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Factor V Leiden, prothrombin G20210A and MTHFR gene mutations in inflammatory bowel disease

inflamatuvar barsak hastalıklarında Faktör V Leiden, protrombin G20210A ve MTFHR gen mutasyon prevelansı

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Background/aims: *Thromboembolic events are more common in patients with inflammatory bowel disease than in the normal population; however, the reason for the increased prevalence is not clear. The aim of this study was to evaluate the prevalence of factor V Leiden, prothrombin G20210A and methylene tetrahydrofolate reductase (MTHFR) gene mutations in IBD patients followed in our outpatient clinic.* ***Methods:*** *Thirty-four patients with ulcerative colitis and 28 patients with Crohn's disease and 80 healthy controls were included in the study. No patient had a history ofprevious thromboembolism. Factor V Leiden, prothrombin G20210A and MTHFR gene mutations were studied.* ***Results:*** *Heterozygote factor V Leiden mutation was found in five (6.25%) control patients and in two (3.2%) IBD patients. Heterozygote MTHFR mutation was obtained in seven (11.3%) IBD patients and in five (6.25%) controls. Heterozygote prothrombin G20210A mutation was found in two (2.5%) and homozygote MTHFR mutation in one (1.25%) control patient. There was no statistical difference between the IBD group and healthy controls.* ***Conclusions:*** *Genetic mutations that could increase the thrombosis risk were not found to be different in IBD versus the normal population in our study.*

Key words: IBD, factor V leiden, MTHFR, prothrombin G20210A

Amaç: *İnflammatuvar barsak hastalıklarında normal popülasyona oranla daha sık tromboembolik olaylara rastlanılmaktadır. Bu artmış sıklığın nedeni tam olarak açıklığa kavuşmamıştır, inflamatuvar barsak hastalıkları polikliniğimizde takip edilen, daha önce tromboembolik olay hikayesi olmayan ulseratif kolit/Crohn hastalarında Faktör V Leiden, protrombin G20210A ve MTHFR mutasyonlarının görülme sıklığını ortaya koymaktadır.* ***Yöntem:*** *Çalışmaya 62 hasta dahil edildi (ülseratif kolit; 34, Crohn hastalığı: 28). Hastaların hiçbirisinde trombolik olay hikayesi mevcut değildi. Hastalardan alınan kan örneklerinde Faktör V Leiden, protrombin G20210A ve MTHFR mutasyonları çalışıldı, kontrol grubu olarak 80 adet sağlıklı kontrol hastası alındı ve aynı mutasyonlar bakıldı.* ***Bulgular:*** *Sağlıklı kontrol grubunda 5 hastada (%6.25) heterozigot olarak Faktör V Leiden mutasyonu, 2 hastada (%2.5) heterozigot olarak protrombin G20210A mutasyonu, 5 hastada (%6.25) heterozigot olarak MTHFR mutasyonu ve 1 hastada (%1.25) homozigot olarak MTHFR mutasyonu tespit edildi. Hasta grubunda ise 7 hastada (%11.3) heterozigot olarak MTHFR mutasyonu, 2hastada (%3.2) ise heterozigot olarak Faktör V Leiden mutasyonu saptandı, hasta grubundaki ve sağlıklı kontrollerde görülen mutasyon sıklığı arasında bir farklılık yoktu.* ***Sonuç:*** *inflamatuvar barsak hastalıklarında tromboz riskini arttıran genetik mutasyonların sıklığında normal populasyona göre bir artış söz konusu değildir.*

Anahtar kelimeler: İBH, Faktör V Leiden, protrombin, G20210A

INTRODUCTION

There is an increased risk of thromboembolism in inflammatory bowel diseases (IBD), (1-3). However, the prevalence of venous thromboembolism is also increased in some other chronic diseases, such as rheumatoid arthritis and celiac disease (4, 5). Therefore, it is uncertain whether the thromboembolism is specific to these IBDs or to chronic inflammation.

Although hereditary and acquired etiological factors have been suggested, the exact mechanism of the venous and arterial thromboembolism in **IBD** remains unknown. In recent years many proteins that play a role in coagulation and fibrinolysis have been studied using molecular biology techniques. In the study of Liebman et al. (6), factor V Leiden mutation was found in 36% of 11 **IBD** patients with a history of thromboembolism and in 4% of 51 IBD patients with no history of thromboem-

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holism. In another study, factor V Leiden and prothrombin G20282A gene mutations were found to be increased in IBD patients with a history of thromboembolism compared to IBD patients without a history of thromboembolism; however, no difference was observed between the patients without thromboembolism history and the normal population (7).

In this study we aimed to evaluate factor V Leiden, prothrombin G20210A and methylene tetrahydrofolate reductase (MTHFR) gene mutations in IBD patients who had no previous history of thromboembolism and to compare the prevalence with that found in healthy controls.

MATERIALS AND METHODS

Sixty-two IBD patients presenting to the Ankara University Medical Faculty Gastroenterology Department, IBD outpatient clinic, between June 2002-July 2003 were included in the study. Eighty healthy subjects without any chronic inflammatory disease such as rheumatoid arthritis or gluten enteropathy served as controls. The patients and control subjects had no history of previous acute or chronic thromboembolism. Serum samples were obtained from all subjects and the presence of factor V Leiden, prothrombin G20210A and MTHFR gene mutations were studied using polymerase chain reaction (PCR) technique.

