Sistemski dejavniki tveganja pri bolnikih mlajših, od 50 let, z zaporo mrežnične vene

Systemic risk factors in patients younger than 50 years with retinal vein occlusionsl

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Key words:
etinal vein occlusion, risk factor, dyslipidemia, thrombophylia

Izvleček

Namen: *Predstaviti dejavnike tveganja pri bolnikih, mlajših od 50 let, z zaporo mrežnične vene (RVO).*
Metode: *Opravljena je bila retrospektivna analiza medicinske dokumentacije bolnikov z zaporo mrežnične vene od januarja 2015 do decembra 2020. Bolniki so bili mlajši od 50 let. Preučili smo podatke o sistemskih in očesnih obolenjih, zdravilih, trombofiliji ali hiperviskoznem sindromu in vaskulitisih. Vsi bolniki so imeli opravljen očesni in sistemski pregled, vključno z določitvijo testov trombofilije.*
Rezultati: *V raziskavo je bilo zajetih 20 bolnikov (22 oči), od tega je bilo 15 moških (71 %) in 6 žensk (29 %). Povprečna starost bolnikov je bila 42 let. Pri 12 očeh (60 %) je bila ugotovljena zapora centralne mrežnične vene (CRVO), pri 10 očeh (40 %) pa zapora veje mrežnične vene (BRVO). Dva bolnika sta imela obojestransko BRVO. Arterijska hipertenzija je bila*

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Abstract

Purpose: *To identify the etiological factors of patients with retinal vein occlusion (RVO) younger than 50 years.*
Methods: *The clinical records of patients with RVO under the age of 50 years seen between January 2015 and December 2020 were analyzed retrospectively. Past medical history, drug use, thrombophilic features, hyperviscosity syndromes, and pathologies that may have caused vasculitis were noted. All patients underwent ocular and systemic examinations, as well as complete screening for thrombophilic risk factors.*
Results: *A total of 20 patients (22 eyes) were recruited in the study, 14 (70%) of whom were male and seven (30%) were female. The mean age was 42 years. The diagnosis was central retinal vein occlusion (CRVO) in 12 eyes (60%) and branch retinal vein occlusion (BRVO) in 10 eyes (40%). Two patients had bilateral BRVO. Hypertension was determined in eight (38%) patients,*

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ugotovljena pri 8 bolnikih (38 %), sladkorna bolezen pri 2 bolnikih (9,5 %) in dislipidemija pri 11 bolnikih (52 %). Pri eni bolnici (5 %) je bila ugotovljena mutacija faktorja V Leiden. Pri 2 bolnikih z RVO sta bili diagnosticirani Behcetova (5 %) in Ealesova bolezen (5 %). 2 bolnika (10 %) sta imela pridružen pigmentni glavkom. Več dejavnikov tveganja je bilo prisotnih pri 10 bolnikih (48 %), medtem ko 4 bolniki niso imeli dejavnika tveganja (19 %).

Zaključek: *Najpogostejši dejavnik tveganja v naši raziskavi je bila dislipidemija. Trombofilija je bila ugotovljena le pri eni bolnici s CRVO. Pri mlajših bolnikih z RVO je pomembno pozorno preučiti dejavnike tveganja.*

diabetes mellitus in two (9.5%) patients, and dyslipidemia in 11 (52%) patients. Mutation of factor V Leiden was found in one (5%) patient. An ocular risk factor was pigmentary glaucoma in two (10%) patients. Other diseases that were also noted included Behcet's (5%) and Eale's disease (5%). Multiple etiological factors were detected in 10 (48%) patients. No risk factors were found in only four (19%) patients.

Conclusion: *Dyslipidemia was the most prevalent risk factor for RVO. Work-up for the etiology of RVO in younger patients may reveal nontraditional risk factors for retinal vein occlusion. It was particularly interesting that thrombophilic disorder was found in only one female CRVO patient. Etiological factors that might result in RVO in young individuals should therefore be investigated in detail.*

INTRODUCTION

Retinal vein occlusion (RVO) is the second most common retinal vascular disease after diabetic retinopathy. Although RVO is frequently seen in people older than 65 years, it is an important reason for vision loss that may also affect young people, and is often associated with arteriosclerotic diseases and glaucoma. A minority of patients, approximately 10%–15%, are typically younger than 50 years of age, representing a significant number of working-age adults (1).

