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Assessment of risk factors affecting thrombosis in patients with essential thrombocytosis

Esansiyel trombositozlu hastalarda trombozu etkileyen risk faktörlerinin değerlendirilmesi

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Abstract

Aim: Arterial and venous thromboembolic complications are the leading cause of morbidity and mortality in Essential thrombocytosis (ET). The mechanism of thrombosis in ET is not fully explained. In present retrospective analysis, we aimed to investigate the association between thrombosis complication and age, gender, disease duration, laboratory findings, janus kinase 2 (JAK2) V617F mutation status in patients with ET.

Methods: Medical database of ET patients whom admitted to outpatient clinics of our institution, between April 2015 and April 2017, were retrospectively analyzed. Patients were divided into two groups, with and without arterial or venous thrombosis history. According to the thrombosis story, general characteristics, laboratory findings and JAK2 V617F mutation status of the groups were compared.

Results: 37 patients with thrombosis history and 15 patients without thrombosis history were detected. The number of leukocyte, platelet and lymphocyte in ET patients with thrombosis history was statistically significantly higher than without thrombosis history patients. JAK2 V617F mutation positivity was statistically significant in ET patients with thrombosis history.

Conclusion: This study confirmed the high leukocyte count, high platelet and lymphocyte count and JAK2 V617F mutation positivity as the thrombosis risk factor in patients with ET. In addition, the characteristics of the patients who applied to our clinic were compared with the literature and the differences were revealed.

Keywords: Thrombosis history, Essential thrombocytosis, Janus kinase 2 mutation, Leukocyte count, Platelet count

Öz

Amaç: Esansiyel trombositozda (ET) arteriyel ve venöz tromboembolik komplikasyonlar morbidite ve mortalitenin en önemli nedenlerdir. ET'de tromboz mekanizması tam olarak açıklanamamıştır. Mevcut retrospektif analizde, ET'li hastalarda tromboz komplikasyonu ile yaş, cinsiyet, hastalık süresi, laboratuvar bulguları, janus kinaz 2 (JAK2) V617F mutasyon durumu arasındaki ilişkiyi araştırmayı amaçladık.

Yöntemler: Nisan 2015 ile Nisan 2017 arasında kurumumuzun kliniğine başvuran ET hastalarının dosyaları retrospektif olarak analiz edildi. Hastalar arteriyel-venöz tromboz öyküsü olan ve olmayan olarak iki gruba ayrıldı. Tromboz öyküsüne göre, grupların genel özellikleri, laboratuvar bulguları ve JAK2 V617F mutasyon durumu karşılaştırıldı.

Bulgular: Tromboz öyküsü olan 37 hasta ve tromboz öyküsü olmayan 15 hasta tespit edildi. Tromboz öyküsü olan ET hastalarında lökosit, trombosit ve lenfosit sayısı tromboz öyküsü olmayan hastalardan istatistiksel olarak anlamlı yüksekti. Tromboz öyküsü olan ET hastalarında JAK2 V617F mutasyon pozitifliği istatistiksel olarak anlamlı idi.

Sonuç: Bu çalışma, ET'li hastalarda tromboz riski faktörü olarak yüksek lökosit sayısı, yüksek trombosit ve lenfosit sayısı ve JAK2 V617F mutasyon pozitifliğini doğrulamıştır. Ayrıca kliniğimize başvuran hastaların özellikleri literatürle karşılaştırıldı, benzerlikler ve farklılıklar karşılaştırıldı.

Anahtar kelimeler: Tromboz hikayesi, Esansiyel trombositoz, Janus kinaz 2 mutasyonu, Lökosit sayısı, Trombosit sayısı

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Introduction

Essential thrombocytosis (ET) is a myeloproliferative neoplasm characterized by clonal proliferation of megakaryocytic lineage in the bone marrow and peripheral thrombosis with high platelet count and an increased risk of thrombosis [1,2]. Gender, age (>60 years), janus kinase 2 (JAK2) V617F mutation, leukocytosis, thrombocytosis, thrombosis history, tobacco use, hypertension (HT) and diabetes mellitus (DM) are predictive factors for thrombosis risk in patients with ET. However, the criteria for risk classification and treatment initiation in ET are thrombosis history and greater than 60 years old [2].

