DOI: 10.14744/eer.2024.22448
Eur Eye Res 2024;4(3):187–192

EUROPEAN EYE RESEARCH

ORIGINAL ARTICLE

Evaluation of hypercoagulability in ocular vascular pathologies

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Abstract

Purpose: The purpose of the study was to evaluate thrombophilic/hypofibrinolytic factors in two ocular vascular pathologies; retinal vein occlusion (RVO) and non-arteritic anterior ischemic optic neuropathy (NAION).

Methods: Prospective study including patients with RVO (n=13), NAION (n=17), and age-sex matched control group (n=14). Clinical history for pre-existing hypertension and diabetes mellitus were recorded. Measured serological thrombophilic markers included Factor V Leiden (FVL) and methyltetrahydrofolate reductase (MTHFR) C677T mutations. Serum Protein C (PC) activity and plasminogen activator inhibitor-1 (PAI-1) levels were also evaluated. P<0.05 was considered statistically significant.

Results: There was no statistically significant difference with demographics between groups. FVL mutation was positive for three patients with RVO (23.1%), two patients with NAION (11.8%), and one subject in the control group (9.1%). MTHFR C677T mutation was found in 12 patients with RVO (92.3%), 15 patients with NAION (88.2%), and three subjects in the control group (27.3%). Even though there was not a statistically significant difference between RVO and NAION groups, this mutation was significantly higher in the patient groups compared to controls (p=0.001). We did not observe a statistically significant difference in PC activity levels between groups (p=0.35). Plasma PAI-1 levels were higher in the patient groups than the control group, however, the difference was not statistically significant (p=0.168) between any of the groups.

Conclusion: MTHFR C677T mutation was more common in both patient groups compared to controls, without a statistically significant difference between RVO and NAION groups. PAI-1 levels were also higher in the patient groups; however, the difference was not statistically significant. The findings of this study underscore the potential role of genetic and serological factors in ocular vascular pathologies. Understanding these associations better could lead to more targeted screening and management strategies for patients at risk of ocular vascular disorders. Further studies including larger cohorts are required to elucidate possible associations.

Keywords: Hypercoagulability; ischemic optic neuropathy; plasminogen activator inhibitor-1; retinal vein occlusion.

Cite this article as: Koseoglu ND, Turgut Cosan D, Musmul A, Ozer A. Evaluation of hypercoagulability in ocular vascular pathologies. Eur Eye Res 2024;4(3):187–192.

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Submitted Date: 01.05.2024 **Revised Date:** 18.08.2024 **Accepted Date:** 04.09.2024 **Available Online Date:** 29.11.2024

Ocular vascular diseases are common reasons for vision impairment, specifically in the elderly population, affecting venous and/or arterial circulation. Retinal vein occlusion (RVO), the second most common ocular vascular pathology after diabetic retinopathy, is associated with risk factors such as age, hypertension (HTN), diabetes mellitus (DM), hyperlipidemia, and atherosclerosis.[1] Non-arteritic ischemic optic neuropathy (NAION), a leading cause of sudden vision loss, shares similar predisposing factors with RVO, leading to circulatory insufficiency in the optic nerve head.[2] However, the role of hypercoagulability in the pathogenesis of RVO and NAION is still debatable.[3-8]

Hereditary and environmental factors contribute to hypercoagulability with Factor V Leiden (FVL) mutation being a common hereditary cause linked to venous and arterial thrombosis.[3,4] This mutation causes resistance to activated protein C (PC), one of the regulatory enzymes in the coagulation cascade, resulting in decreased inactivation of factor Va and increased risk of hypercoagulability.[9] PC deficiency also increases thrombotic risk by impairing the regulation of Factors V and VIII.[7] Methyltetrahydrofolate reductase (MTHFR) gene C677T polymorphism is another hereditary factor, associated with increased thrombosis risk due to hyperhomocysteinemia.[5,6] Conversely, elevated levels of plasminogen activator inhibitor-1 (PAI-1), the main enzyme responsible for inhibition of fibrinolysis, are associated with an increased risk of thromboembolism.[8] Given their functional impact and potential for affecting the fellow eye, we aimed to identify common hypercoagulability factors in RVO and NAION, ocular vascular pathologies with different underlying origins.

