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Interaction Between Glaucoma and Central Retinal Vein Occlusion in a Cohort Study

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Abstract: Objectives: To study the associations of central retinal vein occlusion (CRVO) with glaucoma and cataract before and after the onset of CRVO. **Methods**: This study of 439 fundus photographically verified CRVO cases and a 5:1 set of 2195 registry-based age- and sex-matched control subjects without a record of CRVO examined rates of cataract and glaucoma before and after CRVO based on diagnoses, procedures, and prescriptions and compared odds ratio (OR) and incidence rate ratio (IRR) estimates for 10 years prior to a subject's first CRVO and incident comorbidity after CRVO. **Results**: The median age at the time of presentation of 439 eligible patients with CRVO was 71 years (interquartile range 11 years). In 10 years leading up to the incidence of CRVO, the ORs for glaucoma and cataract were 6.01 (95% confidence interval (CI95) 4.05 to 8.94) and 2.13 (CI95 1.45 to 3.12), respectively. During a mean follow-up of 5.7 years after CRVO, the incidence rate ratios for glaucoma and cataract were 16.7 (CI95 9.32-30.1) and 1.99 (CI95 1.39-2.84), respectively. **Conclusions**: Glaucoma and cataract occurred at elevated rates compared to the background population both before and after the clinical presentation with CRVO. The results fit a model where glaucoma, cataract, and CRVO share a common underlying cause in the form of venous hypertension that converts to classic CRVO when capillary wall integrity has been sufficiently weakened by conditions such as diabetes, cardiovascular disease, and aging to begin leaking, thereby producing retinal haemorrhage and oedema.

Keywords: central retinal vein occlusion; glaucoma; cataract; venous congestion; capillary leakage; venous pressure; retinal perfusion

1. Introduction

Central retinal vein occlusion (CRVO) can present with variable degrees of venous congestion, retinal and optic disc haemorrhage, retinal ischemia, and macular oedema [1,2]. The congestion is caused by compression or thrombosis of the central retinal vein, within or behind the lamina cribrosa. Central retinal vein occlusion can range from mild to severely haemorrhagic, oedematous and/or ischemic [1,3] and it have an insidious onset over months or years [4]. This means that retinal perfusion pressure may have been subnormal for some time before the appearance of CRVO. Central retinal vein occlusion is epidemiologically intertwined with glaucoma, the presence of one being associated with a high risk of having or developing the other. Glaucoma can be preceded by stromal haemorrhage on and around the optic disc [5–8], suggesting that an element of venous congestion may be present early in glaucoma. In this study, we examined rates of glaucoma and cataract before and after CRVO and compared rates of glaucoma and cataract in CRVO patients with the background population.

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2. Materials and Methods

This was a registry-based matched case-control and cohort study including 439 verified CRVO cases assessing ocular risk factors for CRVO with follow-up data from three secondary referral centres, the Rigshospitalet and the Aalborg and Odense hospitals in Denmark, between 1976 and 2010. Reference data were polled from a national database and consisted of 5 optimally matching individuals without a diagnosis of CRVO for every case of CRVO [9]. The study was approved by the Committee on Health Research Ethics of the Capital Region of Denmark (*jr.no. F-24045982*) and conducted in accordance with the Declaration of Helsinki II.

Fundus photographs, fluorescein angiograms and written records from patients registered with the diagnosis of CRVO (code H.348 of the International Classification of Disease 10 and codes 37703, 37708 and 37709 of the International Classification of Disease 8) were reviewed to confirm the diagnosis, which required the presence of disc swelling, macular oedema, dilated retinal veins, intraretinal haemorrhage in all four fundus quadrants, and cotton wool spots. In long-standing cases, the absence of congestion, oedema, haemorrhage, and cotton-wool spots was accepted if chronic changes such as collaterals adjacent to the optic disc were visible. The concomitant finding of diabetic or non-diabetic microvascular retinopathy was accepted if present in both eyes [10]. Patients with more than one CRVO were enrolled based on their first CRVO. All patients were ≥ 40 years of age.