Arterial and venous thromboembolic complications are the leading cause of morbidity and mortality in ET [2,3]. Neutrophil (neu) - white blood cell (WBC) - platelet activation, endothelial activation and inflammation have been suggested in the pathogenesis of thrombosis in ET [4-6]. However, the mechanism of thrombosis in ET is not fully explained.

In present retrospective analysis, we aimed to investigate the association between thrombosis complication and age, gender, disease duration, laboratory findings, JAK2V617F mutation status in patients with ET.

Materials and methods

After the approval of the authority of the institution, medical database of ET subjects who admitted to outpatient clinics of our institution between April 2015 and April in 2017 were retrospectively analyzed. Medical and laboratory data obtained from computerized database and patient file system and recorded. Patients were divided into two groups, with and without arterial or venous thrombosis history. Patients with coronary artery disease, HT, DM, hyperlipidemia, active infection and renal failure were not included in the study.

Statistical analysis

Data were analyzed by SPSS software (SPSS 15.0, IBM Inc., Chicago, IL, USA). Kolmogorov-Smirnov test conducted to observe distribution of variables in study groups. Homogenous variables were expressed as mean ± standard deviation and compared by independent samples t test, whereas, non-homogenous variables were expressed as median (minimum – maximum) and compared by Mann-Whitney U test. Comparison of categorical variables in study groups was conducted with Chi-square test. Correlation between parameters of the study was done with Pearson's correlation analyze test. A p value of <0.05 is considered as statistically significant.

Results

Study population was consisted of 52 subjects, 20 (39%) male and 32 (62%) female. In our study population, the mean age was 58.17±14 years, the mean platelet count was 539±240 K/uL, the mean WBC count was 9±3.5 K/uL, the mean hemoglobin (Hb) level was 13.4±1.6 g/dL, the mean neu count was 6.1±2.9 K/uL, and the mean lym count was 2±0.7 K/uL. JAK2 V617F mutation was positive in 36 patients (70%) and was negative in 16 patients (30%).

In our study, 37 patients with thrombosis and 15 patients without thrombosis were detected. 23 of 37 in with thrombosis history group and 9 of in without thrombosis history group were women. Gender was not statistically different between study groups (p=0.88). Mean age of the patient group with thrombosis history was 63 (21-86) years and mean age of the patient group without thrombosis history was 53 (40-82) years (p=0.75). Similarly, there was no statistically significant difference in disease duration between groups (p=0.63).

The mean WBC count (9.9±0.6 K/uL) in the group with thrombosis history was statistically higher than the mean WBC count (6.7±0.48 K/uL) in the group without thrombosis history (p=0.002). The mean Plt count (484 [297-1369] K/uL) of the group with thrombosis history was significantly higher than that of the group without thrombosis history (363 [170-782] K/uL)(p=0.006). The mean lym count of the patient group with thrombosis story was statistically higher than the group without thrombosis history (p=0.04). However, there was no significant difference between the groups in Hb, hematocrit (hct) and neu counts (p>0.05 for all). The characteristics of the study group and the laboratory data are given in table 1.

In 37 patients with thrombosis history, JAK2 V617F mutation was negative in 7 patients and positive in 30 patients. In 15 patients without thrombosis history, the JAK2 V617F mutation was negative in 9 patients and positive in 6 patients. In JAK2 V617F mutation-positive patients, the thrombotic event was statistically higher than JAK2 V617F mutation-negative patients (p=0.004).

A Pearson's correlation test was revealed that WBC was positively correlated with Plt (r=0.393, p=0.004).

Table 1: General characteristics and laboratory parameters according to the thrombosis history of the essential thrombocytosis patients

		Study Groups		
		With thrombosis history	Without thrombosis history	p
Age (year)		63 (21-86)	53 (40-82)	0.75
Gender	Female	23	9	0.88
	Male	14	6	
JAK2 V617F	Positive	30	6	0.004
mutation status	Negative	7	9	
Duration of disease (year)		4 (1-20)	4 (1-12)	0.63
White blood Cell (K/uL)		9.9±0.6	6.7±0.48	0.002
Platelet (K/uL)		484 (297-1369)	363 (170-782)	0.006
Lymphocyte (K/uL)		2.1 (0.85-5.4)	1.9 (0.89-2.46)	0.04
Neutrophil (K/uL)		5.39 (3.16-16.4)	4.8 (2.25-12.4)	0.06
Hemoglobin (g/dL)		13.7±0.29	12.8±0.28	0.1
Hematocrit (%)		39.6±1	37.7±0.7	0.28

Discussion

We showed in present retrospective study that the number of WBC, Plt and lym in ET patients with thrombosis history was statistically significantly higher than without thrombosis history patients. In this study, we also showed that JAK2 V617F mutation positivity was statistically significant in ET patients with thrombosis history.

