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Central retinal vein occlusion risk profile: a case-control study

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PURPOSE. To identify risk factors for central retinal vein occlusion (CRVO).
METHODS. This clinic-based case-control study included 408 patients with CRVO aged 21 years and older and 566 controls who were seen between January 1, 1990, and December 31, 2001. Multivariate logistic regression analysis was used to adjust for various factors and test potential interactions between the different variables.
RESULTS. An increased risk of CRVO was found in persons with systemic hypertension, but odds ratios were greater for older patients. Risk of CRVO increases with age and also in association with hypercoagulability. Diabetes mellitus, kidney disease, and glaucoma were associated with increased risk for CRVO. A significantly greater prevalence of higher erythrocyte sedimentation rate was present in young adults compared with older patients.
CONCLUSIONS. The results suggest a relationship between CRVO and certain risk factors (systemic hypertension, diabetes mellitus, kidney disease, glaucoma, older age) and support the possibility of an association between CRVO and urban location. The findings also support the potential value of medical treatment of underlying medical conditions in preventing occurrence of CRVO. (Eur J Ophthalmol 2003; 13: 445-52)

KEY WORDS. Central retinal vein occlusion, Risk factors, Case-control study

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INTRODUCTION

Many systemic and ocular risk factors have been reported for central retinal vein occlusion (CRVO) in younger (1-6) and older (7-23) subjects. Although few studies have included adequate control populations, evidence from clinical observations, many case series (17-19), and a few cross-sectional studies with controls (20-23) suggests a cardiovascular risk profile in patients with CRVO. Such a profile is consistent with hypotheses suggesting that a thickened, sclerotic central retinal artery, as occurs in systemic hypertension, may play an important role in the pathogenesis of CRVO (24).

Histopathologic study has shown thrombus formation in the area of the lamina cribrosa in eyes with CRVO (24). Anatomic features make the central retinal vein vulnerable to occlusion at this location. As the optic nerve and the accompanying central retinal artery and vein pass through the sieve-like connective tissue of the lamina cribrosa, the central retinal vein normally narrows, and the dense connective tissue of the lamina cribrosa limits any expansion of the traversing optic nerve and the vessels within. Any thickening of the central retinal artery, which shares a common fibrous tissue sheath with the vein, might easily compress the lumen of the adjacent central retinal vein and start in motion the sequence of events that

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lead to thrombus formation (24). Other factors that might predispose toward thrombus formation include endothelial cell damage (25), increased blood viscosity (26), and changes in the blood constituents (27-33).

CRVO is often classified into ischemic and nonischemic types based on the amount of retinal capillary nonperfusion noted on fluorescein angiography (7). Hayreh (10) suggested that the site of the occlusion in eyes with nonischemic CRVO may not be in the area of the lamina cribrosa but further back in the orbit. The more posterior location of the occlusion would make more collateral channels available for venous blood flow, and this could explain the less dramatic presentation (34) and more benign clinical course of nonischemic CRVO. Differences in the demographic characteristics, clinical manifestations, and clinical courses of ischemic and nonischemic CRVO also suggest that risk factors might differ for the two types of occlusion (14).

The aim of this study was to identify risk factors for CRVO. We also investigated the relationship between CRVO and many other possible risk factors that have been suggested in the literature.

METHODS

This was a clinic-based case-control study of 408 patients with a clinical diagnosis of CRVO and 566 controls, all aged 21 years and older, who were seen in the 12-year period between January 1, 1990, and December 31, 2001. The medical records of patients seen at the Ophthalmologic Centre were reviewed.

Signs of CRVO included flame-shaped, dot, or punctate retinal hemorrhages in all four quadrants of the retina, dilation and increased tortuosity of the retinal veins, and optic disk swelling.

Excluded from case and control groups were persons with severe myopia, vasoproliferative retinopathy, and intermediate or posterior intraocular inflammatory disease.

A person qualified as a control if he or she was free of retinal vascular diseases. Patients with corneal disorders or cataract among controls were eligible if the fundus could be explored and was considered normal despite the anterior segment problems.

