INVITED REVIEW

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Thrombophilia and Screening in Family Medicine Practice

ABSTRACT
Thrombophilia encompasses a group of inherited or acquired disorders that predispose individuals to thrombotic events. The identification of these individuals is essential to guide appropriate management strategies and reduce the risk of complications and the associated increased healthcare costs and mortality. Venous thromboembolism (VTE), encompassing deep vein thrombosis (DVT) and pulmonary embolism (PE), represents a major global health concern due to its substantial morbidity and mortality rates. General practitioners (GPs) play a vital role in the assessment and initial screening of patients for thrombophilia, as they perform their activities at the entrance of the health care system - in primary care. In addition, they serve a heterogeneous group of patients - from newborns to pregnant women and adults, knowing their risk factors and underlying diseases well. In general practice, an enduring doctor-patient relationship is usually established and the medical history is documented and well known, making it possible to carry out screening initiated in general practice with great success. The most common genetic defects that lead to thrombophilia are Factor V Leiden mutation, Prothrombin gene mutation, Protein C deficiency, Protein S deficiency, Antithrombin deficiency. Multiple acquired conditions have also been linked with an increased predisposition towards VTE development, including oral contraceptive use, hormone replacement therapy (HRT), pregnancy, postpartum period and malignancy. Thrombophilia screening in general practice should be guided by clear indications to identify individuals at increased risk of thrombotic events.
Keywords: Thrombophilia, Hereditary, Acquired, Thrombosis, Screening, General Practitioners.

Aile Hekimliği Pratiğinde Trombofili ve Tarama

ÖZET
Trombofili, bireyleri trombotik olaylara yatkın hale getiren bir grup kalıtsal veya edinilmiş bozukluğu kapsar. Bu bireylerin tanımlanması, uygun yönetim stratejilerine rehberlik etmek ve komplikasyon riskini ve buna bağlı olarak artan sağlık hizmeti maliyetleri ve mortaliteyi azaltmak için önemlidir. Derin ven trombozu (DVT) ve pulmoner emboliyi (PE) kapsayan venöz tromboembolizm (VTE), önemli morbidite ve mortalite oranları nedeniyle önemli bir küresel sağlık sorununu temsil etmektedir. Pratisyen hekimler (GP'ler), faaliyetlerini sağlık sisteminin girişinde - birinci basamakta - yerine getirdiklerinden, hastaların trombofili açısından değerlendirilmesinde ve ilk taranmasında hayati bir rol oynamaktadır. Ayrıca yenidoğanlardan hamilelere ve yetişkinlere kadar heterojen bir hasta grubuna, risk faktörlerini ve altta yatan hastalıkları iyi bilerek hizmet veriyorlar. Pratisyen hekimlikte genellikle kalıcı bir doktor-hasta ilişkisi kurulur ve tıbbi geçmiş belgelenir ve iyi bilinir; bu da pratisyen hekimlikte başlatılan taramanın büyük bir başarıyla gerçekleştirilmesini mümkün kılar. Trombofiliye yol açan en yaygın genetik bozukluklar Faktör V Leiden mutasyonu, Protrombin gen mutasyonu, Protein C eksikliği, Protein S eksikliği, Antitrombin eksikliğidir. Oral kontraseptif kullanımı, hormon replasman tedavisi (HRT), hamilelik, doğum sonrası dönem ve malignite dahil olmak üzere birden fazla kazanılmış durum, VTE gelişimine yatkınlığın artmasıyla da ilişkilendirilmiştir. Genel pratikte trombofili taraması, trombotik olay riski yüksek olan bireyleri belirlemek için açık endikasyonlara göre yönlendirilmelidir.
Anahtar Kelimeler: Trombofili, Kalıtsal, Edinsel, Tromboz, Tarama, Pratisyen Hekimler.