ET patients are diagnosed at an average age of 55-60 years [7]. Age, especially over 60 years, is the criterion for both general survival risk factor and risk classification in patients with ET. Patients with ET over the age of 60 years are a criterion for starting medical treatment [8]. We found that the median age of our patient group was consistent with the literature. In our study, the mean age of the group with thrombosis history was higher than the group without thrombosis history. But there was no statistical difference. It is also reported that high age is a risk

factor for leukemic transformation [9]. In patients with ET, only male gender predicted venous thrombosis [8]. It has been reported that gender is not predictive of the risk of arterial thrombosis [8]. The number of female patients in our study was high. There was no difference in gender of the group with and without thrombosis history. Because of this, only male gender is a risk factor for the risk of thrombosis, so our study was considered to have a high number of female patients.

In ET, the effect of WBC on the risk of thrombosis has become increasingly prominent [10, 11]. However, the effect of WBC on the development of thrombosis remains uncertain. Previus studies have shown that activated leukocytes impair blood coagulation by releasing intragranule-associated proteases (i.e., elastase and cathepsin G), which are known to degrade numerous inhibitors of coagulation [12, 13]. In our study, WBC was statistically significantly higher in the group with thrombosis story. We confirmed the association of WBC count with thrombosis in our study. It has also been reported that WBC count >15 K / uL is a risk factor for leukemic transformation [9]. We can say that the risk of leukemic transformation is low because the mean WBC count is 9±3.5 K/uL in our study.

Thrombocytosis is the most prominent clinical feature of ET and persistently elevated thrombocyte activation is continuous [14-16], this suggests that there is a pathogenic relation between platelets and thrombotic complications. Despite uncertainties about the role of thrombocytosis on thrombosis, some evidence supports the contribution of activated platelets to the pathogenesis of thrombosis in ET [14, 17]. In one study, phosphatidylserine (PS) levels in platelets and lymphocytes were elevated significantly in ET patients [18] and this has been suggested to cause abnormal platelet and lym activation or apoptosis [14]. In another study, patients with ET had higher PS levels of platelets than controls, but no statistically significant difference [19]. In our study, platelet levels of the group with thrombosis history were significantly higher than the group without thrombosis history. The mean platelet level was below 1000 Ku/L in the group with thrombosis history. It has been reported that extreme thrombocytosis (> 1500 K/uL) increases the risk of bleeding [20]. In our study, we confirmed that the high platelet count increased the risk of thrombosis. Recent studies have shown that erythrocytes participate in thrombosis in ET [21, 22]. However, relatively little is known about the role of erythrocytes in thrombosis in patients with ET. In our study, Hb and Hct levels were high in the group with thrombosis history, but there was no statistical difference between groups. In our study, the absence of a relationship between thrombosis and the Hb level was thought to be due to the relatively low Hb levels of our patients.

JAK2-V617F mutation, observed in 50–60% of patients with ET, has been an independent risk factor for thrombosis [23] but little is known about the underlying mechanism of this relation [18]. JAK2 exon 12 mutations in ET are rare [24]. Patients with ET also have calreticulin (CALR) (15-24%) or myeloproliferative leukemia virus oncogene (MPL) mutations (4%) [25]. In one study, although the platelet count was lower, the absolute number of PS + platelets was reported to be dramatically higher in JAK2 than in the CALR mutation [18]. In our patient group, JAK2 V617F mutation rate was 69%. The relatively low number of patients suggests that JAK2 V617F caused mutation positivity to be high. In our study, JAK2 V617F positivity was statistically significant in the group with thrombosis history. This finding was consistent with the literature.

This study confirmed the high WBC count, high lym count and JAK2 V617F mutation positivity as the thrombosis risk factor in patients with ET. In addition, the characteristics of the patients who applied to our clinic were compared with the literature and the differences were revealed.

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