Thrombophilia – How Far and How Much to Investigate?

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Abstract Thrombohemorrhagic balance is maintained by complicated interactions between the coagulation and fibrinolytic system, platelets, and the vessel wall. Dr. Virchow provided approach for investigating and managing thrombotic disorders. He proposed stasis, vascular injury, and hypercoagulability as causes for thrombosis. In 1965, antithrombin deficiency was described. After two decades, protein C and protein S deficiencies, mutations of factor V Leiden, and factor II were described. If we distinguish patients at high risk and low risk of thrombosis, we can optimize therapeutic decisions. There is currently no evidence to say that laboratory abnormality should influence intensity of anticoagulation. In this article we reviewed the risk factors and need for thrombophilia screening in patients. Screening general population for thrombophilia is not justified or recommended at this time.

Keywords Thrombophilia 1 · Antithrombin 2 · Protein C 3 · Protein S 4 · Factor V Leiden 5 · Prothrombin 6 · Hyperhomocysteinemia 7 · Antiphospholipid antibody syndrome 8 · Thromboembolism 9

Introduction

Highly regulated proteins take active part in coagulation cascade. These proteins circulate in their inactive form. Coagulation is initiated when factor VIIa binds to the tissue

factor on the surface of endothelial cells or monocytes at the site of vascular injury. Factor VII is the only factor that circulates in substantial quantities in its active form and generates factors Xa and IXa. Small amounts of factors Xa and Va are continuously generated in the vascular system [1]. These activated coagulation components bind to specific platelet receptors to form prothrombinase complex and to activate prothrombin to produce small amounts of thrombin. Antithrombin III and protein C and protein S systems oppose generation of thrombin. Prothrombin is brought in to close contact with prothrombinase complex on platelet surface. Significant amounts of thrombin can thus be generated, which can convert soluble fibrinogen into insoluble fibrin. Thrombin also activates XIII which helps in forming the fibrin polymer. The excess thrombin binds with thrombomodulin and activates protein C, which is a potent anticoagulant locally. Tissue Factor Pathway Inhibitor (TFPI) inhibits factor VIIa and antithrombin III inhibits IXa, Xa, and XIa through a process that can be accelerated 1000-fold by heparin. Mild or moderate deficiencies of the anticoagulant proteins can lead to thrombosis in contrast to bleeding disorders such as hemophilia, which requires marked deficiencies of coagulation proteins before bleeding. Spontaneous life-threatening bleeding is rare until the coagulation factor level falls to less than 1% [2].

In 1995, World Health Organization and International Society of Thrombosis and Hemostasis defined thrombophilia as “unusual tendency towards thrombosis.” The clinical features of patients with thrombophilia include the following:

- (1) Early-age onset of thrombotic events before the age of 40–45 years
- (2) Recurrent episodes of thrombosis or thrombophlebitis
- (3) Strong family history of thrombotic events
- (4) Unusual sites, migratory episodes, or diffuse form of thrombotic events

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- (5) Severity out of proportion to any recognized known stimulus for thrombosis
- (6) Unexplained neonatal thrombosis
- (7) Skin necrosis particularly if on coumarins
- (8) Unexplained, prolonged, activated partial thromboplastin time
- (9) Patients with recurrent fetal loss, idiopathic thrombocytopenia, or SLE

If the above clinical features are noted, the clinician can consider investigating for thrombophilia [3].

Classification of Thrombophilic States

Thrombophilic states can be divided into inheritable and acquired types (Table 1). The inheritable thrombophilic disorders are classified into group 1, group 2, and other disorders. In group 1 inheritable thrombophilia, inhibitors of coagulation are reduced. In group 2 inheritable thrombophilia, coagulation factors are increased or their function has increased. The risk of thrombosis is more in the group 1 thrombophilia patients [4]. But in patients suspected to have thrombophilia, group 2 thrombophilia was detected at least five times more frequently than group 1 disorders [5]. Group 2 thrombophilia is known to be associated with the first episode of deep vein thrombosis (DVT), but may not be a risk factor for the recurrent thrombotic attacks [6].

Group 1 Thrombophilia

Antithrombin III Deficiency

This was the first described congenital thrombophilia. In 1965, Egeberg described a family with reduced levels of the antithrombin and recurrent episodes of venous thrombosis [7]. Antithrombin covalently binds and inactivates

thrombin and factors Xa, IXa, Xia, and XIIa [8]. Antithrombin deficiency is rare (0.2%), but it can be as high as 0.5–7.5% in patients presenting with venous thromboembolism. About 50–60% of patients with antithrombin deficiency develop venous thrombosis episode before 60 years of age.