Control subjects representing the general population were sampled from the Danish Civil Registration System (DCRS), which maintains vital information on all residents in Denmark from the year 1968 and later under unique personal identification numbers [11]. Five unduplicated same-sex control subjects per case (2,195 in total) were automatically retrieved at random among subjects eligible based on their age being within ± 2 years of the case, sex, of them not having a diagnosis of CRVO and on being alive the day CRVO was diagnosed in the case.

Comorbidity data were assessed using data from the Danish National Patient Registry (DNPR) and the Registry of Medicinal Product Statistics (RMPS). Established in 1977, the DNPR covers all private and public hospital admissions in Denmark and related diagnoses, using ICD-8 before 1995 and ICD-10 from 1995 [12]. From 1995 the RMPS has recorded all prescription drug dispensation at pharmacies in Denmark by civil registration number, date, and type of drug (Anatomical Therapeutic Chemical code) [13].

Chronic conditions were classified using hospital discharge diagnoses and drug prescriptions. The presence of glaucoma was inferred if an antiglaucoma eye drop medication had been dispensed, and so on. Isolated events were based on hospital discharge diagnoses. Cataract was assigned if cataract surgery had been registered. Glaucoma and cataract were the only ocular associations that were deemed to be of sufficient prevalence and registry-based diagnostic reliability to be included in the analysis. Registration was per patient, not per eye. The data were not of sufficient granularity to reliably define sidedness of conditions, to differentiate between ocular hypertension and glaucoma, or to differentiate between glaucoma subtypes.

Survival data and migration status up to December 31, 2010, were obtained from the DCRS. Comorbidity data, also obtained up to December 31, 2010, were available from 1968 (DCRS), 1977 (DNPR), 1994 (RMPS) and onwards, respectively. The study period was divided into a 10-year period before the date that CRVO was diagnosed and the period between the date of diagnosis of CRVO and the date of censoring. Patients were censored at the first occurrence of an event within a given category, at the date of their death, or at the end of follow-up on December 31, 2010, whichever came first. Separate analyses were made for each of the two periods. Only patients with a complete set of registry data for a given period were included in the analysis of that period.

Statistics

For each patient and control subject, information on diagnosis, date of birth, gender, index date (date of diagnosis, in patients), age at index date, observation time and outcome events were recorded. To reveal missing data and extreme values, the data set was systematically tested. No extreme values were found. Minor data deficits were found among the socioeconomic variables, but

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in equal proportions in cases and controls. Deletion of the missing data or categorization as unknown did not change the estimates. Hence no changes were made to the data set in terms of deletion or addition.

The study population was divided into five groups by age at index date (<50, 50-59, 60-69, 70-79 and >80 years). Conditional logistic regression was used to evaluate socioeconomic characteristics (income, education, and employment) as potential confounders.

Odds-ratios (ORs) and 95% confidence intervals (95% CI) for each potential risk factor during the 10-year period before CRVO were calculated using conditional logistic regression. The ORs were adjusted for age at the index date (the matched variable), gender, index date and socioeconomic characteristics (income, education, and employment) as categorical variables. Systematic testing did not identify any interactions.

Cox' proportional hazard regression method was used to calculate hazard ratios (HRs) and 95% confidence intervals (CI95), which were interpreted as a measure of incidence rate ratios (IRRs) and used to compare event rates between groups. Initially, the model was constructed using each covariate considered to be potentially influential. In the final model the HRs were adjusted by age at the index date, gender, index date and socioeconomic characteristics with time as the underlying scale. Systematic testing did not identify any interactions.

Data were linked using population-wide unique personal identification numbers and anonymized before being made available for analysis using SAS (version 9.2, SAS Institute, Inc., Cary, North Carolina, USA) on terminals linked to Statistics Denmark.