Traditional risk factors for RVO include advancing age, hypertension, diabetes mellitus, hyperlipidemia, and glaucoma. Several studies have also suggested potential roles of hypercoagulable and inflammatory conditions in the pathogenesis of central retinal vein occlusion (CRVO), although other reports have provided contradicting results (2).

RVOs are classified as central, hemi-central, and branch occlusions according to the level of occlusion. While occlusion is found at the disc level in central and hemi-central vein occlusions, in branch retinal vein occlusion (BRVO) it is at the arteriovenous crossing point (3).

Different types of RVOs share the same characteristics on fundus evaluation, such as vein dilatation, hemorrhage, edema, and vascular stasis, most commonly in the painless eye presenting with variable degrees of vision alterations (4).

CRVO is typically associated with loss of vision in one eye. Retinal vein dilatation and tortuosity due to an increase in the diameter and length of retinal veins and venules are found on fundus examination and color fundus photographs. Variable degrees of hemorrhage from the optic nerve head to the extreme periphery of the retina are present. Hemorrhages can appear flame-shaped (superficial) or as deep blots (ischemic). The optic nerve head and macular edema can also be present as cotton-wool spots (Figure 1, Figure 2). Hemiretinal vein occlusions display similar signs in only half of retinas (4).

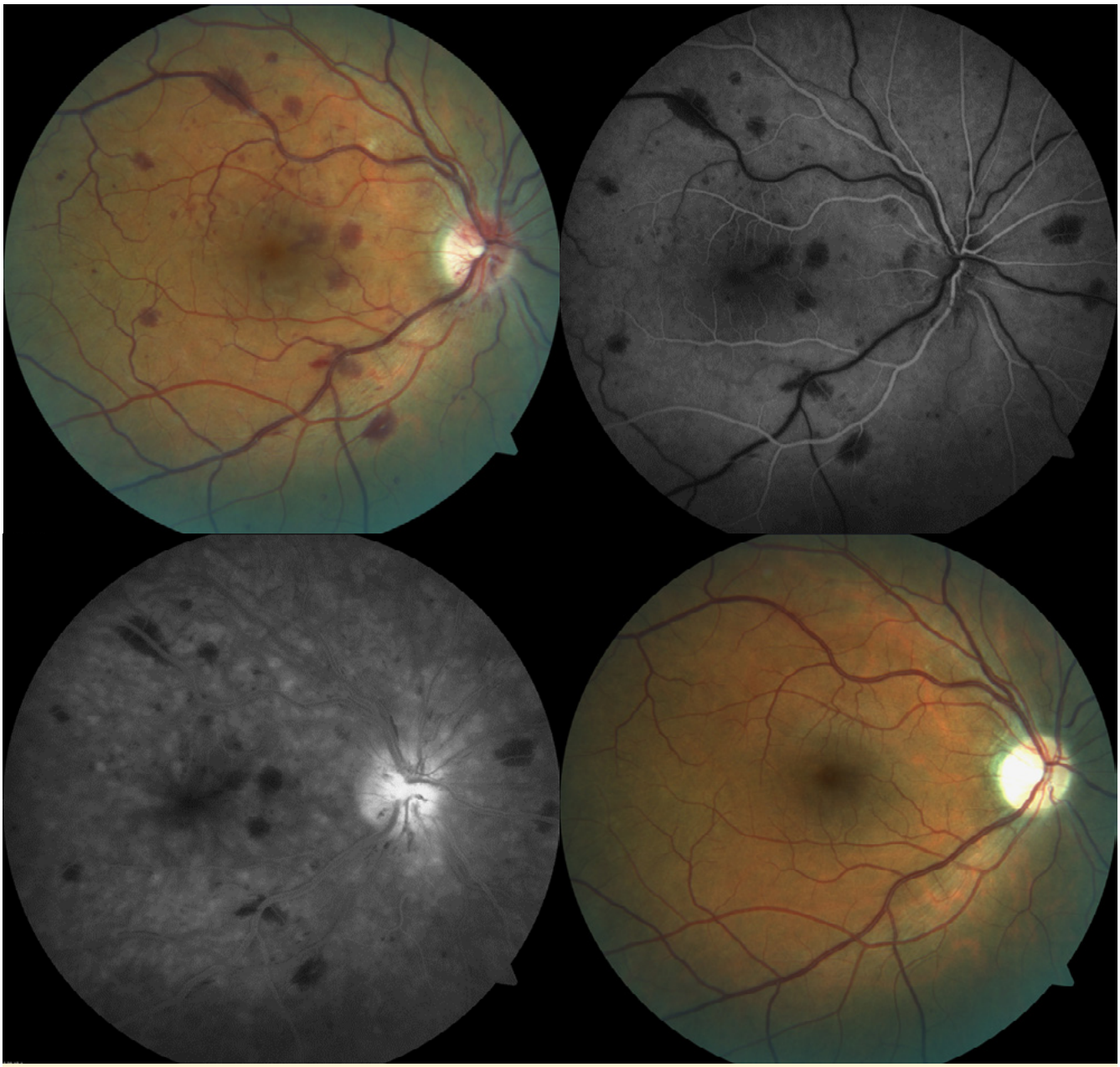

Figure 1. *Non-ischemic central retinal vein occlusion in a 40-year-old man with 20/23 visual acuity in the right eye. A color image of the retina shows retinal vein dilatation and tortuosity and optic nerve head edema but only moderate intraretinal hemorrhaging (top left). Fluorescein angiogram shows a late filling of veins but no signs of non-perfusion (top right). Late image (bottom left) showing staining of the disc and veins. There is also leaking within the macula. The same eye 5 months later (bottom right) with resolution of hemorrhaging and disc edema. Visual acuity was 20/20.*

Patients with BRVO suffer visual field defects or blurred vision. Signs of vein occlusion are found in the fundus in the area upstream of an arteriovenous crossing, which is considered as the site of occlusion. The location and size of the BRVO area differs from a small area upstream of a small venule to the total hemiretina. If macular drainage is not involved and the edema does not reach the macula, visual acuity (VA) can remain normal (4).

MATERIALS AND METHODS

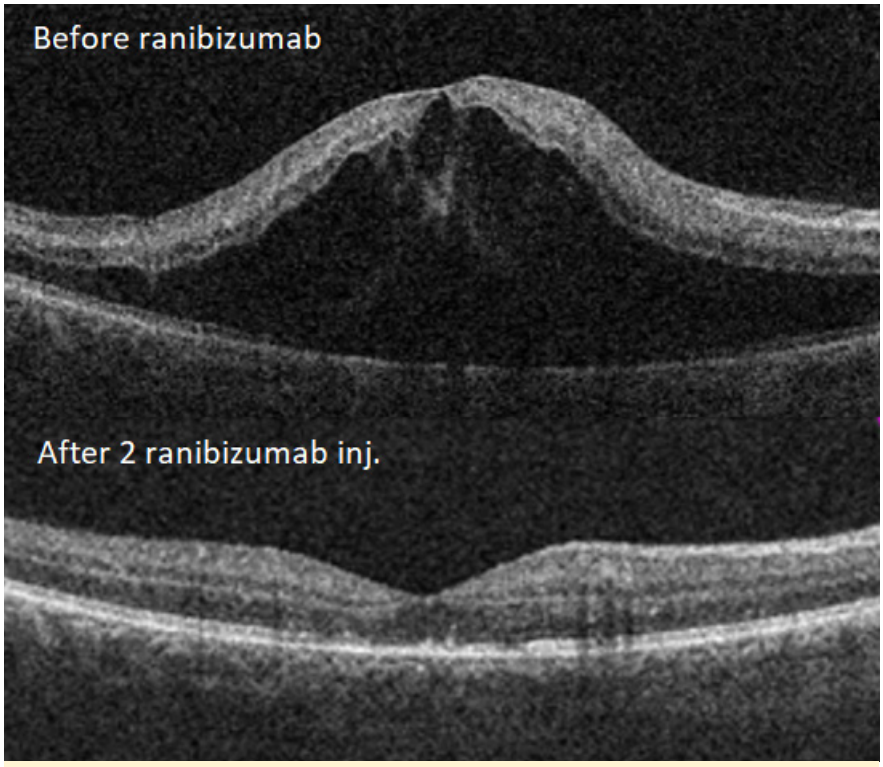

Figure 2. *Optical coherence tomography of the right eye shows macular edema (central foveal thickness: more than 700 µm) Optical coherence tomography of the left eye after 8 weeks after two monthly ranibizumab injections (central foveal thickness: 253µm).*