Protein C Deficiency

Protein C inactivates factors Va and VIIa, along with the cofactor protein S. Its association with venous thrombosis was reported in 1981 [9]. Protein C deficiency is seen in 0.2% of the normal population and 2.5–6% of the patients with venous thrombosis. In patients with venous thrombosis, protein C levels will be 50% of the normal; many patients will have an episode of thrombosis by age 60 years. When there is complete absence of protein C, a condition known as purpura fulminans develops in neonates and becomes fatal if not corrected in time with infusion of protein C [10].

Protein S Deficiency

Protein S circulates in the bound and unbound forms. This deficiency was noted in 1984 [11]. The unbound form is 20%. Protein S deficiency occurs in 1.35% of the patients with venous thrombosis. Only one-third of the patients with protein S deficiency will have venous thrombosis by the time they reach 60 years of age. Purpura fulminans and skin necrosis are also known in patients with protein S deficiency [12].

Other Coagulation Inhibitor Deficiencies

Reduced heparin cofactor II levels, defective fibrinolysis [13], and plasminogen deficiency are known to be associated with venous thrombotic events.

Group 2: Thrombophilia

Activated Protein C Resistance and Factor V Leiden

Activated protein C resistance was first reported in 1994 by Dahlback and Hildebrand. They found that patients with venous thrombosis were resistant to the antithrombotic effects of activated protein C in vivo [14]. It was found that factor V allele was resistant to the proteolytic effect of protein C. About 5% of the healthy people in northern European ancestry and 10% of the patients with venous thrombosis were found to have factor V Leiden. It was found in 30–50% of the investigations in patients with thrombophilia [15]. But it is said to be rare in people of African and Asian descent. Factor V Leiden by itself is a low-risk factor for venous thrombosis. When people with

Table 1 Classification of thrombophilia

Group -1	Group -2
Deficiency of the (CFI) coagulation factor inhibitor	Increased levels or function of the coagulation factors.
1. Protein C deficiency	1. Activated Protein C resistance
2. Protein S deficiency	2. Factor V Leiden
3. Anti thrombin III deficiency	3. Prothrombin gene mutation
	4. Raised levels of VIII,IX,XI factors
	5. Raised Lp(a)
	6. Dysfibrinogenemias

Others- Hyper-Homocysteinemia, Plasminogen deficiency, increased Fibrinolysis inhibitor

factor V Leiden reached 65 years of age, only 6% of them were found to have an event of thrombosis. These patients become high risk candidates to develop venous thrombosis in the perioperative periods after surgery [16].

Factor II Prothrombin Gene Mutation

This mutation was first described in 1996 by Poort and colleagues [17]. They found that 18% of the venous thrombosis patients and 1% of the healthy people had a mutation at base 20210 of the prothrombin gene. Most of the people with this disorder would not have had an episode of venous thrombosis when they have reached age of 50 years. He noticed that 12% of those heterozygous for factor V Leiden were also heterozygous for factor II G20210A, while 23% of patients heterozygous for factor II G20210A were also heterozygous for factor V Leiden. This was much higher than the odds ratios for thromboembolism of 4.9 (95% CI; 4.1–5.9) for the factor V Leiden and 3.8 (3.0–4.9) for the factor II G20210A mutation as single defects [18].

Factors VIII, IX, and XI—Increased Concentrations and Hyperhomocysteinemia

Patients with history of venous thrombosis have shown increased levels of factors VIII, IX, and XI. But it is not clear how the elevated levels of coagulation factors can increase the risk of thrombosis. These elevations of the other coagulation factors may be very weak risk factors for thrombosis, with each 0.1–1.0 U/L of factor VIIIc raise, the risk of venous thrombosis would increase by 10% [19]. When there is combination of these of mutations, then there is higher risk of thrombosis present during the childhood [20].

Acquired Thrombophilic Conditions

Clinical conditions such as hyperviscosity, venous stasis, obesity, post-operative state, aging, trauma, pregnancy, myeloproliferative disorders, cancer, oral contraceptives, nephritic syndrome, paroxysmal nocturnal hemoglobinuria, heparin-associated thrombosis, diabetes mellitus, thrombotic thrombocytopenic purpura, antiphospholipid syndrome, vasculitis, and hyperhomocysteinemia have been identified as the risk factors for thrombosis. These acquired thrombophilia risk factors may be seen a few days and months or persist for very long period in some special situations to increase thrombotic tendency.

