

Impending Central Retinal Vein Occlusion and Cilioretinal Artery Occlusion in a Pediatric Case with MTHFR A1298C Heterozygous Polymorphism and ANA Positivity

MTHFR A1298C Heterozigot Polimorfizimli bir Pediatrik Olguda Santral Retinal Ven Oklüzyonu Tehdidi ve Silioretinal Arter Oklüzyonu

Seher ALTINTAŞ KAŞIKÇI¹, Ebru Nevin ÇETİN², Osman PARÇA³, Gökhan PEKEL², Selcan ZEYBEK⁴, Selçuk YÜKSEL⁵

ABSTRACT

A 13-years old boy presented with impending central retinal venous occlusion followed by ciliary artery occlusion and vitreous hemorrhage. A detailed systemic investigation revealed ANA positivity and heterozygote polymorphism in MTHFR A1298C. Visual acuity immediately improved after starting topical anti-glaucomatous treatment for impending central retinal venous occlusion and remained at 1.0 during the 6-month follow-up.

Key Words: Impending central retinal vein occlusion, cilioretinal artery occlusion, pediatric case, MTHFR A1298C heterozygous polymorphism.

ÖZ

Santral retinal ven oklüzyonu tehdidi ile başvuran 13 yaşında erkek hastada, takiben silier arter oklüzyonu ve vitre hemorajisi gelişti. Ayrıntılı bir sistemik araştırma sonucunda ANA pozitifliği ve MTHFR A1298C heterozigot polimorfizmi saptandı. Santral retinal ven oklüzyonu tehdidi için topikal anti-glokomatöz tedaviye başlandıktan hemen sonra görme keskinliğinin arttığı ve 6. ay kontrolünde 1.0 düzeyini koruduğu izlendi.

Anahtar Kelimeler: Santral retinal ven oklüzyonu tehdidi, silioretinal arter oklüzyonu, pediatrik olgu, MTHFR A1298C Heterozigot Polimorfizm.

INTRODUCTION

Central retinal vein occlusion (CRVO) is rare in individuals aged <30 years with a ratio of 7.5-19.8% in all CRVO cases.¹ It is possible to detect an etiological disorder in the majority of cases and the most common causes are coagulation disorders, cardiologic disorders, migraine, intra-arterial embolism, trauma, sickle cell disease, and hemoglobinopathies.¹ In some cases, CRVO may be accompanied with cilioretinal artery occlusion (CLRAO) and this combination of CRVO and CLRAO are reported to represent 40% of all CLRAO cases.² Two hypotheses regarding the pathomechanisms of

CLRAO combined with CRVO have been proposed: (1) CLRAO occurs secondary to the raised capillary pressure caused by CRVO³⁻⁸ or (2) a primary reduction in perfusion pressure of the cilioretinal and retinal arteries,^{3,5,7,8} leads to decreased retinal circulation and subsequent venous stasis and thrombosis.⁹ Decrease in systemic blood pressure¹⁰ and inflammatory or atherosclerotic retinal arterial disease⁸ have been suggested as possible causes of reduced arterial perfusion pressure.

In this case report, we present a pediatric retinal vascular occlusion case. Detailed systemic work-up revealed methyl-

1- Uz. Dr., Atatürk Public Hospital, Ophthalmology Department, Aydın, Türkiye

2- Doç. Dr., Pamukkale University, Ophthalmology Department, Denizli, Türkiye

3- Assit. Dr., Pamukkale University, Ophthalmology Department, Denizli, Türkiye

4- Uz. Dr., Pamukkale University, Department Of Genetics, Denizli, Türkiye

5- Prof. Dr., Pamukkale University, Department Of Pediatrics, Denizli, Türkiye

Geliş Tarihi - Received: 30.12.2017

Kabul Tarihi - Accepted: 10.01.2018

Ret-Vit 2019; 28: 77-80

Yazışma Adresi / Correspondence Address:

Seher ALTINTAŞ KAŞIKÇI
Atatürk Public Hospital, Ophthalmology Department,
Aydın, Türkiye

Phone: +90 535 629 7128

E-mail: seher_altnts@hotmail.com

enetetrahydrofolate reductase (MTHFR) A1298C heterozygous polymorphism and ANA positivity. MTHFR A1298C heterozygous polymorphism is not infrequent in normal population and ANA positivity is reported as 15% in a general pediatric cohort.¹¹

However, there are few reports of vascular occlusion associated with MTHFR A1298C polymorphism in literature.¹²⁻¹⁴ Therefore, it is unclear whether MTHFR A1298C polymorphism is a risk factor for vascular occlusion and we assume that reporting cases with possible associations may contribute to a better understanding of this issue.

