Central Retinal Vein Occlusion Associated with Hyperhomocysteinemia in a Patient with Heterozygous for the *Methylenetetrahydrofolate Reductase* C677T Mutation: Case Report

Heterozigot *Metilentetrahidrofolat Redüktaz* C677T Mutasyonlu Hastada Hiperhomosisteinemi ile Birlikte Santral Retinal Ven Tıkanıklığı

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ABSTRACT A 19-year-old male patient presented with blurring of vision in his left eye. Central retinal vein occlusion was detected on ophthalmic examination. Clinical examination and laboratory analysis were performed for risk factors predisposing him to retinal vein occlusion. His plasma homocysteine concentration was 14.30 U/mL. No other abnormalities were found in other hematologic tests. C677T heterozygous mutation in the methylenetetrahydrofolate reductase (MTHFR) gene was detected by real-time polymerase chain reaction. A heterozygous mutation was detected in the same gene in the patient's mother, father and one of his sisters, also a homozygous mutation was detected in the other sister. Retinal vein occlusion in young patients may be related to mild hyperhomocysteinemia and a C677T mutation in the MTHFR gene.

Key Words: Hyperhomocysteinemia; 5,10-methylenetetrahydrofolate reductase (FADH2); retinal vein occlusion

ÖZET On dokuz yaşındaki erkek hasta sol gözünde bulanık görme ile başvurdu. Oftalmolojik muayenede santral retinal ven oklüzyonu saptandı. Hastayı santral retinal ven oklüzyonuna predizpoze eden risk faktörleri için klinik muayene ve laboratuar analizleri yapıldı. Plazma homosistein konsantrasyonu 14,30 U/mL'di. Diğer hematolojik analizlerde başka bir anormallik bulunmadı. Gerçek zamanlı polimeraz zincir reaksiyonu ile metilentetrahidrofolat redüktaz (MTHFR) geninde C677T heterozigot mutasyonu saptandı. Hastanın annesinde, babasında ve kızkardeşlerinden birinde aynı gende heterozigot mutasyon saptanırken, ayrıca diğer kız kardeşinde de homozigot mutasyon saptandı. Genç hastalarda retinal ven oklüzyonu hafif hiperhomosisteinemiye ve MTHFR genindeki C677T mutasyonuna bağlı olabilir.

Anahtar Kelimeler: Hiperhomosisteinemi; 5,10-Metilenetetrahidrofolat redüktaz (FADH2); retina ven tıkanıklığı

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Retinal vein occlusion is the most common retinal vascular diseases after diabetic retinopathy[1], but the pathogenesis and risk factors in patients with central retinal vein occlusion (CRVO) are still unclear. CRVO occurs more often in older patients and is typically associated with vascular disease. Systemic risk factors are encountered infrequently in young adults with CRVO.[2]

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The methylenetetrahydrofolate reductase (MTHFR) enzyme catalyzes the transformation of methylenetetrahydrofolate to methyltetrahydrofolate, which is the methyl donor in the remethylation of homocysteine to methionine. Valine is included instead of alanine with the C677T mutation in *MTHFR*, resulting in reduced enzyme activity. A reduction in enzyme activity may increase homocysteine levels, especially when folate intake decreases. Elevated homocysteine can cause oxidative stress in vascular endothelial cells and increase the tendency towards thromboembolic conditions.[3-5]

CASE REPORT

A 19-year-old male patient presented with the complaint of blurred vision in the left eye. The patient previously took an anti-epileptic drug for 3 years, between 4- and 7 years of age. He had no history of eye problems, and his medical history was noncontributory. His family history was unremarkable.

An ophthalmologic examination revealed 20/20 visual acuity, and intraocular pressure was 14 mmHg in both eyes. Biomicroscopical examination was bilaterally normal, and no relative afferent pupillary defect was detected. Fundus examination revealed optic disc swelling, minimal engorgement in the veins and dotted retinal hemorrhage in all retinal areas, consistent with retinal vein occlusion (Figure 1). Fluorescein angiography demonstrated delayed vein filling and engorgement in the venous capillary bed; no ischemia was detected in the retina (Figure 2). No abnormality other than minimal expansion in the blind spot was detected in the visual field examination.

Complete blood count, erythrocyte sedimentation rate, lipid profile, fasting blood glucose, liver and renal function and protein electrophoresis were normal. Prothrombin time, activated partial thromboplastin time, fibrinogen, protein C, protein S and antithrombin III levels were within normal limits. Although vitamin B12 and folate levels were normal, homocysteine level was elevated (14.30 U/mL). Antinuclear antibody, anticardiolipin antibody and lupus anticoagulant were all negative. Coagulation factors were within normal limits, and there was no Factor V Leiden mutation or prothrombin gene *G20210A* polymorphism. No pathology was detected on cranial or orbital magnetic resonance imaging. Orbital Doppler ultrasonography showed increased central retinal vein diameter. Blood pressure was measured as 110/ 60mmHg. The cardiological examination and echocardiography did not reveal any abnormalities. DNA was extracted from whole blood using standard methods, and the *MTHFR* gene mutation was detected by real-time polymerase chain reaction. LightMix kits and

