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REVIEW ARTICLE

A genetical approach to deep venous thrombosis

Derin ven trombozuna genetik yaklaşım

Celal Yavuz

Medical School of Dicle University, Department of Cardiovascular Surgery, Diyarbakir, Turkey

ABSTRACT

Deep venous thrombosis (DVT) is a common disorder that frequently occurs after surgical procedures and trauma and in the presence of cancer or immobilization conditions. However, it can also develop without any of these predisposing factors. This condition directs the researcher's enquiry to investigating the basis of organismal thrombotic predisposition. The common prothrombotic genetic mutations include factor V Leiden, factor II G20210 A, plasminogen activator inhibitor-1, prothrombin A20210, and factor XIII - VIII. Nevertheless, current studies suggest that the thrombotic events are not connected with single gene deletion or homeostatic regulation is also affected by other genetic risk factors. Complex interactions of genetic mutations can be affects different levels of thrombotic system or reinforce each other's effects on homeostatic mechanisms. The analysis of literature, together with the action mechanisms of the classic genetical factors and new suggestions, may contribute significantly to our understanding of the genetic predisposition to venous thrombosis. *J Clin Exp Invest 2012; 3(2): 303-306*

Key words: Venous thrombosis, genetic predisposition, homeostatic mechanisms

ÖZET

Derin ven trombozu (DVT) sıklıkla cerrahi girişimler ve travma sonrası ve kanser veya immobilizasyon koşullarının varlığında oluşur yaygın bir hastalıktır. Ancak aynı zamanda bu predispozan faktörlerin herhangi biri olmaksızın da gelişebilir. Bu durum araştırmacıları, organizmada ki trombotik yatkınlığın temelini soruşturmaya yönlendirmektedir. Faktör V Leiden, Faktör II G20210 A, plazminojen aktivatör inhibitörü-1, protrombin A20210 ve faktör XIII-VIII yaygın protrombotik genetik mutasyonlarıdır. Bununla birlikte, mevcut çalışmalar trombotik olayların sadece tek gen delesyonu veya hemstatik regülasyona bağlı olmadığını, diğer genetik risk faktörlerinden de etkilendiğini göstermektedir. Genetik mutasyonlarının karmaşık etkileşimleri, trombotik sisteminin farklı düzeylerde etkiler veya hemostatik mekanizmaların birbirlerinin etkisini arttırabilir. Literatür analiziyle, klasik genetik faktörlerin ve yeni buluşların etki mekanizmalarının birlikte ele alınması, venöz trombozda genetik yatkınlık anlayışımıza önemli katkıda bulunabilir.

Anahtar kelimeler: Derin ven trombozu, genetik yatkınlık, homeostatik mekanizmalar

HAEMOSTATIC BALANCE AND VENOUS THROMBOSIS

Venous thrombosis usually involving the deep veins of lower extremity is a major worldwide health problem that causes significant mortality and morbidity rates.[1,2] All steps of Virchow triad are important in etiology (Figure 1). However the main factor is deterioration of the homeostatic balance. The venous stasis and leukocyte adhesion to the endothelium triggers the coagulation cascade. Moreover the clotting system must be activated. The basically fibrinolytic, anticoagulant and antiplatelet therapies aim to prevent the hypercoagulation.[1,2]

Factors that causes the disruption of coagulation cascade in favor of hypercoagulation; antithrombin-III, protein-C and protein-S deficiencies that leads to congenital hypercoagulation and acquired hypercoagulation reasons such as oral contraceptives, pregnancy, malignancies, nephrotic syndrome, systemic lupus erythematosus, surgical applications, immobilization etc.[2-4] Congenital and acquired gene mutations may plays role in the formation of thrombosis such as Factor V Leiden gene mutation.[1,5]

Correspondence: Dr. Celal Yavuz
Dicle Medical School Cardiovascular Surgery/ Diyarbakır, Turkey E-mail: celalyav@hotmail.com
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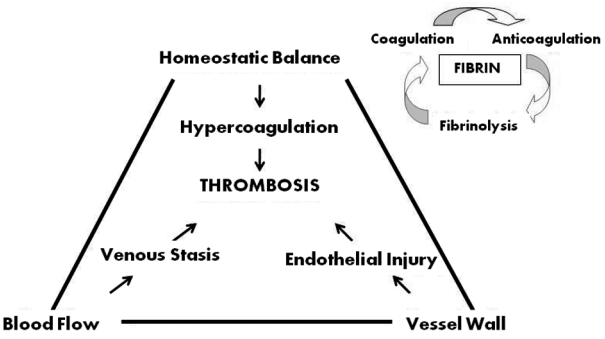

Figure 1. Virchow triad

COMMON PROTHROMBOTIC GENES

Factor V

The common hereditary risk factor activated protein C (APC) resistance is firstly described by Dahlbäck et al in 1993.[5] Bertina et al described genetical defect that known as factor V Leiden mutation.[6] The prevalence of this mutation was detected as 5%-6% in Europe.[7]