Materials and Methods

Participants in this prospective study comprised individuals seen at the Department of Ophthalmology, Eskişehir Osmangazi University School of Medicine between January and October 2015. Informed consent was obtained from all participants. The study was approved by the Ethics Committee of Eskişehir Osmangazi University (8558721/290) and adhered to the tenants of Helsinki declaration. Inclusion criteria were; patients >18 years of age and diagnosed with RVO (branch RVO [BRVO] or central RVO [CRVO]) or NAION within 2 weeks of initiation of symptoms. Control group was selected from age-sex-matched individuals without any known retinal and/or optic nerve pathology. Exclusion criteria for all groups included; previous diagnosis of RVO and/or NAION, symptoms longer than 2 weeks, diagnosis of any known malignancy, and active infection. For diagnostic purposes, all participants received ocular examination including; best correct visual acuity, anterior segment and dilated fundus examinations, and intraocular pressure measurements. In aid of ION diagnosis, patients were also evaluated for relative afferent pupillary defect and color vision. Bloodwork was performed for total blood count, FVL and MTHFR C677T mutations, serum PC activity, and PAI-1 levels. In addition, erythrocyte sedimentation rate and C-reactive protein values were also assessed to rule out arteritic ION. PAI-1 levels were measured using Affymetrix Human PAI-1 Platinum enzyme-linked immunosorbent assay BMS2033/from eBioscience 26 BMS2033TEN branded kits purchased via Eskisehir Osmangazi University scientific research project (BAP no: 201411D25) funding with contribution of Department of Medical Biology. Samples were run in duplicate for verification purposes, using the Thermo brand Multiskan ^{tm}GO Microplate Spectrophotometer available at the Department of Medical Biology. Microplates were prepared according to the manufacturer's guidelines and the absorbance levels read at 450 nm wavelength on the spectrophotometer were presented as ng/mL.

Statistical Analysis

Descriptive statistical analysis was performed with IBM Statistical Package for the Social Sciences (SPSS) Statistics 21.0 (IBM Corp. released 2012. IBM SPSS Statistics for Windows, Version 21.0 Armonk, NY: IBM Corp.). The distribution of continuous variables was tested using Shapiro–Wilk, while categorical variables were analyzed by Fisher's Exact Chi-square test. Normally distributed variables were compared by analysis of variance and Kruskal–Wallis test was used to analyze variables without normal distribution. $P<0.05$ was considered statistically significant.

Results

Of the 13 patients with RVO (n=8 BRVO and n=5 CRVO), 17 patients with NAION and 14 controls, 26 (59.1%) were male and there was no statistically significant difference between groups (p=0.528) (Table 1). Mean age of the total participants was 59.7±12.1 (range: 37–79) and 58.1±12.5

Table 1. Distribution of gender within groups, presented as number of patients (n) and percentage (%)

Group	RVO (%)	NAION (%)	Control (%)	Total (%)	p
Male	6 (46.2)	11 (64.7)	9 (64.3)	26 (59.1)	0.528
Female	7 (53.8)	6 (35.3)	5 (35.7)	18 (40.9)	
Total	13 (100)	17 (100)	14 (100)	44 (100)	

RVO: Retinal vein occlusion; NAION: Non-arteritic ischemic optic neuropathy.

in the RVO group, 57.2±11.4 in the NAION group, and 64.1±12.2 in the control group. There was no statistically significant difference between means of age between groups (p=0.668) (Table 2).

HTN was reported in five out of 13 (45.5%) RVO and nine out of 17 (52.9%) NAION patients. In the control group, seven participants (53.8%) had HTN. DM was present in 1 out of 13 (9.1%) RVO patients, eight out of 17 (47.1%) NAION patients, and two out of 13 (15.4%) controls. Even though DM was more common in the NAION group, we did not find a statistically significant difference between groups for HTN and DM (p=0.904 and p=0.620, respectively) (Table 3).

FVL mutation did not present a statistically significant difference between any of the groups (p=0.628) and was detected in three out of 13 (23.1%) RVO, two out of 17 (11.8%) NAION, and one out of 11 (9.1%) controls. On the other hand, MTHFR C677T mutation was presented in 12 out of 13 (92.3%) RVO and 15 out of 17 (88.2%) NAION patients and was considered statistically significant for patient groups when compared to controls (p=0.001) (Table 4).

PC activity was evaluated according to decreased, normal, and increased activity (N: 70–130%). PC activity was reduced in five out of 13 (38.5%) RVO patients, four out of 17 (23.5%) NAION patients, and one out of 12 (8.3%) controls. There was no statistically significant difference between groups (p=0.350) (Table 5).

Mean PAI-1 levels were found to be 1172.40 ng/mL (±1050.07) for RVO patients, 946.60 ng/mL (±662.50) for NAION patients and 626.20 ng/mL (±367.60) for controls. Even though plasma PAI-1 levels were increased in both NAION and RVO groups compared to controls, all groups presented within the normal range and there was no statistically significant difference between groups (p=0.168).