Data collection included demographic characteristics, associated ophthalmic and systemic conditions, blood pressure, complete blood count, erythrocyte sedimentation rate (ESR), blood sugar, blood coagulability (fibrinogen, recalcification time, plasma tolerance to heparin, prothrombin ratio), and visual acuity.

Data were entered into computer databases using automatic skips and range checks. A commercially available statistical software package (Statistical Analysis System for Windows [SAS], version 6.12, Cary, NC) was used for tabulations and statistical analyses.

Initially, we screened each possible risk factor separately. The number of cases and controls involved in each analysis depended on the availability of risk factor data.

We then computed a multiple logistic model including all variables that were statistically significant ($p<0.05$) in the previous stage of the analysis. Multivariate logistic regression analysis was used to adjust for the various factors; also, various multivariate models were used to test potential interactions between the different variables.

RESULTS

A total of 408 patients with CRVO and 566 controls were included in the study. All cases and controls were white (European origin). The age and sex profile of the cases and controls is shown in Table I.

The most common diagnoses among controls (n = 566) were as follows: corneal disorders (n = 261; 46%), cataract (n = 164; 29%), refractive error (n = 124; 22%), and other (n = 17; 3%).

Several risk factors were significantly associated with CRVO in the screening analyses (Tab. II). We calculated odds ratios to assess the magnitude of these associations, grouping the values for each characteristic (Tab. III). Patients 70 years and older represent the selected population with less likelihood of active vascular event, compared with the 61- to 70-year-old group (in our population, average life expectancy varies between 50 and 60 years).If we compare patients from the 70 years and older age group with any younger group (21-50 years), being 70 years or older is a strong risk factor, but it was decided to have a comparison group of 70 years and older in order to show continuous age-dependent dose response.

The age and sex distribution of patients with CRVO is shown in Table IV. We found a significant positive association of CRVO with older age, female sex, ur-

TABLE I - AGE AND SEX DISTRIBUTION OF CRVO CASES AND CONTROLS

Age, years	CRVO, n (%)	Controls, n (%)
21-30	4 (0.9)	163 (28.8)
31-40	34 (8.3)	71 (12.5)
41-50	35 (8.6)	64 (11.3)
51-60	98 (24)	88 (15.6)
61-70	167 (41)	94 (16.6)
70 or older	70 (17.2)	86 (15.2)
Sex		
M	206 (49.5)	346 (61.1)
F	202 (50.5)	220 (38.9)

CRVO = Central retinal vein occlusion

ban location, history of diabetes, history of cardiovascular disease, kidney disease, systemic hypertension, elevated systolic and diastolic blood pressure, elevated blood sugar, prothrombin ratio, ESR, proteinuria, intraocular pressure level, and history of glaucoma. We found a significant inverse association (decreasing risk) with young age, rural location, and low systolic and diastolic blood pressure. The variables that were significant in the screen were retained in the final multivariate logistic model.

We computed a multivariate logistic regression model for significant characteristics including systemic hypertension, diabetes, kidney disease, glaucoma history, location, and age. Urban location, specifically in the capital, remains a risk factor even after adjustment for age, sex, and systemic disease.

Sex was retained in the final multivariable logistic model taking into account the significant association of sex with CRVO revealed from the screening analysis. Age was used in the model as continuous variable. The annual occurrence of CRVO depending on age and adjusted for sex, location, systemic diseases, and glaucoma is 2.7%.