INTRODUCTION

Thrombophilia encompasses a group of inherited or acquired disorders that predispose individuals to thrombotic events. The identification of these individuals is essential to guide appropriate management strategies and reduce the risk of complications and the associated increased healthcare costs and mortality. Venous thromboembolism (VTE), encompassing deep vein thrombosis (DVT) and pulmonary embolism (PE), represents a major global health concern due to its substantial morbidity and mortality rates. Approximately 10% of cases are fatal within one month after diagnosis, emphasizing the importance of timely detection measures targeting high-risk individuals (1). General practitioners (GPs) play a vital role in the assessment and initial screening of patients for thrombophilia, as they perform their activities at the entrance of the health care system - in primary care. In addition, they serve a heterogeneous group of patients - from newborns to pregnant women and adults, knowing their risk factors and underlying diseases well. In general practice, an enduring doctor-patient relationship is usually established and the medical history is well knonn and documented, making it possible to carry out screening initiated in general medical practice with great success. This review aims to consolidate the current knowledge and evidence on thrombophilia screening in general practice, highlighting the key indications, testing strategies, and implications for patient management.

METHODS

A comprehensive literature search was conducted using electronic databases, including PubMed, Medline, and Cochrane Library, to identify relevant articles published between 2010 and 2021. The search terms included "thrombophilia," "screening," "general practice," and combinations thereof. Only studies published in English and those focusing on thrombophilia screening in general practice were included. Reference lists of selected articles were also reviewed to identify additional relevant studies.

Types of Thrombophilia: Thrombophilia includes heterogeneous types of etiological causes of coagulation disorders, which are divided into two large groups - hereditary and acquired, but often there is a combination of these factors (2).

Hereditary thrombophilia: Hereditary thrombophilia is due to genetic defects, which can be in the homozygous state or a combination of two or more heterozygous factors, and then the clinical manifestation is at an early age. The existence of single heterozygous states is usually established by laboratory testing (3). The coagulation system in humans includes hemostatic and fibrinolytic pathways, and a defect at any one level leads to a disturbed balance and the appearance of a pathological condition. The two systems are enzyme and are interconnected, regulating formation and breakdown of fibrin. The end result of the coagulation cascade is to produce thrombin, which can then convert soluble fibrinogen into fibrin, which forms a clot. Coagulation is initiated when factor VIIa binds to tissue-factor (TF) on the surface of endothelial cells and monocytes at sites of vascular injury. The TF-factor VII complex activates factor IX and X to factors IXa and Xa, respectively. Factor Va and Xa, together, activate prothrombin to thrombin. Thrombin has multiple prothombotic roles: it cleaves soluble fibrinogen to insoluble fibrin that will eventually form the hemostatic plug, and activates factors V, VIII, XI and XIII. Thrombin also acts to produce an anticoagulant effect by forming an enzyme complex with thrombomodulin to activate protein C (4). Activated coagulation factors are modulated by natural inhibitors circulating in the plasma, the most important of which are antithrombin, protein C, and protein S (5). According to data, 15% of patients with pulmonary embolism before 45 years of age have a hereditary deficiency of one of the mentioned factors (5). The imbalance between reduced inhibitors of coagulation and/or increased activation of coagulation factors leads to thrombosis (5). Plasmin plays a central role in the fibrinolytic system, with the ultimate goal being the destruction of thrombi formed in the vascular system. Their basic structure involves thrombin, which is degraded by plasmin. Tissue-type plasminogen activator (t-PA) and urokinase (u-PA) activate plasminogen, which is the inactive form of plasmin. Thrombophilia can also occur with plasminogen deficiency (6). The most common genetic defects that lead to thrombophilia are Factor V Leiden mutation, Prothrombin gene mutation, Protein C deficiency, Protein S deficiency, Antithrombin deficiency. Dysfibrinogenemias and Hyperhomocysteinemia are rare. Most probably there are still undiscovered types, which is why the frequency of hereditary thrombophilia cannot be precisely defined (4).

Characteristics of the most common genetic defects.