CASE REPORT

A 13-year-old boy presented with decreased vision in his left eye for one day. The patient reported no history of previous trauma or systemic illness. In the patient, best-corrected visual acuity at the initial examination was 1.0 in the right eye and 0.4 in the left eye. The intraocular pressure was 19 mmHg in the right eye and 18 mmHg in the left eye. No relative afferent pupil defect was detected. The anterior segment examination was unremarkable. The posterior examination revealed optic disc edema and dilated and tortuous veins in the left eye and normal findings in the right eye. Topical anti-glaucomatous treatment (0.2% brimonidine tartrate + 0.5% timolol maleate) was started with the diagnosis of impending CRVO in the left eye and the patient was scheduled for fundus fluorescein angiography on the next day. The visual acuity in the left eye was found to be 0.7 on the next day, however, there was optic disc edema, superficial retinal hemorrhages in the parapapillary area, small intravitreal hemorrhage on the disc area and papillomacular bundle whitening. No retinal hemorrhage occurred outside the parapapillary region. Fundus fluorescein angiography revealed hemorrhage caused masking around the optic disc and delayed venous filling (Figure 1). Optical coherence tomography showed no macular edema. With the present findings, he was diagnosed as impending central retinal venous occlusion and ciliary artery occlusion in the left eye, and the detailed systemic examination was initiated. At the third day of follow-up, visual acuity was found to be 1.0 despite small vitreous hemorrhage (Figure 2). In the following months, visual acuity remained at 1.0 level and vitreous hemorrhage cleared. At the month 6, visual acuity was 1.0 with no retinal vascular tortuosity or retinal hemorrhage (Figure 3).

Systemic risk factors, especially hematologic, cardiac and rheumatologic diseases, were questioned for CRVO. Laboratory studies included complete blood count, erythrocyte sedimentation rate, C reactive protein (CRP), fasting blood sugar, hemoglobin A1c (HbA1c), renal function tests, liver function tests, electrolytes, platelet count, pro-thrombin time, activated prothrombin time, bleeding time, lipid profile, plasma homocystein, anti-cardiolipin antibody, antiphospholipid antibody, lupus anticoagulant, plasma fi-

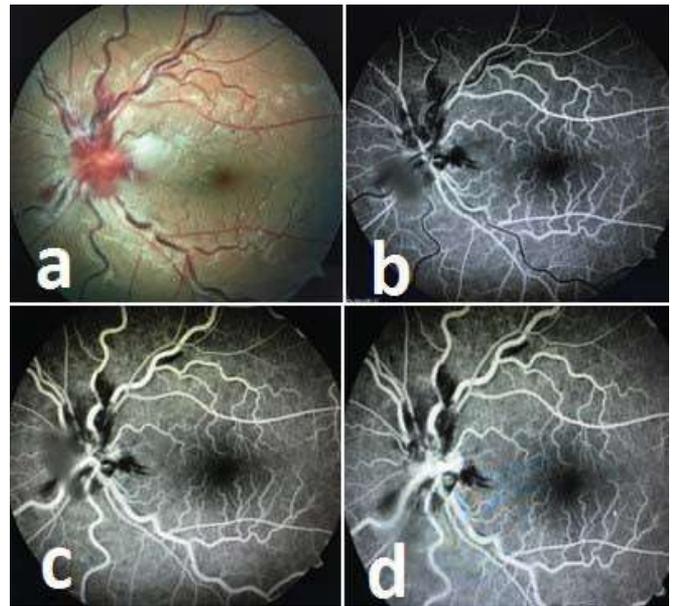


Figure 1. Fundus findings of the left eye. (a) Fundus examination revealed optic disc edema, dilated and tortuous veins, superficial retinal hemorrhages in the parapapillary area, small intravitreal hemorrhage on the disc area and papillomacular bundle whitening. (b,c,d) Fundus fluorescein angiography revealed hemorrhage masking around the optic disc and delayed venous filling.



