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Clinical Characteristics of Patients With CRVO in One Eye With Subsequent RVO in The Fellow Eye: A Retrospective Observational Study

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Abstract

BACKGROUND AND OBJECTIVE: To compare risk factors in patients with a central retinal vein occlusion (CRVO) in the first eye and a subsequent retinal vein occlusion (RVO) in the fellow eye versus those with only unilateral CRVO.

PATIENTS AND METHODS: Records of patients who presented to the Duke Eye Center with unilateral CRVO were evaluated. Logistic regression models were performed to identify potential covariates of subsequent development of RVO in the fellow eye.

RESULTS: Of the 287 patients with CRVO in one eye, 31 (10.8%) developed an RVO in the fellow eye during a mean ± standard deviation follow-up of 36.7 months ± 38.86 months. The conversion rate of unilateral-to-bilateral RVO was 3.4% per year. Several comorbidities were observed to be unique to 25.8% of patients with bilateral RVO. Patients who used oral pentoxifylline ($P = .008$) or those who had an ischemic CRVO in the first eye ($P = .001$) were less likely to develop an RVO in the fellow eye.

CONCLUSION: This information may be used to develop a predictive model to assess the risk of developing bilateral RVO in patients with unilateral CRVO.

INTRODUCTION

Retinal vein occlusion (RVO) is a common cause of unilateral vision loss that most often afflicts persons older than 45 years of age.[1,2] Among the various types, branch retinal vein occlusion (BRVO) is the most common, followed by central retinal vein occlusion (CRVO), and hemiretinal vein occlusion (HRVO).[3,4] Although the exact pathophysiology of RVO remains unclear, there have been established risk factors in the literature;[5,6] the strongest risk factors for development of RVO include hypertension, diabetes mellitus, hyperlipidemia, cigarette smoking, atherosclerosis, and nephropathy.[5–8] For CRVO, glaucoma is an additional risk factor.[9] The most common sight-threatening sequelae of RVO is the development of macular edema.[10,11]

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The Central Retinal Vein Occlusion Study (CVOS) identified 1.4% of 581 patients with a prior CRVO in first eye who developed a CRVO in the second eye during the course of the study, whereas an additional 1.2% developed some other type of vascular occlusion in the fellow eye during follow-up.[11] The CVOS identified a 0.9% risk per year of any vascular occlusion developing in the fellow eye of patients with a CRVO in the first eye. Several other population studies have reported that up to 35% of patients with CRVO had bilateral RVO findings, but these are population studies based on fundus photographs and were not designed to examine patients with bilateral disease.[12,13] We undertook a retrospective review to study patients with CRVO in the first eye who subsequently developed any RVO in the fellow eye and to investigate risk factors observed in those with unilateral versus bilateral disease.

The primary aim of our study is to identify factors that may predispose patients with CRVO in the first eye to develop a subsequent RVO in the fellow eye over time. The secondary aims are to identify the unilateral-to-bilateral conversion rate, to observe for any unique comorbidities found in patients with bilateral RVO, and to identify if ischemic CRVO in the first eye is associated with the development of RVO in the fellow eye.

PATIENTS AND METHODS

The current analysis utilized a large, retrospective database of patients with CRVO that was created with approval by the Duke University Institutional Review Board and in adherence with the Health Insurance Portability and Accountability Act and all tenets of the Declaration of Helsinki. In order to populate this database, the electronic medical records of all patients who visited the Duke Eye Center between January 1, 2009, to July 1, 2016, were searched using Duke Enterprise Data Unified Content Explorer (DEDUCE) for International Classification of Diseases 9 and 10 coding for CRVO. Patients were excluded if the duration of CRVO onset was unknown or the initial assessment at Duke occurred during a 1-year period following the development of CRVO. The medical records identified by this search were then reviewed to identify patients with a CRVO in the first eye and no RVO in the second eye for our observational study. We retrieved information on and analyzed patient demographics; comorbidities; oral medication use such as beta blockers, antiplatelet agents, anticoagulants, angiotensin-converting-enzyme (ACE) inhibitors, and pentoxifylline; and CRVO perfusion status in the first eye of all study patients. A CRVO was classified as ischemic if the eye had one of the following findings: 1) neovascular sequelae attributable to the CRVO or 2) counting fingers visual acuity (VA) or worse plus a physician-confirmed afferent pupillary defect clinically attributed to the presence of the CRVO.[14] Antiplatelet medication was defined as the daily use of aspirin and/or clopidogrel (Plavix; Bristol-Myers-Squibb, New York, NY). Anticoagulant medication was defined as the daily use of warfarin, rivaroxaban (Xarelto; Janssen, Beerse, Belgium), dabigatran (Pradaxa; Boehringer Ingelheim, Ridgefield, CT), or apixaban (Eliquis; Bristol-Myers-Squibb, New York, NY).

