetrahydrofolate with the presence of B12 as a cofactor, while in transsulfuration pathway, homocysteine is converted to cystathionine by the action of cystathionine-β-synthase (CBS) enzyme with B6 as a cofactor.\[^{16}\] Inherited severe hyperhomocysteinemia diagnosed by homocysteine plasma level >100 µmol/l usually is caused by homozygous methyltetrahydrofolate reductase (MTHFR) or CBS deficiencies or rarely inherited B12 abnormal metabolism.\[^{17}\]

Homzygous hereditary deficiency of CBS is a very rare defect that results in hyperhomocysteinemia, homocystinuria, atherosclerosis, and arterial and venous thrombosis at a young.\[^{18}\]

Mild-to-moderate hyperhomocysteinemia diagnosed by homocysteine plasma level 15–100 µmol/l results frequently from C677T mutation in the gene coded for MTHFR enzyme and less frequent from heterozygous MTHFR and CBS deficiencies. C677T is a single point mutation with cysteine-to-thymine substitution at nucleotide 677, inherited as an autosomal recessive trait.\[^{17}\]

Plasma homocysteine when increased may lead to many changes such as endothelial dysfunction, increased low-density lipoprotein oxidation, and stimulation of smooth muscle cell proliferation in addition hypercoagulable state.\[^{19}\]

**Activated protein C resistance and Factor V Leiden**

APC is a potent inhibitor of the coagulation system. Its function is cleaving the activated forms of Factors V and VIII. FVL is the most common known type of inherited thrombophilia, with a prevalence of 3%–8% in Caucasian population, 1.2% in African Americans, and infrequent in native African, Japanese, and Chines populations.\[^{20}\]

The FVL mutation is a point mutation in the exon 10 of Factor V gene in chromosome 1, single-nucleotide substitution (guanine to adenine) at nucleotide 1691 in Factor V gene leads to an amino acid arginine substituted by glutamine at position 506, as showing in Figure 1 Leiden name refers to the city in the Netherlands that was FVL first identified in it.\[^{21}\] The effect of such mutation is that the Factor V is unsusceptible to cleave by APC at position 506, so more FVa existing within the prothrombinase complex and more thrombin production that lead to hypercoagulable state.\[^{22}\]

Around 95% of APC-R identified to be cause by FVL, heterozygote type of FVL has 3–7-fold increased risk of venous thromboembolism (VTE), while the homozygotes have an 80-fold, in addition to that the presence of other thrombophilic risk factors in a heterozygous FVL person synergistically increases the risk of VTE.\[^{23}\] The inheritance of FVL is an autosomal dominant fashion with incomplete dominance, which means that many people carrying the mutation do not suffer any consequence.\[^{24}\] Other genetic causes of APC-R are a rare mutations in Factor V including Factor V Cambridge, Factor V Hong Kong, and Factor V HR2 Haplotype. In Factor V Cambridge, the arginine (AGG) at position 306 was altered to threonine (ACG), but the risk of thrombosis is the same with FVL.\[^{25}\] Factor V Hong Kong, this type of mutation which found only in Hong Kong Chinese, has two different genotypes: type 1 and Type 2. The Factor V Hong Kong Type 1 is a substitution of Arg 485 to Lys at exon 10 which is the result of G1691A mutation while Factor V Hong Kong Type 2 is a substitution of Arg 306 to Gly resulting from an A1090G mutation, and both types increased the risk of thrombosis.\[^{26}\] Factor V HR2 haplotype is characterized by 6 base substitutions in exons 13 and 16 and 2 amino acid alterations. If this mutation found in person with FVL, there is a further 3–4-fold increased risk of VTE than person with FVL mutation only.\[^{27}\]

**Increased plasma coagulation factor levels**

Factor I (fibrinogen) frequently elevated in hospitalized patients because it is also an acute phase protein and high levels of fibrinogen usually associated with increased risk for arterial thrombosis. Factor II (prothrombin) also is an acute phase protein and high levels associated with increased risk of VTE.\[^{28}\]
Factor VIII is an acute phase protein and it is found to be elevated in plasma in many situations, as stress, exercise, pregnancy, and oral contraceptive pills use, and it is unknown if high FVIII level caused by an acute events or leads to it, but elevated FVIII is a known independent strong risk factor for recurrent thrombosis.\(^{[29]}\)

The activated Factor IX needs to FVIIa as a cofactor in the activation of Factor X and the last is an important factor in the thrombin generation, so it is essential that high IXa increases the risk of VTE.\(^{[30]}\)

