Retinal vessel occlusion (RVO) is an eye disease that leads to decreased visual acuity, ultimately resulting in blindness. It is observed in 1%-2% of individuals above the age of 40 years. The etiology of RVO remains unclear. However, the most widely recognized risk factors include age, hypertension, hyperlipidemia, atherosclerosis, cardiovascular diseases, and diabetes. The number of patients with RVO among the young population has increased in recent years; hence, more attention has been focused on the genetic factors. Polymorphisms in the genes encoding proteins involved in the vitamin K cycle are among the genetic factors that may influence RVO. According to literature, the G1639A polymorphism in the vitamin K epoxide reductase complex subunit 1 (vKoRc1) is a possible risk factor for RVO. Purpose. To estimate the association between carriers of the G1639A form of vKoRc1 and the development of venous RVO (VRVO) and arterial RVO (ARVO). Materials and methods. The study included 126 patients aged between 40 and 80 years, mean age 61.5 years. Genotyping for the presence of the G1639A polymorphism of vKoRc1 was performed using polymerase chain reaction, and statistical analysis was performed using the Instat program. Results. The GG genotype of G1639A was found to be significantly more common in patients with VRVO or ARVO than in those of the control group (VRVO, 42.6%; ARVO, 60%; control group, 32%; p = 0.0449 for VRVO, and p = 0.0925 for ARVO). However, the AA genotype was significantly less common in patients with VRVO or ARVO than in those of the control group (VRVO, 9.8%; ARVO, 6.7%; control group, 28%; p = 0.0238 for VRVO and p = 0.1593 for ARVO, RR 2.015, 95% confidence interval 1.011-4.16). Conclusions. Our study demonstrates that the GG genotypic form of the G1639A polymorphism of VKORC1 is associated with the development of VRVO and possibly ARVO. However, the AA genotypic form of this polymorphism is not closely associated with the development of VRVO or ARVO.

Key words: retinal vessel occlusion; vitamin K; genotyping; thrombosis; vKoRc1-gene.
BACKGROUND

Retinal vessel occlusion (RVO) (including artery occlusion and vein occlusion) is a severe multifactorial eye disorder that leads to permanent vision loss. RVO is associated with cardiovascular diseases, such as hypertension, atherosclerosis, and diabetes mellitus [1, 2]. Nearly 16 million of the world's adults suffer from this disease, and most of the afflicted are over 40 years old. Besides decreasing visual acuity, this pathological condition can also lead to severe complications, such as neovascular glaucoma, hemophthalmos, and cystoid macular edema, which can cause disability [3]. The main factors in RVO pathogenesis are mechanical compression of the central retinal vein, changes in the vessel wall, increased blood viscosity, intravascular factors, hypercoagulability syndrome, and thrombophilia [4]. Women taking oral contraceptives or undergoing hormonal therapy, as well as those who are pregnant or in the postpartum period are at increased risk of thrombosis [5, 6].

Hereditary factors also play an important role in the development of RVO; a growing incidence of acute circulatory disorders in retinal vessels among younger populations has been observed in recent years. Therefore, greater attention has been focused on polymorphisms in genes encoding proteins that regulate blood coagulation, which could lead to changes in hemodynamics [7–10]. In recent years, researchers have paid particular attention to the role of polymorphisms in the genes involved in the vitamin K cycle in the development of RVO. Vitamin K is a necessary cofactor for the clotting factors II, VII, IX, and X, as well as for proteins C and S in the anticoagulant system. According to currently available data, the 1639G4A polymorphism in the gene encoding vitamin K epoxide reductase complex subunit 1 (VKORC1) is a new possible risk factor for RVO [11]; however, detailed data for arterial RVO are lacking.

Objective: To estimate the association between different VKORC1 genotypes (based on the detection of G1639A polymorphism) and the development of arterial and venous RVO.

MATERIALS AND METHODS

One hundred and twenty patients aged 40-80 years (mean age, 61.5 years) were enrolled. The first group comprised 61 patients with venous RVO (VRVO); of these, 48 had ischemic thrombosis and 13 had non-ischemic thrombosis. The second group comprised 15 patients with arterial RVO (ARVO). The third group was a control one and included 50 people with no vascular pathology in the retina. Detection of the G1639A polymorphism in the VKORC1 gene was conducted using PCR-RFLP (restriction fragment length polymorphism) after initial isolation of DNA from peripheral blood leukocytes. Nonparametric statistical methods (bilateral exact Fisher test, chi-square) were used to assess the significance of the observed differences. The analysis was performed using the Instat program.
RESULTS

Among patients with VRVO, 26 (42.6%) had the GG genotype, 29 (47.5%) the GA genotype, and 6 (9.8%) the AA genotype. Among patients with ARVO, 9 (60%) had the GG genotype, 5 (33.5%) the GA genotype, and 1 (6.6%) the AA genotype. The distribution of genotype frequency in all patient groups was in accordance with the Hardy–Weinberg law \((p > 0.05)\). In the control group, 16 (32%) individuals had the GG genotype, 20 (40%) the GA genotype, and 14 (28%) the AA genotype (Table 1).

