Received: 5 December 2019 | Revised: 16 March 2020 | Accepted: 2 April 2020

DOI: 10.1002/mgg3.1273

CLINICAL REPORT

Molecular Genetics & Genomic Medicine Open Access WILEY

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

**Ahra Cho**[1,2] | **Sara D. Ragi**[1,2] | **Jin Kyun Oh**[1,3,4] | **Jose Ronaldo Lima de Carvalho Jr**[1,4,5,6] | **Joseph Ryu**[1] | **Ber-Yuh Yang**[7] | **Stephen H. Tsang**[1,4,8,9]

[1]Department of Ophthalmology, Columbia University, New York, NY, USA

[2]Institute of Human Nutrition, Vagelos College of Physicians and Surgeons, New York, NY, USA

[3]State University of New York at Downstate Medical Center, Brooklyn, NY, USA

[4]Jonas Children's Vision Care and Bernard & Shirlee Brown Glaucoma Laboratory, New York, NY, USA

[5]Department of Ophthalmology, Empresa Brasileira de Servicos Hospitalares (EBSERH) – Hospital das Clinicas de Pernambuco (HCPE), Federal University of Pernambuco (UFPE), Recife, Brazil

[6]Department of Ophthalmology, Federal University of São Paulo (UNIFESP), São Paulo, Brazil

[7]New York-Presbyterian Hospital Queens, Flushing, NY, USA

[8]Department of Pathology and Cell Biology, Columbia University, New York, NY, USA

[9]Stem Cell Initiative (CSCI), Institute of Human Nutrition, Vagelos College of Physicians and Surgeons, New York, NY, USA

**Correspondence**
Stephen H. Tsang, Edward S. Harkness Eye Institute, Columbia University Medical Center, 635 W. 165th St, Box 212, New York, NY 10032, USA
Email: sht2@cumc.columbia.edu

**Funding information**
Funding for this research was supported by the Jonas Children's Vision Care and Bernard & Shirlee Brown Glaucoma Laboratory and by the National Institutes of Health [P30EY019007, U01EY030580, U54OD020351, R24EY027285, 5P30EY019007, R01EY018213, R01EY024698, R01EY026682, and R21AG050437], National Cancer Institute Core [5P30CA013696], Foundation Fighting Blindness [TA-NMT-0116-0692-COLU], the Research to Prevent Blindness (RPB) Physician-Scientist Award, and unrestricted funds from RPB, New York, NY, USA. S.H.T. is a member of the RD-CURE Consortium and is supported by Kobi and Nancy Karp, the Crowley Family Fund, the Rosenbaum Family Foundation, the Tistou and Charlotte Kerstan Foundation, the Schneeweiss Stem Cell

## 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 funduscopic examination, digital color fundus and ultrawide-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

Fund, New York State [C029572], and the Gebroe Family Foundation.

hypercoagulable state. Prescription of low-dose aspirin and atorvastatin for hypercholesterolemia resulted in no further neovascularization, leakage, or vein occlusion. **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

## 1 | INTRODUCTION

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, methyltetrahydrofolate. 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.

## 2 | 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 hypercoagulability assessment. Examination of the retinal vasculature was performed through funduscopic examination, and digital color fundus and ultrawide-field color fundus photography (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 history of branched retinal vein occlusions (BRVO) and a medical 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 episode 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 homozygous 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 previously (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 hypoautofluorescent punctate blocking defect in the superior temporal arcades of the right eye (Figure 1) along with a hyperfluorescent 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).

**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 | <7[a] |
| Plasma creatinine (mg/dl) | 0.7 | 0.5–0.99 |
| BUN (mg/dl) | 10 | 7–25 |
| BUN/ creatine ratio | Normal | Normal |
| GFR (ml $min^{-1}$ 1.73 $m^{-2}$) | >60 | >60[b] |

[a]Normal value for patients diagnosed with diabetes, as reported by the laboratory.

[b]Normal value for patients of race respective to that of the patient.

### 3.2 | Progression

One year after the patient's initial visit, she endorsed a subjective 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 appreciated to have increased in diameter and the arterioles narrowed based on ophthalmic examination.

