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Systemic Hypertension and the Eye: Highlighting a Comorbidity

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Abstract

Purpose: To identify ocular comorbidity in systemic hypertension.

Methods: Research findings include data of 566 patients with RVO (retinal vein occlusion) 408 and 158 patients with the central retinal vein occlusion (CRVO) and branch retinal vein occlusion (BRVO) respectively, representing a cases and and 566 controls, all aged 31 years and older. Excluded from case and control group were persons with degenerative changes of retina and ocular inflammation. At the baseline examination blood pressures was measured and were tested fibrinogen, recalcification time, plasma tolerance to heparin, prothrombin ratio for evaluation of blood coagulability. A statistical analysis was conducted by a commercially available statistical software package.

Results: Among our cases hypertension was more prevalent with an elevated systolic and diastolic blood pressures comparing to controls.

Hypercoagulability represented by elevated prothrombin ratio has shown a close association with age and RVO, evidencing higher risk of vasoocclusion in older persons with hypercoagulability. It was found that higher blood pressure: systolic blood pressure (OR, 8.49; 95% CI, 4.81 to 15.13) and diastolic blood pressure (OR, 9.37; 95% CI, 6.34 to 13.89); prothrombin ratio (OR, 4.0; 95% CI, 2.17 to 7.7) after adjusting for age and sex, plays a significant role in the development of RVO. Assessing an impact of systemic hypertension duration on RVO frequency it was evidenced direct relationship indicating increased cases of RVO in patients suffering from systemic hypertension 5-10 years and more obvious impact in case of longer duration–more than 10 years.

Conclusions: The study emphasized the need for enhanced collaboration between specialties to ensure appropriate management of patients with systemic hypertension and ocular comorbidity in order to prevent occurrence of retinal vein occlusion.

Keywords: Systemic hypertension; Duration of hypertension; Systolic blood pressure; Diastolic blood pressure; Retina; Retinal vein occlusion

Introduction

Accumulating evidence based on aging population suggests a worldwide epidemic of systemic hypertension, which represents a major risk factor for cardial, cerebral vascular disease. In the United States approximately 75 million adults are affected by systemic hypertension [1].

According to a new analysis of data from the Nationwide Emergency Department Sample [2] it was evidenced increase by quarter emergency rooms visits for essential hypertension during 2006-2011 years. The prevalence of systemic hypertension dramatically increases in patients older than 60 years [3], reaching 50% in many countries. It is recognized that there is a drive towards increased cases worldwide up to 20% of adult population. Present definition of hypertension is a systolic blood pressure (SBP) of 140 mm Hg or higher, or a diastolic blood pressure (DBP) of 90 mm Hg or higher, or taking antihypertensive medication [4].

Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure [5] highlights that in persons older than 50 SBP serves as an important cardiovascular disease (CVD) risk factor in case of more than 140 mm Hg comparing to diastolic BP. Systemic hypertension starts from asymptomatic silent period, which converts into clinically evidenced hypertension with secondary involvement of different organs, such as heart, kidneys, retina and brain. The results from the Atherosclerosis Risk in Communities (ARIC) study [6,7] based on findings of 2907 hypertensive patients suggest that retinal changes due to hypertension as predictive for stroke, even in case of compensated BP and directly corresponds to severity of hypertensive retinopathy reaching 1.35 and 2.37 for mild and moderate/severe cases respectively.

Retinal vein occlusion (RVO) is the most common retinal disease, second in prevalence only after diabetic retinopathy, in which arterial risk factors play a dominant role comparing to venous factors. [8,9] representing a major cause of visual disability [10].

A recent study assessing worldwide finding indicated 0.52% RVO prevalence, translating to approximately 16 million persons suffered from RVO [11].

Despite being recognized in the 19th century (first central retinal vein occlusion (CRVO) report by Richard Liebreich in 1855 [12], first

branch retinal vein occlusion (BRVO) report by Theodor Leber in 1877 [13]) occlusion of the central retinal vein and its branches still requires an understanding of pathophysiological mechanisms, taken into account complicated and multifactorial process of occlusion. The clinical features and risk factors for RVO were examined in multiple case-control studies [14-20].

It is recognized that systemic vascular disease, hypertension, diabetes mellitus, hyperlipidemia and glaucoma are the risk factors for RVO [10]. Primary hypercoagulable states with a defect in the physiological anticoagulant mechanism [21-24] and secondary hypercoagulable states, which are conditions, also are associated with an increased risk of thrombosis [25-30].

Retinal vein occlusion is classified as either central retinal vein occlusion (CRVO), branch retinal vein occlusion (BRVO), based on the specific occlusion site.

CRVO is caused by obstruction of the central retinal vein that leads to a backup of blood and fluid in the retina. Central retinal artery and central retinal vein are surrounded by common fibrotic sheath, and in case of sclerotic arterial changes associated with systemic hypertension or arteriosclerosis, artery causes a pressure on vein, which predisposes to thrombus formation. If thrombus is formatted into any of branches of central retinal vein it is diagnosed as a BRVO.

