Genetic polymorphism associated with thromboembolic risk in ophthalmic and autoimmune disorders: A case report

RUXANDRA ANGELA PIRVULESCU1,2, HORIA TUDOR STANCA1, MIHAELA OANA ROMANITAN3, MATEI POPOA-CHERECHEANU4, SIMONA STANCA5 and RALUCA IANCU1,2

1Department of Ophthalmology, ‘Carol Davila’ University of Medicine and Pharmacy, 050474 Bucharest; 2Ophthalmology Clinic, University Emergency Hospital, 050098 Bucharest, Romania; 3Department for Emergency Internal Medicine and Neurology, Stockholm South General Hospital, 11883 Stockholm, Sweden; 4Cardiovascular Surgery Clinic, ‘Prof. Dr. Agrippa Ionescu’ Emergency Clinical Hospital, 011356 Bucharest; 5Department of Pediatrics, ‘Carol Davila’ University of Medicine and Pharmacy, 050474 Bucharest, Romania

Received January 22, 2021; Accepted February 22, 2021

DOI: 10.3892/etm.2021.10081

Abstract. The aim of the present study was to discuss genetic polymorphism and its association with thromboembolic retinal venous disorders, such as central/hemi-retinal vein occlusion (CRVO/HRVO), and possible correlations with other ocular findings (such as closed angle glaucoma), but also with autoimmune general disorders. To reinforce the literature data analysis we report the case of a 56-year-old female patient, previously known with rheumatoid polyarthritis, oscillating blood pressure and several spontaneous miscarriages, who presented to the ER with sudden vision loss in the right eye and severe headache. The patient was diagnosed with upper HRVO in the right eye, and acute angle closure glaucoma in both eyes. Given the ophthalmological context and the medical background, the patient underwent extensive genetic analysis which identified two mutations, PAI-1 4G allele and MTHFR A1298C mutation in heterozygosity. These results confirmed the increased risk of the patient to develop venous thromboembolism (VTE) or myocardial infarction, especially when associated with rheumatoid polyarthritis. Being aware of all the aspects of a complex medical situation, including the genetic one, may raise the patient's awareness for being at risk for thromboembolic episodes and for managing them promptly and properly in the future.

Introduction

Retinal venous occlusive disease is the second most frequent retinal vascular disorder after diabetic retinopathy, with a prevalence of 0.7-1.6%. Depending on the site of the venous blockage, retinal vein occlusions (RVO) are classified as central RVO (CRVO), branch RVO (BRVO) and hemi-retinal vein occlusion (HRVO) (1).

The pathogenesis of RVO remains partially unclear. The condition may occur due to three combined systemic changes known as Virchow's triad: i) Hemodynamic changes (venous stasis), ii) degenerative changes of the vessel wall, and iii) blood hypercoagulability (2).

Among the elements of Virchow's triad, the contribution of thrombogenesis or hypercoagulability of the blood to the pathogenesis of CRVO has not been as well investigated as the other two factors. Therefore, the implications of various hematological abnormalities in the etiopathogenesis and treatment of CRVO remain partially unclear and there are contrasting clinical results (3).

Although Virchow's triad explains the systemic changes leading to CRVO, this condition may be caused by both local and systemic causes. The etiopathogenetic mechanisms can be divided into conditions that produce a physical blockage at the level of the lamina cribrosa and conditions in which hemodynamic factors contribute to obstructing the blood flow (3,4).

When a retinal venous occlusion occurs, a thrombus develops, usually at the level of the lamina cribrosa (especially when we refer to the central retinal vein), leading to the obstruction of the retinal blood supply, causing local ischemia, retinal edema and decreased visual acuity. The condition has several triggers; with age, lamina cribrosa loses its elasticity, causing a compression of the vascular wall, Furthermore, degenerative processes that arise from the central retinal artery (atherosclerosis) may induce rigidity of the central retinal artery, which causes compression of the venous wall, the resulting turbulent flow disturbs blood hemodynamics and determines endoluminal thrombus formation (3,4).