Hypercoagulability represented by elevated prothrombin ratio was significantly associated with age and CRVO in the screening analysis. This factor was chosen for inclusion into the regression model for patients younger than versus older than 40 years (Tab. V). An increased risk of CRVO was found in older persons with hypercoagulability. In Table V, two different models with various variables are presented: for the younger age group (≤40 years), sex, location, and high pro-

TABLE II - RISK FACTORS INCLUDED IN THE ANALYSIS OF CRVO AND RESULTS FROM THE SCREENING ANALYSIS

Factor	Association with CRVO, direction (p)*
Age, years	
21-30	↓ (<0.001)
31-40	↓ (<0.05)
41-50	(0.13)
51-60	(0.13)
61-70	↑ (<0.001)
Sex	
F	↑ (0.001)
Location (urban/rural)	↑ (0.001)
Systemic disease	
Diabetes history (yes/no)ψ	↑ (0.001)
Cardiovascular disease history (yes/no)‡	↑ (0.001)
Cerebrovascular disease history (yes/no)§	(0.07)
Kidney disease¶	↑ (0.001)
Atherosclerotic vascular disease ω	(0.06)
Systemic hypertension (yes/no)††	↑ (0.001)
Duration, years	
5-10	(0.2)
More than 10	(0.1)
Systolic blood pressure, mmHg	↑ (<0.001)
Diastolic blood pressure, mmHg	↑ (<0.001)
Biochemical data	
Glucose, mmol/L	↑ (<0.001)
Fibrinogen, g/L	↑ (<0.05)
Recalcification time, sec	↓ (<0.05)
Plasma tolerance to heparin, min	↓ (<0.05)
Prothrombin ratio, %	↑ (<0.001)
Erythrocyte sedimentation rate, mm/h	↑ (<0.001)
Urine analysis	
Proteinuria (yes/no)	↑ (<0.01)
Glaucoma history (yes/no)‡‡	↑ (<0.001)
Intraocular pressure, mmHg	↑ (<0.004)

* Each factor was analyzed in a logistic regression. Direction of association shown only for p<0.05.

ψBlood sugar 6.1 mmol/L or more, or taking insulin or hypoglycemics.

‡One or more of the following: congestive heart failure, heart surgery, or stroke.

§Thrombotic or hemorrhagic stroke.

¶Primary renal parenchymal disease, renal stones, or diabetic nephropathy.

ωIschemic heart disease.

††Systolic pressure of 160 mm Hg or more, or diastolic pressure of 90 mm Hg or more, or taking antihypertensive medication.

‡‡Primary open angle glaucoma: evidence of optic nerve damage or visual field loss, intraocular pressure of 21 mmHg or more, or controlled glaucoma.

CRVO = Central retinal vein occlusion;
↑ = Direct relationship;
↓ = Inverse relationship

TABLE III - OR (95% CI) FOR CRVO

Factor	CRVO/controls, OR (95% CI)
Age, years	
21-30	0.03 (0.00-0.18)
31-40	0.59 (0.34-1.02)
41-50	0.67 (0.39-1.17)
51-60	1.38 (0.88-2.17)
61-70	2.21 (1.44-3.38)
70 and older	1.0
Sex	
M	1.0
F	1.55 (1.19-2.03)
Location	
Urban	1.0
Rural	0.47 (0.33-0.67)
Systemic disease	
Diabetes	
No	1.0
Yes	13.57 (4.57-45.27)
Cardiovascular disease	
No	1.0
Yes	7.15 (1.93-31.26)
Cerebrovascular disease	
No	1.0
Yes	3.75 (0.9-17.9)
Kidney disease	
No	1.0
Yes	32.15 (4.60-643.56)
Atherosclerotic vascular disease	
No	1.0
Yes	2.0 (0.9-4.52)
Systemic hypertension	
No	1.0
Yes	16.35 (11.24-23.83)
Duration, years	
Less than 5	1.0
5-10	1.54 (0.66-3.69)
More than 10	5.5 (0.75-112.82)
Systolic blood pressure, mmHg	
<120	0.27 (0.14-0.51)
120-140	1.0
150	5.71 (3.38-9.69)
160	8.49 (4.81-15.13)
170	7.84 (3.41-18.49)
180	10.78 (4.62-26.04)
>180	11.43 (4.93-27.49)
Diastolic blood pressure, mmHg	
≤70	0.26 (0.14-0.47)
71-89	1.0
90-100	9.37 (6.34-13.89)
>100	11.47 (5.18-26.17)
Biochemical data	
Glucose, mmol/L	
<6.0	1.0
6.1-9.0	5.32 (2.4-12.17)
>9.0	4.99 (1.26-23.01)
Prothrombin ratio, %	
60-75	1.0
80-100	4.0 (2.17-7.7)
Erythrocyte sedimentation rate, mm/h	
8-14	1.0
15-20	4.06 (2.17-7.7)
>20	8.72 (2.81-30.71)
Proteinuria	
No	1.0
Yes	2.2 (1.1-4.39)
Glaucoma	
No	1.0
Yes	6.1 (3.8-9.1)
Intraocular pressure, mmHg	
≤21	1.0
>21	13.46 (1.75-284.97)

