ETIOLOGICAL EVALUATION OF PATIENTS WITH VENOUS THROMBOEMBOLISM

VENÖZ TROMBOEMBOLİLİ HASTALARIN ETİYOLOJİK DEĞERLENDİRİLMESİ

Esra SARIBACAK CAN

Ministry of Health, Ankara Dışkapı Yıldırım Beyazıt Training and Research Hospital, Department of Internal Medicine, Division of Hematology, Ankara, TURKEY

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ABSTRACT

INTRODUCTION: Venous thromboembolism (VTE) as a frequently seen public health problem has a broad clinical presentation spectrum. It includes many different presentations of the same disease process such as deep vein thrombosis (DVT), pulmonary embolism (PE), ischemic stroke, and rarely thromboembolism of upper extremities and pelvic veins. The purpose of this study is to assess the risk factors and clinical features in patients with VTE.

METHODS: In this study, we evaluated the factors which can play a role for etiology in 83 patients with VTE who were admitted to Hematology outpatient clinic between the years 2009 and 2012 retrospectively.

RESULTS: The median age of 83 patients with VTE was 38, with the ranged of 18 to 57. Thirty-five of the patients were men (42.2%) and 48 (57.8%) were women. According to the thrombosis sites in the patients, pulmonary embolism was detected in 34 patients (41%), DVT in 29 patients (39%), SVT (sinus vein thrombosis) in 9 patients (10.8%), RVT (retinal vein thrombosis) in 7 patients (8.4%), and intra-abdominal vein thrombosis in 4 patients (4.8%). In the classification of thrombosis location of the patients with venous thrombosis according to the age groups, pulmonary embolism and DVT were more frequent in the age group of >40 (p=0.016) and that of ≤40 (P:0.009) respectively. There was not statistically significant difference among the age groups for sinus thrombosis (p=0.297). No significant statistical difference was found between the age groups in terms of FV Leiden and PTG mutations (p: 0.089, p:0.090 respectively).

CONCLUSİON: Venous thromboembolism is a disease that has potentially high mortality and morbidity. Inherited and acquired risk factors of VTE must be systematically evaluated in an appropriate manner. Defining those risk factors is important because of the possibility of preventing VTE by modifying the risk factors and the life style of individuals.

Key words: *Venous thromboembolism, inherited risk factors, acquired risk factors, thrombophilia.*

ÖZET

AMAÇ : Sık görülen bir halk sağlığı problemi olan venöz tromboemboli (VTE), geniş bir klinik spektruma sahiptir. Derin ven trombozu (DVT), pulmoner emboli (PE), iskemik inme ve çok nadir olarak da üst ekstremite ve pelvik venlerde tromboemboli aynı hastalığın değişik prezentasyonlarıdır. Çalışmamızın amacı VTE'li hastaların faktörleri ve klinik özellikleri yönünden değerlendirmektir.

YÖNTEM : Bu çalışmada, 2009-2012 yılları arasında hematoloji polikliniğine başvuran VTE'li 83 hasta retrospektif olarak değerlendirildi.

BULGULAR: VTE'li toplam 83 hastanın yaş aralığı 18 ile 57 arasındaydı medyan yaş 38'di. Hastaların 35'I erkek (% 42.2) ve 48'i (% 57.8) kadındı. Tromboz bölgesine göre gruplandırıldığında 34 hastada pulmoner emboli (% 41), 29 hastada DVT (% 39), 9 hastada sinus ven trombozu (%1 0.8), 7 hastada retinal ven trombozu (%8.4), 4 hastada da intraabdominal ven trombozu (% 4.8) saptandı. Venöz trombozlu hastalar yaş grupları ve tromboz yerine göre sınıflandırıldığında 40 yaşın üzerinde PE'nin 40 yaşında ve daha küçük olanlarda ise DVT'nin daha sık görüldüğü saptandı (p:0.016 ve p:0.009). Sinus ven trombozu olan hastalar arasında yaş gruplarına göre istatistiksel anlamlı bir fark izlenmedi (p=0.297). Yaş grupları arasında faktör V Leiden ve protrombin G20210A mutasyonu varlığı yönünden anlamlı bir fark yoktu (p:0.089 ve p:0.090).

