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Associations with retinal vascular occlusions in a diverse, urban population

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ABSTRACT

Purpose: Retinal vascular occlusions can lead to sudden and permanent visual impairment or blindness. Few epidemiological studies on retinal vascular occlusions have been conducted, especially on diverse populations.

Methods: This is a retrospective case-control study of all incident retinal vascular occlusions occurring during a three and one-half year study period at Montefiore Medical Center, capturing all potential cases by diagnosis codes. Patients with retinal venous occlusions (RVO) and retinal arterial occlusions (RAO) were analyzed separately and compared to age-matched control groups.

Results: All potential charts (n = 700) were reviewed, confirming 214 RVO and 35 RAO incident cases. In multivariable analyses, RVO was associated with type 2 diabetes mellitus (OR 2.41, p < 0.001), history of cerebrovascular accident (OR 2.14, p = 0.011), hypertension (OR 1.83, p = 0.004), glaucoma (OR 6.91, p < 0.001), black race (OR 3.72, p < 0.001), and male gender (OR 2.19, p < 0.001). RAO was significantly associated with current and former smoking combined (OR 8.95, p = 0.021) and male gender (OR 2.56, p = 0.038).

Conclusion: Cardiovascular risk factors and glaucoma are reaffirmed as significant predictors of retinal vascular occlusions in a diverse patient population. Retinal vascular occlusions are more common in certain races and ethnicities, and further study into this may help identify high-risk individuals based on demographics.

KEYWORDS

Diverse population; epidemiology; retinal artery occlusion; retinal vein occlusion; risk factors

Introduction

Retinal vascular occlusions, either arterial or venous, are relatively uncommon. The occlusion can be of the central or branch vessels. Both retinal vein occlusions (RVO) and retinal arterial occlusions (RAO) can lead to sudden and permanent visual impairment or blindness. The devastating consequences and limited response of available treatments make understanding risk factors associated with development of retinal vascular occlusions pertinent to clinical practice.

Relatively few epidemiological studies have been conducted on both of these diseases. The prevalence of RVO is estimated to be 520/100,000 people from 11 pooled studies conducted in the USA, Europe, Asia, and Australia.1 The incidence of RVO is 153–333/100,000 person-years annually,2,5 the incidence of central RAO (CRAO) is 0.7–1.87/100,000 person-years annually.6,7 Retinal vascular occlusions are known to generally afflict older individuals,8 and several studies have suggested associations with cardiovascular risk factors and glaucoma.2,9–13

Most epidemiological studies on retinal vascular occlusions are conducted on predominately white or Asian populations.2,3,14,15 Serving approximately one-third of the residents of Bronx, New York, Montefiore Medical Center (MMC) offers an opportunity to study a more diverse population with substantial proportions of black and Hispanic or Latino patients. The Bronx also has a relatively high rate of HIV infection, compared to elsewhere.16 Here, we analyze outpatient data from the clinics of the Department of Ophthalmology and Visual Sciences at MMC to determine risk factors and strengths of associations for RVO and RAO.

Materials and Methods

This was a retrospective case-control study, covering a three and one-half year study period from 1st April 2012 to 30th September 2015. The study population consists of patients seen in the outpatient ophthalmology clinics of MMC. This study was conducted in adherence to the principles of the Declaration of
Helsinki. It was approved by the Albert Einstein College of Medicine Institutional Review Board (IRB). Consent was not obtained from patients as the IRB provided a waiver of consent.

Potential RVO and RAO cases were identified using International Classification of Diseases, Ninth Revision (ICD-9) diagnosis codes in Montefiore’s Clinical Looking Glass (CLG), which is a software tool that allows searching of patient data based on specified parameters. The ICD-9 codes used in the search were: 362.30 Retinal Vascular Occlusion, Unspecified; 362.31 Central Retinal Artery Occlusion; 362.32 Retinal Arterial Branch Occlusion; 362.33 Partial Retinal Arterial Occlusion; 362.34 Transient Retinal Arterial Occlusion; 362.35 Central Retinal Vein Occlusion; 362.36 Venous Tributary (Branch) Occlusion; 362.37 Venous Engorgement. Self-reported demographic data were obtained via CLG search. All charts were reviewed for confirmation of the diagnosis and additional clinical information. Inclusion criteria consisted of patients with 1) a home zip code in Bronx County, New York 2) who presented for initial evaluation at MMC and 3) who were given the diagnosis of retinal vascular occlusion (arterial or venous) within the target study period. Patients with retinal vascular occlusion occurring outside the target study period or those diagnosed by ophthalmologists outside the MMC system were excluded.