A previously published report described mortality and systemic risk factors in the same study population [9]. No ophthalmic risk factor was found to be independently associated with mortality.

3. Results

Of 439 CRVO cases (52 % males, 48 % females), the majority were 60 to 79 years of age when diagnosed with CRVO (Table 1). No significant difference was found in socioeconomic characteristics between patients and controls.

Table 1. Characteristics of central retinal vein occlusion cases and controls matched for sex and age.

	CRVO cases (%) (n=439)	**Controls (%) (n=2,195)**
Age [y]*		
<50	55 (12.5)	273 (12.4)
50-59	60 (13.7)	304 (13.8)
60-69	111 (25.3)	554 (25.2)
70-79	139 (31.7)	679 (31.1)
≥80	74 (16.9)	385 (17.5)
Gender		
Male	230 (52.4)	1,150 (52.4)
Female	209 (47.6)	1,045 (47.6)

CRVO = Central retinal vein occlusion. *at time of each CRVO index case diagnosis. Income, employment and education characteristics were comparable between cases and controls [9].

Significant ocular risk factors for CRVO present in the period 0-10 years before CRVO were glaucoma (OR 6.01, CI_{95} 4.05-8.94) and cataract (OR 2.13, CI_{95} 1.45 to 3.12) (Table 2). Mean follow-up was 5.1 years after CRVO and 5.7 years for control subjects. A higher-than-normal risk of developing a condition following the diagnosis of CRVO was found for both glaucoma (IRR 16.74; CI_{95} 9.32-30.11) and cataract (IRR 1.99; CI_{95} 1.39-2.84) (Table 3).

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Table 2. Risk factors present 10 years before central retinal vein occlusion.

	CRVO cases (%)	Controls (%)	Odds ratio (95% CI)*	Odds ratio (95% CI)†	Odds ratio (95% CI)‡	p-value‡
Glaucoma§	62 (23.94)	72 (5.56)	5.35 (3.69-7.75)	6.03 (4.08-8.92)	6.01 (4.05-8.94)	<0.0001
Cataract	48 (11.16)	137 (6.37)	1.85 (1.31-2.61)	2.05 (1.40-3.00)	2.13 (1.45-3.12)	0.0001

CRVO = Central retinal vein occlusion. CI = confidence interval. *Logistic regression estimating crude odds ratio (OR) for risk factors associated with central retinal vein occlusion. †Logistic regression estimating odds ratio (OR) adjusted for age, gender and index date for risk factors associated with central retinal vein occlusion. ‡ Logistic regression estimating odds ratio (OR) adjusted for age, gender, index date and socioeconomic characteristics. § Glaucoma diagnosis based on both hospital discharge diagnoses and drug prescriptions, cataract only on the former.

Table 3. Risks of incident ocular comorbidity after central retinal vein occlusion.

	CRVO cases (%)	Controls (%)	IRR (95% CI)*	IRR (95% CI)†	p-value†
Glaucoma§	34 (13.9)	21 (1.38)	15.91 (9.02-28.08)	16.7 (9.32-30.1)	<0.0001
Cataract	42 (11.6)	150 (7.81)	1.93 (1.36-2.75)	1.99 (1.39-2.84)	0.0002

CRVO = Central retinal vein occlusion CI = confidence interval. * Cox regression model estimating incidence rate ratio (IRR) with time as underlying timescale adjusted for sex, age and index date as categorical variables. † Cox regression model estimating incidence rate ratio (IRR) with time as underlying timescale adjusted for sex, age, index date and socioeconomic characteristics as categorical variables. § Glaucoma diagnosis based on hospital discharge diagnoses and drug prescriptions, cataract on the former.