This retrospective study included patients diagnosed with BRVO or CRVO presenting at the Department of Ophthalmology over a period of 5 years, from January 2015 to December 2020. Patients 50 years of age and younger were included. The primary aim of this study was to evaluate systemic and ocular risk factors for RVO, specifically in young adults between 18 and 50 years of age. The secondary goal was to determine demographic variables associated with RVO. All patients had undergone ocular and systemic investigations to identify possible associations with systemic risk factors.

The following data were obtained: age, sex, history of smoking, history of using/taking oral contraceptive pills in female patients, association with systemic diseases, fundus appearance, type of RVO, site of occlusion, best-corrected visual acuity (BCVA) (baseline and at the most recent follow-up), glaucoma, occurrence of intraocular neovascularization (NV), and the results of treatment. The attending internists, cardiologists, and rheumatologists confirmed definite diagnoses of the associated systemic abnormalities.

All RVO patients underwent the following ocular and systemic investigations.

Ocular examination

All patients underwent a full ophthalmological examination, including BCVA, measurement of intraocular pressure (Goldmann applanation tonometry), attention to the absence or presence of an afferent pupillary defect, an iris examination and gonioscopy to eliminate neovascularization, and a fundus examination. The diagnosis of RVO was made clinically at the time of patient presentation. The diagnosis of CRVO was made clinically at the time of patient presentation based on venous dilation and tortuosity, four quadrants of intraretinal hemorrhage, and angiographic evidence of the impaired venous return. In BRVO, signs of vein occlusion were found in the fundus area upstream of an arteriovenous crossing, which was considered as the site of the occlusion. The diagnosis of RVO was confirmed in all cases by review of fluorescein angiograms or color fundus photographs. An intravenous bolus injection of sodium fluorescein solution (2 mL of 25% solution) was given when performing the flourescein angiography (FA). According to the Central Retinal Vein Occlusion Study, photographs were taken of the central fundus and of the midperiphery in all four quadrants. The disc area (DA) was used as a reference area when evaluating the degree of ischemia. Less than 10 DA of capillary

dropout was considered as non-ischemic CRVO. FA was performed in 20 patients. The patients studied were subdivided into the two groups: non-ischemic and ischemic RVO.

Systemic investigation

The systemic work-up for patients with retinal vein occlusions included a thorough medical history, including the history of any previous thrombotic events (such as deep vein thrombosis, pulmonary embolism, or miscarriage), oral contraceptives, alcohol intake, fasting, and intense exercise at the initial visit. The systemic examination included a general physical examination, routine blood and urine tests, a hematological work-up, fasting serum glucose and lipid levels, blood pressure, and an electrocardiogram, as well as clinical consultations with a cardiologist, rheumatologist or neurologist if required. Systemic hypertension, diabetes mellitus, and hyperlipidemia were defined as pre-existing diseases for which patients were treated. All patients underwent complete screening for thrombophilic risk factors, including factor V Leiden and prothrombin gene mutation, protein C, S and antithrombin deficiency, and analysis of homocysteine, anticardiolipin antibodies and lupus anticoagulant. Dehydration was confirmed if a patient developed CRVO following an episode of dehydration as a result of high alcohol intake or intense exercise without proper rehydrating, and if general medical examinations as well as analyses of thrombophilic factors were negative.

RESULTS

A total of 20 patients (22 eyes) were recruited in the study. Twelve patients were diagnosed with CRVO and eight patients were diagnosed with BRVO. Two patients had bilateral BRVO. This resulted in 12 CRVO eyes (60%) and 10 BRVO eyes (40%) for investigation.