SONUÇ: VTE yüksek mortalite ve morbiditeye yol açabilen bir hastalıktır. VTE'nin kalıtsal ve kazanılmış risk faktörleri uygun bir şekilde sistematik olarak değerlendirilmelidir. Bu risk faktörlerini tanımlamak, risk faktörlerini ve bireylerin yaşam tarzını değiştirerek VTE'yi önleme olasılığından dolayı önemlidir.

Anahtar Kelimeler: *Venöz tromboemboli, kalıtsal risk faktörleri, kazanılmış risk faktörleri, trombofili.*

Sorumlu Yazar / Corresponding Author:
Esra SARIBACAK CAN
T.C. Sağlık Bakanlığı, Sağlık Bilimleri Üniversitesi, Dışkapı Yıldırım Beyazıt Eğitim ve Araştırma Hastanesi, Şehit Ömer Halisdemir Caddesi, Dışkapı/ANKARA
Gsm: +90 532 327 47 39 **E posta:** esracanercan@hotmail.com

INTRODUCTION

Venous thromboembolism (VTE) is the general name for all pathological thrombosis which occurs in the venous circulation. VTE as a frequently seen public health problem has a broad clinical presentation spectrum. It includes many different presentations of the same disease process such as deep vein thrombosis (DVT), pulmonary embolism (PE), ischemic stroke, and rarely thromboembolism of upper extremities and pelvic veins. The most important and life threatening form of VTE is pulmonary embolism (1, 2).VTE is seen generally as DVT in community with the rate of 1-2/1000 annually. Its incidence increases with the age. While its frequency is 1/10000 below the age of 40, it reaches as high as 1/100 over the age of 60. It is foreseen that 2-5 out of every 100 people will have VTE at least once during their lives (3).

VTE is a multifactorial disease and can be found in patients with multiple risk factors simultaneously. Not only inherited risk factors such as thrombophilia but also acquired ones can lead to VTE. The more risk factors the patient has, the greater is the risk for VTE (4). Defining those risk factors is important because of the possibility of preventing VTE by modifying the risk factors and the life style of individuals.

In this study, we aimed to assess the risk factors and clinical features in patients with VTE who referred to our clinic between the years 2009 and 2012.

MATERIALS AND METHODS

We collected the data of 83 patients with VTE who were admitted to the hematology outpatient clinic between 2009 and 2012, retrospectively. The patients were evaluated at the time of application for other co-morbidities which may cause thrombosis such as diabetes, dyslipidemia, obesity, central catheter, active malignancy, myeloproliferative disease, paroxysmal nocturnal hemoglobinuria, Behcet's disease. The patients were documented whether they had DVT history or thromboembolism, and the number of thrombosis attacks. History of thrombosis was investigated in the family history.

Thrombophilia testing was applied after 4 weeks following withdrawal of warfarin, after 15 days following withdrawal of heparin or its derivatives, and after 3 months in the patients with a history of acute thrombosis. The test was repeated for the positive results. Protein S (PS) antigen and activity, antithrombin III activity, activated protein C resistance (APC-R), Factor V Leiden G1691A mutation (FV Leiden), prothrombin G20210A mutation (PTG), and factor VIII level was examined for the etiology of thrombophilia, and anti-phospholipid antibodies (anti-cardiolipin antibodies IgG and IgM), lupus anticoagulant (LA), (screening and confirmation) were examined for acquired thrombophilia reasons. FV Leiden and PTG mutations were examined with G20210A Roche kit. The examination was made in the "Light Cycler 1.5 ROCHE" (Real Time PCR) device. Blood samples were taken into tubes after 12 hours of fasting for examining PC, PS, antithrombin III, (LA), APC-R and factor VIII level. APC-R (Dade Behring proC global kit), PC, PS, ATIII, FVIII (Dade Behring) kits were used for the examination. Samples were examined in Dade Behring BCS device. Anti-phospholipid antibodies (IgG and IgM) were examined in microbiology-ELISA laboratory of our hospital with Biomaster device and Intec cardiolipin IgG and IgM kits and ELISA method.