Figure 2. At the third day of follow-up, vitreous hemorrhage slightly increased.

brinogen, D-dimer, factor V Leiden, factor 8, factor 9, anti-thrombin III, protein C, protein S, Von Willebrand factor antigen, peripheral smear, antinuclear antibody (ANA), anti-histone antibody, nucleosome, anti-SSA, anti-SSB, anti-SCL70, anti-JO1, anti-SM, serological tests including hepatitis A, hepatitis B, hepatitis C, human immunodeficiency virus (HIV), toxoplasma, cytomegalovirus (CMV), rubella, herpes, venereal disease research laboratory (VDRL), rapid

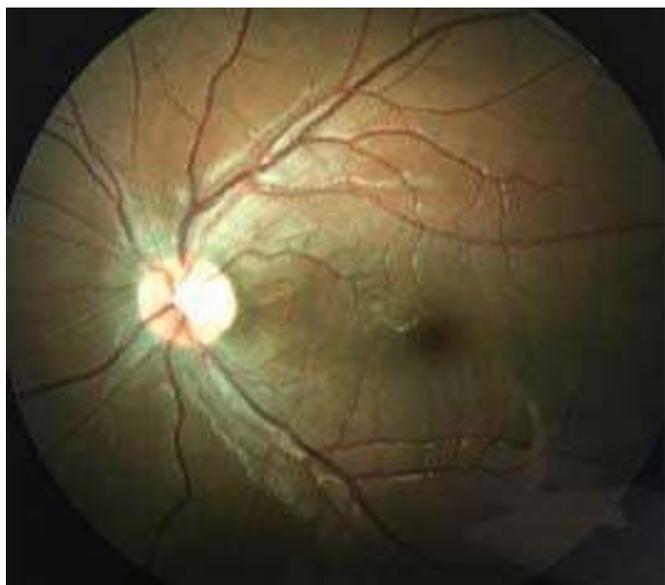


Figure 3. At the month 6, the vision was 1.0 and vitreous hemorrhage totally regressed.

plasma reagin (RPR), treponema pallidum hemagglutination assay (TPHA) and pathergy test. Of these ANA was positive.

Radiological studies included chest x-ray, echocardiography, cranial magnetic resonance imaging and angiography, orbital magnetic resonance imaging, bilateral renal color Doppler sonography, carotid and vertebral Doppler sonography. In addition, since her mother had a history of multiple miscarriages, genetic consultation also was obtained. Genetic analysis was performed using primers specific to the gene regions of F II G20210A, FV G1691A, MTHFR C677T, MTHFR A1298C, PAI-1 4G/5, β - Fibrinogen G455A, FXIII V34L, Glycoprotein IIIa L33P. Molecular genetic analysis revealed heterozygous polymorphism in the MTHFR A1298C gene.

DISCUSSION

The majority of patients with CRVO are adults, with mean age at onset of 58.5 years and are usually associated with systemic vascular disease.¹ CRVO patients are known to have one or more of the following risk factors: diabetes mellitus, hypertension, hyperlipidemia, smoking habit or glaucoma.¹⁵ CRVO is rare in individuals aged <30, and most of these patients have some detectable systemic or ocular disorders.¹ Of the reported cases of young patients with CRVO, 86%–90% are Caucasian, while few are Asian.¹⁶ It has been reported that younger patients are affected more frequently by impending CRVO (venous stasis retinopathy) which is characterized by enlarged retinal veins and disc swelling with little or no loss of vision.¹⁷⁻¹⁹ Combined CRVO and CLRAO are reported to represent 40% of CLRAO.² It appears that the CLRAO occurs subsequent and secondary to CRVO. Since the perfusion pressure in a cilioretinal artery is

lower than in a retinal artery,^{6,8,20} a CLRAO is more likely to be caused by optic disc swelling and/or reduced cilioretinal artery perfusion following CRVO.

The causes associated with RVO in the pediatric age group are Behçet's Disease,²¹ systemic lupus erythematosus,²² sarcoidosis,^{23,24} cyanotic heart disease causing elevated hematocrit,²⁵ infectious endocarditis,²⁶ cat scratch disease,²⁷ antiphospholipid antibody syndrome²⁸ and hyperhomocysteinemia.²⁹

