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Is İt İn Our Genes That We're Going To Have Pulmonary Embolism?

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ABSTRACT

Pulmonary thromboembolism is a disease with high mortality and morbidity, which can be recurrent, difficult to diagnose, yet preventable and treatable. In this study, our aim was to evaluate comorbidities, risk factors, laboratory results, and clinical scoring in patients diagnosed with pulmonary embolism. Our primary goal was to detect genetic mutations in cases of pulmonary embolism with acquired risk factors.

Our study is a prospective study that includes clinical information, laboratory tests, Wells scoring, admission, and the prospective history of 60 patients with no previous history of venous thromboembolism (VTE) and no history of anticoagulation use. These patients were admitted to the chest diseases outpatient clinic, emergency department, or hospitalized for another reason and diagnosed with pulmonary thromboembolism.

The mean age of the patients was 59.9 ± 18.7 years. The most common presenting complaints were shortness of breath and sharp chest pain. Nearly half of the patients had at least one comorbid disease. There was at least one genetic/congenital risk factor in all cases, and at least two risk factors were present in more than half of the cases. The most common mutations were plasminogen activator inhibitor type 1 (PAI-1) and Methylenetetrahydrofolate Reductase (MTHFR) heterozygote mutations.

Pulmonary embolism continues to be a more prevalent disease with increasing age and associated risk factors. Since there is at least one acquired risk factor in all of our cases, we believe that almost every patient may have an acquired risk factor if the history is thoroughly investigated. We also believe that genetic or thrombophilic conditions may be detected in almost all cases diagnosed with pulmonary embolism. It has been concluded that immobilization and obesity are the most common preventable risk factors associated with VTE.

Keywords: Pulmonary Embolism; Anticoagulants; Deep Vein Thrombosis; Risk Factors; Thrombophilia; MTHFR defeciency

Introduction

Pulmonary Embolism (PE) can be defined as obstruction of the pulmonary artery or its branches with various substances such as thrombus, tumor, or air. Pulmonary thromboembolism (PTE) typically manifests as an early complication of deep vein thrombosis (DVT), involving fragments that detach from thrombi, which commonly originate in the deep veins of the legs. Pulmonary thromboembolism and DVT often coexist (1). Factors contributing to intravascular coagulation were delineated by Virchow in 1856 as "1. Vascular endothelial damage, 2. Hypercoagulability, 3. Stasis." Acquired and/or inherited factors leading to one of these three conditions are present in 75% of VTE cases (2).

Numerous risk factors have been identified that increase susceptibility to venous thromboembolism. Among the most frequently reported risk factors in studies are a previous history of VTE, active cancer, major trauma, surgery, recent hospitalization, long flights, immobility, obesity, and concomitant heart diseases (3,4). In addition to environmentally acquired factors that predispose to venous thromboembolism, hereditary risks also play a role. Studies have reported a detection rate of thrombophilia varying between 10-50%, depending on the characteristics of the selected population. The most commonly identified mutations include factor V Leiden and prothrombin gene mutations, followed by protein C, S, and antithrombin III deficiencies (5-7). Studies conducted in our country on hereditary

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thrombophilia have indicated that factor V Leiden mutation is the most prevalent hereditary factor, with carrier rates ranging from 2-12% in the healthy population and 5-35% in the VTE group. Elevated factor VIII and protein C deficiency have also been found to be significant in VTE cases. However, homocysteinemia and methylene tetrahydrofolate reductase (MTHFR) gene mutation were not deemed significant risk factors in our country due to their high prevalence in the healthy population (8-12).

In this study, our aim was to identify genetic mutations in patients with VTE. Additionally, we examined the risk factors, laboratory results, and clinical scoring associated with the condition.

Materials and Methods

This study is a prospective research that includes the clinical characteristics and laboratory test results of patients diagnosed with PTE confirmed by computed tomography angiography (CT angiography) who have no history of venous thromboembolism (VTE) and anticoagulation use. The research was conducted between November 27, 2017 and August 27, 2018 and it includes patients aged 18 and above who were diagnosed with Pulmonary Embolism through CT angiography for definitive diagnosis. These patients consist of individuals who presented to the chest diseases outpatient clinic or emergency department, were evaluated with a preliminary diagnosis of PTE while hospitalized for another reason, and subsequently received a definitive diagnosis of PTE through pulmonary CT angiography. This prospective study, which examined the data of a total of 60 patients, aims to evaluate the clinical characteristics and laboratory test results of patients diagnosed with PTE.