In most cases, these mechanisms do not occur individually, they most likely coexist in many patients with RVO (5).
Several studies indicate that primary thrombosis is quite rare; more often, thrombosis may occur as an end-stage phenomenon, complicating other causing mechanisms in the obstructive process (5).

Among the findings, RVO is especially associated with CRVO, the most common being atherosclerosis, age, diabetes mellitus, systemic hypertension, vasculitis (sarcoidosis), coagulopathies, blood hyper viscosity, due to changes in the coagulating factors in the blood (genetic polymorphism, with deficiency of thrombolytic factors and/or increase in clotting factors), migraine and smoking. The majority of these conditions may lead to other retinal or optic nerve disorders, making the differential diagnosis of RVO challenging, at some point (Table I). However, there are also several ocular comorbidities that may be associated to RVO, such as chronic glaucoma (1,6,7).

Glaucoma is a multifactorial optic neuropathy with environmental and genetic causes and a leading cause of blindness worldwide. In the glaucomatous disease, there is a characteristic loss of nerve fibers, which leads to progressive and eventually irreversible loss of vision. Primary glaucoma is classified in primary open angle glaucoma (POAG), primary congenital glaucoma (PCG) and primary angle-closure glaucoma (PACG). There are several studies that support that genetic polymorphism, such as the variant MTHFR A1298C, may increase the risk for developing glaucoma, especially in the heterozygote model (8,9). However, while there are meta-analyses supporting this idea, other studies are yet to be extended, given the fact that, while some of these studies tried to maintain a heterogeneity of the assessed patients, other studies were made on specific ethnic groups (9).

In addition, recent findings suggest that there may be a strong connection between primary angle closure (PAC) or primary angle closure glaucoma (PACG) and RVO (mainly CRVO). This association could be explained not only by genetic predisposition, but also by the fact that mechanical changes on lamina cribrosa in eyes with PAC/PACG contribute to the onset of RVO. PACG combined with the genetic polymorphism of such patients may increase even further the risk for RVO/CRVO onset (10).

The MTHFR gene may undergo different mutations (or variants). The most frequent one, C677T, is linked to hyperhomocysteinemia (HH) and occlusive vascular pathology. Mutation A 1298C is still not very well studied. What is known is that the A1298C polymorphism of the MTHFR gene refers to: i) Substitution of adenine (A) with cytosine (C) in the position 1298 in the MTHFR gene area on the DNA chain; ii) substitution of glutamic acid with alanine in the position 429 in the polypeptide chain of the enzyme (Glu429Ala).

Polymorphism in the MTHFR gene may decrease the activity of methylenetetrahydrofolate reductase, leading to a mild increase of homocysteine in the blood (11). This may cause problems within blood vessels and is considered a risk factor for thromboembolism. However, it has been shown that there are individuals with MTHFR mutations who have normal homocysteine levels, and are therefore not at risk for developing blood clots. Thus, the MTHFR mutation by itself does not cause clotting disorders, but the coexistence of different mutations may further increase the risk for thromboembolic accidents (12).

Symptoms caused by MTHFR mutations may vary among individuals and depend on the type of mutation. Patients are usually not aware they have a MTHFR mutation unless they experience severe symptoms or undergo genetic testing. One or two MTHFR mutations can slightly increase the levels of homocysteine in the blood. Depending on how severe this condition is, the possible consequences may be abnormal blood clotting, seizures, poor coordination, anemia, cardiovascular (CV) diseases, strokes, heart attacks, depression or behavior disorders (13,14).

Vieira et al studied MTHFR polymorphism, in order to highlight thrombophilic and cardiovascular risk factors (CRF) for RVO (15). The retrospective study analyzed 60 consecutive case series of patients with RVO, tested for CRF, HH, lupic anticoagulant, antiphospholipid antibody and 5 gene variants: Factor V (FV) Leiden (G1691A), factor II (PT G20210A), 5,1-methylenetetra-hydrofolate reductase (MTHFR; 677 C>T and 1298 A>C), and plasminogen activator inhibitor 1 (PAI-1; 4 G/5 G). More than 1 CRF were present in 60% of the patients, and had a significantly higher mean age at diagnosis (66.7±12.9 vs. 59.5±13.7 with ≤1 CRF; [t(57)]=−2.05, P=0.045, d=0.54); d is the Cohen's score and represents a statistic term; its value (0.54) indicates a statistic relevance of the higher mean age of the patients in and for this particular study.