Table 2. Distribution of age within groups, presented as number of patients (n) and percentage (%)

Group	RVO (%)	NAION (%)	Control (%)	Total (%)	p
<50 years of age	2 (15.4)	5 (29.4)	3 (21.4)	10 (22.7)	0.668
≥50 years of age	11 (84.6)	12 (70.6)	11 (78.6)	34 (77.3)	
Total	13 (100)	17 (100)	14 (100)	44 (100)	

RVO: Retinal vein occlusion; NAION: Non-arteritic ischemic optic neuropathy.

Table 3. Distribution of HTN and DM within groups, presented as number of patients (n) and percentage (%)

Group	RVO (%)	NAION (%)	Control (%)	Total (%)	p
HTN	5 (45.5)	9 (52.9)	7 (53.8)	21 (51.2)	0.904
DM	1 (9.1)	8 (47.1)	2 (15.4)	11 (26.8)	0.620
Total	13 (100)	17 (100)	14 (100)	44 (100)	

RVO: Retinal vein occlusion; NAION: Non-arteritic ischemic optic neuropathy; HTN: Hypertension; DM: Diabetes mellitus.

Table 4. Distribution of FVL and MTHFR C677T mutations within groups, presented as number of patients (n) and percentage (%)

Group	RVO (%)	NAION (%)	Control (%)	Total (%)	p
FVL	3 (23.1)	2 (11.8)	1 (9.1)	6 (14.6)	0.628
MTHFR	12 (92.3)	15 (88.2)	3 (27.3)	30 (73.2)	0.001*
Total	13 (100)	17 (100)	11 (100)	41 (100)	

RVO: Retinal vein occlusion; NAION: Non-arteritic ischemic optic neuropathy; FVL: Factor V Leiden; MTHFR: Methyltetrahydrofolate reductase. *Indicates statistical significance.

Table 5. Distribution of Protein C activity levels (%) within groups, presented as number of patients (n) and percentage (%)

Group (%)	RVO (%)	NAION (%)	Control (%)	Total (%)	p
<70	5 (38.5)	4 (23.5)	1 (8.3)	10 (23.8)	0.350
70–130	7 (53.8)	13 (76.5)	10 (83.3)	30 (71.4)	
>130	1 (7.7)	0 (0.0)	1 (8.3)	2 (4.8)	
Total	13 (100)	17 (100)	12 (100)	42 (100)	

RVO: Retinal vein occlusion; NAION: Non-arteritic ischemic optic neuropathy.

Discussion

In this prospective study, we evaluated hypercoagulability in two pathologies of venous and arterial vascular origin of the eye. Pathophysiology of RVO is thought to be similar to venous thrombosis elsewhere in the body including endothelial injury, hypercoagulability, and stasis (Virchow triad).[10] Whereas NAION is considered to be caused by transient hypoperfusion/infarct, or in rare occurrences due to embolism, of the optic nerve head circulation specifically short posterior ciliary arteries.[10,11] The association with vasculopathic systemic diseases (i.e., HTN, DM, and hyperlipidemia) has been well-established for both RVO and NAION.[12-15] However, there are still conflicting results when it comes to the possible role of thrombophilic factor in the pathogenesis.

FVL is the most common hereditary cause of thrombophilia and has been detected in 15–20% of patients who present with first episode of deep venous thrombosis and around

50% of patients with recurrent venous thrombosis.[16] This mutation has also been subject to a number of studies investigating its role on the risk of RVO and NAION.[3,17-20] Most of these studies did not report any association with FVL mutation and an increased risk of RVO or NAION.[19,21,22] In line with these reports, our study also did not yield a difference between the patient groups and the control group. There were only two patients in the RVO group, three patients in the NAION group, and one individual with FVL mutation in the control group (p=0.628). On the contrary, there are also multiple studies and case reports, describing FVL as a risk factor specifically in patients without any other predisposing causes and younger individuals.[19,23-25] Some of these case studies also report concurrent involvement of arterial and venous pathways.[26,27] Mahmoud et al. identified heterozygous FVL mutation in a young female patient who presented with simultaneous CRVO, NAION, and branch retinal artery occlusion.[26] Similarly, Lemos et al. also described a case of combined retinal artery and venous thrombosis in a patient with FVL mutation.[27] These inconsistent results still warrant further investigations with larger cohorts to elucidate the possible association of FVL and ocular occlusive pathologies.