Data Collection: The study was conducted in the Department of Pulmonology of our hospital after obtaining approval from the ethics committee. After obtaining consent from patients diagnosed with PTE, their demographic data, clinical history, risk factors for PTE, and genetic tests (MTFHR C677T, PAI-1, MTFHR A1298C, factor 13, prothrombin, Factor V Leiden mutation) were examined and recorded in the data collection forms. Sections were obtained using a 128-detector computed tomography scanner in the computed tomography angiography protocol. Wells scoring was calculated based on the presence of symptoms and signs of deep vein thrombosis, low probability of alternative diagnosis, tachycardia (> 100/minute), history of immobilization or surgery in the last 4 weeks, previous history of deep vein thrombosis or pulmonary embolism, hemoptysis, and presence of cancer (13). According to the binary scoring system in Wells scoring, values >4 points were classified as 'PTE probable' and ≤4 points as 'PTE not probable'. In the triple scoring system, values < 2 points were classified as 'low clinical probability', values between 2.0-6.0 points as 'moderate clinical probability', and values ≥ 6 points as 'high clinical probability'.

Data Analysis: Descriptive statistics for continuous variables in question were expressed as mean, standard deviation, minimum and maximum values, and those for categorical variables are expressed as numbers and percentages. Statistical significance level was taken as 5% in the calculations and SPSS statistical package program was used for the calculations.

Results

The study included 60 cases, of which 26 were male (43.3%) and 34 were female (56.7%). When evaluating the ages of the cases, the youngest was 18 and the oldest was 91 years old. The mean age was 59.9±18.7 years. 51.6% of the cases were aged 65 and above.

A total of 47 cases (78.3%) had at least one comorbid disease in their medical history. The most prevalent comorbid conditions were hypertension, accounting for 31.6% (n: 19), followed by cardiac diseases at 20% (n: 12), respectively. Chronic obstructive pulmonary disease (COPD) was the most prevalent among the concurrent diseases in the medical history of the cases, at 13.3%. Table 1 illustrates the frequency of other comorbid conditions.

All cases had at least one risk factor, and 76.6% of cases (n: 46) had at least two risk factors, with a mean number of risk factors being 2.5. The most common risk factor was immobilization, present in 35 cases (58.3%), followed by obesity and advanced age, each at a rate of 48.3% (n: 29). Table 2 displays the frequency of other risk factors.

The average Wells score of the cases was found to be 4.9 points. According to the binary scoring system, 'PTE probable' was found in 36 cases (60%), while 'PTE not probable' was found in 24 cases (40%). In the triple scoring system, low clinical probability was detected in 7 cases (11.6%), moderate clinical probability in 38 cases

Table 1: Comorbid Conditions

Comorbidities	Frequency (%,n)
Hypertension	%31,6 (19)
Cardiac disease (chd, cag, chf)	%20 (12)
COPD	%13,3 (8)
Diabetes Mellitus	%13,3 (8)
Other	%13,3 (8)
Malignancy	%10 (6)
Stroke	%8,3 (5)
Hematologic Malignancy	%3,3 (2)

Table 2: Frequency of Acquired Risk Factors

Acquired Risk Factors	Frequency (%,n)	Acquired Risk Factors	Frequency (%,n)
İmmobilization	%58,3(35)	Prolonged travel(>8 hours)	%8,3(5)
Obesity	%48,3(29)	Central venous catheter	%6,6(4)
Aging	%48,3(29)	Miyocardial infarction	%6,6(4)
Cancer	%20(12)	Chemotherapy	%6,6(4)
Major surgery	%18,3(11)	Pregnancy/Postpartum	%5(3)
Trauma	%10(6)	Contraceptive therapy	%5(3)
Stroke	%10(6)	Congestive heart failure	%3,3(2)

(63.3%), and high clinical probability in 15 cases (25%).

