FAKTÖR V LEİDEN MUTASYONU VE RENİTAL VEN TIKANIKLIĞI: TÜRKİYE'NİN DOĞUSUNDAKİ BÖLGESEL ÇALIŞMA

FACTOR V LEIDEN MUTATIONS AND UNILATERAL RETINAL VEIN OCCLISION: A REGIONAL STUDY OF EASTERN PART OF TURKEY

Orhan ATES, Orhan BAYKAL

Department of Opthalmology, Medical Faculty, Ataturk University, Erzurum, Turkey

Özet

Amaç: Retina ven tıkanıklığı olan olgularda factor V Leiden mutasyonunu rolü araştırıldı.

Metod: Retina ven tıkanıklığı (RVT) tanısı konmuş 30 hastadan alınan periferik kanlarından elde edilen DNA örneklerinde factor V Leiden mutasyonu araştırıldı. Olguların onikisinde santral retinal ven tıkanıklığı, 18'inde retinal ven dal tıkanıklığı vardı. Sağlıklı 30 kişiden kontrol gurubu oluşturuldu. Fisher's exact testi kullanılarak hasta grubu ile kontrol grubu arasında factor V Leiden mutasyonunun sıklığı karşılaştırıldı.

Bulgular: DNA analizi sonucunda yalnızca 2 hastada (%6.6) heterezigot faktör V leiden mutasyonu taşıyıcılığı tespit edildi. Hiçbir hastada homozigot gen tespit edilmedi. Kontrol grubunda, 2 (%6.6) olguda heterezigot faktör V leiden mutasyonu taşıyıcığı bulundu. Hasta ve kontrol grubunda faktör V leiden mutasyonu sıklığı açısından istatiksel fark bulunmadı.

Sonuç: Bu çalışmada retina ven tıkanıklığı ile factor V Leiden mutasyonu arasında anlamlı bir ilişki gösterilemedi.

Anahtar kelimeler: *Santral retinal ven tıkanıklığı, Retinal ven dal tıkanıklığı, Factor V Leiden mutasyonu*

Summary

Piırpose: We investigated the role of factor V Leiden mutation in patients with retinal vein occlusion (RVO).

Method: Factor V Leiden mutation was investigated in DNA obtained from the peripheral blood of 30 patients, diagnosed with retinal vein occlusion. Twelve of the patients had central retinal vein occlusion (CRVO), and 18 patients had branchal retinal vein occlusion (BRVO). The control groups comprised of 30 healthy individuals. The frequencies of factor V Leiden was compared between the patients and the controls using Fisher's exact test.

Results: DNA analysis showed that only 2 patients (6.6%) were heterozygous carriers of factor V Leiden. None of the patients were found to be homozygous. In the control group, 2 (6.6%) were heterozygous carriers of factor V Leiden. The difference in frequencies of factor V Leiden mutation between the patients and the controls was not statistically significant.

Conclusion: We could not showed a significant association between retinal vein occlusion and the factor V Leiden mutation.

Key words: *Central retinal vein occlusion, Branchal retinal vein occlusion, Factor V Leiden mutation*

Table 1. *Demographic Data of Patients and Control Group*

	CRVO (n=12)	BRVO (n=18)
age(yrs)	57.9	58.1
gender(F/M)	4/8	10/8
hypertensionn(%)	5/30(%16.5)	8/30 (%26.4)
diabetes mellitus(%)	2/30 (%6.6)	7/30 (%23.1)
primary open-angle glaucoma	1(%3.3)	-

CRVO: Central retinal vein occlusion-hemispheric retinal vein occlusion, BRVO: Branch retinal vein occlusion

Introductıon

Retinal vein occlusion is the most common retinal vascular disorder following diabetic retinopathy (1,2). The pathogenesis and the risk factors of thrombosis of retinal vein have not been clearly understood. It is often associated with many systemic and ocular conditions such as hypertension,diabetes, hyperlipidemia, and glaucoma (2-5)

In previous studies, association of retinal vein occlusion with many hereditary and acquired risk factors for thrombosis were reported.

Recently, mutations that increase tendency to thrombosis such as factor V Leide have been identified (6).

In this study, we aimed to analyse the freguency of factor V Leiden mutations in group of patients with unilateral retinal vein occlusion from eastern region of turkey.

Materials and Methods

Thirty patients with RVO consisted of the study group. After systemic exemination, all patients underwent a full haematological and ophthalmologic evaluation in terms of diabetes mellitus and systemic hypertension. Blood pressure of patients without a history of hypertension were monitored for 2 weeks and patients with a value higher than 140/90mm were accepted as hypertensive. Ophthalmologic exeminations revealed the lokalisation of the occlusion in retinal vein as central, branchal or hemispheric. Peripheral blood samples were obtained from patients after informed consent was obtained. Genomic DNA recovered from blood of patients was amplified by polimerase chain reaction (PCR). The fragment was cleaved by Mnl I and Hind III endonuclease restriction for factor V Leiden mutations. The bands which were formed by agarose gel electrophoresis were evaluated.