RVO and RAO cases were analyzed separately with their own control groups. Unilateral and bilateral cases were grouped together; for instance, if a person had a unilateral case of RVO or a bilateral case of RVO, they were coded as having RVO. Cases were compared to age-matched controls using Wald’s test for conditional logistic regression for both univariable and multivariable analysis. P-values for univariable analyses were corrected for multiple testing using the False Discovery Rate procedure.17 This procedure involved first sorting the p-values from smallest to largest and giving a number for its place in the order (i.e. the smallest p-value is 1, the second smallest 2, etc). Each p-value was then compared to a new critical p-value derived by dividing its number on the ordered list by the total number of tests and multiplying it by the desired standard (0.05). The first p-value that was bigger than its critical value was considered non-significant at corrected levels and all subsequent, larger p-values on the ordered list were considered non-significant as well. Only risk factors (including both demographic and disease risk factors) that survived the correction were considered significant. Each multivariable model examined one disease risk factor that was significant in the univariable analysis and controlled for all significant demographic and smoking variables.

Age-matched controls (±5 years) were chosen randomly from a CLG search for all outpatient visits during the corresponding study period in a 4:1 control to case ratio. Hematological abnormalities (sickle cell disease and hemophilia) were matched in the RVO controls but not the RAO controls. A standard alpha of 0.05 was used to determine significance. All medical conditions were found through chart review. Table 1 shows medical conditions considered. Glaucoma was defined as nerve related damage with or without intracranial hypertension. Coronary artery disease encompassed stable angina, unstable angina, and myocardial infarction. Lack of notation of a medication condition (e.g. HIV) was considered as absence of that medical condition. Smoking was the only exception where lack of information was coded as unknown.

**Table 1. Potential risk factors predicting retinal vascular occlusion diagnosis.**

<table>
<thead>
<tr>
<th>Risk Factors Considered</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 2 Diabetes Mellitus</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
</tr>
<tr>
<td>Coronary Artery Disease</td>
</tr>
<tr>
<td>Hepatitis C Virus</td>
</tr>
<tr>
<td>Cerebrovascular Accident</td>
</tr>
<tr>
<td>Cancer</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
</tr>
<tr>
<td>Obesity</td>
</tr>
<tr>
<td>Asthma</td>
</tr>
<tr>
<td>Atopic Dermatitis</td>
</tr>
<tr>
<td>Glaucoma</td>
</tr>
<tr>
<td>HIV</td>
</tr>
<tr>
<td>Sickle Cell Disease</td>
</tr>
<tr>
<td>Smoking</td>
</tr>
<tr>
<td>Race</td>
</tr>
<tr>
<td>Ethnicity</td>
</tr>
<tr>
<td>Gender</td>
</tr>
</tbody>
</table>

**Results**

A total of 700 charts had at least one of the target diagnostic codes and were reviewed to confirm the diagnosis, yielding 214 incident RVO cases and 35 incident RAO cases. Conditional logistic regressions were run as described in the methods. This led to RVO multivariable analyses controlling for gender and race and RAO multivariable analyses controlling for gender, ethnicity, and current+former smoking. For instance in the RVO outcome, one multivariable model assessed if type 2 diabetes mellitus (which was significant in a corrected univariable analysis) retained its significance after considering the effects of gender and ethnicity (also significant demographic variables). Significant results are shown in the tables but further nonsignificant data can be found in the supplementary tables.
Retinal vein occlusion

Of the 214 RVOs, 33.2% (n = 71) were central retinal vein occlusions (CRVO) and 66.8% (n = 143) were branch retinal vein occlusions (BRVO). 1.4% (n = 3) were bilateral CRVO and 0.93% (n = 2) were bilateral BRVOs.