Patients with thrombophilic MTHFR forms with decreased enzyme activity (T677T or C677T/A1298C) had a significant lower mean age (57.6±15.1) than patients with normal MTHFR enzyme activity (68.5±10.2). The study also highlights the fact that, although severe HH is rare, mild HH occurs in ~5% of the general population (mild HH is an independent risk factor for venous thromboembolism) and that there may be an association between HH, coronary heart disease, deep venous thrombosis and CRVO. MTHFR compound heterozygosity C677T/A1298C was found in 26.7% of patients. MTHFR polymorphisms were found in 55 patients (91.7%) (Table II) (15).

Another mutation possibly linked with many different disorders, including thromboembolic disorders is the PAI-1 (plasminogen activator inhibitor type 1) 4G allele mutation. Several meta-analyses suggested an association between PAI 1 4G and both rheumatoid arthritis (RA) and CV risk (16).

The plasminogen activator inhibitor-1 (PAI-1) 4G/5G polymorphism has been associated with increased risk of VTE; however, the existing evidence remains scarce. Different meta-analyses have been performed, to verify and possibly prove this connection.

Wang et al (17) developed a systematic search in PubMed, EMBASE, Wanfang,China National Knowledge Infrastructure (CNKI) and Cqvip databases to identify relevant studies published prior to March 6th, 2014. The odds ratios (ORs) with 95% confidence intervals (CIs) were pooled using the fixed/random-effects model using Review Manager 5.1 and STATA 12.0. A number of 34 studies with 3,561 cases and 5,693 controls were analyzed. The studies included in that study contained both Caucasian and Asian patients. Summing up, a significant association between the PAI-1 4G/5G variant and VTE risk in the total population was observed. This variant was also related to the deep vein thrombosis risk. In the subgroup analyses on ethnicity, significant results were obtained for both Asians and Caucasians. Regarding subgroup analyses about co-existence of other thrombotic risk factors,
Table I. Main features to be considered regarding differential diagnosis of retinal vein occlusion (RVO).

| Central/retinal vein occlusion | Papillophlebitis | Ocular ischemic syndrome | Papillitis | Anterior optic ischemic neuropathy | Diabetic retinopathy | Hypertensive retinopathy |
|--------------------------------|------------------|-------------------------|-----------|----------------------------------|---------------------|-------------------------|
| Age: Variable Usually, history of vascular disease Unilateral Optic disc: Edema Macular edema Veins: Dilated and tortuous Hemorrhages: Flame shaped, in all quadrants, in nerve fiber layer, in the affected quadrant +/-Cotton wool spots/rarely hard exudates | Age: <50 (usually women 25-35 y.o.) Clinical features of CRVO, no history of vascular disease Misdiagnosed, may lead to CRVO with macular edema and poor acuity. | Age: 50-80 Uni/bilateral Optic disc: Normal Hemorrhages: Dot, in mid periphery and deep retinal layers Microaneurysms | Age: Variable Unilateral | Non-arteritic Age: >50 Uni/bilateral Optic disc: Hyperemic edema Usually related to inflammatory/infectious/demyelinating diseases | Age: Variable, usually 50-80 Bilateral Optic disc: Normal/rarely diabetic papillopathy | Age: Variable Bilateral Optic disc: Normal/edema Macular edema in advanced stages |
|                                |                  |                        |           |                                  |                     |                         | Veins: Dilated, tortuous Salus/Gunn/ Bonet signs Hemorrhages, retinal hard exudates or cotton wool spots |

ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.
the PAI-1 4G/5G polymorphism was significantly associated with venous thrombosis risk in patients with factor V Leiden mutation, but not in patients with cancer or surgery. The results of this meta-analysis revealed the role of PAI-1 4G/5G polymorphism as a risk for VTE susceptibility, especially in patients with other genetic thrombophilic disorders (17).