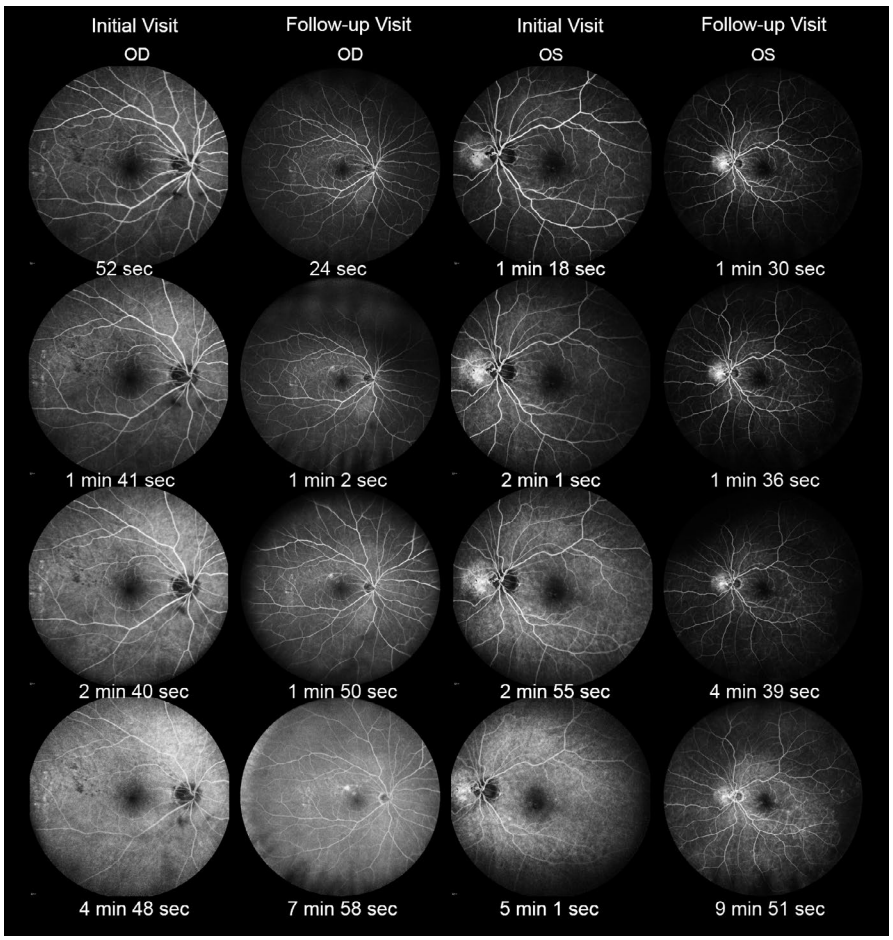


**FIGURE 1** Fluorescein Angiography at the Initial and Most Recent Visits. Fluorescein angiography of the right eye at the initial visit demonstrates the presence of a hypofluorescent punctate blocking defects in the superior temporal arcade along with hyperfluorescent window defect at the temporal periphery. On follow-up examination, the blocking defects resolved but the window defect persisted. Moreover, hyperfluorescent staining of microaneurysms in the superior and inferior temporal arcades was seen. On the left eye, the angiography demonstrated a hyperfluorescent staining of the radial neurotomy scar at the nasal border of the optic disk. Hyperfluorescent aneurysms can be appreciated at the temporal arcades at both visits

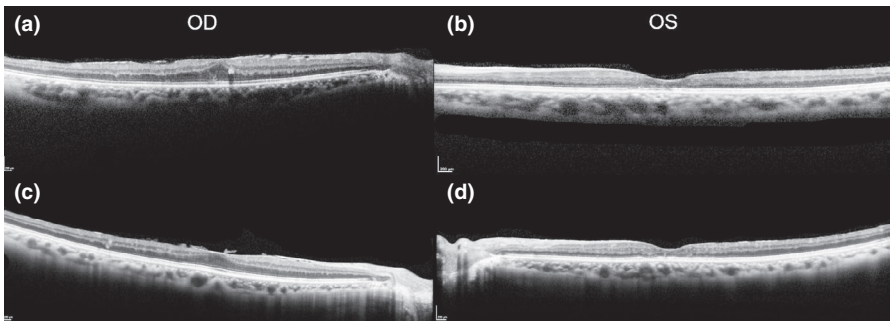


**FIGURE 2** Optical Coherence Tomography at the Initial and Most Recent Visit. Optical coherence tomography demonstrates the presence of an epiretinal membrane in the right eye at the initial visit that had resolved at the recent examination (a & c). Hyperreflective dot was seen in the right parafovea at initial visit with complete resolution at follow-up (a & c). Granular interruption of the ellipsoid zone line can be appreciated at the fovea in both eyes at initial visit that has since resolved (a–d). Furthermore, retinal thinning due to inner layers atrophy was seen in both eyes in addition to an atrophy of the outer nuclear layer in the left eye (a–d)