4. Discussion

In clinical practice, the term CRVO is used without detailed consideration of the degree to which the outflow of venous blood through the central retinal vein is impaired. Angiographically, most cases of CRVO show preserved perfusion of the central retinal vein as it enters the lamina cribrosa. Hence, a categorical shift from an open to a closed central retinal vein cannot be verified and the term occlusion is a simplification. We will therefore use CRVO as a classification entity only. At the mechanistic level, we propose that the transition to clinical CRVO can be triggered either by an isolated decrease in vessel wall resistance that in itself leads to haemorrhage, exudation, macular oedema and visual loss, or by an isolated increase in outflow resistance, or by a combination of the two.

Insidious onset of CRVO is seen in clinical practice, beginning with a few retinal haemorrhages, and then progressing gradually to clinical CRVO with macular oedema [4,14]. So is the progression from a few peripapillary retinal splinter haemorrhages to wedge-shaped retinal nerve fibre layer defects with arcuate scotomata of the classical glaucoma type [5–8]. Also documented in clinical practice is the local aggravation of diabetic retinopathy by venous congestion [4,15]. These observations are compatible with a general role of venous congestion as a risk factor for retinal disease and with a large variation in retinal venous pressure in the healthy human eye. The existence of an unrecognized risk factor for retinal vascular disease is also suggested by the 8% prevalence of retinal microaneurysms and haemorrhages that meet the definition of diabetic retinopathy in 8% of people without diabetes [10]. Venous hypertension is therefore a candidate for being such a silent risk factor.

The pressure in the central retinal vein in healthy eyes appears to vary from being near the intraocular pressure, in eyes where the central retinal vein is pulsating with the heartbeat, to levels

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near the diastolic arterial blood pressure in eyes where venous backflow during the cardiac diastole can be demonstrated [16]. Variation in retinal venous pressure is also evident from the absence of spontaneous pulsation of the retinal veins on the optic disc in CRVO [17], compared with it being present in 75-98% of healthy subjects, and in 51-64% of glaucoma patients [18–20], consistent with glaucoma eyes having higher-than-normal retinal venous blood pressure.

In the present study, glaucoma was six times more common and cataract two times more common in people who later went on to develop CRVO than in controls. These results agree with prior studies and add a considerable amount of data to the volume of risk factor observations, while also adding new information about the temporal relation of events [21–29].

The association between glaucoma and subsequent CRVO was 2-4 times stronger than for any of the systemic risk factor reported in the study cohort, which were diabetes (OR 2.08), arterial hypertension (OR 2.03), heart disease (OR 1.57), peripheral artery disease (OR 3.21), peripheral vein disease (OR 2.10), and cerebrovascular disease (OR 1.77) [9]. Although some of these systemic risk factors may be competing representations of a smaller set of underlying causal factors, the relative weight of the intraocular posterior pole risk factors should be enough to prompt further investigation of intraocular disease mechanisms for glaucoma and CRVO.

The predominant unilaterality of CRVO suggests that it may be primarily an eye disease and to a lesser degree a complication of systemic disease [3]. The rate of bilaterality of CRVO at presentation has been found to be 1.6% [30] and the conversion rate from unilateral CRVO to bilateral unspecified RVO only 3.4% - 4.4% per year over 3 years [30,31].

The empirical association of CRVO with cardiovascular disease, diabetes, and increasing age may be taken to indicate that thrombosis is a common cause of CRVO. An alternative hypothesis is that venous congestion comes first, whereas conversion to CRVO happens when retinal vessel integrity has been sufficiently weakened by chronically high venous pressure, the weakening being promoted by diabetes, cardiovascular disease, and aging [32,33]. In this scenario, CRVO is a product of capillary frailness rather than thrombosis.

The effect of intravitreal pharmaceutical inhibition of vascular endothelial growth factor (VEGF) on macular oedema secondary to CRVO is profound. Reduction of leakage is evident on fluorescein angiograms, supporting that relapse of CRVO problems are driven by vessel wall frailty rather than recurrent thrombosis of the central retinal vein. Of note, the suppression of macular oedema can last for many months [34], despite intravitreal drug half-life being only 7 days [35]. This supports that leaky retinal vessels regain structural integrity, enabling them to withstand high venous pressure well beyond the intraocular lifetime of the VEGF-inhibitor.