Thirty healthy volunteers without of any personal or family history of thrombosis formed the control groups. The freguency of factor V Leiden mutations between study and control groups was compared by Fisher‘s exact test.

Results

The mean age of the patients were 58.2 years (range 32-77,median 57years) and 16 were (%57) male. Of 30 RVO patients, 12 (40%) had central retinal vein occlusion, 18 (60%) had branchal retinal vein occlusion. Demographic data of the patients and control cases are given in tablo 1. In 41% (5/12) of patients from CRVO group, and in 44%(8/18) patients from BRVO group, at least one systemic or oculer risk factor for retinal vein occlusion was detected. Two case (%6.6) from study groups and 2 case (%6.6) from control groups had factor V Leiden mutations. All had heterozygous mutations. One of patients with factor V leiden mutations had CRVO and one had BRVO. Also all patients with factor V leiden mutations had an additional risk factor; diabetes mellitus in two and hypertension in two.

The freguency of factor V leiden mutations was not statistically different between study and control groups ($p>0.05$)

Discussion

Thrombotic events are occured by multiple interactions between different genetic and environmental components (7,8). Factor V Leiden mutation which causes activated protein C resistance (APCR) is the most common among the known genetic defects causing thrombophilia (9 10). Protein C plays an important role in coagulation. After its activation on the surface of endothelial cells via thrombin-thrombomodulin complex, activated protein C (APC) inhibits coagulation by selectively degrading coagulation factors Va and VIIIa. The concept of APC resistance was first introduced by Dahlback et al. (1993), who reported a poor anticoagulant response to the addition of APC in the plasma of some young patients with thrombosis (11). In 95% of the

patients,phenotype of APC resistance was shown to be associated with a single point mutation in factor V gene (G to A substitution at nucleotide position 1691) on chromosome 1, the mutant being called factor V Leiden (12-14).

In previous studies, the prevalence of the mutation in the healthy population and in patients with thrombosis are 1–7% and 20–60% and in the general population, because of the high prevalence of this mutation, it is accepted as a most common genetic defect for patients with venous thrombosis (15).

Heterozygosity for factor V Leiden is associated with a 5–10 fold increased risk of thrombosis compared with a normal individual, while homozygosity is associated with a 50–100 fold increased risk (16). The rate of activated protein C resistance was found to be higher in patients with CRVO compared to normals and was thought to contribute to the etiopathogenesis of CRVO (17).

Ciardella et al. (18) reported that APC resistance were 45% in the patients and 9% healthy controls group as positive. In this patients tested for factor V Leiden, 3% was a heterozygous carrier of the Arg506GIn mutation and 2% of the controls was a heterozygous carrier. No homozygous individuals were identified in either the study or the control groups. According to this study that the difference in frequencies of APC resistance in patients and controls was statistically significant .

Similarly, Dhote et al. (19) presented case reports describing CRVO patients with a heterozygous state for factor V Leiden, Dorval et al. (20) reported one patient heterozygous for factor V Leiden with BRVO,Williamson et al. (15) analysed APC resistance in 56 patients with CRVO and demonstrated that a higher percentage of the patients (12%) had APC resistance than controls (5%).

In a retrospective study, Fong et al. (7) demonstrated that the prevalence of APC resistance in 31 patients younger than 50 years was 26% (more than four times the normal incidence of 2–7%) and recommended that the APC resistance was the most common known cause of CRVO in younger patients.

In Recent years, studies show that, the frequency of the mutation in CRVO patients was not found to be higher than in the normal controls (21).

Johnson et al.(22) found Factor V Leiden mutations in patients with CRVO as 2.3% and healthy control group as 3.5%. By this results it showed that there is no significant association between the presence of factor V Leiden and CRVO

Similarly Kalaycı et al.(1) found Factor V Leiden mutation in 8% of all patients, 4% of the CRVO-HRVO group and 11% of the BRVO patients. Factor V Leiden have been previously found in 7% of the healthy controls. The differences of frequencies between the patients and the controls were not statistically significant.

As in recent studies, we did not find higher statistically significant rate of mutation in the RVO patients than in the healthy controls.

We included patients of all age groups with associated systemic or ocular pathologies in our study. All four patients with RVO who had factor V Leiden mutation were associated with systemic pathologies that may be considered as risk factors. We think that this approach might have underestimated the role of factor V Leiden in RVO as it is possible that this mutation may contribute to the development of thrombosis only in the presence of other risk factors such as hypertension or diabetes mellitus which are clearly more frequent in the elderly population.

As the RVO patients with factor V Leiden mutation also had other associated pathologies, it is prudent to search for the role of factor V Leiden by comparing the relative risk of vein thrombosis with and without other risk factors.