The mean age was 42 years (range, 29–50 years),

Table 1. *Demographic data of patients*

	CRVO (n=12), n(60%)	BRVO (n=8), n(40%)
Gender		
Male	9 (75%)	5 (62.5%)
Female	3 (25%)	3 (37.5%)
Age		
≤30	1 (8%)	
31-40	2 (17%)	3 (37.5%)
41-50	9 (75%)	5 (62.5%)
Mean age	43	44

BRVO = branch retinal vein occlusion; CRVO = central retinal vein occlusion.

Table 2. *Distribution of etiological factors.*

Etiological factors	CRVO (n=12)	BRVO (n=8)	RVO (n=20)
No systemic diseases	3		3 (15%)
Atherosclerotic diseases			
Hyperlipidemia	6	5	11 (55%)
Hypertension	3	4	7 (35%)
Diabetes mellitus	1	1	2 (10%)
Thrombophilic disorders			
Factor V Leiden mutation	1		1 (5%)
Other diseases			
Bechet's disease		1	1 (5%)
Dehydration	1		1 (5%)
Ocular findings		1	1 (5%)
Glaucoma			3 (15%)
POAG		1	
PG	1	1	
Retinal vasculitis (Eales disease)		1	1 (5%)

RVO = retinal vein occlusion; POAG = primary open angle glaucoma; PG = pigmentary glaucoma.

14 (70%) of whom were male and six (30%) were female. The mean age of the patients was 43 years in the CRVO group and 44 years in the BRVO group. The youngest patient in the CRVO group was a male patient 29 years of age and in the BRVO group, a male patient 37 years of age. Subgroup analysis was further performed on both CRVO and BRVO patients. The patients were divided into three subgroups depending on the age at presentation (ages ≤ 30, 31–40, and 41–50 years). It was noted that CRVO and BRVO increased with increasing age. The demographic data of these patients are shown in Table 1.

Fundus findings were similar to RVO in the elderly. There were diffuse retinal vein tortuosity and retinal hemorrhage in CRVO, and localized lesions in BRVO patients. Disc swelling was noted in nine (75%) CRVO cases. In BRVO eyes, the common site of occlusion was the superotemporal branch in five eyes, the inferotemporal branch in two eyes, the inferonasal branch in one eye, and the superonasal branch in one eye. Twelve eyes (60%) were nonischemic at the time of presentation and 10 eyes (40%) had evidence of retinal ischemia on fluorescein angiograms at presentation. Three patients with ischemic BRVO developed neovascularization of the posterior segment, and were subsequently treated with retinal photocoagulation.

Systemic abnormalities associated with RVO are shown in Table 2. In six of the 20 patients (30%), a systemic disease was known at the time of presentation. Hypertension was determined in seven (35%) patients, diabetes mellitus in two (10%) patients, and hyperlipidemia in 11 (55%) patients. Multiple etiological factors were detected in 10 (50%) patients. In 14 patients with no known systemic disease at presentation, a systemic medical evaluation was performed and a systemic abnormality was discovered in 10 patients. No risk factors were only found in three (15%) patients. One patient with nonischemic BRVO had a history of stroke at the age of 28 years, and was treated with systemic anticoagulant therapy. One patient with ischemic BRVO had coronary artery disease and a history of myocardial infarction at the age of 45 years. Mutation of factor V Leiden was found in one (5%) female patient with CRVO. Protein C and protein S deficiencies were not found in any patient. One patient with CRVO suffered from dehydration resulting from intense exercise. Other diseases that were also noted included Behcet's and Eale's diseases. There were two smokers in both groups. Most patients had missing data on smoking history.

It was noted that atherosclerotic diseases remained the major associated systemic diseases in both CRVO and BRVO patients. Furthermore, it increased with advancing age. Hyperlipidemia and hypertension were the most common systemic diseases in both CRVO and BRVO patients. It was particularly interesting that thrombophilic disorder was found in only one female patient, whose age was 42 years.