Age

Venous thrombosis is strongly age dependent. It is extremely uncommon in childhood (1 in 100,000/year) and raises to

nearly 1%/year in the old age [21]. One of the strongest risk factors for thrombosis is age. Incidence is thousandfold higher in the very old than in the very young. It is not clear why the age is a strong risk factor for thrombosis. It could be due to decreased mobility, decreased muscle tone, aging of the veins and valves, and acquisition of risk enhancing diseases.

Surgery and Trauma

50% of the patients may develop thrombosis following major surgeries. Venous thrombosis is high in multiple trauma, head and spine injury, pelvic, femoral, and tibial fractures [22]. Thromboprophylaxis reduced these incidences. It was found that 18% of the venous thrombosis patients had given history of some forms of surgery prior to development of venous thrombosis. It means surgery increased the risk of thrombosis by sixfold [23]. When 4000 patients with the first venous thrombosis were analyzed, there was a fourfold increase in the symptomatic thrombosis following orthopedic and major nonorthopedic surgery [24].

Immobilization

Stasis is a major cause of venous thrombosis in all circumstances such as bed rest, plaster casts, prolonged travel, and paralysis where stasis is known acts as a risk factor for thrombosis. Immobilization in sitting position confers higher risk than in the other positions. During the Second World War in London, there was a sixfold increase in pulmonary embolism shortly after air raids as people were sitting in deck chairs in the underground. It is interesting note that the incidence went down after changing deck chairs with bunks [25]. Young people sitting near computer for more than 12 h a day regularly are found to be at risk of developing DVT, and it is termed “e-thrombosis.”

Long Distance Travel

The first reports of venous thrombosis after long-haul air travel were noted in 1954. In 1986, a study conducted in Heathrow airport showed the arrival hall had more pulmonary embolism deaths than the departure hall (relative risk of sixfold) [26]. Similarly another study from CDG airport in Paris found 50fold difference in the risk between flights less than 2500 km and those over 10,000 km. A study showed that recent air travel doubled the risk of thrombosis and was over 14fold in those with thrombophilia or women who used oral contraceptive pills (OCPs). Travel was associated with threefold increase in DVT without much difference in modes of travel.

Cancer

Recurrent migratory thrombophlebitis is known to be associated with occult cancers. Some cancers produce procoagulant state due to secretion of humoral factors, compression of the veins, less mobility, central venous catheters. About 10% of the patients with the central venous catheter develop symptomatic venous thrombosis of the upper extremity [27]. Thrombotic risk to lung cancer patients is 20-fold higher than the general population. In a Swedish study, 19% of the patients with venous thrombosis had a known malignancy at the time of diagnosis, an additional 5% diagnosed to have cancer in the following year [28]. The presence of distant metastasis led to a further 20-fold increase in the risk of thrombosis. Factor V Leiden and factor II gene mutation combination with cancer increased the risk of thrombosis more than 12-fold.

Oral Contraceptive Pills

In 1959, OCPs entered the market and the first pulmonary embolism was noted in a nurse using OCPs for endometriosis [29]. They increased the risk of thrombosis two- to fivefold. The Estrogen dose in oral pill has been reduced to 50–30 µg. The absolute risk of thrombosis in young women of reproductive age is less than 1 per 10,000/year. In 1995, there were reports measuring the venous thrombotic risk to be twofold higher with the third-generation OCPs (30/10,000 per year) [30]. Obese, older and thrombophilic people are at higher risk of thrombosis with OCPs. The congenital thrombophilia in association with OCPs can greatly increase risk of thrombosis (>15 to 30-fold)

Pregnancy and Puerperium

In both these physiological states, there is increased risk of thrombosis. If there are other acquired risk factors or inherited risk factors, the incidence of thrombosis will be high. In a study from Scotland, 62 venous thrombotic events were noted in 72,000 deliveries. The risk of about 1 venous thrombotic event per 1000 deliveries is at least a 10-fold increase when compared to the nonpregnant women. In a Scottish study, 12% of the women had antithrombin deficiency and so increased the risk of thrombosis [31].

Antiphospholipid Antibodies

In the Leiden thrombophilia study of consecutive patients with the first DVT, a lupus anticoagulant was seen in 3.1% of patients and 0.9% of controls. Anti-beta2 Gp1 antibodies are associated with increased risk of thrombosis [32].

The inherited and acquired thrombophilic conditions may coexist in the same patient. Patients with still undiagnosed

cancer who present with Venous Thrombo Embolism (VTE) may also be the carriers of thrombophilic polymorphisms such as factor V Leiden mutation or prothrombin variant.