## 3.3 | Recent visit

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

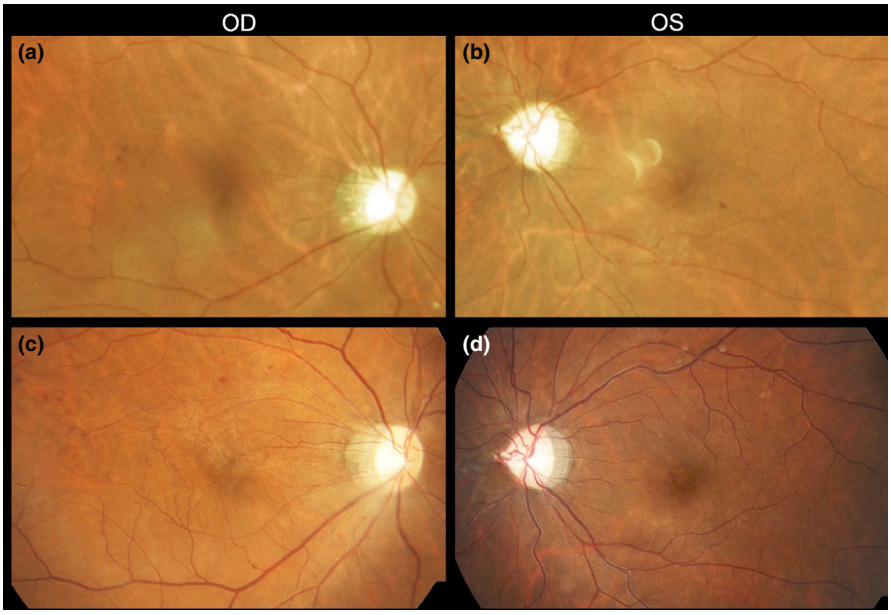


**FIGURE 3** Color Fundus Photography at the Initial and Most Recent Visit. Color fundus photography at the initial visit demonstrates the presence of small microaneurysms found at the tip of the temporal arcades of the right eye (a). Radial optic neurotomy scar can be appreciated at the nasal aspect 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 ey

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 $B_6$, 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 noncompliance 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).

**TABLE 2** Levels of homocysteine, vitamin B12, and folate over time

| | Patient results | | | |
|---|---|---|---|---|
| **Test** | **2009** | **2019** | **2020** | **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.

## ACKNOWLEDGMENTS

None.

## 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.

## ORCID

*Stephen H. Tsang* https://orcid.org/0000-0001-9082-2427

## REFERENCES

Alasil, T., Lee, N., Keane, P., & Sadda, S. (2009). Central retinal vein occlusion: A case report and review of the literature. *Cases Journal*, *2*, 7170. https://doi.org/10.1186/1757-1626-2-7170

Blair, K., & Czyz, C. N. (2019). *Central retinal vein occlusion*. Treasure Island, FL: In StatPearls.

Cugati, S., Wang, J. J., Knudtson, M. D., Rochtchina, E., Klein, R., Klein, B. E. K., … Mitchell, P. (2007). Retinal vein occlusion and vascular mortality: Pooled data analysis of 2 population-based cohorts. *Ophthalmology*, *114*(3), 520–524. https://doi.org/10.1016/j.ophtha.2006.06.061

D'Angelo, A., & Vigano D'Angelo, S. (2008). Protein S deficiency. *Haematologica*, *93*(4), 498–501. https://doi.org/10.3324/haematol.12691

denHeijer, M., Koster, T., Blom, H. J., Bos, G. M. J., Briët, E., Reitsma, P. H., … Rosendaal, F. R. (1996). Hyperhomocysteinemia as a risk factor for deep-vein thrombosis. *New England Journal of Medicine*, *334*(12), 759–762. https://doi.org/10.1056/NEJM199603213341203

Friberg, T. R., Smolinski, P., Hill, S., & Kurup, S. K. (2008). Biomechanical assessment of radial optic neurotomy. *Ophthalmology*, *115*(1), 174–180. https://doi.org/10.1016/j.ophtha.2007.03.013

Frosst, P., Blom, HJ, Milos, R., Goyette, P., Sheppard, CA, Matthews, RG, … Rozen, R. (1995). A candidate genetic risk factor for vascular disease: A common mutation in methylenetetrahydrofolate reductase. *Nature Genetics*, *10*(1), 111–113. https://doi.org/10.1038/ng0595-111

Hayreh, S. S., Zimmerman, M. B., Beri, M., Podhajsky, P. (2004). Intraocular pressure abnormalities associated with central and hemicentral retinal vein occlusion. *Ophthalmology*, *111*(1), 133–141. https://doi.org/10.1016/j.ophtha.2003.03.002

Kim, J., Kim, H., Roh, H., & Kwon, Y. (2018). Causes of hyperhomocysteinemia and its pathological significance. *Archives of Pharmacal Research*, *41*(4), 372–383. https://doi.org/10.1007/s12272-018-1016-4

Klein, R., Klein, B. E., Moss, S. E., & Meuer, S. M. (2000). The epidemiology of retinal vein occlusion: The Beaver Dam Eye Study. *Transactions of the American Ophthalmological Society*, *98*, 133–141; discussion 141–133.