The patients included into the study were divided into two groups according to age, namely ≤40 years, and >40 years. Then comparisons were made between the age groups in terms of the demographic and clinical characteristics.

Data analysis was performed using SPSS for Windows 11.5 package software. Descriptive statistics were shown as median (minimum-maximum) for continuous variables and as number of cases and (%) for categorical variables. Categorical variables were examined with Pearson's Chi-Square, Fisher's exact test or likelihood ratio test. A p value below 0.05 was considered as statistically significant.

RESULTS

A total of 83 patients were included to the study. Median age of them was 38 with the range of 18 to 57. Thirty-five of the patients (42.2%) were male and 48 (57.8%) were female. Demographic and clinical characteristics of the patients are summarized in **Table 1.**While no statistically significant difference was observed between the age groups of the patients in terms of family history of thrombosis, immobilization and smoking state (p values 0.346, 0.607, 0.518 respectively), disease story was more common in the age group of >40 years (p: 0.001).

Table.1 Demographic and clinical characteristics of the patients with venous tromboembolism included into the study.

Characteristics	n percent
Age, median, range	38(18-57)
Male/Female	35/48 (42.2/57.8%)
Disease history	22 (26.5%)
Smoking history	23 (27.7%)
Operation history	2 (2.4%)
Immobilization	7 (8.4%)
Family history for VTE	2 (2.4%)

As for venous thrombosis patients, it was found that when age groups are compared according to the place

of thrombosis, there was a significant difference in terms of pulmonary embolism (p: 0.016) between the age groups. Pulmonary embolism was more common in the age group of >40 years compared to the age group of ≤40 years (p: 0.025, **Table 2**). Also DVT prevalence was more common in the age group of ≤40 years compared to other group significantly (p: 0.009). Although smokers had a tendency to develop PE, it did not reach statistical significance (p: 0.076). Smoker and non-smoker groups were not different from each other in terms of thrombosis sites such as PE, DVT, SVT (p values 0.076, 0.113, 0.107 respectively). However, in the smoker group the mostly seen type of thrombosis was PE significantly (p: 0.025).

Table.2 Distribution of the thrombosis site according to age groups of the patients with venous thrombosis.

Thrombosis site	≤40 Age (n:49)	>40 Age (n:34)	Total (n:83)	p
Pulmonary Embolism	15 (30.6 %)[a]	19 (55.9 %)[a]	34	0,025
DVT	23 (46.9 %)[a]	6 (17.6 %)	29	0,009
SVT	7 (14.3 %)	2 (5.9 %)[a]	9	0,297
RVT	2 (4.1 %)	5 (14.7%)	7	0,117
IAVT	2 (4.1 %)	2 (5.9%)	4	0,544

DVT: Deep Venous Thrombosis, SVT: Sinus Vein Thrombosis, RVT: Retinal Vein Thrombosis,
IAVT: Intraabdominal Venous Thrombosis

a: The difference between the age groups of ≤40 and >40 years was statistically significant (p<0,05). In the age group older than 40, the most common thrombosis type was PE compared to the other age group (p: 0.016) and likewise DVT was the most common in the age group lower and equal to 40.

In the patients with sinus thrombosis, there was no difference between the age groups in terms of prevalence (p: 0.297). The rates of smoking were similar between the patients with SVT and the others (p: 0.107). There was no correlation with SVT and the presence of FV Leiden mutation (p: 0.713).