Pediatric Patients: In the pediatric population, genetic defects in coagulation lead to neonatal purpura fulminans, renal vein thrombosis, vena cava thrombosis and hepatic venous thrombosis, pulmonary embolism, Legg Calve Perthes and cerebral palsy (7). In homozygous individuals with protein C or S deficiency, the clinical picture is neonatal purpura fulminans and disseminated intravascular coagulation with an incidence of about 1 in 16,000–360,000 (8). Newborns with hereditary forms of thrombophilia have demonstrated a higher risk for thromboembolic complications compared to older children. It was established that their frequency decreases significantly after the first year of life, with a second peak during puberty and adolescence

and is associated with reduced fibrinolytic activity (4).

Factor V Leiden Mutation (V Q506 or Arg506Gln): In this type of defect, there is an allele that makes factor V resistant to the proteolytic effect of protein C. A transition (guanine to adenine) at nucleotide 1691 results in the replacement of arginine by glutamine. Thus, the cleavage at position 506 by activated protein C becomes impossible, and as a result, the availability of factor Va and thus the synthesis of thrombin increases, resulting in a hypercoagulable state. The main clinical manifestation is deep venous thrombosis with or without pulmonary embolism, as well as thrombosis of placental vessels with a probable association with recurrent pregnancy loss (9). In a study of 34 families with this mutation, it was found that by the age of 50, 25% of them will develop thrombotic complications. Homozygous carriers have an 80-fold higher risk of these events and will develop at least one by the end of their lives (10). These results are supported by another study of 306 individuals from 50 Swedish families, in which 40% of homozygotes had a thrombotic event by age 33 compared with 20% in heterozygotes and 8% in healthy controls. According to data from European studies, the frequency of heterozygotes is 5-8% and up to 15% in some areas of Greece, Sweden and Lebanon.

Prothrombin Gene Mutation (G20210A): In a study of 28 families from the Netherlands who survived venous thromboembolism, a substitution of guanine to adenine at nucleotide 20210 in the 3' untranslated region of the prothrombin gene was identified (11). Prothrombin (factor II) has procoagulant, anticoagulant and antifibrinolytic activities, which is why the mutation leads to the manifestation of multiple defects in coagulation. Patients with this type of mutation have an increased risk of venous thrombosis, but less than that of factor V Leiden (10). In them, 30% higher plasma levels of prothrombin were found compared to healthy people. According to data from 11 European centers, the frequency of this mutation is 0.7-4.0%

Protein C Deficiency: The gene for protein C is located on chromosome 2 (2q13–14) and the defect is inherited in an autosomal dominant manner. There are two major subtypes of heterozygous protein C deficiency, and more than 160 genetic abnormalities have been identified (12). In homozygotes, purpura fulminans has been observed in the neonatal period (13). An increased risk of warfarin-induced skin necrosis has been reported in heterozygotes (14). In pregnant women, this type of genetic defect is associated with the development of DVT, preeclampsia, intrauterine growth restriction and recurrent pregnancy loss (15). According to data from studies in the Netherlands, in most patients, the appearance of thrombotic complications increases towards the age of 50 and up to 20 years of age they are usually asymptomatic (16). A study of 277 Dutch patients with this defect found an 8.3% incidence of venous thrombotic complications compared with 2.2% in healthy controls (17).

Protein S Deficiency: The inheritance of the genetic defect is autosomal-dominant and 3 phenotypes of Protein S deficiency have been established, all of which are associated with change in the functional activity of protein C. In heterozygotes, in which the functional activity is between 15-50% of the norm, thrombotic complications occur. A study was conducted among 122 members of a Swedish family, 44 of whom had a proven genetic defect. The data indicate a low thrombotic risk up to 15 years of age, but upon reaching 30 years of age only 50% had no thrombosis (18).