Comparison of the vKoRc1 genotype distribution (based on the detection of G1639A polymorphism) in the groups showed that the GG genotype was significantly more common in patients with VRVO than in those with no vascular pathology in the retina \((42.6\text{ vs } 32\%, p = 0.0449)\). The frequency of the GG genotype was higher in patients with ARVO than in the controls \((60\text{ vs } 32\%, p = 0.0925)\). No differences in genotype frequency were observed between VRVO and ARVO groups \((p = 0.4810)\).

Among patients with VRVO, 6 (9.8%) had the AA genotype and 55 (90.2%) had non-AA genotypes \((26 \text{ had GG, 29 GA})\). Among patients with ARVO, 1 (6.7%) had the AA genotype and 14 (93.3%) had non-AA genotypes \((9 \text{ had GG, 5 GA})\). The distribution of genotype frequency in all patient groups was in accordance with the Hardy–Weinberg law \((p > 0.05)\) (Table 2).

The AA genotype of the vKoRc1 gene was found to be significantly less common in patients with VRVO than in those with no retinal vascular pathology \((9.8 \text{ vs } 28\%, p = 0.0238, RR = 2.015, 95\% \text{ CI } 1.011-4.16)\).

The AA genotype was less common in patients with ARVO than in controls \((6.7 \text{ vs } 28\%, p = 0.1593)\). There was no significant difference in AA genotype frequency between patients with venous RVO and arterial RVO \((42.6 \text{ vs } 32\%, p = 1)\).

Among patients with VRVO, 26 (42.6%) had the GG genotype and 35 (57.4%) had non-GG genotypes \((29 \text{ had GA, 6 AA})\). Among patients with ARVO, 9 (60%) had the GG genotype and 6 (57.4%) had non-GG genotypes \((5 \text{ had GA, 1 AA})\). The distribution of genotype frequency in all patient groups was in accordance with the Hardy–Weinberg law \((p > 0.05)\) (Table 3).

<table>
<thead>
<tr>
<th>Genotype</th>
<th>VRVO (n = 61)</th>
<th>ARVO (n = 15)</th>
<th>Control group (n = 55)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GG</td>
<td>26 (42.6%)</td>
<td>9 (60%)</td>
<td>16 (32%)</td>
</tr>
<tr>
<td>GA</td>
<td>29 (47.5%)</td>
<td>5 (33.5%)</td>
<td>20 (40%)</td>
</tr>
<tr>
<td>AA</td>
<td>6 (9.8%)</td>
<td>1 (6.6%)</td>
<td>14 (28%)</td>
</tr>
</tbody>
</table>

VRVO – venous retinal vessel occlusion, ARVO – arterial retinal vessel occlusion; \(p > 0.05\) according to the Hardy–Weinberg law in all groups

<table>
<thead>
<tr>
<th>Genotype</th>
<th>VRVO</th>
<th>ARVO</th>
</tr>
</thead>
<tbody>
<tr>
<td>AA</td>
<td>6 (9.8%)</td>
<td>1 (6.7%)</td>
</tr>
<tr>
<td>GA + GG</td>
<td>55 (90.2%)</td>
<td>14 (93.3%)</td>
</tr>
</tbody>
</table>

VRVO – venous retinal vessel occlusion, ARVO – arterial retinal vessel occlusion; \(p > 0.05\) According to the Hardy–Weinberg law in all groups
Comparison of the vkOrCl genotype distribution (based on the detection of G1639A polymorphism) in the groups showed that the GG genotype was more common in patients with arterial RVO compared to individuals with no retinal vascular pathology (60 vs 32%, $p = 0.0708$). No statistically significant difference was observed in the frequency of the GG genotype between patients with venous RVO and the controls (42.6 vs 32%, $p = 0.3258$). There was also no difference in genotype frequency between patients with VRVO and those with ARVO ($p = 0.2592$).

**CONCLUSION**

The GG genotype of the vkOrCl gene (based on the detection of G1639A polymorphism) was found to be more common in patients with retinal vein occlusion; this is in agreement with previously published data from our foreign colleagues [12, 13]. Similar genotyping results were obtained in patients with ARVO; however, the difference was not statistically significant due to the small number of cases. The study demonstrated that carriage of the mutant A allele (GA and AA genotypes) is equally common in patients with retinal vascular disorders and in healthy people. However, the AA genotype was significantly less frequent among individuals with RVO, especially in cases of arterial embolism. Since the 1639AA genotype of the vkOrCl gene is associated with a hypercoagulation shift in hemostasis, we can hypothesize that the presence of this mutation reduces the risk of RVO, and is a protective genetic factor.

**REFERENCES**

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