Sequential multiple retinal vein occlusions and transient ischemic attack in MTHFR polymorphism and protein S deficiency

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Abstract

Background: The C677T variant of the MTHFR (5,10-Methylenetetrahydrofolate reductase) gene is associated with increased susceptibility to homocystinuria (OMIM#236250), neural tube defects (OMIM#601634), schizophrenia (OMIM#181500), thromboembolism (OMIM#188050), and vascular diseases. Protein S deficiency is also associated with an increased risk of thromboembolism from reduced thrombin generation. In this report, we describe the case of a patient who presented with multiple retinal vein occlusions likely caused by an underlying combination of a homozygous MTHFR C677T variant and protein S deficiency.

Methods: We performed 8 years of continuous ophthalmic follow-up of one patient diagnosed with central retinal vein occlusion. Peripheral blood was collected for metabolic evaluation and hypercoagulability assessment. Targeted gene sequencing was used for genetic diagnosis. Examination of the retinal vasculature was performed through dilated funduscopy, digital color fundus and ultra-wide-field color fundus photography, spectral domain optical coherence tomography, and fluorescein angiography.

Results: Sequential retinal vein occlusions and a transient ischemic attack were observed during the follow-up period. Targeted gene sequencing by PCR identified the homozygous MTHFR C677T variant. The metabolic profile indicated low-protein S activity, high levels of vitamin B6, and LDL cholesterol consistent with her
Central retinal vein occlusion (CRVO) is a common cause of severe vision impairment affecting 1 in 1,000 people in the U.S. (Klein, Klein, Moss, & Meuer, 2000). While its prevalence is correlated with advanced age, with the highest risk after the age of 60, recent studies indicate that angiographic findings consistent with CRVO are also observed in younger patients (Blair & Czyz, 2019; Recchia, Carvalho-Recchia, & Hassan, 2004). On fundoscopic examination, CRVO is characterized by optic disc edema, diffuse nerve fiber layer thickening, intraretinal hemorrhage, and cotton wool spots (Alasil, Lee, Keane, & Sadda, 2009). Glaucoma and ocular hypertension are common comorbidities in patients with CRVO compared with the general population (Hayreh, Zimmerman, Beri, & Podhajsky, 2004). CRVO is classified into two distinct categories: nonischemic and ischemic CRVOs. Nonischemic CRVO accounts for about 70% of cases accompanied by good visual acuity (Blair & Czyz, 2019). Unlike the milder nonischemic CRVO, ischemic CRVO often accompanies much poorer visual prognosis and generates secondary neovascular glaucoma, which can, in extreme circumstances, lead to enucleation of the eye (Lahey, Kearney, & Tunc, 2003).

Patients who experience CRVO are typically found to be in a hypercoagulable state due to an imbalance between anticoagulation and thrombosis in the blood. This hypercoagulable state may not only predispose them to recurrent episodes of retinal vein occlusions but also systemic ischemic events, such as stroke. Two common risk factors for a hypercoagulable state are hyperhomocysteinemia and protein S deficiency. The main cause of hyperhomocysteinemia is a dysfunction of key enzymes of homocysteine biosynthesis (Kim, Kim, Roh, & Kwon, 2018), such as methylenetetrahydrofolate (MTHFR) enzyme. The most commonly reported polymorphism of this enzyme is the MTHFR (OMIM# 607093) C677T variant, which is associated with an increased susceptibility to primary open-angle glaucoma, coronary artery disease, neural tube defects, psychiatric diseases, and pregnancy complications (Lewis, Zammit, Gunnell, & Smith, 2005; Moll & Varga, 2015). This polymorphism leads to the synthesis of a thermolabile form of the enzyme (Frosst et al., 1995), which limits the remethylation cycle of homocysteine metabolism by diminishing the production of the methyl donor, methylenetetrahydrofolate. The resulting hyperhomocysteinemia can be controlled by promoting the transulfuration cycle of homocysteine metabolism with sufficient supplementation of vitamin B6 (Liew & Gupta, 2015; Maron & Loscalzo, 2009). Protein S is a vitamin K-dependent single-chain glycoprotein that modulates the coagulation cascade by inhibiting factors Va and VIIIa through the activation of protein C (Miyoshi et al., 2019). Reduced activity of protein S is associated with recurrent deep vein thrombosis, pulmonary embolism, nephrotic syndrome, and pregnancy complications (ten Kate & van der Meer, 2008; Vigano-D’Angelo et al., 1987).