No significant statistical difference was found between the age groups in terms of FV Leiden and PTG mutations (p: 0.089, 0.090) **(Table 3)**.Venous thrombosis reasons according to the age groups, distribution of patients according to the place of thrombosis and the number of etiological risk factors, were given in Tables 4 and 5, respectively. No statistically significant difference was found between the age groups for the levels of d-dimer, homocysteine, anti-cardiolipin antibodies IgG and IgM, and LA. As the number of patients was not sufficient for some variables, no statistical comparisons could be made between the age groups **(Table 4).**

Table.3 Distribution of genetic characteristics of patients with venous thrombosis according to the age groups.

Genetic risk factors	≤40 Age n:49	>40 Age n: 34	Total n:83	p
FV Leiden mutation	21 (42.9%)	11 (32.5%)	32 (38.6)	0.089
Heterozygote	14 (28.6%)	9 (26.5%)	23 (27.7%)	
Homozygote	7 (14.3%)	2 (5.9%)	9 (10.8%)	
PTG mutation	7 (14.3%)	1 (2.0%)	8 (16.3%)	0.090
Heterozygote	6 (12.2 0%)	1 (2.0%)	7 (14.3%)	
Homozygote	1 (2.0%)	0	1 (2.0%)	

FV Leiden; Factor V Leiden mutation, PTG: Prothrombin G20210A mutation

Table.4 Venous thrombosis reasons according to the age groups in our cohort

Risks	≤40 Age (n:49)	>40 Age (n: 34)
Protein C	1 (2%)	-
Protein S	-	1 (2.9%)
AT3	1 (2%)	1 (2.9%)
APCR	3 (6.1 %)	-
FVIII	1 (2 %)	2 (5.8%)
ANA	4 (8.1%)	1 (2.9%)
Anti-dsDNA	5(10.2%)	-

ANA: Anti-nuclear antibody, APCR: Activated protein C resistance, AT3: Anti-thrombin 3

Table.5 Distribution of thrombosis site according to the number of risk factors

Risk factors	PE	DVT	SVT	RVT	IABD	Total
No risk factor	3	3	1	-	2	9 (10.8 %)
1 risk factor	15	23	4	6	-	48 (57.8 %)
>1 risk factors	16	3	4	1	2	26 (31.4 %)
Total	34	29	9	7	4	83 (100 %)

Risk factors include presence of FV Leiden, PTG mutations, and elevated levels of factor VIII, d-dimer, fibrinogen, and homocysteine.

DISCUSSION

Since VTE which refers to as a big majority PE and DVT, could be potentially fatal in one- thirds of the patients,

defining the risk factors for VTE and by means of this a possibility of preventing VTE had become a point of interest for the researchers. There are both genetic and acquired risk factors associated with VTE. Older age, diabetes mellitus, obesity, arterial hypertension, hyperlipidemia and smoking habit are considered acquired risk factors for VTE. And also there exist some other genetic risk factors proposed to be associated with VTE such as FV Leiden, PTG mutations (2, 5).

In this study, we found that the median age of overall patients with VTE was 38 in contrast to the literature findings. In the literature it was reported that both PE and DVT had been the diseases seen above the age of 50. However, PE patients were older, while DVT was more common in the younger patients in our study cohort. PE was more frequent in the >40 age group compared to the other group similar to the literature (5-11). Older age and presence of co-morbid diseases may give rise to PE which is a more serious form of VTE.