Similar to that of FVL, there are also many conflicting reports for MTHFR mutation.[21-23,28] In our study, MTHFR C677T mutation was more frequent in both RVO and NAION patient groups compared to controls and the difference was statistically significant (p=0.001). This result is comparable to that of Ferrazzi et al. where the MTHFR mutation was more common in RVO patients however, was not recognized as a certain risk factor.[29] Another study by Glueck et al. showed a similar association between NAION and MTHFR C677T mutation in a small sample size of 12 patients and 36 controls.[30] In contrast, there are numerous studies reporting a lack of direct association between MTHFR mutation and RVO or NAION. These studies describe elevated levels of homocysteine (hyperhomocysteinemia), a metabolite of methionine amino acid regulated by MTHFR enzyme, as a risk factor for these vascular occlusive diseases.[21,31-34] Even though MTHFR enzyme is a part of the homocysteine-methionine cycle, this hypercoagulative effect of hyperhomocysteinemia independent from the presence of MTHFR mutation, is speculated to be influenced by other confounding factors in the cycle; folate and Vitamin B12.[32,35] The lack of homocysteine levels can be considered a limitation of this current study, however higher frequency of MTHFR C677T mutation in our patient groups is similar to current literature.

While clinically significant PC deficiency is rare (1 in 20.000 individuals), the incidence of mild deficiency is considerably higher (1 in 200–500 individuals).[36] Even though PC deficiency is related to thromboembolism in significantly deficient individuals, the risk is reported to be higher in patients presenting with other predisposing factors such as; immobility, pregnancy, or surgery.[37] There are only a few case reports describing PC deficiency as a potential risk factor for RVO and NAION.[38-40] In general, more recent studies with larger sample sizes do not report a similar association between PC deficiency and RVO or NAION.[20,41-43] In line with these more current reports, there was no statistically significant difference between groups in our prospective study.

PAI-1 is a major inhibitor of fibrinolysis and high levels of PAI-1 activity have been associated with an increased risk of coronary disease, stroke, and thromboembolism due to hypofibrinolysis.[8] Even though there are several studies investigating the PAI-1 polymorphisms (4G/4G and 4G/5G) as a risk factor for RVO and NAION, most of these studies did not report PAI-1 levels.[22,44-47] Thus, there is limited data for the association of PAI-1 levels and RVO and even less data about the relationship between PAI-1 and NAION. While both Glueck et al. and Prisco et al. showed that high levels of PAI-1 were an independent risk factor for RVO, there has only been a single case report associated with high PAI-1 levels in a patient with NAION that presented concurrently with CRVO, to the best of our knowledge.[5,48,49] In this current study, while PAI-1 levels were higher in both RVO and NAION groups, the difference did not reach statistical significance, which may be attributed to the small sample size.

Age is another significant contributor to both pathologies and has been extensively researched in large epidemiological studies. The Beaver Dam Eye Study, a landmark epidemiological study, concluded that while the incidence of BRVO/CRVO increased with age, there was no statistically significant difference in the frequency of the disease between male and female participants.[13] In another study evaluating 1229 patients with BRVO/CRVO, Hayreh et al. observed that 51% of the patients were aged 65 and above.[12] Similarly, another study by Hayreh found that the incidence of NAION was 11% in patients under the age of 45, 49% between the ages of 45 and 65, and 40% in those aged 65 and above. In our study, while there was no difference in the mean age between groups, 84.6% (n=11) of patients with RVO and 70.6% (n=12) of patients with NAION were over the age of 50.[11] Considering the effects of aging on the vascular system, it is notable that the incidence of both pathologies increase with older

ages. However, it should not be forgotten that various predisposing factors including DM, HT, and thrombophilic diseases may lead to encountering these conditions at earlier ages as well.

Study Limitations

A small number of participants in each group and also lack of homocysteine levels and PAI-1 polymorphisms can be considered as major limitations of this current study.

Conclusion

In this prospective study, MTHFR C677T mutation was the only thrombophilic etiology more frequent in RVO and NAION patients compared to controls. Even though PAI-1 levels were also higher in these groups, the difference did not reach statistical significance. The role of thrombophilic factors in ocular vascular diseases still remains controversial and further studies with larger cohorts are necessary to clarify these associations.

Ethics Committee Approval: This study was approved by Eskisehir Osmangazi University Faculty of Medicine Ethics Committee (November 24, 2014; IRB number: 80558721/290).

Peer-review: Externally peer-reviewed.

Authorship Contributions: Concept: N.D.K., D.T.C., A.M., A.O.; Design: N.D.K., D.T.C., A.M., A.O.; Supervision: N.D.K., D.T.C., A.M., A.O.; Resource: N.D.K.; Materials: N.D.K., D.T.C.; Data Collection and/or Processing: N.D.K., A.O.; Analysis and/or Interpretation: N.D.K., D.T.C., A.M.; Literature Search: N.D.K.; Writing: N.D.K.; Critical Reviews: A.O.

Conflict of Interest: None declared.

Use of AI for Writing Assistance: Not declared.

Financial Disclosure: The authors declared that this study received no financial support.

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