A topic that also needs to be explored involves patients with RA who are particularly exposed to CV risk; CV diseases in such patients appear to be the most common cause of premature mortality. The main cause involved in this outcome may be the result of an accelerated atherosclerotic process. Both RA and atherosclerosis are complex polygenic diseases, and both are chronic inflammatory diseases with similar pathophysiological mechanisms (8), indicating a strong genetic component of susceptibility. RA has an estimated heritability of ≤60% and CV disease in the general population of ≤30-60%. In addition, a specific genetic background may contribute to the development of both diseases (16-18).

Several studies have already confirmed the role of genetic factors in the development of atherogenesis in RA patients. Nevertheless, despite research effort to unlock the genetic basis of CV disease in RA, further studies are necessary to further establish the genetic influence in the increased risk of CV events observed in patients with RA (18).

Another side of these genetic disorders to be taken into consideration is that PAI-1 is the main inhibitor of fibrinolysis; according to the latest studies, high levels of PAI-1 may increase the risk of CV disease. The 4G/5G polymorphism affects PAI-1 gene transcription with lower levels of plasma PAI-1 in the presence of the 5G allele (19).

Conversely, while assessing thromboembolism, one should consider the general medical background of the patient, for example the existence of an inflammatory autoimmune disorder, such as RA; in this particular case, the risk of developing CRVO may increase. Previous findings showed that there is an increased risk of developing VTE for RA patients compared with non-rheumatoid arthritis patients. The same studies show that the risk can be attenuated, but it remains elevated even after adjusting for various risk factors for venous thromboembolism (20).

Detecting RVO and associated systemic and local conditions as early as possible may strongly improve the visual outcome of the patient and both the long-term visual acuity and ocular morbidity. It is crucial, when encountering a patient with such a complex pathology, to explore all the possible causes, to treat them promptly and efficiently, in order to prevent further vascular occlusions and to preserve a good long term visual acuity.

### Case report

The case/study was approved by the University Emergency Hospital Ethics Committee in Bucharest. Written informed consent obtained from the patient prior to publication.

We present the case of a 56-year-old woman, previously known with several miscarriages (25 years prior) and rheumatoid polyarthritis. The patient was previously diagnosed with RA at age 38, being occasionally under non-steroidal anti-inflammatory drugs, and had also been diagnosed with oscillating systemic blood pressure. The patient presented to the Ophthalmological ER with severe headache and blurred vision in the right eye, with sudden onset, 2 days before. At that time, prior to presenting in our clinic, the patient had the eyes examined in another facility and the suspicion of anterior ischemic optic neuropathy was raised.

Upon admission, the optimal corrected visual acuity in the right eye was 20/20 (0 logMAR), with difficulty, with correction (+3.5 spherical lens) and in the left eye it was also 20/20 (0 logMAR) with correction (+2.75 spherical lens).

Intraocular pressure was 65 mmHg in the right eye and 31 mmHg in the left eye (using Goldmann aplanotonometry). Slit lamp examination of the anterior segment highlighted epithelial corneal edema in the right eye, anterior chamber depth significantly decreased in both eyes, a non-reactive semi-mydriatic pupil was observed in the right eye, while in the left eye the pupil was miotic and reactive.

Fundus examination revealed an elevated hyperemic blurred optic disc in the right eye, with a suprachoroidal flame-shaped haemorrhage, tortuous and engorged retinal veins, macula with foveolar reflex (Fig. 1A and B). In the left eye, the optic disc had a normal aspect, with cup/disc ratio 0.2, a normal aspect macula and normal configured retinal vessels (Fig. 2).