Gender was not considered as a risk factor in the literature. Likewise we also did not find any significant difference between the male and female group of our patients with VTE (5-11). Approximately one-fourth of the patients (26.5 %) had a chronic disease such as hypertension, obesity, and diabetes mellitus. This finding was compatible with the literature. Various studies reported that there was an increased risk of DVT and/or PE in people with obesity (12, 13), and the risk decreased in people with low weight (14). Smoking is one of the controversial issues as a risk factor for VTE, in the literature. Although no significant relationship between VTE and smoking was reported in Leiden group (15), ARIC and CHS (12) studies, and a meta-analysis including the Norwegian study (16), the other five studies showed that there was a relative relationship between VTE and smoking (relative risk between 1.3 and 3.3) (12, 17). In another study, it was reported that high/pack year factor in young people who smoke causes high venous thrombosis risk compared to the young people who do not smoke (18). Rate of smoking was 27.7% in our study. When we compared the smoker and non-smoker group in terms of thrombosis sites (PE, DVT, and SVT) we did not find any difference between the groups (p values 0.076, 0.113 and 0.107 respectively). Although PE was seen more frequently in the smokers, this was not statistically significant (p: 0.076).

In the literature there are some studies reporting that the major reasons for VTE had been major surgery, long term hospitalization and immobilization (19). In contrast to those studies immobilization and history of surgery was relatively rare in our study group. This could be explained by the distribution of our patients who were mostly from the outpatient clinic.

It is believed that the risk of VTE further increases in case of FV Leiden, PTG mutations (19, 20). The FV Leiden and PTG mutations were the most common genetic risk factors in our cohort too, with the rate of 42.3 and 16.9 percent respectively, compatible with the literature. The presence rates of those risk factors in normal population were reported 8 and 4 percent respectively in the population based incidence studies in the literature (21). Since the rates we found were much more than those numbers, it can be proposed that FVL and PG gene mutations play a role in the pathogenesis of VTE.

In our cohort the majority of the patients also had at least one or more genetic risk factors such as presence of FV Leiden, PTG mutations, and elevated levels of factor VIII, d-dimer, fibrinogen, and homocysteine. Only 10.8 percent of the patients had no genetic risk. This finding also supports the importance of genetic anomalies in development of VTE (23).

Deficiencies of PC and PS were reported to be associated with the VTE in the literature (22). Protein S deficiency prevalence has been reported as 1/33000 in healthy people (24). It was considered to be responsible for 2 % of the VTE cases (25). In our study, deficiencies of PC, PS, and antithrombin, activated protein C resistance, high factor VIII levels and the positivity of anti-nucleic acid and anti-ds DNA was diagnosed in 1.2, 1.2, 1.2, 3.6, 6, 6, 2.4 % of the patients respectively. Those findings were compatible with the literature.

The main limitations of this study are its retrospective design, relatively small number of study participants, and the lack of a control group.

CONCLUSION

VTE is a disease that has potentially high mortality and morbidity. Inherited and acquired risk factors of VTE must be systematically evaluated in an appropriate manner in order to determine the etiologic risk factors. Defining modifiable risk factors for VTE may serve us in order to prevent first attack of the disease by means of changing life style. Defining present genetic risk factors may help in defining the duration of treatment and preventing the recurrence.

Conflict of Interests:Authors declare that there is no conflict of interests.

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REFERENCES

1.)Segal JB, Eng J, Janckes MW, et al. Diagnosis and treatment of deep venous thrombosis and pulmonary embolism. Agency for Healthcare Research and Quality Publication No. 03-E016, 2003:1-169.
2.)Goldhaber SZ. Risk factors for venous thromboembolism. J Am Coll Cardiol. 2010 Jun 29; 56(1):1-7
3.)Devecioğlu Ö, Dündar S, Demir M, et al. Tromboz El Kitabı. Türk Hematoloji Derneği Yayınları 2004, Ankara.
4.)Türk Toraks Derneği Pulmoner Tromboembolizm Tanı ve Tedavi Uzlaşı Raporu. http://www.toraks.org.tr/news.php =1288, 2009.
5.)Andersen FA, Spencer FA. Risk factors for venous thromboembolism. Circulation. 2003; 107:I-9-I-16