Screening Families for Inherited Thrombophilia

Screening the general population is not justified. It has been shown that among members of families of symptomatic patients with inherited thrombophilia, there are many who have already experienced thrombosis at the time of the laboratory screening. Because of the autosomal dominant inheritance of most thrombophilic defects, both male and female patients may be affected by the disease. Thus, if family screening for thrombophilia is to be performed, extensive laboratory testing should be considered for both symptomatic and asymptomatic family members. Needless to say, other still unknown thrombophilia defects can be present in families with severe VTE manifestations [33].

Screening for Thrombophilia and Recurrent Thromboembolism

The most important causes of recurrences after a first episode of VTE are probably the presence of active cancer and antiphospholipid antibodies. Meta-analyses were in favor of a potential role, at least of factor V Leiden. Ho et al. presented the most updated view on this topic in an exhaustive meta-analysis of all available studies [34]. Pooled results from 10 studies involving 3104 patients with the first VTE revealed that the presence of heterozygous factor V Leiden is associated with increased odds of recurrent VTE.

Unusual Site Thrombosis and Thrombophilia Screening

There is evidence to suggest that thrombosis in unusual sites, such as cerebral sinus venous thrombosis, mesenteric vein thrombosis, portal vein thrombosis, and suprahepatic veins thrombosis (Budd–Chiari syndrome), in young individuals is also associated with inherited thrombophilia. On the basis of some studies, it is felt that screening patients with unusual site thrombosis is useful except in retinal vein thrombosis patients [35].

Thrombosis in Children and Thrombophilia Screening

There seems to be no benefit of screening for thrombophilia in otherwise healthy family members younger than 15 years. In contrast, in children who develop VTE, the prevalence of thrombophilic defects can vary depending on the selection criteria of the population. An “off-limit” and rare situation in which thrombophilia screening in pediatric age can be helpful is the neonatal purpura fulminans, often associated with severe deficiency (homozygous) of protein C or protein S.

Replacement therapy with protein C concentrates may be lifesaving [36].

Role of Thrombophilia Screening in Women Receiving Hormones

Female members of families of symptomatic probands with thromboembolism who are carriers of thrombophilia may take advantage of screening for inherited thrombophilia. In majority of cases, asymptomatic women identified following family screening are carriers of the less severe thrombophilic defects. Selective screening before administration of hormone replacement therapy is the cost-effective approach. The recommendation for screening is based on how much one is willing to spend to prevent one VTE event [37].

Pregnancy Complications and Thrombophilia Screening

Despite clear evidence of increased risk of VTE in women with congenital thrombophilia, routine universal screening of pregnant women for these defects is not recommended. Screening pregnant women who have had VTE can be reasonable in order to offer antepartum and postpartum thromboprophylaxis if a thrombophilia is identified [38]. Women with inherited thrombophilic defects may present with an increased risk of other pregnancy complications such as fetal loss, Intra Uterine Growth Retardation (IUGR), preeclampsia, or Hemolysis, Elevated Liver enzymes, Low Platelet count (HELLP) syndrome [39]. Thrombophilia also seems to play a role in vascular disorders of the placenta and has shown a result of eightfold increase in preeclampsia, abruption, or IUGR in carriers of thrombophilia as compared with noncarriers.

Patients presenting with DVT or pulmonary embolism are often tested for the thrombophilic defects. Due to the existence of multiple tests for these disorders, there is a potential for confusion about which tests to order and when to order them. Indeed, Somma et al. found that a significant proportion of orders appeared not to be clinically indicated in their study of 200 consecutive thrombophilia panel orders at an academic medical center [40].

Conclusion

Venous thrombosis is a multicausal disease [41]. Venous thrombosis is caused by the interplay of genetic and acquired risk factors. Thrombophilia screening can be recommended in patients with a history of recurrent VTE; a first VTE at an age of less than 50 years; a first unprovoked VTE at any age; a first VTE at an unusual site; a first VTE related to pregnancy and puerperium, oral contraceptives, or hormonal replacement therapy. In addition, it can be recommended in women with two or more pregnancy losses and in

children with VTE or arterial thrombosis. Thrombophilia screening may also be indicated in asymptomatic adult family members of probands with known clotting inhibitor defect or factor V Leiden mutation; asymptomatic female family members belonging to thrombophilic families who are pregnant or are considering hormone therapies or pregnancy; selected women with unexplained severe eclampsia, IUGR, HELLP syndrome, abruptio placentae; and patients older than 50 years with a first unprovoked VTE. Screening general population for thrombophilia is not justified and so it is not recommended at this time.

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