Patients were divided into two groups: those with unilateral CRVO in the first eye but no prior or subsequent RVO in the fellow eye (Group 1), and those with CRVO in the first eye and subsequent RVO in fellow eye (Group 2). Patients in Group 2 were also analyzed for any pre-existing comorbidities that were absent in Group 1.

Statistical Analysis

Continuous variables were summarized as mean with standard deviation (SD), and categorical variables were summarized as frequency with percentages. The statistical differences between the two groups were tested using unequal variances Student *t*-test or Mann-Whitney U test for continuous variables, and Chi-square test or Fisher's exact test for categorical variables. Univariate logistic regression analyses were used to identify the associations between potential covariates and the likelihood of developing RVO in the fellow eye. Covariates that were statistically significant or clinically relevant from the univariate logistic regression analyses were subsequently added into the multivariate logistic regression model in an attempt to establish any independent associations, with the removal of confounders. Associations from the logistic regression models were characterized using odds ratio (OR) and corresponding 95% confidence interval (95% CI). The unilateral-to-bilateral conversion rate of RVO was calculated by dividing the frequency of RVO in the fellow eye by the mean duration of follow-up in the entire cohort. Significance level was set at .05 and all tests were two-tailed. IBM SPSS Statistics version 24.0 software (IBM Data Analytics, Chicago, IL) was used for the analysis.

RESULTS

Two hundred eighty-seven patients with a CRVO in the first eye were identified, of whom 256 (89.2%) had only a unilateral CRVO and did not develop a RVO in the fellow eye over time (Group 1), whereas 31 patients (10.8%) developed a subsequent RVO in the fellow eye (Group 2). Among the 31 patients with bilateral RVO, 20 patients (64.5%) developed a CRVO, eight patients (25.8%) developed a BRVO, and three patients (9.7%) developed a HRVO in the fellow eye over time. After adjusting for 56 patients lost to follow-up, the mean ± SD follow-up was 36.7 months ± 38.86 months (95% CI, 31.70–41.78). The unilateral-to-bilateral conversion rate of RVO was calculated to be 3.4% per year.

Table 1 shows the distribution of patient demographics between the two groups of patients. We found that 74.2% of bilateral RVO patients had an ischemic CRVO in the first eye. This is in contrast to the 43.4% of unilateral RVO patients with an ischemic CRVO in the first eye ($P = .001$). We also found that the distribution of races between the two groups was significantly different ($P = .023$), with more Caucasians in Group 1 and more African-Americans and "other" races in Group 2. In addition, the use of oral anticoagulants and oral pentoxifylline between the two groups were also significantly different ($P = .019$ and $P = .012$, respectively), with more use in Group 2. However, whereas Table 1 displays the proportion of patients in each group with the reflected variables and the significant differences between the two groups, conclusions on each variable's true association with the development of an RVO in the fellow eye requires logistic regression analyses.

Univariate and multivariate logistic regression analyses are presented in Table 2. Univariate logistic regression analyses showed that the use of oral anticoagulants, use of pentoxifylline, and the presence of an ischemic CRVO in the initial eye were statistically associated with a higher likelihood to develop any RVO in the fellow eye. To determine the independent association of each selected variable with the development of RVO in the fellow eye, multivariate logistic regression analysis was performed to remove confounders and revealed

a significant inverse association between the use of pentoxifylline and subsequent development of any RVO in the fellow eye (adjusted odds ratio [OR]: 0.099; 95% CI, 0.018–0.550; $P = .008$). We also found a negative association between an ischemic CRVO in the first eye and subsequent development of RVO in the fellow eye (adjusted OR: 0.143; 95% CI, 0.044–0.466; $P = .001$) on the multivariate logistic regression analysis. On the other hand, covariates of the multivariate logistic regression analyses such as age of CRVO onset in the study eye; smoking status; history of hypertension, diabetes mellitus, and open angle glaucoma; and the use of oral beta blockers, antiplatelets, anticoagulants, and ACE inhibitors did not show any significant independent association with the development of any RVO in the fellow eye.