6.)Silverstein MD, Heit JA, Mohr DN, et al. Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study. Arch Intern Med 1998; 158:585 Blood, 2007 110: 3097-3101
7.)Silverstein RL, Bauer KA, Kushman M, et al. Venous thrombosis in the elderly: more questions than answers Blood.2007 Nov 1;110(9):3097-101. Epub 2007 Aug 7
8.)de Bruijn SF, Stam J, Koopman MM, et al. Case-control study of risk of cerebral sinus thrombosis in oral contraceptive users and in (correction of who are) carriers of hereditary prothrombotic conditions. The Cerebral Venous Sinus Thrombosis Study Group. BMJ 1998; 316:589.
9.)Castoldi E, Brugge JM, Nicolaes GA, et al. Impaired APC coFaktör activity of Faktör V plays a major role in the APC resistance associated with the Faktör V Leiden (R506Q) and R2 (H1299R) mutasyonus. Blood 2004; 103:4173.
10.)Simioni P, Castoldi E, Lunghi B, et al. An underestimated combination of opposites resulting in enhanced thrombotic tendency. Blood 2005; 106:2363.
11.)Bezgin T, Kaymaz C, Akbal Ö, et al. Thrombophilic gene mutations in relation to different manifestations of venous thromboembolism: a single tertiary center study. Clin App Throm Hemostasis. 2016;1-7
12.)Ageno W, Becattini C, Brighton T, et al. Cardiovascular risk factors and venous thromboembolism: a meta-analysis. Circulation 2008; 117:93.
13.)Holst AG, Jensen G, Prescott E. Risk factors for venous thromboembolism: results from the Copenhagen City Heart Study. Circulation 2010; 121:1896.
14.)Eichinger S, Hron G, Bialonczyk C, et al. Overweight, obesity, and the risk of recurrent venous thromboembolism. Arch Intern Med 2008; 168:1678.
15.)Helmerhorst FM, Bloemenkamp KW, Rosendaal FR, et al. Oral contraceptives and thrombotic disease: risk of venous thromboembolism. Thromb Haemost 1997; 78:327.
16.)Nijziel MR, van Oerle R, Christella M, et al. Acquired resistance to activated protein C in breast cancer patients. Br J Haematol 2003; 120:117.
17.)Severinsen MT, Overvad K, Johnsen SP, et al. Genetic susceptibility, smoking, obesity and risk of venous thromboembolism. Br J Haematol 2010; 149:273.
18.)Tormene D, Simioni P, Prandoni P, et al. The risk of fetal loss in family members of probands with factor V Leiden mutation. Thromb Haemost 1999;82(4):1237–9.
19.)Pomp ER, le Cessie S, Rosendaal FR, et al. Risk of venous thrombosis: obesity and its joint effect with oral contraceptive use and prothrombotic mutations. Br J Haematol 2007; 139:289.
20.)Delluc A, Mottier D, Le Gal G, et al. Underweight is associated with a reduced risk of venous thromboembolism. Results from the EDITH case-control study. J Thromb Haemost 2009 Apr;7(4):728-9. doi: 10.1111/j.1538-7836.2009.03280.x. Epub 2009 Jan 13
21.)Türk Hematoloji Derneği.Edinsel Kanama Bozuklukları ve Kalıtsal Trombofili Tanı ve Tedavi Kılavuzu 2011;1:75-98
22.)Lensen RP, Rosendaal FR, Koster T, et al. Apparent different thrombotic tendency in patients with factor V Leiden and protein C deficiency due to selection of patients. Blood 1996; 88:4205
23.)Ganesan V, McShane MA, Liesner R, et al. Inherited prothrombotic states and ischaemic stroke in childhood. J Neurol Neurosurg Psychiatry 1998; 65:508.
24.)Mommertz G, Sıgala F, Glowka TR, et al. Differences of venous thromboembolic risks in vascular general and trauma surgery patients J Cardiovasc Surg 2007 ;48:727-733
25.)de Visser MC, Rosendaal FR, Bertina RM. A reduced sensitivity for activated protein C in the absence of Faktör V Leiden increases the risk of venous thrombosis. Blood 1999; 93:1271.