Of the 214 cases, 9.3% (n = 20) were white, 42.5% (n = 91) were black or African American, 6.5% (n = 14) were multiracial, 33.1% (n = 71) were other race, 9.0% (n = 47) were Hispanic or Latino, and 46.7% (n = 100) were male gender. Of the 856 controls, 22.7% (n = 194) were white, 29.0% (n = 248) were black or African American, 11.1% (n = 95) were multiracial, 21.7% (n = 186) were other race, 26.6% (n = 228) were Hispanic or Latino, and 34.8% (n = 298) were male gender. On presentation, 9.8% (n = 21) of cases had a relative afferent pupillary defect (rAPD). 41.6% (n = 89) had macular edema on optical coherence tomography (OCT). Only 56.5% (n = 121) of RVO cases received OCT testing.

Table 2 describes the significant results of the RVO univariable analyses. Male gender was associated with increased odds of RVO in both univariable (OR = 1.65, p = 0.001) and multivariable analyses controlling for race (OR = 2.19, p < 0.001). Black and “other race” had significantly increased odds of RVO compared to White participants in univariable analysis (OR = 3.38, p < 0.001; OR = 3.86, p < 0.001 respectively) but not if multivariable analysis. Hispanic or Latino ethnicity was tending towards a negative association with RVO (OR = 0.71, p = 0.098).

Type 2 diabetes mellitus was associated with an increased risk for RVO (OR = 2.58, p < 0.001) and retained its significance when controlling for gender and race (OR = 2.41, p < 0.001). The same was true of history of cerebrovascular accident (univariable: OR = 2.39, p < 0.001; controlling for gender and race: OR = 2.14, p = 0.011), hypertension (univariable: OR = 2.25, p < 0.001; controlling for gender and race: OR = 1.83, p = 0.004), and glaucoma (univariable: OR = 8.6, p < 0.001; controlling for gender and race: OR = 6.91, p < 0.001). Hypercholesterolemia was initially associated with increased risk of RVO in univariable analysis (OR = 1.38, p = 0.041), but this did not survive False Discovery Rate correction. Multivariable analyses controlling for gender and race were run as shown in Table 4.

Retinal artery occlusion

Of the 35 RAO cases, 54.3% (n = 19) were unilateral CRAOs, 37.1% (n = 13) were unilateral branch retinal artery occlusions (BRAO), 2.9% (n = 1) were bilateral CRAOs, and 5.7% (n = 2) were bilateral BRAOs.

Of the 35 cases, 8.6% (n = 3) were white, 40.0% (n = 14) were black or African American, 5.7% (n = 2) were multiracial, 28.6% (n = 10) were other race, 17.1% (n = 6) were Hispanic or Latino, and 62.9% (n = 22) were male gender. Of the 140 controls, 15.7% (n = 22) were white, 27.1% (n = 38) were black or African American, 15.0% (n = 21) were multiracial, 20.7% (n = 29) were other race, 33.6% (n = 47) were Hispanic or Latino, and 35.0% (n = 49) were male gender. Among RAO cases, 34.3% (n = 12) of cases had a rAPD on presentation, while 8.6% (n = 3) had macular edema on OCT. A minority of RAO cases (n = 8; 22.9%) received OCT testing.

Table 3 describes the significant results of the RAO univariable analyses. In univariable analysis, Hispanic or Latino ethnicity was associated with decreased odds of RAO (OR = 0.20, p = 0.015), male gender was

**Table 2. Demographics and potential risk factors that were significant in univariable analysis for retinal vein occlusion cases.**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Frequency</th>
<th>Percentage</th>
<th>Univariable Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>Controls</td>
<td>Cases</td>
</tr>
<tr>
<td>Total</td>
<td>214</td>
<td>856</td>
<td>109%</td>
</tr>
<tr>
<td>Type 2 Diabetes Mellitus</td>
<td>110</td>
<td>248</td>
<td>51.4%</td>
</tr>
<tr>
<td>Cerebrovascular Accident</td>
<td>25</td>
<td>45</td>
<td>11.7%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>163</td>
<td>518</td>
<td>76.2%</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>107</td>
<td>363</td>
<td>50.0%</td>
</tr>
<tr>
<td>Glaucroma</td>
<td>58</td>
<td>36</td>
<td>27.1%</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White†</td>
<td>20</td>
<td>194</td>
<td>9.3%</td>
</tr>
<tr>
<td>Black or African American</td>
<td>91</td>
<td>248</td>
<td>42.5%</td>
</tr>
<tr>
<td>Other</td>
<td>71</td>
<td>186</td>
<td>33.1%</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not Hispanic or Latino</td>
<td>113</td>
<td>424</td>
<td>52.8%</td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>47</td>
<td>228</td>
<td>9.0%</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female†</td>
<td>114</td>
<td>558</td>
<td>53.3%</td>
</tr>
<tr>
<td>Male</td>
<td>100</td>
<td>298</td>
<td>46.7%</td>
</tr>
</tbody>
</table>