Table 3 reflects the comorbidities observed in patients with bilateral RVO but not in patients with unilateral RVO. Eight patients (25.8%) in Group 2 had the following pre-existing comorbidities, some patients with more than one: hyperhomocysteinemia, non-Hodgkin's lymphoma, CREST syndrome, giant cell arteritis, polymyalgia rheumatica, protein C deficiency, chronic oral steroid use, retinal vasculitis, inflammatory bowel disease, Sjogren syndrome, and Behçet disease.

DISCUSSION

We found the conversion rate of unilateral-to-bilateral RVO to be 3.4% per year in patients with a CRVO in the first eye and subsequent development of any RVO in the second eye. Although a greater proportion of bilateral RVO patients was observed to use oral pentoxifylline compared to unilateral CRVO patients, multivariate analyses revealed that oral pentoxifylline use is inversely associated with the development of any RVO in the fellow eye of patients with an existing CRVO in the first eye. Similarly, though, there was a greater proportion of bilateral RVO patients observed to have an ischemic CRVO in the initial eye compared to unilateral CRVO patients, subsequent multivariate analyses revealed that ischemic CRVO does not significantly increase the risk of developing any RVO in the fellow eye. Finally, we found that many bilateral RVO patients had unique comorbidities, absent from unilateral CRVO patients.

Pentoxifylline is a xanthine-derived hemorheologic agent that has been used for decades. Though the exact mechanism is unclear, it has been used in the treatment of intermittent claudication in peripheral arterial disease and venous stasis leg ulcers by decreasing blood viscosity and platelet aggregation.[15] A large study in 2011 investigating 585 eyes showed that the use of antiplatelets and anticoagulants was associated with a poorer visual outcome secondary to more intraretinal hemorrhage in eyes with CRVO and HRVO.[16] Interestingly, a 2007 retrospective study suggested favorable effects of oral pentoxifylline on reducing cystoid macula edema in eyes with CRVO, although VA did not improve in that series.[17] However, no previous studies have explored the potential benefits of pentoxifylline on the fellow eye in persons with CRVO in the first eye. The potential protective effects of pentoxifylline on the fellow eye suggested in this study imply that further evaluation may be warranted.

Although our findings suggest that patients with bilateral RVO have higher proportions of ischemic CRVO in the initial eye, our multivariate logistic regression analysis showed that having an ischemic CRVO did not increase the risk of developing any RVO in the fellow eye. We recognize that ischemic CRVO is associated with poorer clinical outcomes such as decreased VA[2] and encourage future studies to further investigate the relationship between ischemic CRVO in one eye and the subsequent development of CRVO or any RVO in the fellow eye. It is plausible that our study patients who developed loss of vision in one eye from an ischemic CRVO subsequently had improved management of systemic risk factors.

The incidence of bilateral RVO reported in our study was 10.8%, similar to that reported in prior studies, with 9% of patients in the CVOS having bilateral retinal vascular occlusion at study entry.[11,12] Our study has also found the conversion rate of unilateral-to-bilateral RVO to be 3.4% per year, which is slightly higher than that found in a study by Brown et al. at 1.5% per year,[18] and slightly lower than a previous study that found a unilateral-to-bilateral conversion rate among CRVO patients to be 5%.[19] However, this may be attributed to our criteria-based selection of study participants where we only analyzed patients with CRVO in the first eye to determine which ones then later developed any subsequent RVO in the fellow eye, since eyes with CRVO are known to have an increased risk for any RVO in the fellow eye.[2,11] This is in contrast to the study by Brown et al. that analyzed the bilateral conversion from a variety of unilateral RVO types in the first eye that included CRVO, BRVO, and HRVO,[18] and not just CRVO in the first eye in patients as our study evaluated.