Lahey, J. M., Kearney, J. J., & Tunc, M. (2003). Hypercoagulable states and central retinal vein occlusion. *Current Opinion in Pulmonary Medicine*, *9*(5), 385–392. https://doi.org/10.1097/00063198-200309000-00008

Lewis, S. J., Zammit, S., Gunnell, D., & Smith, G. D. (2005). A meta-analysis of the MTHFR C677T polymorphism and schizophrenia risk. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics: The Official Publication of the International Society of Psychiatric Genetics*, *135B*(1), 2–4. https://doi.org/10.1002/ajmg.b.30170

Liew, S. C., & Gupta, E. D. (2015). Methylenetetrahydrofolate reductase (MTHFR) C677T polymorphism: Epidemiology, metabolism and the associated diseases. *European Journal of Medical Genetics*, *58*(1), 1–10. https://doi.org/10.1016/j.ejmg.2014.10.004

Maron, B. A., & Loscalzo, J. (2009). The treatment of hyperhomocysteinemia. *Annual Review of Medicine*, *60*, 39–54. https://doi.org/10.1146/annurev.med.60.041807.123308

Miyoshi, T., Oku, H., Asahara, S., Okamoto, A., Kokame, K., Nakai, M., … Miyata, T. (2019). Effects of low-dose combined oral contraceptives and protein S K196E mutation on anticoagulation

factors: A prospective observational study. *International Journal of Hematology*, *109*(6), 641–649. https://doi.org/10.1007/s12185-019-02633-x

Mohamed, Q., McIntosh, R. L., Saw, S. M., & Wong, T. Y. (2007). Interventions for central retinal vein occlusion: An evidence-based systematic review. *Ophthalmology*, *114*(3), 507–519. https://doi.org/10.1016/j.ophtha.2006.11.011

Moll, S., & Varga, E. A. (2015). Homocysteine and MTHFR Mutations. *Circulation*, *132*(1), e6–e9. https://doi.org/10.1161/CIRCULATIONAHA.114.013311

Newman, A., Andrew, N., & Casson, R. (2018). Review of the association between retinal microvascular characteristics and eye disease. *Clinical and Experimental Ophthalmology*, *46*(5), 531–552. https://doi.org/10.1111/ceo.13119

Previtali, E., Bucciarelli, P., Passamonti, S. M., & Martinelli, I. (2011). Risk factors for venous and arterial thrombosis. *Blood Transfusion*, *9*(2), 120–138. https://doi.org/10.2450/2010.0066-10

Recchia, F. M., Carvalho-Recchia, C. A., & Hassan, T. S. (2004). Clinical course of younger patients with central retinal vein occlusion. *Archives of Ophthalmology*, *122*(3), 317–321. https://doi.org/10.1001/archopht.122.3.317

Stuhlinger, M. C., Tsao, P. S., Her, J. H., Kimoto, M., Balint, R. F., & Cooke, J. P. (2001). Homocysteine impairs the nitric oxide synthase pathway: Role of asymmetric dimethylarginine. *Circulation*, *104*(21), 2569–2575. https://doi.org/10.1161/hc4601.098514

tenKate, M. K., & van derMeer, J. (2008). Protein S deficiency: A clinical perspective. *Haemophilia*, *14*(6), 1222–1228. https://doi.org/10.1111/j.1365-2516.2008.01775.x

Vigano-D'Angelo, S., D'Angelo, A., Kaufman, C. E.Jr, Sholer, C., Esmon, C. T., & Comp, P. C. (1987). Protein S deficiency occurs in the nephrotic syndrome. *Annals of Internal Medicine*, *107*(1), 42–47. https://doi.org/10.7326/0003-4819-107-1-42

Vine, A. K. (2000). Hyperhomocysteinemia: A new risk factor for central retinal vein occlusion. *Transactions of the American Ophthalmological Society*, *98*, 493–503.

**How to cite this article:** ChoA, RagiSD, OhJK, et al. Sequential multiple retinal vein occlusions and transient ischemic attack in *MTHFR* polymorphism and protein S deficiency. *Mol Genet Genomic Med*. 2020;8:e1273. https://doi.org/10.1002/mgg3.1273