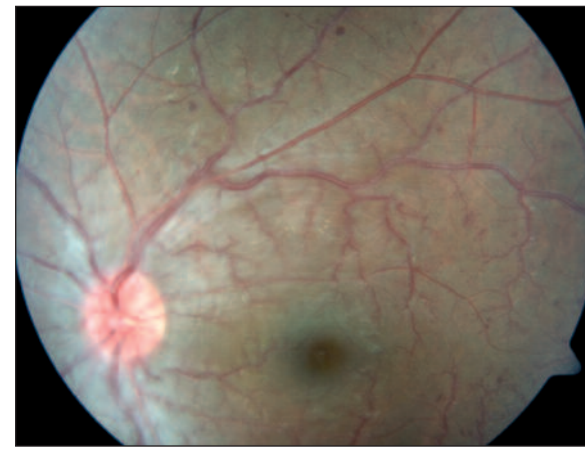

FIGURE 1: Color fundus photograph showing mild optic disc head swelling, minimal vein engorgement, and dotted retinal hemorrhages in all retinal areas of the left eye.
(See for colored from http://tipbilimleri.turkiyeklinikleri.com/)

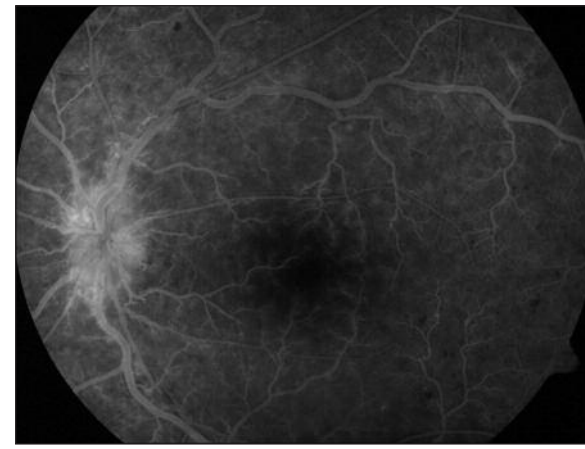

FIGURE 2: Fluorescein angiography showing engorgement in the venous capillary bed of the right eye.

LightCycler FastStart DNA Master HybProbe were used to detect human *MTHFR* (C677T). Heterozygous C677T mutation of the *MTHFR* gene was detected. Same mutation was also detected in the mother, father and one sister of the patient. In addition, homozygous mutation of the same gene was detected in another sister. Written informed consent was obtained from patient and the family members before clinical assessment and laboratory analyses.

DISCUSSION

Diabetes mellitus, hypertension, aging, cardiovascular risk profile and glaucoma are risk factors for retinal vein occlusion. It has recently been debated whether hyperhomocysteinemia and the C677T mutation in the *MTHFR* gene are risk factors for retinal vein occlusion. Moderately elevated level of plasma homocysteine is a risk factor for venous thrombosis and cardiovascular disease.[4-9] Homocysteine is a sulfur amino acid that arises during methionine metabolism. Homocysteine is metabolized via two pathways: Transsulfuration to cystathionine and cysteine or remethylation to methionine.[10-11] Remethylation occurs primarily by 5-methyltetrahydrofolate, which is formed by 5,10 methylenetetrahydrofolate reductase, with folate as a cosubstrate.[9] Severe hyperhomocysteinemia is caused by genetic defects resulting in deficiencies in cystathionine beta synthase. Mild hyperhomocysteinemia that occurs in fasting conditions is due to mild impairment in the methylation pathway, and an MTHFR deficiency usually results in mild hyperhomocysteinemia. Kang et al. found a new variant of the MTHFR enzyme with 50% residual activity and distinctive thermolability under specific conditions of heat inactivation.[3] This thermolabile variant of the enzyme was identified by Frosst et al. as a sequence change resulting from a single amino acid substitution caused by a C677T nucleotide change.[12] Hyperhomocysteinemia appears to act independently of other risk factors. This effect may be caused by the known toxic effect of homocysteine on the vascular endothelium and on the clotting cascade. Because it is a highly reactive amino acid, it is toxic to the vascular endothelium and can potentiate auto-oxidation of low-density lipoprotein cholesterol and promotes thrombosis.[4,13] In some studies, it has been suggested that a plasma homocysteine level exceeding 14.83 μmol/L is associated with an odds ratio of 5.29 for central retinal vein occlusion.[11,14,15] In our case, mild hyperhomocysteinemia might have been associated with retinal vein occlusion. Moreover, the *MTHFR* gene mutation may be triggered by hyperhomocysteinemia.

Loewenstein et al. reported a case with bilateral central retinal vein occlusion.[16] The *MTHFR* C677 homozygous gene mutation was found and no other was abnormalities were foundin a hematological analysis. In another study, Loewenstein et al. showed that the prevalence of *MTHFR* homozygosity increased in a series of patients with retinal vein occlusion.[13] In contrast, Larsson et al. stated that neither hyperhomocysteinemia nor the MTHFR gene mutation are important risk factors for retinal vein occlusion.[17] Di Crecchio et al. suggested that hyperhomocysteinemia, along with the *MTHFR* gene mutation, were not a prime reason, but could be a determinant of atherosclerosis.[18] These studies show that the relationship between the MTHFR gene mutation and thromboembolic events is still uncertain.

Consequently, it may be beneficial to analyze homocysteine levels and the *MTHFR* gene mutation in young patients with retinal vein occlusion. It should be noted that the plasma folate level is important in patients with the *MTHFR* gene mutation because decreased folate intake can cause hyperhomocysteinemia, followed by retinal vein occlusion. In this condition, folic acid supplementation can reduce homocysteine level and might prevent further thrombosis and worsening of retinal vascular changes.

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