*Insufficient data or not applicable reference group

**p-value was no longer significant after False Discovery Rate correction.
associated with increased odds of RAO (OR = 3.24, p = 0.004), and Black or African American race was tending towards increased odds of RAO relative to White individuals (OR = 3.00, p = 0.11).

Table 4 shows results of multivariable analyses. As with RVO, univariable analyses were initially conducted and any significant predictors were then further examined in multivariable models. Multivariable models controlled for gender, ethnicity, and smoking status (i.e. if the participant was a current or former smoker). In univariable analysis, both current and current+former smoking combined were associated with increased odds of RAO (OR = 2.98, p = 0.049; OR = 7.79, p < 0.001), however after False Discovery Rate correction, only current+former smoking remained significant. Coronary artery disease was significant in a univariable analysis (OR = 5.81, p = 0.002) and tending towards significance in multivariable analysis (OR = 6.27, p = 0.068). The same was true of history of cerebrovascular accident (univariable: OR = 8.93, p = 0.010; multivariable: OR = 8.33, p = 0.096). Type 2 diabetes mellitus was associated with RAO initially in a univariable analysis (OR = 2.48, p = 0.035); however, the p-value was no longer significant after the False Discovery Rate correction. Only current+former smoking (OR = 8.95, p = 0.021) was significantly associated with RAO in all multivariable models it was included in.

Among the RAO cases, 14.3% (n = 5) were found to have sickle cell disease. Logistic regression was not possible because 0 controls had sickle cell disease. The age range of these sickle cell cases was 17–35 (median = 23, SD = 7.3). Of the sickle cell cases, 3 were male, 3 had bilateral occlusion, and 1 was a current smoker. Additionally, 1 had history of hypertension, 0 had history of type 2 diabetes mellitus, and 1 had a history of cerebrovascular accident.

**Discussion**

In this study, incident cases of RVO and RAO over a three and one-half year period were retrospectively reviewed and compared to age-matched controls in conditional logistic regression models.

In a series of multivariable analyses, RVO was significantly associated with type 2 diabetes mellitus, cerebrovascular accident, hypertension, glaucoma, black race, and male gender, and RAO was significantly associated with current+former smoking and male gender.

There were substantial percentages of black (29.0% of controls) people in this study. Black race was associated with increased odds of RVO compared to other races, a finding that has previously been reported. For ethnicity, there were also significant percentages of Hispanic or...
Latinos (26.6% of controls) people; however, no association was found between RVO and Hispanic or Latino ethnicity.

The present study found potential associations with RVO to include type 2 diabetes mellitus (OR = 2.41, p < 0.001), cerebrovascular accident (OR = 2.14, p < 0.001), hypertension (OR = 1.83, p < 0.001), glaucoma (OR = 6.91, p < 0.001), and male gender (OR = 2.19, p < 0.001). Multiple studies have previously reported associations with RVOs. The Eye Disease Case-Control Study Group found increased risk of CRVO associated with hypertension, type 2 diabetes mellitus, and open-angle glaucoma.9 When adjusting for sex, race, age, and site, they found odds ratios of 3.8 (95% CI 2.3–6.5) for history of systolic blood pressure greater than or equal to 152 mmHg, 2.0 (95% CI 1.3–2.9) for history of diabetes mellitus, and 5.3 (95% CI 3.5–8.0) for history of glaucoma. They also found increased risk of BRVO associated with hypertension (OR = 7.2, 95% CI 3.8–13.7), history of cardiovascular disease (OR = 1.8, 95% CI 1.3–2.5), increased BMI at 20 years of age, and history of glaucoma (OR = 2.3, 95% CI 1.5–3.8).10 Koh et al similarly found increased risk of RVO to be associated with hypertension (OR = 4.26, 95% CI 2.02–10.5) and history of myocardial infarction (OR = 2.34, 95% CI 1.18, 4.33).20 Klein et al reported associations with RVO including glaucoma (OR = 3.17, 95% CI 1.50–6.69) and current smoking (OR = 1.88, 95% CI 1.05–3.35).5 Other studies have also found associations between RVO and hypertension, increased age, history of cardiovascular disease, and history of glaucoma.10,11,15,21,22 These associations support the abundance of evidence, including in the present study, that cardiovascular risk factors and glaucoma contribute to increasing the risk for RVO, including in black and Hispanic or Latino populations.