A total of 58 cases were examined for genetic mutations, while 2 cases could not be examined due to death. No mutations were detected in only 3 of the cases. In all the remaining cases, at least 1 mutation, with an average of 2 mutations, was observed. Heterozygous mutations were the most common, with the PAI-1 mutation being the most frequently observed one. The PAI-1 mutation was found to be homozygous in 27.6% (n:16) and heterozygous in 51.7% (n:30) of the cases. On average, the PAI-1 mutation was observed in 4 out of 5 patients. Factor V Leiden mutation was heterozygous in 7 patients (12.1%), while Prothrombin 20210A mutation was heterozygous in only 3 patients (5.2%). The rate of cases with the MTHFR A1298c homozygous mutation was 19% (n: 11), while the rate of cases with heterozygous mutations was 29.3% (n: 17). Figure 2 shows the frequency of mutations.

Discussion

The primary objective of our study was to assess the genetic-congenital risk status of all patients, irrespective of whether they had acquired risk factors. It is not common practice to explore genetic-congenital conditions in patients with acquired risk factors. However, given that PTE was not observed in all individuals with acquired risk factors, and only a subset of them presented with PTE, we structured our study under the assumption that there might be a genetic-congenital risk factor even among those with acquired risk factors.

In a study conducted by Koyden et al. involving 132 PTE patients, hypertension (HT) was identified as the most prevalent comorbidity (37%), followed by coronary artery disease (CAD) at 15.9%, chronic obstructive pulmonary disease (COPD) at 12.1%, diabetes at 9.8%, congestive heart failure (CHF) at 7.6%, and cerebrovascular events (CVO) at 6.1% (14). Similarly, in the EMPEROR study, hypertension was reported in 45.6% of cases, COPD in 8.5%, and heart failure in 7.5% (15). However, the rates observed in the Swedish cohort study by Andersson and Sodenberg, which included 5793 cases, differed from those in our study, although hypertension remained the most common comorbidity, followed by subsequent cardiac diseases (16). Consistent with the literature, our study also found hypertension to be the most prevalent comorbidity, with a rate of 31.6%, followed by cardiac diseases such as CAD and CHF at 20%. The similarity in comorbidities between the literature and our study can be attributed to the increasing incidence of cardiac diseases like HT, COPD, and CAD with advancing age. While the cancer rate in our study generally aligns with the literature, differences are observed in other risk

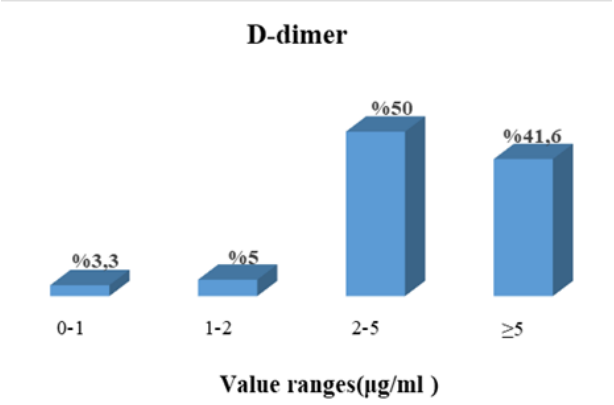

Fig.1. Case frequencies according to categorized D-dimer value ranges

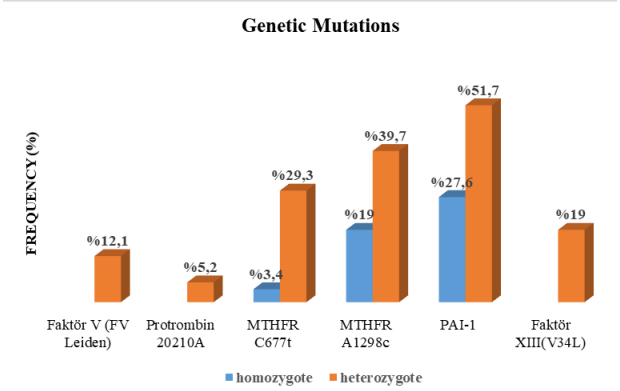

Fig.2. Frequency of genetic mutations

factors such as immobilization and obesity. We believe that the high number of cases aged over 65 years and socio-economic and regional factors in our study may have influenced these differences.

An investigation in Turkey revealed that in cases diagnosed with proven PTE, using the triple scoring system, low probability was determined in 39.5%, moderate probability in 50.6%, and high probability in 9.9% according to Wells scoring (17). In a comprehensive review of a total of 29 studies and 31,215 cases, it was found that among cases with low clinical probability, 5.7% had proven PTE, among those with moderate clinical probability, 23.2% had proven PTE, and among those with high clinical probability, 49.3% had proven PTE (18). In our study, "Low Clinical Probability" was detected in 11.6% of cases with proven PTE.