The pathogenesis of RVO is thought to mirror the principles of Virchow's triad for thrombogenesis involving damage to the vessel wall, intravascular stasis, and hypercoagulability.[1] Just as how it has been extensively shown that inflammatory rheumatological diseases are associated with significantly higher rates of thromboembolism, [20] these diseases are also thought to contribute to the development of RVO.[1] Similarly, conditions that result in a hypercoagulable state also contribute to Virchow's triad and consequently to the development of RVO.[1] With this information, it may be prudent to counsel patients with systemic vasculitides on the risk of developing retinal vasculitis and therefore retinal vascular occlusions. We found that many of our patients who developed bilateral RVO had certain comorbidities that were unique to Group 2 patients and absent from Group 1 unilateral CRVO patients. These comorbidities, reflected in Table 3, have been previously studied to show evidence of contributing to Virchow's triad through inflammatory mechanisms or hypercoagulability. Comorbidities unique to Group 2 that result in hypercoagulability include hyperhomocysteinemia,[21] non-Hodgkin's lymphoma,[22] Protein C deficiency,[23] and chronic glucocorticosteroid use.[24] As alluded to earlier, inflammatory conditions can also predispose to Virchow's triad through integration of inflammatory and coagulation pathways, increasing the risk of RVO development. Inflammatory conditions unique to the Group 2 bilateral RVO patients that have been shown to contribute to venous thrombogenesis include CREST syndrome, giant cell arteritis, polymyalgia rheumatica, retinal vasculitis, inflammatory bowel disease, Sjogren syndrome, and Behçet disease.[25,26] Moreover, chronic oral steroid use in the treatment of these conditions may also predispose to venous thromboembolism.[24]

Our patient list of unique comorbidities is not exhaustive of all the comorbidities that can potentially contribute to thrombogenesis and thus RVO development. Although the aforementioned comorbidities may cause thrombogenesis and subsequent RVO, little is known regarding their role in bilateral RVO. Hence, it is noteworthy that these conditions found in the bilateral RVO patients in our study were absent from the unilateral CRVO patients.

We recognize the limitations of our study. As a retrospective study, the data are limited and may be subject to bias. As a tertiary referral center, the patient population may be different than that found in other community-based practices. In addition, the results from our study are largely observational, and further studies would be necessary to establish whether these conclusions hold true in larger prospective studies and across different populations.

In conclusion, our retrospective, observational study compared patients who had a CRVO in only one eye to those who had a CRVO in the first eye followed by the development of any subsequent RVO in the fellow eye and found no significant differences in terms of age at initial CRVO event; gender; race; smoking status; presence of hypertension, diabetes mellitus, or open angle glaucoma; or use of oral beta blockers, antiplatelet agents, anticoagulants, or ACE inhibitors. However, we found that there is a significant inverse association between the use of oral pentoxifylline and the development of any RVO in the fellow eye. We also found that ischemic CRVO in the first eye did not increase the risk of developing any RVO in the fellow eye. In addition, we found the conversion rate of unilateral-to-bilateral RVO to be 3.4% per year. Finally, we observed several comorbidities that were unique to our study's bilateral RVO patients, possibly playing a yet unknown role in the development of bilateral RVO that lends to further investigation.

This retrospective, observational study can serve as a primer for future research with larger population sizes, as the knowledge of the aforementioned risk factors and predisposing conditions may be useful in developing a predictive model to assess the risk of developing any RVO in the fellow eye in individuals with a CRVO in the first eye.

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TABLE 1

Demographics, Comorbidities, and Medication Use in Patients With Unilateral CRVO (Group 1) Compared to Those With CRVO in First Eye and Any RVO in the Fellow Eye (Group 2)