The most prevalent ocular risk factors were pigmentary glaucoma (PG) and primary open angle glaucoma (POAG), which were found in three (15%) patients with RVO (two had PG and one had POAG). Of the 12 patients studied, 10 (75%) had non-ischemic CRVO and two (25%) had ischemic CRVO. Seven patients with non-ischemic CRVO and one patient with ischemic CRVO had no systemic disease or other conditions associated with CRVO at the time of presentation. Of those seven patients, no risk factors were found in three patients. In the ischemic CRVO patients, one patient without known diseases was found to have hyperlipidemia and hypertension, and one patient had known but nontreated hypertension.

DISCUSSION

Systemic diseases and RVO

RVO is rising due to an increase of systemic vascular risk factors in the elderly, and systemic hypertension is the vascular pathology that is most associated with RVO in this group. Other important systemic risk factors for RVO are hyperlipidemia and diabetes mellitus. However, distribution of risk factors in RVO patients under the age of 50 years significantly varies and should be evaluated in a broader perspective. Compared to older adults, hypertension and diabetes mellitus are not prevalent in young adults with RVO. Our study presented the etiological results in terms of

RVO in young patients who were diagnosed before the age of 50 years.

RVO is the result of thrombus formation at an anatomically vulnerable location. In the case of CRVO, the central retinal artery and vein have a close relationship, sharing a common fibrous sheath as they course through the optic nerve. Normal laminar flow in the central retinal vein is compromised, whether from anatomic variations in the relationship between the artery and vein, or atherosclerotic disease in the artery compressing the vein with thrombus potentially forming. The location of thrombus is critical, because locations more posterior to the lamina cribosa are typically less ischemic than a thrombus nearer the lamina cribosa due to the availability of venous tributaries, which are nearly nonexistent at the lamina cribosa (1).

In our study, hypertension was determined in eight (38%) patients, diabetes mellitus in two (9.5%) patients, and hyperlipidemia in 11 (52%) patients. These results are very similar to those reported by Chen et al. in which traditional risk factors such as hypertension and diabetes mellitus did not pose significant risks, whereas hyperlipidemia was a significant risk factor (2).

In contrast, a study published by Wittstrom reported the results of 22 Swedish CRVO patients aged 50 years or younger. More than half of the patients had a treatable systemic disease, with systemic hypertension being the most prevalent systemic risk factor for CRVO, followed by diabetes mellitus and hyperlipidemia (5, 6). These results are very similar to those reported by Fong et al. and Klein et al. (7,8). Quinlan et al. also found systemic hypertension to be the most predominant underlying condition for CRVO in patients under 50 years of age (9). In two previous studies of younger CRVO patients, the prevalence of systemic hypertension was almost the same as in the present study, but hyperlipidemia was reported as the predominantly associated medical condition (10,11).

Hypercoagulable states and CRVO

In younger patients without known cardiovascular risk factors or significant atherosclerosis, the pathophysiology of CRVO remains unclear. However, it was hypothesized that unprovoked thrombus formation in the central retinal vein secondary to a hypercoagulable state may contribute to developing CRVO in these patients. The most common of these conditions include hyperhomocysteinemia, anticardiolipin antibodies, protein C or protein S deficiencies, Factor V Leiden, prothrombin mutation, and others. Extensive hypercoagulability work-up is usually suggested if older patients do not possess any of the traditional risk factors, if the patient is younger than 50 years, has bilateral CRVO or a prior history, or a family history of thrombosis (12).

We analyzed the hypercoagulable state in all patients comprising primary and secondary causes of hypercoagulability; however no cases of secondary hypercoagulable state were identified. In our study, a heterozygous factor V mutation was detected in one female patient with CRVO, who was treated with anticoagulant medication.

Contradictory findings have been reported in laboratory evaluations of patients with RVO. Gottlieb at al. found no increase in the prevalence of resistance to activated protein C (APC) or factor V Leiden in a study of blood samples from CRVO patients younger than 50 years. Their finding of APC resistance in only one of 21 patients (4.7%) was similar to that found in a general population and in our study (10). In contrast, Lahey et al. found that the percentage of positive hypercoagulable tests was higher in a study population with CRVO than age-matched controls. Fifteen of 55 patients (27%) younger than 56 years of age had one positive test result, which suggested hypercoagulability. They found that hyperhomocysteinemia and antiphospholipid antibodies were significantly more common in CRVO patients than in age-matched controls (13).