The MTHFR C677T variant and protein S deficiency give rise to a high level of plasma homocysteine and disruption of the coagulation cascade, respectively. Strikingly, both conditions have been associated with venous thrombosis in the literature, but the exact pathophysiologic mechanism remains unclear (D’Angelo & Vigano D’Angelo, 2008; den Heijer et al., 1996; Lahey et al., 2003).

Hereby, we present a rare case of CRVO followed by a transient ischemic attack in a 51-year-old Asian woman secondary to both the homozygous MTHFR C677T variant and protein S deficiency. Close monitoring of patients with these conditions, as well as their family members, is imperative, as the history of CRVO can predict other impending thromboembolic episodes.

**Conclusion:** Retinal vein occlusions associated with the MTHFR C677T variant and protein S deficiency may signal impending systemic thromboembolic episodes and warrant aggressive preventative measures.

**Keywords:** central retinal vein occlusion, hypercoagulability, MTHFR, protein S, thrombosis

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**METHODS**

Eight years of continuous follow-up was performed of one patient diagnosed with CRVO who presented to the Applied Genetics Clinic at Edward S. Harkness Eye Institute, Columbia University Irving Medical Center. The study followed the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board (Protocol number AAAR8743). Written consent was not required as analysis was performed through retrospective review and there was no more than minimal risk to the patient. No information or image is identifiable to the patient. The patient’s peripheral
blood was used for metabolic evaluation and hypercoagu-
ibility assessment. Examination of the retinal vasculature
was performed through funduscopic examination, and digi-
tal color fundus and ultrawide-field color fundus photograph-
(y (Optos, Dumfermline, UK). Spectral domain optical
coherence tomography (SD-OCT) images and fluorescein
angiography were acquired using a confocal scanning laser
ophthalmoscope (cSLO; Spectralis HRP + OCT, Heidelberg
Engineering). Targeted gene sequencing by PCR identified
the homozygous MTHFR C677T variant.

3 | CASE PRESENTATION

3.1 | Initial presentation

A 51-year-old woman of Asian descent with an ocular his-
tory of branched retinal vein occlusions (BRVO) and a medi-
cal history of hyperlipidemia was referred to the Edward S.
Harkness Eye Institute at Columbia Irving Medical Center
(New York, NY, USA) for reported blurry vision, flashes,
and floaters. Prior to her initial visit, she experienced one epi-
sode of BRVO in her right eye 1 year prior and two episodes
of CRVO 20 years and 7 years prior. She had a prior optic
neurotomy performed in the left eye.

Targeted genetic sequencing by PCR revealed a homozy-
gous C677T polymorphism in the MTHFR gene which was
consistent with the patient's history of central and branched
retinal vein occlusions. The metabolic profile (Table 1)
from the peripheral blood indicated low protein S activity,
high levels of vitamin B6, LDL cholesterol, and free antigen
against protein S while normal homocysteine level, likely due
to vitamin B6 supplementation.

Ophthalmic history was significant for multiple CRVOs
and optic nerve neurotomy in the left eye performed pre-
viously (Figures 2 and 3). At the initial visit, the patient's
best-corrected visual acuity was 20/20 in the right eye and
20/60 in the left. Fundus angiography revealed a hypoauto-
fluorescent punctate blocking defect in the superior temporal
arcades of the right eye (Figure 1) along with a hyperfluores-
cent window defect at the temporal periphery. Notably, the
left eye demonstrated hyperfluorescent staining of the radial
neurotomy scar nasal to the optic disk (Figure 1).