Antithrombin Deficiency: The genetic defect is inherited in an autosomal dominant manner, and 3 subtypes have been established, 1 and 2 are associated with reduced functional activity, and in 3rd disturbed interaction between antithrombin and heparin has been established. Thrombotic events are rare before puberty, but with aging the risk increases. At the age of 50 years carriers developed such complications in 70% (19). In a study of 2132 patients with thromboembolism in Spain, 12.9% were found to be deficient in anticoagulant proteins - 7.3% protein S, 3.2% protein C, and 0.5% with antithrombin respectively (6). There are known data on the risk of thrombosis depending on the type of defect. In patients with protein S deficiency it is 8.5 times higher than in healthy individuals, in antithrombin type 1 deficiency it is 8.1 times, 7.3 for protein C deficiency, and 2.2 for factor V Leiden (20)

Acquired Thrombophilia Risk Factors: Apart from inherited factors, multiple acquired conditions have also been linked with an increased predisposition towards VTE development, including oral contraceptive use, hormone replacement therapy (HRT), pregnancy and postpartum period. Furthermore, malignancy has been recognized as a significant contributory factor affecting clotting dynamics.

Screening is a method in which tests are applied to detect individuals at increased risk of various diseases, without having complaints or clinical manifestations. If the result is positive, additional tests are followed and preventive actions are taken.

Indications for Thrombophilia Screening: Thrombophilia screening should be considered in specific clinical scenarios, including unprovoked VTE, recurrent VTE, VTE at a young age (<50 years), VTE in unusual sites, and family history of thrombosis (21). In patients with recurrent miscarriages, thrombophilia screening may be warranted to identify underlying causes and guide management decisions (22). However, routine

screening of asymptomatic individuals without a clear indication is not recommended due to limited evidence supporting its clinical utility (23).

Testing Strategies: Several laboratory tests are available for thrombophilia screening, including genetic and acquired markers. The most commonly performed tests include factor V Leiden mutation analysis, prothrombin gene mutation analysis, antithrombin activity, protein C activity, and protein S activity (24). Genetic testing for thrombophilia is usually performed using polymerase chain reaction (PCR) or real-time PCR techniques. Additionally, laboratory tests assessing acquired thrombophilia markers, such as antiphospholipid antibodies, lupus anticoagulant, and anticardiolipin antibodies, may be considered in specific clinical scenarios (25).

Implications for Patient Management: Identifying individuals with thrombophilia can have significant implications for patient management, including the initiation of appropriate thromboprophylaxis, lifestyle modifications, and family screening. Anticoagulant therapy is the cornerstone of management in individuals with thrombophilia and a history of VTE (26). However, the duration and intensity of therapy may vary based on the underlying thrombophilia subtype, clinical context, and individual patient factors. Additionally, counseling regarding lifestyle modifications, such as weight management, regular exercise, smoking cessation, and avoidance of estrogen-containing contraceptives, is crucial to reduce the risk of thrombotic events (27).

CONCLUSION

The general practitioner occupies a central place in the health care systems in most European countries. The specificity of the work of these doctors is related to close contact with patients and detailed information for their risk factors and concomitant diseases, which makes it possible to apply preventive and screening methods in primary care. Knowledge of coagulation disorders is essential for the correct selection of patients to be screened, with the aim of early identification of people at risk of thrombotic complications and initiation of prevention with the aim to reducing morbidity and mortality. Further preventive interventions tailored according to individual need can be implemented promptly if identified earlier via systematic testing protocols or population-wide programs. Thrombophilia screening in general practice should be guided by clear indications to identify individuals at increased risk of thrombotic events. The appropriate use of laboratory tests for thrombophilia, along with clinical assessment and evaluation of risk factors, can aid in the management and prevention of thrombotic complications. However, routine screening of asymptomatic individuals without a clear indication is not recommended. Despite advancements in our understanding regarding genetic and acquired risk factors contributing towards venous blood clots formation there remains considerable unresolved debate surrounding the overall clinical utility, prognostication, predictive value and benefit. Laboratory staff, techs subject, expense, quantity sample collection, timing, interpretation, effective communication, follow-up, preventive interventions, established therapy, clinical decision and influenced cost-benefit considerations still evolving controversy . Future research should focus on better identification of high-risk individuals, with an emphasis on tailored prophylactic measures rather than universal screening. Further research is needed to establish the clinical utility and cost-effectiveness of thrombophilia screening in general practice.

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