In a study by Bezgin et al., the MTHFR A1298C heterozygote mutation rate was 42.6% in the healthy population and 42.8% in patients with VTE. The MTHFR C677T heterozygote rate was 44.6% in the healthy control group and lower in the VTE group at 38%. In the same study, the PAI-1 homozygote (4G/4G) mutation rate in healthy individuals was 28%, and the heterozygote (4G/5G) mutation rate was 47.4%, whereas they were found to be 23% and 47% in VTE patients, respectively (19). Kupeli et al. detected the MTHFR C677T homozygote mutation rate as 5.9% and the heterozygote mutation rate as 33.3% in cases with PTE. In the same study, the Factor V Leiden heterozygote mutation was found to be 7.8%, and the Prothrombin 20210A heterozygote mutation was found to be 9.8%, while the PAI-1 homozygote and heterozygous mutation rates were found to be 30% and 47.5%, respectively (20). In a study of 46 cases, including proven VTE cases by Tug et al., the Factor V Leiden heterozygous mutation rate was found to be 30.8%, while the prothrombin 20210A mutation could not be detected (21). Factor V Leiden heterozygote mutation was found to be 26%, and prothrombin 20210A heterozygote mutation was found to be 6.8% in another study, which included 146 cases presenting with thrombosis (22). In our study, the Factor V Leiden heterozygote mutation was found to be 12.1%, and the Prothrombin 20210A heterozygote mutation was found to be 5.2%. Although the rate of Prothrombin 20210A heterozygote mutation is similar to those in the literature, we can say that the rate of heterozygote mutation in the literature is lower than those of the studies conducted in our society. However, the limitation of the number of cases in the studies conducted in the world results in a wide range of rates. There are a great number of studies on PAI-1 4 Guanosine/5 Guanosine (4G/5G) polymorphism in relation to VTE formation. The results differ from study to study, and publications on this topic are conflicting. All reported effects in all studies are more pronounced for the 4G allele. The PAI-1 data in our study are similar to those in the literature; the homozygote mutation rate is 27.6%, and the heterozygote mutation rate is 51.7%. Community screening studies conducted in Turkey showed that the overall C677T homozygote incidence for MTHFR was around 5%, while the C677T heterozygote incidence was around 35% (23). In our study, the C677T mutation homozygote and heterozygote rates were found to be 3.4% and 29.3%, respectively. The mutation rates of A1298C were found to be 19% in homozygotes and 39.7% in heterozygotes. We could not compare these rates because we did not have a healthy control group, but when we examine other studies conducted in our country and in the world, we can say that the results are similar. In many studies conducted in this context, we can say that MTHFR and PAI-1 mutation rates

are very close to each other in patient groups and healthy individuals, and even higher in healthy individuals in some studies, with or without pulmonary thromboembolism, deep vein thrombosis, ischemic stroke, or any focal thrombosis. Although we have reached this conclusion with the available and worldwide data for heterozygous mutations of these two genetic anomalies, homozygous mutations have statistically more significant results and may have a slightly higher relationship with thrombosis. Since there are many factors and risk factors leading to thrombosis, we believe that studies with very large patient series with no risk factors should be performed to clarify this issue.

The most important limitation of our study was the absence of a control group. Therefore, we could not compare risk factors and comorbidities in individuals without VTE. In addition, the data of our study are limited in terms of generalizability because genetic mutation rates in healthy and VTE patients differ between populations and geographical regions.

It is known that there are many genetic and acquired factors leading to the development of pulmonary thromboembolism. It is evident that VTE does not develop in all immobilized and obese patients. In addition to genetic mutations that increase the risk of thrombosis and lead to VTE, there are also mutations that have not yet been proven to increase thrombosis and VTE risk. We believe that Factor V Leiden and Prothrombin 20210A should be considered as the first step in the cases planned for genetically advanced examination. Considering the studies conducted in the literature and our own study, we think that MTFHR and PAI heterozygote mutations should not be effective in the decision of prolonged treatment or prophylaxis of VTE; however, we also believe that the presence of these mutations along with other genetic mutations increases the tendency to thrombosis in association with acquired risk factors.

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