Carotid artery stenosis is thought to be the main etiology of thrombotic plaques that embolize and cause RAO, and patients are at increased risk of stroke and acute myocardial infarction just after CRAO occurrence.23,24 Previous studies have reported associations between RAO and type 2 diabetes mellitus as well as other cardiovascular risk factors.25,26 Hayreh et al found increased risk of RAO associated with type 2 diabetes mellitus, hypertension, ischemic heart disease and cerebrovascular accident.27 Additionally, Calway et al studied risk factors for RAO during cardiac surgery and found increased associations with embolic stroke (OR = 4.43, 95% CI 3.05–6.42), male gender (OR = 1.30, 95% CI 1.12–1.52), and several other diseases.28 Interestingly, smoking was found to decrease odds of RAO perioperatively (OR = 0.82, 95% CI 0.70–0.97). In the present study, the only risk factors for cardiovascular disease found to be associated with increased odds of RAO were current/former smoking (OR = 8.95, p = 0.21) and male gender (OR = 2.56, p = 0.038). History of coronary artery disease and cerebrovascular accident were tending towards association (p = 0.068 and p = 0.096 respectively), so perhaps a larger sample size would reveal significance. Univariable analysis found several other associations with RAO; however, none of these individual associations remained significant after the False Discovery Rate correction or when adjusting for gender and race.

Hispanic or Latino ethnicity was found to be tending towards an association with decreased odds of RAO in this study (OR = 0.28, p = 0.054). Because no previous studies on epidemiology of RAO have been conducted on populations with large numbers of Hispanic or Latino people, there have not been any studies that have looked into this association. Hoki et al did report that the prevalence of retinal emboli was lower in a Latino population-based study compared to previous non-Latino population-based studies.29 Why Hispanic or Latino individuals would have lower risk for RAO, even when controlling for other contributing factors, remains unknown.

While several case reports in the literature have reported RVOs serving as the initial presentation for HIV,30–32 HIV was not associated with either RVO or RAO in this analysis. Regardless of RVO status, there were few cases with HIV in this study. This is surprising given its relatively high prevalence in the Bronx.16 However, this may be because the sample size was not large enough to capture enough HIV cases.

Sickle cell disease was seen in 14.3% (n = 5) of RAO cases and 0.0% (n = 0) of RAO controls. While logistic regression was not possible, descriptively this suggests a strong association. The pathogenesis of RAO can often be similar to that of neurological ischemic strokes, which are known to occur in young sickle cell patients.33

There are limitations to this study. Due to its retrospective nature, many patients did not receive testing for medical conditions such as HIV, but were considered negative in this analysis. For smoking, this resulted in a large number of unknown cases. This was especially true in the RVO and RAO cases (15.9% and 5.7% respectively) compared to the RVO and RAO controls (3.9% and 2.9% respectively). Additionally, there are other potential risk factors that were not examined as part of this study due to the limitations of retrospective analysis. Finally, we also need to consider the role that Berkson’s bias may have had in these findings, as our cases and controls were selected from a pool of participants who were treated in a clinical setting. Research subjects recruited from a clinical setting may have increased exposure to occurrence of disease compared...
to a healthy population, potentially resulting in a distortion of the odds ratios.

To our knowledge, this is the first epidemiological study of retinal vascular occlusions conducted on a population with significant percentages of black and Hispanic or Latino people, and it is the first to report strengths of associations between retinal vascular occlusions and race and ethnicity. The sample size for RVO cases was fairly large, and cases were age-matched to better control for known associations with increased age. There have been some epidemiological studies reported investigating RVO, and fewer studying RAO. Most of these studies have been conducted on white or Asian populations. Future studies should investigate the role of race, ethnicity, and genetics in retinal vascular occlusions to further elucidate harmful and protective factors.

Declaration of Interest
None of the authors have any proprietary interests or conflicts of interest, financial or otherwise, related to this submission.

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