It was postulated that activated Factor XI has procoagulant and antifibrinolytic roles in coagulation process, FXIa participates in fibrin formation in addition to protect it from break down, and thus, the higher the FXIa level, the greater the risk of thrombosis.\(^{[28]}\)

**Factor XII deficiency**

The XII is also known as Hageman factor. It is apart from contact activation reactions that initiate intrinsic blood coagulation *in vitro*; deficiency of Hageman factor in its sever type inherited as an autosomal recessive trait. *In vivo* XII deficiency presented with obvious prolongation of activated partial thromboplastin time (APTT) and a high-risk thrombosis.\(^{[7]}\)

**Factor XIII polymorphisms**

There are four common polymorphic forms of Factor XIII, resulting in amino acid changes at Va134Leu, Pro564Leu, Va1650Ile, and Glu651Gln. The Va134Leu polymorphism results from a G100T coding alteration, such that alteration occurs at position 34 which located about 3 amino acids from thrombin cleaving site (Arg37-Gly38) on polypeptide chain that associated with a risk of thrombosis.\(^{[31]}\)

**Dysfibrinogenemia**

Dysfibrinogenemia has two types, congenital and acquired. The congenital dysfibrinogenemia can be defined as a relatively rare inherited fibrin molecule abnormality that leads to defect in fibrin clot formation.\(^{[32]}\) Congenital dysfibrinogenemia is an autosomal dominant inheritance caused by mutations in the coding region of the fibrinogen alpha, beta, or gamma, named after the city where the patient was first identified and when there are many dysfibrinogenemia cases from the same city, roman numerals added after the city name (e.g., Caracas V).\(^{[33]}\) The presentation of this disorder varying from asymptomatic to life threatening, 40% of patients are asymptomatic, 50% have a bleeding disorder, and the remaining 10% have a thrombotic disorder or combined thrombotic and bleeding presentation. In general, congenital dysfibrinogenemia is considered as a rare cause of thrombophilia. The acquired type of dysfibrinogenemia often called dysfibrinogenemia of a liver disease; it occurs with hepatoma, liver cirrhosis, and hepatitis, but the most common presentation of this disorder is a bleeding tendency.\(^{[34]}\)

**Reduced tissue factor pathway inhibitor**

Tissue factor pathway inhibitor (TFPI) is the first inhibitor in the coagulation process, synthesized by the endothelial cells. About 60%–80% of TFPI found within endothelium and only 20% were free in the circulation.\(^{[35]}\) New data suggest that low TFPI levels have a risk of thrombosis. Fortunately, different forms of TFPI gene will be recognized and lead to elevation TFPI levels.\(^{[36]}\)

**Reduced protein Z and Z-dependent protease inhibitor**

PZ is a Vitamin K-dependent protein found in plasma and acted as a cofactor to enhance the inhibition of Xa by protein ZPI. Some clinical studies found an association between reduced PZ plasma levels and thromboembolic disease.\(^{[37]}\) ZPI not only inhibits Factor Xa but also directly inhibits Factor Xla. Indeed, ZPI appears to be the most potent inhibitor of Factor Xla in plasma in the absence of heparin.\(^{[38]}\) Therefore, the more severe ZPI deficiency, in contrast to PZ deficiency, is most likely due to the loss of regulation of both Factor Xa and Factor Xla in ZPI deficiency but only regulation of Factor Xa in PZ deficiency.\(^{[37]}\)

**Plasminogen deficiency**

It may be a congenital cause and is of autosomal recessive inheritance, or it may be acquired like in patients with generalized atherosclerosis, and these patients exhibit a decreasing in plasminogen activity caused by atherosclerotic damage to vascular intima.\(^{[39]}\) Theoretically, plasminogen deficiency thought to be a risk for thrombosis but the recent studies and cumulative data show that such deficiency does not lead to an increasing in the risk of thrombosis.\(^{[40]}\)

**Tissue plasminogen activator deficiency**

tPA synthesized in endothelial cells, it responsible for conversion of plasminogen to plasmin. Theoretically, decreasing in tPA production leads to increase the risk of thrombosis, but in practice, not all studies found such an association.\(^{[41]}\)

**Increased plasminogen activator inhibitor-1**

PAI-1 is a primary inhibitor of plasminogen activation in plasma. Theoretically, increased PAI-1 leads to increase the risk of thrombosis, only few studies identify such association, but other several studies fail to support this theory.\(^{[40]}\)

**Increased thrombin-activatable fibrinolysis inhibitor**

Increased levels of thrombin during the coagulation process are important for both clot formation and prevention of clot breakdown, but with a very high thrombin level, there is an activation of TAFI that acts to
stop clot breakdown. Theoretically, increased levels of TAFI may prevent the normal clot breakdown and may increase the tendency for thrombosis, but not all studies shown this relation.