As a result of detailed systemic investigation in our case, no evidence other than ANA positivity and heterozygous polymorphism in MTHFR A1298C was detected. The prevalence of A1298C polymorphism in MTHFR gene was found to be 39.2% for AA homozygous; 38.6% for AC heterozygous; and 22.2% for CC homozygous in a study including 1015 healthy individuals from 13 populations distributed widely from north to south in China.³⁰ In a study conducted on 90 healthy individuals with mean age of 47 in Turkey, MTHFR A1298C homozygous and heterozygous polymorphism were found in 12 (13.3%) and 30 (33.3%) participants, respectively.³¹ The role of factor MTHFR A1298C mutation was evaluated in Turkish patients with clinical venous thrombosis (270 patients) compared with healthy controls (114 subjects). MTHFR A1298C was equally distributed in the patient group compared with the control group.³² On the other hand, only a heterozygous MTHFR A1298C mutation has been reported as an etiologic cause in a 21-year-old case of cerebral venous sinus thrombosis.¹² In another 55-year-old patient without any known history of neurological or vascular diseases diagnosed as non-ischemic CRVO, MTHFR A1298C heterozygote mutation and a slightly elevated cholesterol level was detected.¹³ Scheufele TA et al. found a combined CRVO and CLRAO in a 16-year-old girl with multiple miscarriages and early cerebrovascular events in the family history. Laboratory testing revealed a compound heterozygous mutation (C677T and A1298C) in the methylenetetrahydrofolate reductase (MTHFR) gene and an elevated factor VIII level.¹⁴

ANA was positive in our case, however, there was no sign of intraocular inflammation or systemic finding that could be associated with vasculitis. So, it is possible that it could be the first finding of future rheumatoid disorder. On the other hand, it was reported that ANA positivity was up to 15% in a general pediatric cohort, with a higher rate of positivity among females.¹¹

In literature, it has been reported that the majority of cases with impending CRVO are young patients and that the patients recover without any specific treatment.¹⁸ Spontaneous recovery was also observed when impending CRVO and CLRAO were associated.¹⁹ In our case, topical anti-glaucomatous treatment was initiated in order to reduce intraocular

pressure and to increase perfusion by considering impending CRVO since the patients had reduction of visual acuity, disc swelling and venous engorgement but not macular edema and concomitant retinal hemorrhages. In the follow-up, CLRAO developed but the current treatment continued because of the increased visual acuity. In our case, a vitreous hemorrhage occurred which did not affect visual acuity during the follow-up period. No additional ocular or systemic pathology occurred after vitreous hemorrhage, and there was no decrease in visual acuity during the 6-months of follow-up.

In conclusion, there are controversial findings regarding the heterozygote mutation of MTHFR A1298C as a cause of vascular occlusion in literature. In our case, no pathology except MTHFR A1298C heterozygote mutation and ANA positivity was detected as a result of a detailed investigation performed due to impending CRVO and CLRAO. There was no additional laboratory or physical findings that supported any rheumatologic etiology. The possible association between MTHFR A1298C heterozygous mutation and vascular occlusion should be supported by more data.