The macular OCT showed a RNFL within normal limits in both eyes (Figs. 3 and 4). The anterior segment OCT revealed

---

Table II. MTHFR polymorphisms.

| MTHFR mutations | CRVO (%) | BRVO (%) | Total RVO (%) | Age (M ± SD) |
|-----------------|----------|----------|--------------|-------------|
| T677T           | 4 (11.4) | 5 (20.0) | 9 (15.0)     | 52.3±17.4   |
| C677T/A1298C    | 10 (8.6) | 6 (24.0) | 16 (26.7)    | 60.6±13.3   |
| C1298C          | 1 (2.9)  | 4 (16.0) | 5 (8.3)      | 66.4±10.5   |
| C677T           | 12 (34.3)| 3 (12.0) | 15 (25.0)    | 69.1±8.30   |
| A1298C          | 4 (11.4) | 6 (24.0) | 10 (16.7)    | 67.1±12.0   |
| Total           | 31 (88.6)| 24 (96.0)| 55 (91.6)    | 64.0±13.5   |
| No polymorphism | 4 (11.4) | 1 (4.0)  | 5 (8.3)      | 71.6±14.0   |

MTHFR, methylenetetrahydrofolate reductase; CRVO, central retinal vein occlusion; BRVO, branch retinal vein occlusion; RVO, retinal vein occlusion; M, mean; SD, standard deviation.
a 4-degree closed angle in the right eye and a 1-degree closed angle in the left eye (Figs. 5 and 6).

The general examination revealed no abnormal findings, the patient had normal weight and the systemic blood pressure was 130/60 mmHg.

Based on the clinical and paraclinical aspects, the preliminary diagnosis was CRVO (in the right eye), bilateral acute closed angle glaucoma and rheumatoid polyarthritis.

The patient was administered osmotic diuretic i.v. (Mannitol 15%) 250 ml, oral carbonic anhydrase inhibitors, antiplatelet drugs (Aspirin), Sulodexide 250 USL, Clexane 2000 UI/day injected subcutaneously, and received topical β-blockers and carbonic anhydrase inhibitors. After lowering the intraocular pressure, pilocarpine 2% eye drops were instilled and laser iridotomy was performed after 12 h on each eye, followed by the stabilization of the IOP within normal values.

The perimetric eye exam with Optopol Visual Field Analyser, Fast Threshold algorithm, showed an inferior altitudinal defect in the right eye, with no impairment of the central vision, but also multiple false-negative errors, due to the patient's weak cooperation. However, after subsequent examination, the aspect was improved. In the left eye, the visual field showed a small enlargement of the blind spot.

Given the fact that our patient had an autoimmune inflammatory disease, a history of miscarriages, which added to the ocular pathology, further examinations were performed. CV exam highlighted, at the time of the examination, elevated blood pressure (for which a conversion enzyme inhibitor was recommended), and cord ultrasonography was within normal limits. The neurology exam was normal, as well as the head contrast MRI. The echo Doppler of right and left carotid and ophthalmic arteries did not reveal any pathological findings.

The blood exam revealed elevated levels of CRP 158.4% (normal range 70‑140%) and slightly elevated levels of free Protein S, 116.1% (normal range 60.1‑113.6%). The resistance to activated C protein was 1.14% (normal range >0.8%). The blood test was performed by Protein C global assay and indicated Factor V Leyden-normal; thus, it excluded any type of anomaly that increased resistance to activated C protein, including any anomaly of Factor V Leyden. Coagulation tests (APTT, PT, Fibrinogen, ESR) were normal. CBC (except a small increase in hemoglobin (14.8 g/dl) and the biochemical profile were within normal range, and a series of additional tests were performed, to exclude a possible infectious cause: Anti toxoplasma and anti toxocara antibodies, Ag HBS, Ag HVC, HSV1 and HSV2 antibodies, VDRL and HIV tests, which were all negative. Antibodies associated with acquired thrombophilia (anti‑phospholipidic antibodies, anti‑cardiolipin antibodies, β 2 glicoprotein-I antibodies, and Lupic anticoagulant) were negative.

Based on the clinical and paraclinical examinations, the final diagnosis was upper HRVO (in the right eye), bilateral
acute closed angle glaucoma, rheumatoid polyarthritis, and systemic arterial hypertension.