The active form of factor V plays an important role in the formation of thrombosis. APC prevents the formation of excessive thrombus by inactivating active form of factor V. Factor V Leiden mutation localized to one of the major points of APC departure. Because of this the negative-feedback mechanism is disrupted by APC resistance in this gene mutation. APC resistance is responsible for the 20% of familial venous thromboses. Surgical applications and oral contraceptive usage is increases the further venous thrombosis risk in individuals that carrying this mutation.[6] Heterozygote form of this mutation is increases the thrombosis risk [5-10] fold and this rates increases 80-100 folds according to general population in homozygote carriers.[8]

Prothrombin

Poort et al. firstly described the prothrombotic mutation of prothrombin gene (the arrival of adenine instead of guanine 20210th nucleotide in prothrombin gene) in 1996.[9] This mutation is the second most common causes of hereditary thrombophilia.[9,10] The plasma prothrombin concentration is increasing by about 30% by the reason of mutation and the venous thrombosis risk is increased when the plasma concentration of prothrombin level is exceeds 115 IU/dL.[10]

Attia et al reported that the prothrombin gene mutation can be leading the recurrent venous thrombosis and it is more common in positive family history of DVT.[11]

Factor XIII

Factor XIII is a kind of transglutaminase that can detect at many macrophages and monocytes in plasma, responsible for fibrin cross-binding. This enzyme exhibits high activity in homozygote mutation of factor XIII V34L gene and it is activity moderately increases in heterozygote mutation.[12] However the change of valine-leucine in 34th position of factor XIII gene is protective effect against DVT with an unknown mechanism. Indeed, the factor XIII V34L gene mutation was observed more frequently in healthy control groups against DVT subjects.[12]

β-Fibrinogen

β-Fibrinogen is a kind of plasma protein that plays an important role in tissue regeneration and coagulation. Elevated fibrinogen levels may increases the DVT risk such as atherothrombosis. However, the mechanism of this situation cannot clarify with current evidences. The in-vitro increased fibrinogen levels do not increased the mortality and morbidity in animal models.[13,14]

The most common G/A polymorphism have shown in the 455th area of fibrinogen gene. The presence of A allele leads to increase fibrinogen levels. Most of the studies cannot show any relationship between DVT and this gene mutation such as Renner et al. and Rasmussen et al.[13,14]

PAI-1

Plasminogen Activator Inhibitor 1 (PAI-1) also plays a role in fibrinolytic activity. PAI levels are increased by the reason of the 4G gene deletion in the 675th position of the promoter region of the PAI gene. Thus, fibrinolytic activity is deteriorated and the predisposition to thrombotic events is increased.[15] PAI-1 is an important physiological inhibitor of the tissue plasminogen activator and uroplasminogen activator in the modulation of fibrinolytic habits. So it acts variable roles in thrombotic events, such as coronary heart disease, deep-vein thrombosis, and obesity.[16] Additionally, there are innumerable studies in the literature claiming an association between the 4G allele and the atherogenic lipid profile in different ethnicities.[16] To sum up, prior studies show that combined or alone mutation of the PAI gene may cause the DVT.[15]

MTHFR

Current studies show that the hyperhomocysteinemia due to the genetical defect in Methylenetetrahydrofolate reductase (MTHR) gene may cause atherosclerosis and vascular problems. These da-

ta's suggest that the T allele of the MTHFR C677T gene can reduced the plasma folate concentration and increased homocysteine levels. At the other hand plasma homocysteine level is highly evaluated in MTHFR A1298C gene mutation.[17,18]

There are different opinions in the MTHFR C677T v A1298C gene mutations which progress with highly homocysteine levels in DVT. Some researchers have opposing views regarding deletions of this gene increases the risk of DVT. Despite controversial opinions, these mutations have been shown to increase susceptibility to thrombotic events.[19,20]

ACE

Renin-angiotensin system is a complex modulator of to blood pressure, homeostasis, cardiovascular remodeling, and vascular tone. his system consists of angiotensinogen, angiotensin converting enzyme (ACE), angiotensin II and key proteins which includes homeostatic receptors . Angiotensin I converted to the Angiotensin II through the endothelial ACE. Angiotensin II is stimulating PAI-1, which is responsible for down-regulation of the fibrinolysis.[21]

ACE, reduces fibrinolysis and increases the thrombotic risk by reducing bradykinin which is an important mediator of tissue-type plasminogen (t-PA).[22] There are three genetical variations in ACE gene. There are three genotypic variations in ACE gene: DD, DI, and II. ACE levels are being highest in DD, intermediate in DI, and lowest in II.[23] The studies which include various ethnic groups reported that ACE DD gene deletion may be effective in venous thrombosis development.[24]

CONCLUSION

Current advances are focused on the genetical predisposing factors in the cardiovascular events especially thrombotic disorders. The recent findings are concentrated for the improvement of the new treatment and diagnostic strategies for these events.

To sum up, Prothrombotic gene mutations increase the DVT risk with affected the coagulation factors by disrupts homeostasis in favor of coagulation, directly or indirectly. The preventive and therapeutic methods for the DVT can be developed by clarifying the singled or combined effects of effects of these genes. However, collaborative studies should be planned to reveal the systematic effects of these genes.

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