CRVO = Central retinal vein occlusion; OR = Odds ratio; CI = Confidence interval

thrombin ratio were used; for the older age group (>40 years), sex, high prothrombin ratio, and systemic hypertension were used. This gives us the opportunity to compare the impact of high prothrombin ratio between the two age groups adjusted for all other important factors. Thus, systemic hypertension was included as a variable in the multifactorial model for the older group; location was used in the multifactorial model only for the younger group.

CRVO in young adults is thought to be a different entity from CRVO in older patients. The multivariable analysis disclosed some differences in risk factors for younger versus older patients (Tab. VI). Systemic hypertension and elevated ESR show associations with CRVO independent of age, but the odds ratios are greater for hypertension in older patients and for ESR in young adults. An increased risk of CRVO was found in young adults with systemic hypertension and elevated ESR.

TABLE IV - UNIVARIATE ANALYSIS OF AGE-DEPENDENT RISK OF CRVO STRATIFIED BY SEX

	Male	Female
Age group, years	OR (95% CI)	OR (95% CI)
21-30	0.04 (0.0-0.3)	0.28 (0.01-2.08)
31-40	0.40 (0.18-0.9)	0.89 (0.39-2.0)
41-50	0.44 (0.19-0.99)	1.04 (0.47-2.31)
51-60	1.12 (0.56-2.2)	1.62 (0.87-3.02)
61-70	1.89 (0.99-3.6)	2.43 (1.35-4.38)
70 or older	1.00	1.00

CRVO = Central retinal vein occlusion;
OR = Odds ratio;
CI = Confidence interval

TABLE V - MULTIVARIATE LOGISTIC REGRESSION ANALYSIS OF CRVO IN DIFFERENT AGE GROUPS

	Age group, y, OR (95% CI)	
Factor	≤40	>40
Sex	1.212 (0.14-10.6)	2.545 (1.31-4.93)
Location	1.761 (0.15-20.84)	—
High prothrombin ratio	2.838 (0.34-23.68)	4.818 (2.53-9.17)
Systemic hypertension	—	8.572 (4.12-17.85)

CRVO = Central retinal vein occlusion;
OR = Odds ratio;
CI = Confidence interval

DISCUSSION

In this clinic-based case-control study, we identified several possible risk factors for CRVO. Increased risk was found with systemic hypertension, diabetes mellitus, kidney disease, history of glaucoma, older age, and urban location.

The findings are consistent with hypotheses of an underlying cardiovascular risk profile for persons with CRVO (17-23, 35-37). As in a previous study (29), significantly higher levels of systolic and diastolic blood pressure were noted in our patients. Patients with a history of systemic hypertension had a more than fivefold increase in risk of CRVO. These findings are consistent with suggestions from case series and findings from previously conducted, smaller case-control studies. Many case series (17-19) have reported rates of systemic hypertension that are higher than might be expected for the age groups involved, but results from case series are difficult to interpret without appropriate control groups. In four previously conducted clinic-based studies (20-23) with control groups, systemic hypertension was significantly more common in patients with retinal vein occlusion than in controls.