REFERENCES

- Fong ACO, Schatz H. Central retinal vein occlusion in young adults. *Surv Ophthalmol* 1993;37:393-417.
- Kácerik M, Mikuláš AM, Lipková B. Combined occlusion of central retinal vein. *Cesk Slov Oftalmol* 2009;65(5):187-189.
- McLeod D, Ring CP. Cilio-retinal infarction after retinal vein occlusion. *Br J Ophthalmol* 1976;60:419-427.
- Zylbermann R, Rozenman Y, Ronen S. Functional occlusion of a cilioretinal artery. *Am Ophthalmol* 1981;13:1269-1272.
- Glacet-Bernard A, Gaudric A, Touboul C et al. Occlusion of the central retinal vein with occlusion of a cilioretinal artery: apropos of 7 cases. *J Fr Ophthalmol* 1987;10:269-277.
- Schatz H, Fong AC, McDonald HR et al. Cilioretinal artery occlusion in young adults with central retinal vein occlusion. *Ophthalmology*.1991;98:594-601.
- Brazitikos PD, Pournaras CJ, Othenin-Girard P et al. Pathogenetic mechanisms in combined cilioretinal artery and retinal vein occlusion: a reappraisal. *Int Ophthalmol* 1993;17:235-242.
- Keyser BJ, Duker JS, Brown GC et al. Combined central retinal vein occlusion and cilioretinal artery occlusion associated with prolonged retinal arterial filling. *Am J Ophthalmol* 1994;117:308-313.
- Hayreh SS. Pathogenesis of occlusion of the central retinal vessels. *Am J Ophthalmol* 1971;72:998-1011.
- Hayreh SS. Classification of central retinal vein occlusion. *Ophthalmol* 1983;90:458-474.
- Somers EC, Monrad SU, Warren JS et al. Antinuclear antibody prevalence in a general pediatric cohort from Mexico City: discordance between immunofluorescence and multiplex assays. *Clin Epidemiol* 2016 Dec;20:9:1-8.
- Shah JH, Salagre KD, Sahay RN et al. Heterozygous MTHFR A1298C Mutation causing Cerebral Venous Sinus Thrombosis. *J Assoc Physicians India*. 2016 Nov;64(11):76-77.
- Fişuş AD, Pop DS, Rusu MB, et al. Nonischemic Central Retinal Vein Occlusion Associated With Hereditary Thrombophilia. *Rom J Ophthalmol*. 2015 Jul-Sep;59(3):172-176.
- Scheufele TA, Pieroni CG, Baurnal CR. Methylenetetrahydrofolate reductase gene mutation in a 16-year-old girl with combined central retinal vein occlusion/cilioretinal artery occlusion. *Retin Cases Brief Rep*. 2007;1(3):134-137.
- Lahey JM, Kearney JJ, Tunc M. Hypercoagulable states and central retinal vein occlusion *Curr Opin Pulm Med* 2003 Sep;9(5):385-392
- Fong ACO, Schatz H, McDonald HR et al. Central retinal vein occlusion in young adults (papillophlebitis). *Retina* 1992;12(1):3-11.
- Gass JDM. *Diagnosis and Treatment*. 4th ed. St. Louis: CV Mosby; Stereoscopic atlas of macular diseases; 1997;546-555.
- Lee DH, Lee SJ, Yoon leN. *Clinical Progress in Impending Central Retinal Vein Occlusion*. *Korean J Ophthalmol*. 2010 Apr;24(2):83-88.
- Bottós JM, Aggio FB, Dib E et al. Impending central retinal vein occlusion associated with cilioretinal artery obstruction. *Clin Ophthalmol*. 2008 Sep;2(3):665-668.
- Murray DC, Christopoulou D, Hero M. Combined central retinal vein occlusion and cilioretinal artery occlusion in a patient on hormone replacement therapy. *Br J Ophthalmol* 2000;84:549-550.
- Citirik M, Berker N, Songur MS et al. Ocular findings in childhood-onset Behcet disease. *J AAPOS* 2009;13:391-395.
- Korematsu S, Goto H, Gotoh C et al. Central retinal vein occlusion in a pediatric patient with SLE and antiphospholipid antibodies without anti-cardiolipin or anti $\beta 2$ glycoprotein I antibodies. *BMC Pediatr*. 2014 May 3;14:116.
- Ohara K, Okubo A, Sasaki H et al. Branch retinal vein occlusion in a child with ocular sarcoidosis. *Am J Ophthalmol* 1995;119:806-807.
- Momtchilova M, Pelosse B, Ngoma E et al. Branch retinal vein occlusion and sarcoidosis in a child: a case report. *J Fr Ophthalmol*. 2011 Apr;34(4):243-247.
- VanderVeen DK, Pasquale LR, Fulton AB. Central retinal vein occlusion in a young child with cyanotic heart disease. *Arch Ophthalmol* 1997;115:1077.
- Kato T, Takeda Y, Matsuyama S et al.. Photo essay: combined-occlusion of the central retinal artery and vein in a pediatric patient secondary to infective endocarditis. *Arch Ophthalmol* 2001;119:1868-1869.
- Taylor RH, Smith RA, Issa M. Possible cat scratch disease causing neuroretinitis and CRVO in a child. *Eye (Lond)* 2002;16:189-190.
- Hartnett ME, Laposata M, Van Cott E. Antiphospholipid antibody syndrome in a six-year-old female patient. *Am J Ophthalmol* 2003;135:542-544.
- Rosenbaum PS, Srinivasan S, Zelefsky JR et al. Branch retinal artery occlusion and non-ischemic central retinal vein occlusion due to hyperhomocysteinemia in a 14-year-old child. *J Pediatr Ophthalmol Strabismus*. 2010 Jul 22;47 Online:e1-4.
- Mao R, Fan Y, Chen F et al. Methylenetetrahydrofolate reductase gene polymorphisms in 13 Chinese ethnic populations. *Cell Biochem Funct*. 2008 Apr;26(3):352-358.
- Ekim M, Ekim H, Yılmaz YK. The prevalence of Factor V Leiden, prothrombin G20210A, MTHFR C677T and MTHFR A1298C mutations in healthy Turkish population. *Hippokratia* 2015 Oct-Dec;19(4):309-313.
- Dölek B, Eraslan S, Eroğlu S et al. Molecular analysis of faktor V Leiden, factor V Hong Kong, factor II G20210A, methylenetetrahydrofolate reductase C677T, and A1298C mutations related to Turkish thrombosis patients. *Clin Appl Thromb Hemost*. 2007 Oct;13(4):435-438.