The differential diagnosis (Table I) was a challenge. We suspected the occlusive cause for many reasons. First, we excluded anterior ischemic optic neuropathy; eye vision was 20/20, no visual field loss, no history of DM or dyslipidemia; the inflammatory markers were low, excluding a possible arteritic cause. Papillophlebitis was also not an option, considering that it usually appears in younger age and there were no infectious, inflammatory or demyelinating findings. DM was also excluded, given the normal blood sugar levels, and the clinical fundus aspect, which was normal in the left eye. Ocular ischemic syndrome was also ruled out, given the clinical aspect and the normal carotid Echo Doppler exam along with the exclusion of dyslipidemia and vascular stenosis (21,22). The reasons for eventually tipping the balance in favor of the upper HRVO (instead of CRVO) were the arcuate inferior defect in the visual field, along with the upper flame hemorrhages.

Taking into consideration the medical history of the patient, especially the rheumatoid arthritis, the miscarriages and the CRVO, genetic tests were performed, to further investigate the patient complex condition.

DNA was extracted from the peripheral blood sample. Twelve gene mutations and alleles associated with the genetically determined risk of thrombophilia and/or CV diseases were screened using multiplex PCR with biotinylated primers followed by a reverse hybridization assay (CVD Strip Assay, IVD). The mutations screened using this technique were: Factor V Leiden (1691G>A; R506Q), Factor V H1299R (R2), Prothrombin (PTH; Factor II) 20210G>A, 5,10-Methylenetetrahydrofolate reductase (MTHFR) C677T and A1298C, Factor XIII V34L, Plasminogen...
Figure 4. Macular OCT aspect; normal macular thickness in the left eye.

Figure 5. Anterior segment OCT of the right eye reveals 4° irido-corneal angle closure.
Activator Inhibitor 1 (PAI-1, Serpin E1) 4G/5G, β-fibrinogen (FGB)-455G>A, Angiotensin-Converting Enzyme (ACE) 287 bp insertion/deletion (I/D), Human Platelet Antigen 1 (HPA 1 α/β; GpIIIa, integrin β3 L33P), Apolipoprotein B (Apo B) R3500Q, Apolipoprotein E (Apo E) E2/E3/E4. The results of the genetic testing of the patient detected PAI-1 4G allele and MTHFR A1298 C mutation in heterozygosity (Table III), indicating an increased risk for thromboembolic incidents.

The patient was followed up monthly and remained on lowering IOP medication—a combination of prostaglandin analogue and β-blocker was administered once a day, permanently. The patient maintained good visual acuity and a good clinical aspect of the eye fundus (Fig. 7), as well as a good optic nerve and macular OCT aspect (Fig. 8: Optic nerve OCT images) and an improved visual field aspect, even though a small inferior arcuate defect persists.

**Discussion**

One of the first important issues to consider in this case was to decide whether there was a CRVO, which was revealed in its early stages, or an upper HRVO. Even though all vein branches were engorged and dilated, and the optic nerve was swollen, the fact that there were visual field changes inferiorly, correlated with hemorrhages in the upper quadrants, led us to believe there was an upper HRVO (21,22); most likely, it was preceded by the angle closure, and the lowering of the...
IOP, together with anticoagulant and antiaggregant treatment prevented further development of this condition.

The particular features of this case are the sudden onset of bilateral acute angle closure, along with the HRVO in a hypertensive patient with rheumatoid polyarthritis and a history of multiple miscarriages, whose genetic tests revealed specific mutations (MTHFR A1298C and PAI-1 4G heterozygote) that increased, not only the risk for developing venous thromboembolism, but also the risk of developing chronic glaucoma.

In our patient case, the mutation MTHFR A1298C indicates a heterozygote mutation, which means that there is a mutation on just one chromosome out of two. This kind of mutation...
may cause a decrease in the enzymatic capacity of ≤20%, with slightly elevated levels of homocysteine. That, combined with PAI-1G mutation, may submit the patient to an even higher risk of blood clotting, even further in the future.