3.2 | Progression

One year after the patient's initial visit, she endorsed a sub-
jective decrease in color and near vision despite stable retinal
examination. The following year, she experienced a transient
ischemic attack, resulting in a left-sided weakness of the arm

and gait impairment, which resolved with aspirin. Seven
years after the initial visit, the patient's retinal veins were ap-
preciated to have increased in diameter and the arterioles nar-
rrowed based on ophthalmic examination.

| TABLE 1 | Metabolic evaluation and hypercoagulability assessment at first visit |
| Test | Patient results | Reference range |
| Prothrombin time (s), INR | 12.1, 1.0 | 10.3–14.1, <1.5 |
| Activated partial | | |
| thromboplastin time (s) | 34.7 | 28.9–38.1 |
| Antiphosphatidylserine IgG (phospholipid units) | 0 | ≤16 |
| Antiphosphatidylserine IgM (phospholipid units) | 4 | ≤22 |
| Anticardiolipin IgG (phospholipid units) | 6 | <23 |
| Anticardiolipin IgM (phospholipid units) | 3 | <11 |
| Anticardiolipin IgA (phospholipid units) | 5 | <22 |
| Antithrombin III activity (Xa based) (%) | 80 | 80–120 |
| Protein C activity (%) | 153 | 74–172 |
| Protein S activity (%) | 42 | 62–136 |
| Protein S antigen, free (%) | 134 | 65–125 |
| MTHFR C677T polymorphism | Positive, homozygous | Negative |
| Factor V Leiden polymorphism | Negative | Negative |
| Prothrombin polymorphism | Negative | Negative |
| Homocysteine (μmol/L) | 11.36 | 3.7–13.9 |
| Folate (ng/ml) | >20 | ≤4.8 |
| Vitamin B6 (nmol/L) | 308 | 20–125 |
| LDL cholesterol (mg/dl) | 105 | <100 |
| Plasma glucose (mg/dl) | 112 | 65–139 |
| HgA1c (%) | 6.1 | <7a |
| Plasma creatinine (mg/ dl) | 0.7 | 0.5–0.99 |
| BUN (mg/dl) | 10 | 7–25 |
| BUN/ creatinine ratio | Normal | Normal |
| GFR (ml min−1 1.73 m−2) | >60 | >60b |

aNormal value for patients diagnosed with diabetes, as reported by the laboratory.
bNormal value for patients of race respective to that of the patient.
The following year, the patient was diagnosed with two new microaneurysms in the right eye and one in the left eye. At the most recent visit, the patient's best-corrected visual acuity was 20/30 in the right eye and 20/40 in the left. Follow-up fundus angiography of the right eye revealed that previously observed blocking defects had resolved and the hyperfluorescent window defect persisted. Moreover, hyperfluorescent staining of microaneurysms in the superior parafoveal arcade was present. On the other hand, the left eye progressed with hyperfluorescent staining secondary to microaneurysms in the inferior temporal arcade in addition to an area of non-perfusion at the inferior temporal periphery of the retina. Color fundus photography at this visit revealed multiple microaneurysms located along the superior arcades of the right eye as well as one microaneurysm along the arcades of the inferior retinal vein and at the superior retinal vasculature in
FIGURE 3  Color Fundus
Photography at the Initial and Most Recent Visit. Color fundus photography at the initial visit demonstrates the presence of small microaneurysms found at the tip of the temporal arcades of the right eye (a). Radial optic neuretomy scar can be appreciated at the nasal aspect of the optic disc in the left eye (b). At a recent visit, an increased number of microaneurysms can be appreciated along the superior arcades of the right eye as well as one along the arcades of the inferior retinal vein (c). Microaneurysms can be appreciated along the superior and inferior retinal vasculature of the left eye (Figures 2 and 3). No signs of neovascularization, leakage, or vein occlusion were observed.

4  RESULTS

Metabolic assessment at the initial visit showed abnormalities in protein S activity, free protein S antigen, serum folate, Vitamin B6, and LDL levels (Table 1). A hypercoagulability assessment identified a polymorphism in the MTHFR (C677T) gene. The patient’s plasma homocysteine was controlled prior to her initial visit with supplementation of vitamin B6 (Table 1). However, the patient reported non-compliance with her anticoagulant therapy, mainly due to the inconvenience of the periodic injections. Low-dose aspirin and atorvastatin for hypercholesterolemia were added to her medication regimen. Metabolic evaluation at recent visits showed consistently controlled levels of homocysteine (7.5 and 7.6 µmol/L) (Table 2).

| Test                  | Patient results | Reference range |
|-----------------------|-----------------|-----------------|
| Homocysteine (µmol/L) | 11.36 7.5 7.6   | 3.7–13.9        |
| Vitamin B12 (pg/ml)   | N/A 1522 530    | 200–1100        |
| Folate (ng/ml)        | >20 >20 >20     | >4.8            |

Note: The values reported for the year 2009 reflect the patient’s results at the initial visit.
Abbreviation: N/A = not available.