Chronic venous congestion that precedes CRVO will have a negative effect on retinal perfusion that are more subtle than CRVO. While autoregulation can compensate for fluctuations in arterial pressure, there is no similar mechanism on the venous side. Vascular remodelling may help, by forming vein-to-vein collaterals, but the process is slow and erratic. The manifestation of high central retinal vein pressure can be subtle, as when localized ischemic retinopathy develops in the supply area of a low-pressure cilioretinal artery [36,37]. Finally, simple flow mechanics explain how arterial hypotension can combine with venous congestion to reduce optic disc and peripapillary retina blood flow, produce optic disc hemorrhages, and induce glaucoma [38].

The hypothesis of venous congestion and retinal hypoxia predating CRVO is also the background for analysing the temporal relation between cataract and CRVO. We hypothesized that cataract would be more common than in the background population not only after, but also before CRVO and both were confirmed. One possible confounding mechanism is an intraocular inflammation associated with cataract surgery that may have promoted the development of CRVO by reducing retinal vessel wall resistance [39,40].

The study was limited by the diagnosis of glaucoma being based on prescription data for pressure-lowering eye drops, by lack of registration of glaucoma subtype, ocular hypertension, anterior chamber neovascularization [41], and lack of information about the laterality of CRVO and glaucoma. Laterality information was unavailable in the study and may have led to overestimation

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of odds ratios by counting glaucoma and cataract in the fellow eye of the incident CRVO eye [42,43]. The data are from before the introduction of intravitreal VEGF-inhibition medication for CRVO and studies from the current era may find a lower incidence of neovascular glaucoma after CRVO.

Our observations of a link between glaucoma and CRVO fit a model where constitutively high retinal venous pressure imparts risk of vascular leakage and outbreak of macular oedema and retinal haemorrhage that makes CRVO symptomatic and where low perfusion pressure promotes retinal nerve fibre loss and glaucoma. The hypothesis of a unifying role of venous congestion may assist the design of targeted investigations of vessel patterns, perfusion, pulsation, oxygenation, haemorrhage, oedema, and ischaemia in clinical practice to help map the transition from healthy conditions to CRVO and glaucoma.

Author Contributions:

AUTHOR NAME	RESEARCH DESIGN	DATA ACQUISITION AND/OR RESEARCH EXECUTION	DATA ANALYSIS AND/OR INTERPRETATION	MANUSCRIPT PREPARATION
Abdullah Amini	☐	☒	☒	☒
Mette Bertelsen Vardrup	☐	☒	☒	☒
Anne-Sofie Petri	☐	☐	☐	☒
Allan Linneberg	☐	☐	☐	☒
Henrik Vorum	☐	☐	☐	☒
Michael Larsen	☒	☒	☒	☒

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Institutional Review Board Statement: The study was approved by the Committee on Health Research Ethics of the Capital Region of Denmark (jr.no. F-24045982).

The study was conducted in accordance with the Declaration of Helsinki and approved by the Committee on Health Research Ethics of the Capital Region of Denmark (jr.no. F-24045982).

Informed Consent Statement: Not applicable for this anonymized registry-based study.

Data Availability Statement: The source data are curated by Danmarks Statistik.

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Conflicts of Interest:

AA: Bayer (Speaker); ML: Bayer, Roche (speaker and investigator), Novo Nordisk (consultant), Stoke (consultant and investigator); HV (Novartis, Roche, Bayer).

The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

Abbreviations

The following abbreviations are used in this manuscript:

CRVO	Central retinal vein occlusion
OR	Odds ratio
IRR	Incidence rate ratio
CI	Confidence interval
DCRS	Danish Civil Registration System
DNPR	Danish National Patient Registry
RMPS	Registry of Medicinal Product Statistics
ICD	International Classification of Disease
HR	Hazard ratio

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VEGF Vascular endothelial growth factor

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