Another interesting aspect about this case is the possible association between rheumatoid polyarthritis and thrombosis. Previous findings suggested that the MTHFR 1298 A>C gene polymorphism may increase the risk for subclinical atherosclerosis and CV episodes in patients with RA. As already indicated, patients with rheumatoid arthritis are more exposed to CV risk due to the accelerated atherosclerosis they may develop. Adding genetic disorders to the chronic inflammation increases again the risk of thromboembolic events, regardless of the presence of usual CRF (23).

There are also issues to consider regarding the possible connection between PAC or PACG and RVO. As previously shown, this association may be explained, not only by genetic predisposition, but also by mechanical changes on lamina cribrosa in eyes with PAC/PACG, and these changes are believed to contribute even further to the onset of RVO (10). In addition, PACG combined with the genetic polymorphism of such patients, may increase even further the risk for RVO/CRVO onset, which may explain the clinical condition of our patient (10).

Complex clinical cases such as the one presented in this study increase the awareness regarding, not only thromboembolic ocular events, but also their association with other ocular pathologies, and with general disorders. These cases require a wide approach and thorough research in order to establish the best treatment and follow up for the patient, to preserve as much as possible a good visual outcome and a satisfactory health status.

Acknowledgements

Professional editing, linguistic and technical assistance performed by Irina Radu, Individual Service Provider, certified translator in Medicine and Pharmacy (certificate credentials: Series E no. 0048).

Funding

No funding was received.

Availability of data and materials

All data and materials supporting the results of the present case are available in the published article.

Authors' contributions

All authors had equal contribution in this study. RAP contributed to the conception and design of the article, the acquisition, analysis, and interpretation of data, the drafting of the work, revision and editing all data to cover all aspects for the proper intellectual content. RI contributed to the acquisition, the analysis and interpretation of data of the study, to the drafting of the work and its critical revision for important intellectual content. HTS contributed to the conception and design of the study, the acquisition, analysis, and interpretation of data of the study, as well as to the drafting of the work and its critical revision for important intellectual content. MPC and SS contributed to data analysis, the drafting of the work and its critical revision for important intellectual content, as well as interpretation of data in the study. MOR contributed to data acquisition and analysis, drafting of the work and its critical revision for important intellectual content and interpretation of data in the study. All authors read and approved the final version of the manuscript and agreed to be accountable for all aspects presented in the paper in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics approval and consent to participate

The case/study was approved by the University Emergency Hospital Ethics Committee in Bucharest. Written informed consent was obtained from the patient prior to publication.

Patient consent for publication

Written informed consent was obtained from the patient prior to publication.

Competing interests

The authors declare that they have no competing interests.