As a result, we found no significant association between retinal vein occlusion and the factor V Leiden mutation. Our data implies that factor V Leiden is not risk factors in RVO.

References

1. Kalaycı D, Gürgey A, Güven D, Parlak H, Hasıpiri H. Faktör V Leiden and Protrombin 20210 A mutations in patients with control and branch retinal vein occlusion. Acta Ophtholmol Scand 1999; 77: 622-624
2. Hansen L, Kristensen HL, Bek T, İngerslenv J. Markers trombophilia in retinal vein trombosis. Acta Ophthalmol Scand 2000; 78: 523-526
3. Fegar CD. Central retinal vein occlusionu trombobphilia. Eye 2002; 16:98-106
4. Lahey JM, Tunc M, Kearney J, Modlinski B, Koo H, Johnson RN, Tanaka S. Laboratoriy Evalvation of hypercoagulaple statesion patient with central retinal vein occlusion who are less than 56years, of Age. Ophthalmology 2002;109:126-131
5. Rath EZ, Frank RN, Shin DH, Kim C. Risk factors for retinal vein occlusion. A case-control study. Ophthalmology 1992; 99: 509-514
6. Bertina RM, Koeleman BPC, Koster T, Rosendaal FR, Dirven RJ, de Ronde H, vandervelden PA, Reitsma PH. Mutationin blood coagulation factor V associated with resistance to activated protein C. Nature 1994;369: 64-67
7. Fong ACA, Schatz H. Central retinal vein occlusion in young adults. Surv Opthalmol 1993;37:393-414
8. Williamson TH, Rumley A, Lowe GDO. Blood viscosity, coagulation, and activatedprotein C resistance in central retinalvein occlusion: a population controlled study. Br J Ophthalmol 1996;80: 203-208
9. Rees D, Cox M, Clegg J. World distribution of factor V Leiden. Lancet 1995;346:1133-1134

10. Larsson J, Sellman A , Bauer B. Activated protein C resistance in patients with central retinal vein occlusion. Br J Ophthalmol 1997;81: 832-834
11. Dahlback B. Physiological anticoagulation:resistance to activated protein C andvenous thromboembolism. J Clin Invest 1994; 94:923-927
12. Gottlieb JL, Blice JP, Mestichelli B, Konkle BA, Benson WE. Activated protein C resistance, factor V Leiden, and central retinal vein occlusion in young adults. Arch Ophthalmol 1998;116: 577-579
13. Hodgkins PR, Perry DJ, Sawcer SJ, Keast-Butler J. Factor V and antithrombin gene mutations in patients with idiopathiccentral retinal vein occlusion. Eye 1998; 9: 760-762
14. Marcucci R, Bertini L, Giusti B, Brunelli T, Fedi S, Cellai AP, Poli D, Pepe G, Abbate R, Prisco D. Thrombophilic risk faktors in patients with central vein occlusion. Tbromb Haemost 2001; 86: 772-776
15. Larsson J, Olafsdottir E, Bauer B: Activated protein C resistance in young adults with central retinal vein occlusion. Br J Ophthalmol 1996; 80: 200-202
16. Hunt BJ. Activated protein C and retinalvein occlusion. Br J Ophthalmol 1996; 80: 194
17. Greiner K, Hafner G, Dick B, Peetz D, Prellwitz W, Pfeiffer N. Retinal vascular occlusion and deficiencies in the protein C pathway. Am J Ophthalmol 1999;128:69-74
18. Ciardella AP, Yannuzzi LA, Freund KB, DiMichele D, Nejat M, De Rosa JT, Daly JR, Sisco L. Factor V Leiden, activated protein C resistance, and retinal vein occlusion. Retina 1998;18:308-315
19. Dhote R, Bachmeyer C, Horellou MH, Toulon P, Christoforov B. Central retinal vein thrombosis associated with resistance to activated protein C. Am J Ophthalmol 1995; 120:388-389
20. Dorval I, Lellouche F, Ribaute E. Thromboses veineuses oculaires: relation avec la mutation G1691A sur le gene du facteur V. Presse Medicale 1995; 24: 1272
21. Weger M, Renner W, Steinbrugger I, Cichocki L, Temmel W, Stanger O, El-Shabrawi Y, Lechner H, Schmut O, Haas A. Role of thrombophilic gene polymorphisms in branch retinal vein occlusion. Ophthalmology 2005 ;112:1910-1915
22. Johnson TM, El-Defrawy S, Hodge WG, Leonard BC, Kertes PJ, Taylor SAM, Lillicrap DP. Prevalence of factor V Leiden and activated protein C resistance in central retinal vein occlusion.Retina 2001;21:161-166

Corresponding adres:
Orhan ATES MD

Department of Opthalmology,
Medical Faculty, Ataturk University,
Erzurum, Turkey
Tlf: +90 442 2361212-1618
e-posta:orhanates@atauni.edu.tr