Different studies have reported that factor V Leiden and prothrombin gene mutations are associated with the development of RVO (14,15,16). Among these, factor V Leiden mutation is the genetic factor that causes thrombosis most frequently. This mutation is seen in 5% of Caucasians. When this mutation occurs, protein C becomes resistance to enzymatic degradation and causes hypercoagulability. It was reported that this mutation increased the risk of thrombosis 3–8-

fold in patients who were heterozygous and 80-fold in patients who were homozygous. Turelo et al. detected heterozygous factor V mutations in 8.2% of patients with RVO (17).

Prothrombin gene mutation may increase the thrombosis risk 3-fold by causing excess prothrombin production. It is the most frequent mutation seen after Factor V Leiden mutation.

Inflammatory conditions and CRVO

Systemic inflammatory disorders that cause retinal vasculitis including Behcet's disease, polyarteritis nodosa, sarcoidosis, granulomatosis with polyangiitis (Wegener's disease) and Goodpasture's syndrome may also be responsible for RVO (4).

BRVO secondary to retinal vasculitis associated with systemic disorders was found in our study in one patient with Behcet's disease and in one patient with Eale's disease. Historically, CRVO in younger patients (typically less than 45 years of age) was named papillophlebitis, and the condition was thought to arise from localized vasculitis. However, histopathological studies of eyes from younger patients in which CRVO was diagnosed showed no evidence of vasculitis, but instead showed chronic inflammatory changes in the vessel walls, which was similar to older patients. Other than vein occlusion secondary to retinal vasculitis associated with systemic disorders (sarcoidosis, Behcet's disease, and syphilis), the majority of CRVOs in younger patients are therefore not thought to result from a vasculitis process (1,17,18, 19).

In the development of RVO, another risk factor is sex. As in other vascular diseases, male patients are more susceptible to RVO. In their studies consisting of 103 cases, Fong et al. reported that 64% of the patients were male (7). In our study, 71% of the patients were male and 29% of them were female. However, there are studies indicating that RVO is more common in females (8).

Standard work-up for younger patients with RVO should consist of the normal battery of ophthalmic testing as described above. Systemic testing should focus on identifying those patients who present with a negative medical history, assessing for hypertension, hypercholesterolemia, diabetes mellitus, body mass index (BMI), and smoking status. Several studies in younger patients with CRVO or BRVO have shown that systemic risk factors such as hypertension, hyperlipidemia, elevated BMI, and diabetes are found less frequently than in older patients, but still occur in significant numbers (19,20, 21). Screening for the aforementioned diseases is probably more effective than characterizing a hypercoagulable defect, which may or may not have any clinical relevance. Naturally, in patients with a previous thrombotic history or strong family history of thrombophilia, laboratory work-up is appropriate (1, 22).

CONCLUSION

The results in our study provided some indications that young RVO patients had clinical manifestations and associated systemic diseases not much different from RVO in elderly patients. Atherosclerotic diseases remain a major problem in the same way as reported in the elderly. The association of RVO with systemic cardiovascular diseases emphasizes the need to investigate cardiovascular risk factors in these younger patients. Evaluations should include a screening for hypertension, diabetes mellitus, and lipid abnormalities.

Thrombophilias are typically rare and sporadic in younger patients, but should also be considered when no obvious atherosclerotic diseases are found or if the patient is younger than 40 years, and has a history of thrombosis or a family history of thrombosis. For those at increased risk, laboratory work-up is warranted, and involvement of the patient's primary care provider is critical in optimizing systemic therapies.