References

1. Bucan K, Pustina Borjan I, Bucan I, Paradzik Simunovic M and Borjan I: Genetic background of a recurrent unusual combined form of retinal vein occlusion: A case report. Case Rep Ophthalmol 9: 248-253, 2018.
2. Kolar P: Risk factors for central and branch retinal vein occlusion: A meta-analysis of published clinical data. J Ophthalmol 2014: 724780, 2014.
3. Cevik MO and Cevik SG: Effects of common thrombophilia factor mutations in central retinal vein occlusion. Beyoglu Eye J 4: 23-27, 2019.
4. Blair K and Czyz CN: Central retinal vein occlusion. StatPearls [Internet], Treasure Island (FL), StatPearls Publishing, 2020. https://www.ncbi.nlm.nih.gov/books/NBK430685/. Accessed September 12th, 2020.
5. Duane's Ophthalmology on CD-ROM, 2006 Edition, Lippincott, Williams & Wilkins, http://www.oulco.com/downton/05221/epook/duanes/index.html. Accessed September 12th, 2020.
6. Babak A, Soheila Z and Pouria S: Is central retinal vein occlusion (CRVO) due to hereditary ischemia risk factors? Case report. J Neurol Neurorehabil Res 3: 9-11, 2018.
7. Borke J: Drugs & diseases emergency medicine, retinal vein occlusion (RVO). Updated September 20, 2019. https://emedicine.medscape.com/article/798583-overview. Accessed September 12th, 2020.
8. Gohari M, Mirjaldi SA, Akbarian-Bafghi MJ, Jarahzadeh MH, Zare-Shenhe M and Neamatzadeh H: Association of MTHFR C677T and A1298C polymorphisms with glaucoma risk: A systematic review meta-analysis based 42 case-control studies. Rom J Ophthalmol 63: 107-118, 2019.
9. Kadhim MR and Clement CI: Homocysteine in the pathogenesis of chronic glaucoma. In: The Mystery of Glaucoma. Tomas Kubena (Eds.). InTechOpen, 2011. https://www.intechopen.com/books/the-mystery-of-glaucoma/homocysteine-in-the-pathogenesis-of-chronic-glaucoma. Accessed September 6th, 2011.
10. Xu K, Wu L, Ma Z, Liu Y and Qian F: Primary angle closure and primary angle closure glaucoma in retinal vein occlusion. Acta Ophthalmol 97: e564-e572, 2019.
11. https://medlineplus.gov/genetics/gene/mthfr/#conditions. Accessed September 12th, 2020.
12. Ferrazzi P, Di Micco P, Quaglia I, Rossi LS, Bellatorre AG, Gaspari G, Rota LL and Lodigiani C: Homocysteine, MTHFR C677T gene polymorphism, folic acid and vitamin B 12 in patients with retinal vein occlusion. Thromb J 3: 13, 2005.
13. https://www.medicalnewstoday.com/articles/326181#symptoms. Accessed September 12th, 2020.
14. Cho K, Amin ZM, An J, Rambaran KA, Johnson TB and Alzghari SK: Methyleneetetrahydrofolate reductase A1298C polymorphism and major depressive disorder. Cureus 9: e1734, 2017.
15. Vieira MJ, Campos A, do Carmo A, Arruda H, Martins J and Sousa JP: Thrombophilic risk factors for retinal vein occlusion. Sci Rep 9: 18972, 2019.
16. Muñoz-Valle JF, Ruiz-Quezada SL, Oregón-Romero E, Navarro-Hernández RE, Castañeda-Saucedo E, De la Cruz-Mosso U, Illades-Aguilar B, Leyva-Vázquez MA, Castro-Alarcón N and Parra-Rojas I: PAI-1 mRNA expression and plasma level in rheumatoid arthritis: Relationship with 4G/5G PAI-1 polymorphism. Rheumatol Int 32: 3951-3956, 2012.
17. Wang J, Wang C, Chen N, Shu C, Guo X, He Y and Zhou Y: Association between the plasminogen activator inhibitor-1 4G/5G polymorphism and risk of venous thromboembolism: A meta-analysis. Thromb Res 134: 1241-1248, 2014.
18. Rodríguez-Rodríguez L, López-Mejías R, García-Bermúdez M, González-Juanatey C, González-Gay MA and Martín J: Genetic markers of cardiovascular disease in rheumatoid arthritis. Mediators Inflam 2012: 574817, 2012.
19. Hoekstra T, Geleijnse JM, Kluft C, Giltay EJ, Kok FJ and Schouten EG: 4G/4G genotype of PAI-1 gene is associated with reduced risk of stroke in elderly. Stroke 34: 2822-2828, 2003.
20. Kim SC, Schneeweiss S, Liu J and Solomon DH: The risk of venous thromboembolism in patients with rheumatoid arthritis. Arthritis Care Res (Hoboken) 65: 1600-1607, 2013.
21. https://eyewiki.aao.org/Ocular_Ischemic_Syndrome#Differential_410diagnosis. Accessed September 12th, 2020.
22. https://rarediseases.org/rare-diseases/papillitis/. Accessed September 12th, 2020.
23. Palomino-Morales R, Gonzalez-Juanatey C, Vazquez-Rodriguez TR, Rodriguez L, Miranda-Filloy JA, Fernandez-Gutierrez B, Llorca J, Martin J and Gonzalez-Gay MA: A1298C polymorphism in the MTHFR gene predisposes to cardiovascular risk in rheumatoid arthritis. Arthritis Res Ther 12: R71, 2010.