	Group 1 (N = 256)	Group 2 (N = 31)	*P* Value*
Age at Initial CRVO Event, Years	65.7 ± 14.51	62.6 ± 16.09	.371
Gender			.367
Male	121 (47.3%)	12 (38.7%)	
Female	135 (52.7%)	19 (61.3%)	
Race			**.023**
Caucasian	168 (65.6%)	16 (51.6%)	
African-American	53 (20.7%)	8 (25.8%)	
Multiracial	5 (1.95%)	0	
Other	30 (11.7%)	7 (22.6%)	
Smoking Status	43 (16.8%)	5 (16.1%)	.912
Comorbidities			
Hypertension	187 (73.0%)	22 (71.0%)	.901
Diabetes mellitus	77 (30.1%)	12 (38.7%)	.210
Open angle glaucoma	72 (28.1%)	11 (35.5%)	.281
Oral Medications			
Beta blockers	71 (27.7%)	8 (25.8%)	.822
Antiplatelet agents	112 (43.8%)	9 (29.0%)	.117
Anticoagulants	18 (7.0%)	6 (19.4%)	**.019**
Pentoxifylline	8 (3.1%)	4 (12.9%)	**.012**
ACE inhibitors	80 (31.3%)	7 (22.6%)	.412
CRVO Perfusion Status in the First Eye			**.001**
Ischemic	111 (43.4%)	23 (74.2%)	
Non-ischemic	145 (56.6%)	8 (25.8%)	
Duration of follow-up, months	36.3 ± 38.41	41.4 ± 43.57	.739

*Student t-test or Mann-Whitney U test for continuous variables, and Chi-square test or Fisher's exact test for categorical variables, whichever appropriate. Values are either in mean ± SD or frequency (proportion).

Statistically significant P values highlighted in bold (P < 0.05).

CRVO = central retinal vein occlusion; RVO = retinal vein occlusion; ACE = angiotensin converting enzyme

TABLE 2

Univariate and Multivariate Logistic Regression Models of Covariates of Development of Any RVO in Fellow Eye

Variables	Univariate Logistic Regression		Multivariate Logistic Regression	
	Unadjusted OR (95% CI)	*P* Value	Adjusted OR (95% CI)	*P* Value
Age	0.986 (0.961 – 1.012)	.287	0.994 (0.959 – 1.030)	.727
Gender (Ref: Females)	0.705 (0.328 – 1.512)	.369		
Race (Ref: Caucasian)		.319+		
African-American	0.408 (0.155 – 1.076)	.070		
Multiracial	0	1.000		
Other	0.647 (0.213 – 1.961)	.441		
Smoking status	1.059 (0.384 – 2.922)	.912	3.127 (0.573 – 17.046)	.188
Comorbidities				
Hypertension	0.944 (0.385 – 2.316)	.901	1.133 (0.376 – 3.409)	.825
Diabetes mellitus	0.604 (0.273 – 1.338)	.214	0.838 (0.299 – 2.351)	.737
Open angle glaucoma	0.643(0.287 – 1.441)	.284	0.740 (0.251 – 2.184)	.585
Oral Medications				
Beta blockers	0.903 (0.373 – 2.189)	.822		
Antiplatelet agents	1.901 (0.842 – 4.290)	.122		
ACE inhibitors	1.456 (0.591 – 3.588)	.414		
Anticoagulants	0.315 (0.115 – 0.867)	.025	0.571 (0.123 – 2.644)	.474
Pentoxifylline	0.157 (0.043 – 0.570)	.005	0.099 (0.018 – 0.550)	**.008**
Ischemic CRVO in initial eye	0.266 (0.115 – 0.618)	.002	0.143 (0.044 – 0.466)	**.001**

Statistically significant P values highlighted in bold (P < .05).

RVO = retinal vein occlusion; CRVO = central retinal vein occlusion; CI = confidence interval; ACE = angiotensin converting enzyme

TABLE 3

Comorbidities Unique to Patients With CRVO in First Eye and Any RVO in Second Eye But Absent in Those With Unilateral CRVO

Comorbidity	N (%)
Hyperhomocysteinemia	3 (9.7%)
Non-Hodgkin's lymphoma	2 (6.5%)
CREST syndrome	1 (3.2%)
Giant cell arteritis	1 (3.2%)
Polymyalgia rheumatica	1 (3.2%)
Protein C deficiency	1 (3.2%)
Chronic oral steroid use	1 (3.2%)
Retinal vasculitis	1 (3.2%)
Inflammatory bowel disease	1 (3.2%)
Sjogren syndrome	1 (3.2%)
Behçet disease	1 (3.2%)

Values are in frequency (proportion) in relation to Group 2 patients.

CRVO = central retinal vein occlusion; RVO = retinal vein occlusion