REFERENCES

1. Lindsell LB, Lai MM, Fine HF. Current concepts in managing retinal vein occlusion in young patients. Ophthalmic Surgery, Lasers and imaging retina. 2015;46(7):695-701.
2. Chen TY, Uppuluri A, Zarbin MA, Bhagat N. Risk factors for central retinal vein occlusion in young adults. Eur J Ophthalmol. 2021 Sep;31(5):2546-2555.
3. Nalcaci S, Degirmenci C, Akkin C, Mentes J. Etiological factors in young patients with retinal vein occlusion. Pak J Med Sci. 2019:35(5):1397-401.
4. Schmidt-Erfurth U, Garcia-Arumi J, Gerendas BS, Midena E, Sivaprasad S, Tadayoni R et al. Guidelines for the Management of Retinal Vein Occlusion by the European Society of Retina Specialists (EURETINA). Ophthalmologica. 2019;242(3):123-62.
5. Lai MM. Retinal vein occlusions in younger patients are strongly associated with systemic risk factors. Retina today.2008;68-9.
6. Wittstrom E. Central retinal vein occlusion in younger swedish adults: case reports and review of the literature. Open ophthalmology journal. 2017;11:89-102.
7. Fong A, Schatz H. Central retinal vein occlusion in young adults. Survey of ophthalmology. 1993;37(6):393-417.
8. Klein R, Moss SE, Meuer SM, Klein BE. The 15-year cumulative incidence of retinal vein occlusion: the Beaver Dam Eye Study. Arch Ophthalmol. 2008;126(4):513-8.
9. Quinlan PM, Elman MJ, Bhatt AK, Mardesich P, Enger C. The natural course of central retinal vein occlusion. Am J Ophthalmol. 1990;110:118-23.
10. Dodson PM, Kirtzinger EE. Underlying medical conditions in young patients and ethnic differences in retinal vein occlusion. Trans Ophthalmol Soc UK. 1985;104:114-9.
11. Kuo JZ, Lai CC, Ong FS, Shih CP, Yeung L, Chen TL et al. Central retinal vein occlusion in young Chinese population: risk factors and associated morbidity and mortality. Retina. 2010;30:479-84.
12. Gottlieb JL, Blice JP, Mestichelli B, Konkle BA, Benson WE. Activated protein C resistance, factor V Leiden, and central retinal vein occlusion in young adults. Arch Ophthalmol.1998:116(5):577-79.
13. Lahey JM, Tunç M, Kearney J, Modlinski B, Koo H, Johnson RN et al. Laboratory evaluation of hypercoagulable states in patients with central retinal vein occlusion who are less than 56 years of age. Ophthalmology.2002;109(1):126-31.
14. Ahluwalia J, Rao S, Varma S, Gupta A. Thrombophilic risk factors are uncommon in young patients with retinal vein occlusion. Retina. 2015;35:715-9.
15. Fernandez LP, Treguerres FF, Bueso ES, Frances FS, Martinez-de-la-casa JM, Feijo JG et al. Hyperhomocysteinemia in chronic alcoholism: a case with retinal manifestations. Arch soc esp oftalmol. 2014;89(8):336-9.
16. Battaglia Parodi M, Di Crecchio L. Hyperhomocysteinemia in central retinal vein occlusion in young adults. Seminars in ophthalmology. 2003;18(3);154-9.
17. Turello M, Pasca S, Daminato R, Dello Russo P, Giacomello R, Venturelli U et all. Retinal vein occlusion: evaluation of »classic« and »emerging« risk factors and treatment. J Thromb Thrombolysis. 2010;29:459-64.
18. Roca MF, Mesquida M, Pelegrin L, Liorens V, Fontenia JR, Adan A. Retinal vasculopathy in systemic lupus erythematosus: a case of lupus vasculitis and a case of non-vasculitis venous occlusion. Arch soc esp oftalmol. 2014;89(2):66-9.
19. Yahalomi T, Pikkel J, Arnon R, Pessach Y. Central retinal vein occlusion in a young healthy COVID-19 patient: a case report. American journal of ophthalmology case reports. 2020;20:100992.
20. Rothman AL, Thomas AS, Khan K, Fekrat S. Central retinal vein occlusion in young individuals: A comparison of risk factors and clinical outcomes. Retina. 2019;39(10):1917-24.

21. Recchia FM, Carvalho-Recchia CA, Hasan TS. Clinical course of younger patients with central retinal vein occlusion. Arch Ophthalmol. 2004;122:317-22.

22. Sinawat S, Bunyavee C, Ratanapakorn T, Sinawat S, Laovirojjanakul W, Yospaiboon Y. Systemic abnormalities associated with retinal vein occlusion in young patients. Clinical ophthalmology 2017;11:441-7.