Additionally, the charts of patients were reviewed for disease type, disease activity and extension, duration of disease and medical history for other chronic inflammatory diseases.

Relationship between gene mutations and type, activity and the duration of the disease was also determined.

In statistical analysis, chi-square and Student's t tests were used. A p value less than 0.05 was accepted as statistically significant.

RESULTS

Thirty-four (21 women, 13 men, 54.8%) of the patients had ulcerative colitis and 28 (11 women, 17 men, 45.2%) of the patients had Crohn's disease. The mean (±SD) age was 37.7±12.6 years. 62.5% of the patients with ulcerative colitis had pancolitis, and 37.5% had only left colon involvement. 66.7% of the patients with Crohn's disease had ileocolitis, and 33.3% had only colon involvement. The demographic characteristics of the patients are summarized in (Table 1).

Table 1. General characteristics of the IBD patients

	Ulcerative Colitis	Crohn's Disease
Patient #	34	28
Gender (Male/Female)	13/21	17/11
Age (Years ± SD)	38.1±13.3	36.7±10.7
Disease Localization		
Pancolitis/left side	62.5% / 37.5%	
Ileocolitis/Colitis		66.7% / 33.3%

Heterozygote factor V Leiden mutation was found in two (3.2%) IBD patients, both of whom had Crohn's disease. Heterozygote MTHFR mutation was determined in seven (11.3%) IBD patients; six of the patients had ulcerative colitis and one had Crohn's disease. There was no association between the duration and the activity of the diseases.

Heterozygote factor V Leiden mutation was found in five (6.25%) control subjects. Heterozygote MTHFR mutation was obtained in five (6.25%), and homozygote MTHFR mutation in one (1.25%) control subject. Also, heterozygote prothrombin G20210A mutation was found in two (2.5%) control subjects. However, there was no statistical difference in the overall mutation frequency between the two groups (14.5 % vs. 16.2 %, $p>0.05$).

DISCUSSION

We determined in this study heterozygote MTHFR mutation in 11.3% and factor V Leiden mutation in 3.2% of IBD patients who had no history of previous acute or chronic thromboembolism. Neither homozygote MTHFR mutation nor prothrombin G20210A mutation was found in the patient group. In a study from Duke University, factor V Leiden, prothrombin G20210A and MTHFR mutations were found to be 2.8%, 1.7%, and 24.7%, respectively in IBD patients under 21 years of age. These ratios were not different from the general population (8). Factor V Leiden, prothrombin G20210A and MTHFR mutations were 1.5%, 1.1% and 45.1%, respectively, in IBD patients without a history of thromboembolism in another study, and these ratios were not found to be different than in the general population (9). Furthermore, these mutations were not related to the patients' age or gender.

Turri et al. (10) investigated the prothrombin and factor V Leiden mutations in IBD patients with and without a history of thromboembolism and in healthy subjects. They reported that none of the patients with a history of thromboembolism had mutations and that heterozygote factor V Leiden

mutation was obtained in 2.2% of patients without a history of thromboembolism. However, factor V Leiden and prothrombin mutations were found in 5% and 2%, respectively, of the healthy control group.

In a study including 614 patients, homozygote MTHFR mutation was found to be higher in patients with a history of arterial (n=191) and venous (n=127) thromboembolism compared to the control group (n=296), and it was suggested that the presence of homozygote mutations of this gene may be a risk for both arterial and venous thromboembolism (11). In addition to these contradictory results, the frequencies of the mutations that may increase the tendency to thromboembolism show differences between different regions of the world. In a study in which 1,180 healthy control subjects from China were investigated, homozygote MTHFR mutation was found in 11.3% and heterozygote MTHFR mutation in 39.6% (12). However, prothrombin G20210A mutation was not found in any subjects in the same study. In another study from Greece, factor V Leiden, prothrombin G20210A and MTHFR mutations were found in 2.5%, 2.2%, and 35.3%, respectively, in 160 healthy subjects (13). Studies from our country have revealed that homozygote MTHFR mutation was determined in 10%, and prothrombin G20210A mutation in 2.7% in the healthy population (14, 15). In our study we obtained heterozygote factor V Leiden mutation in 6.25%, heterozygote prothrombin G20210A mutation in 2.5% and MTHFR mutation (both homozygote and heterozygote) in 7.5% in the healthy controls.

In summary, gene mutations which are implied as predisposing factors for venous and arterial thrombosis are seen less in the Turkish population than in other countries. We found similar frequencies of genetic mutations between the IBD population and control subjects, which is consistent with the previous studies. In our study, we included patients without any previous thromboembolic events; therefore, it is difficult to consider whether or not factor V Leiden, prothrombin G20210A and MTHFR mutations have a role in thromboembolic processes in IBD. However, if we consider all studies, including the current one, we can conclude that thromboembolic processes in the IBD population may not depend only on these kinds of mutations and that these events should be considered as multi-factorial.

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