5  DISCUSSION

This case report illustrates a rare case of CRVO followed by a systemic ischemic episode in a patient with a simultaneous presentation of the homozygous MTHFR C677T variant and protein S deficiency. It demonstrates the potential for an ocular condition to serve as a principal indicator of the development of a systemic impairment. We propose that the reduced functions of MTHFR and protein S deficiency triggered the interplay between two components of Virchow’s Triad—hypercoagulability and endothelial damage—in the development of CRVO. Homocysteine inhibits the synthesis of nitric oxide, an antiatherogenic substance, an absence of which indicates vascular disease and mortality (Stuhlinger et al., 2001). Although the pathophysiology is controversial, hyperhomocysteinemia is also strongly associated with endothelial damage, which exposes the subendothelial matrix and initiates thrombus activation (Vine, 2000).

Consistently, prior studies have identified hyperhomocysteinemia as a risk factor for recurrent venous thrombosis, with women at a higher risk (OR 7.0, 95% CI 1.6–30.8) than men (OR 1.4, 95% CI 0.6–3.4) across all ages (den Heijer et al., 1996). In our patient, serum hypercoagulability coupled with endothelial damage resulted from the MTHFR polymorphism and protein S deficiency contributed to the development of the transient ischemic attack 2 years postdiagnosis. In addition to the MTHFR variant and protein S deficiency, medical history of hypertension, diabetes, and hyperlipidemia also increased the patient’s susceptibility to thrombosis (Previtali, Bucciarelli, Passamonti, & Martinelli, 2011).

The narrowing of both the retinal vein and artery noted on fundoscopic examination at 6 years posttransient ischemic attack represented significant risk factors for future retinal occlusions (Newman, Andrew, & Casson, 2018). These
findings suggest an etiology for the development of the microaneurysms in the right and left eyes in the following year. Furthermore, they indicate an impending venous occlusion and a high possibility of aneurysms or leakage elsewhere in the body, such as vein thrombosis, pulmonary embolism, acute coronary syndrome, or myocardial infarction (Liew & Gupta, 2015).

The precise pathogenesis of CRVO is yet to be established but is expected to be multifactorial (Cugati et al., 2007). We suggest that the reduced activity of MTHFR and protein S in combination with patient's medical conditions likely caused a synergistic development of the hypercoagulable state. Radial optic neurotomy, which the patient received to relieve the tension in the optic nerve head, is one of the treatment options for patients with CRVO. However, its biomedical effect on ameliorating the signs of CRVO has been reported as negligible (Friberg, Smolinski, Hill, & Kurup, 2008). While other options include intravitreal triamcinolone, anti-VEGF agents, chorioretinal anastomoses, and vitrectomy (Mohamed, McIntosh, Saw, & Wong, 2007), there has not been an ample number of randomized controlled trials to evaluate their safety and efficacy. Retinal vein occlusion is correlated with higher risk of cardiovascular and cerebrovascular mortality for all ages (Cugati et al., 2007). Therefore, retinal occlusions warrant special attention for signaling the possible development of subsequent thromboembolic episodes in other body vasculature and consequently the need to initiate aggressive preventative therapeutic measures.

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CONFLICT OF INTEREST
The authors report no conflicts of interest in this work.

AUTHOR’S CONTRIBUTION
SHT and JRLC contributed to the conception of the work. AC and JRLC directed the project. AC, SDR, and JKO contributed to data collection, analysis, and interpretation. SDR created the figures. AC, SDR, and JKO drafted the manuscript. JRLC, JKO, and JR performed critical revision of the manuscript. SHT and BY reviewed and provided final approval of the work.

DATA AVAILABILITY STATEMENT
The patient’s written consent was waived due to the nature of this study. Therefore, supporting data are not available due to ethical restrictions.

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