**Indications for Thrombophilia Testing**

- Unexplained VTE at a young age (<50 years)
- Recurrent spontaneous VTE
- Unexplained VTE at an unusual site (portal, mesenteric, splenic, hepatic, cerebral, renal, and retinal veins)
- Unusually extensive spontaneous VTE
- Family history of spontaneous VTE
- Asymptomatic individual with a positive family history of known thrombophilia: AT deficiency, protein C deficiency, PS deficiency, homozygous FVL, homozygous prothrombin mutation, and compound thrombophilia
- Recurrent VTE while adequately anticoagulated
- Unexplained arterial thromboembolism in a young patient who has no significant arteriosclerosis risk factors and no cardioembolic source
- Three or more than three unexplained pregnancy losses before week 10 or one or more than after week 10,

**Investigation of Thrombophilia**

- Complete blood count done to exclude any evidence of polycythemia vera, essential thrombocytopenia, PNH, and herapin-induced thrombocytopenia
- Blood film can help to exclude any feature of DIC and TTP such as schistocyte red cells, presence of sickle cells, and leukoerythroblastic picture which suggests the involvement of bone marrow by tumor
- Erythrocyte sedimentation rate and C-reactive protein as indicators of inflammation, connective tissue disorders, or multiple myeloma
- Global coagulation tests: PT, APTT, and fibrinogen
- Protein C deficiency tests: Functional assay is the first diagnostic step and identifies both Types (I and II) of deficiency. Immunochemical assay (for protein C antigen measurement) is the second diagnostic step but should not be performed without functional assay because Type II deficiency will not be detected
- Test for APC-R and FVL mutation: First diagnostic step is coagulation-based functional assay with Factor V deficient plasma. The second diagnostic step is the DNA analysis for FVL mutation
- Prothrombin G20210A mutation detection by DNA analysis
- Test for antiphospholipid antibodies: including lupus anticoagulant, anticardiolipin antibodies (IgG and IgM) in addition to estimation of anti-B2 glycoprotein I if a strong clinical suspicion of APS is present
- Homocysteine testing: Patients assayed for plasma homocysteine, Vitamin B12, and folic acid levels and genetic detection of MTHFR C677T gene polymorphism
- Additional tests: Consider when above tests given a negative results and the clinical suspicion for hypercoagulable state remains high, these tests, for examples, hemoglobin electrophoresis in suspected persons, functional assay for Factor VIII, test for dysfibrinogenemia, test for plasminogen antigen and activity, liver function tests, serum protein electrophoresis, and looking for sepsis and cancers by microbiological investigations, computed tomography scan, and magnetic resonance imaging.

**Conclusion**

Increased knowledge about the clinical presentation, etiology, and investigations of thrombophilia whether secondary or primary types is important, especially in areas with low resources like ours. Thrombophilia investigations represent an important part of hemostasis laboratories and focus should be toward the patients with thrombophilia such as those with bleeding disorders. Thrombophilia investigations should be done according to recommended guidelines regarding types of patients, time of investigation, and type of methods to reach appropriate design for those are candidates for testing. Inappropriate testing without the recommended guidelines becomes harmful and can leading to misdiagnosis and loss of many resources. Good and well-trained laboratories will help the clinicians to proper testing in association with recommended guidelines. Laboratory investigations for thrombophilia can identify the cause in most of the patients and fail in substantial proportion of cases or may be miss the association of >1 cause of thrombophilia in the same patient and even there may be new risk factors remain to be discovered. Multifactorial pattern of association between hereditary and acquired cause of thrombophilia may hidden the expression of disorder in the absence of other interacting transient risk factors. Future studies need to include both genetic and phenotypic assessments of risk factors and should be a shifted from the restricted idea of a single cause toward the fact of multiple risk factors.
Treatment of thrombophilia may persist for many years and even for life in some irreversible cause, so it needs proper diagnosis and dependable laboratory tests.

Low evidence based medicine on the etiology of thrombophilia in our society is the main problem due to low resources and limited thrombophilia investigations especially those required genetic level of study and many cases remain undiagnosed. In addition to few data achieved from postgraduate thesis focused on thrombophilia and its causes and investigational issues.

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