We found that diabetes mellitus was significantly more common among our cases than controls. The proportion of patients with diabetes in various case series of CRVO varies widely (16, 38-40). In these studies, definitions of diabetes are rarely given. In their clinic-based case-control study, Elman et al (20) used two control groups: patients without CRVO from the same clinic and a control group drawn from the National Health Interview Survey. Diabetes was a significant risk factor when CRVO cases were compared with the National Health Interview Survey population, but not when compared with the clinic controls.

TABLE VI - MULTIVARIABLE LOGISTIC REGRESSION ANALYSIS OF THE VARIABLES WITHIN THE COMPARISON OF YOUNGER VERSUS OLDER PATIENTS WITH CRVO

	Age group, years, OR (95% CI)	
Factor	≤40	>40
Sex	0.7 (0.3-1.6)	1.3 (0.89-1.92)
Location	1.29 (0.55-3.02)	2.1 (1.44-3.11)
Systemic hypertension	7.34 (1.48-36.39)	12.47 (8.24-18.86)
Elevated erythrocyte sedimentation rate	13.07 (3.5-48.6)	3.17 (1.6-6.2)

CRVO = Central retinal vein occlusion;
OR = Odds ratio;
CI = Confidence interval

An elevated prevalence of kidney disease was present in the CRVO cases. Also, our findings suggest that urban location, specifically in the capital, may be a risk factor for CRVO. Likely explanations for these factors are that 1) kidney disease may cause renal origin arterial hypertension, which is significantly associated with CRVO, and 2) a significantly greater prevalence of systemic hypertension due to stress may exist among the urban population compared with the rural population.

Many risk factors have been associated with CRVO onset at various ages. In patients over 50 years of age, cardiovascular risk factors predominate (36). The present findings confirm that a stronger cardiovascular risk profile was observed in older patients.

Coagulation parameter testing showed hypercoagulability. Increased thrombin formation and impaired fibrinolysis may be contributing factors in the pathogenesis of retinal vein occlusion (26-33, 41-43). An increased risk of CRVO was found in older persons with hypercoagulability. Older age itself is a risk factor for CRVO.

ESR were significantly higher in cases than controls, but the odds ratios were greater for young adults. In a comparison of patients with CRVO and branch retinal vein occlusion, Appiah and Trempe (44) reported significantly higher ESR in the CRVO cases. They suggest that a higher ESR might cause changes in the shear forces and viscosity of plasma and that such changes in hemodynamics might contribute to occlusion of the central retinal vein. A likely explanation for a stronger association between elevated ESR and CRVO in young persons is that in the majority of cases inflammation of the central retinal vein has been proposed as a cause of occlusion in young adults; for that reason, it has been called papillophlebitis (5).

CRVO sometimes is divided into a nonischemic type and a more disabling ischemic form (7, 14). Comparisons of patients with ischemic and nonischemic CRVO are problematic in cross-sectional studies because the nonischemic type of CRVO can convert to the ischemic form.

The important ocular finding was an association between CRVO and a history of open-angle glaucoma. Our finding of significantly higher intraocular pressure in the eyes of cases than in controls provides additional support for the glaucoma association.

Widely varying, but seemingly high, prevalences of open-angle glaucoma have been reported in series of cases with CRVO (12, 45, 46). The lack of controls and the frequent absence of age-specific data and disease definitions make it difficult to interpret and compare prevalence data in these case series. In a case-control study (22), open-angle glaucoma was significantly more common among the cases (odds ratio 5.4; 95% confidence interval 3.5 to 8.5). It has been suggested (24) that by compressing and stretching the lamina cribrosa, elevated intraocular pressure might interfere with blood flow (46) and cause endothelial damage to the traversing central retinal vein (47).

Our data suggest differences in risk factors for young versus older patients with CRVO.

The results from this case-control study suggest a relationship between CRVO and increased risk factors (systemic hypertension, diabetes mellitus, kidney disease, glaucoma, older age) and support the possibility of an association between CRVO and urban location. Our data also support the potential value of medical treatment of underlying conditions in preventing occurrence of CRVO.

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