Taking into consideration the high prevalence of hypertension in the population and potentially linked pathologies, the aim of this study was to identify an ocular comorbidity in systemic hypertension.

Methods

Research findings include data of 566 patients with RVO (retinal vein occlusion)-408 and 158 patients with the central retinal vein occlusion (CRVO) and branch retinal vein occlusion (BRVO) respectively, representing a cases and and 566 controls, all aged 31 years and older. Diagnosis of CRVO and BRVO was established by ophthalmologist using direct ophthalmoscope and ophthalmobiomicroscopy with 90 D Fundus lens at the initial visit of patient. CRVO was diagnosed if fundus examination revealed flame-shaped, dot, or punctuate retinal hemorrhages in all four quadrants of the retina, dilated and tortuous retinal veins, and optic disc swelling. The same findings in one quadrant corresponded to the branch of central retinal vein indicated the BRVO. Excluded from case and control group were persons with degenerative changes of retina and ocular inflammation. A person qualified as a control if he or she was free of retinal vascular disease. 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. 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%). The age and sex profile of the cases and controls is shown in Table 1. At the baseline examination blood pressure was measured and was tested fibrinogen, prothrombin time, recalcification time, plasma tolerance to heparin, for evaluation of blood coagulability.

Age, years	**RVO, n (%)**	**Controls, n (%)**
21-30	6 (0.9)	163 (28.8)
31-40	47 (8.3)	71 (12.5)
41-50	48 (8.6)	64 (11.3)
51-60	136 (24)	88 (15.6)
61-70	232 (41)	94 (16.6)
70 or older	97 (17.2)	86 (15.2)
Sex		
M	280 (49.5)	346 (61.1)
F	286 (50.5)	220 (38.9)
RVO = Retinal vein occlusion		

Table 1: Age and sex distribution of RVO cases and controls.

The prothrombin time test belongs to a group of blood tests that assess the clotting ability of blood. The prothrombin test specifically evaluates the presence of factors VIIa, V, and X, prothrombin, and fibrinogen. Prothrombin is a protein in the plasma that is converted to thrombin as part of the clotting process. Fibrinogen is a type of blood protein called a globulin; it is converted to fibrin during the clotting process. Recalcification time is a measure of the time taken for clot formation in recalcified blood. Plasma tolerance to heparin represents the patient's clotting response to graded doses of heparin solution.

Statistical analyses were conducted by a commercially available statistical software package.

Results

Several risk factors were significantly associated with RVO in the screening analyses (Table 2).

Factor	Association with RVO, 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)
Systemic disease	
Systemic hypertension (yes/no) &	↑ (0.001)
Systolic blood pressure, mmHg	↑ (<0.001)
Diastolic blood pressure, mmHg	↑ (<0.001)
Kidney disease	↑ (0.001)
Diabetes history (yes/no)	↑ (0.001)
Biochemical data	
Fibrinogen, g/L	↑ (<0.05)
Recalcification time, sec	↓ (<0.05)

Plasma tolerance to heparin, min	↓ (<0.05)
Prothrombin ratio, %	↑ (<0.001)
Urine analysis	
Proteinuria (yes/no)	↑ (<0.01)
* Each factor was analyzed in a logistic regression. Direction of association shown only for p<0.05 & Systolic pressure of 160 mmHg or more, or diastolic pressure of 90 mm Hg or more, or taking antihypertensive medication, RVO = Retinal vein occlusion. ↑ = Direct relationship, ↓ = Inverse relationship	

Table 2: risk factors included in the analysis of RVO and results from the screening analysis.

We calculated odds ratios to assess the magnitude of these associations (Table 3).

Factor	**RVO/ 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
Sex	
M	1
F	1.55 (1.19-2.03)
Systemic disease	
Systemic hypertension	
No	1
Yes	8.6 (4.12-17.85)
Systolic blood pressure, mmHg	
<120	0.27 (0.14-0.51)
120-140	1
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)
Factor	RVO/controls, OR (95% CI)
Diastolic blood pressure, mmHg	
≤ 70	0.26 (0.14-0.47)
71-89	1
90-100	9.37 (6.34-13.89)
>100	11.47 (5.18-26.17)
Kidney disease	
No	1
Yes	13.57 (4.57-45.27)
Diabetes	
No	1.0
Yes	13.57 (4.57-45.27)
Prothrombin ratio, %	
60-75	1.0
80-100	4.0 (2.17-7.7)
Proteinuria	
No	1
Yes	2.39 (1.01-5.60)
RVO = Retinal vein occlusion; OR = Odds ratio; CI = Confidence interval	

Table 3: Odds ratios to assess the magnitude (95%CI) for RVO.

Among our cases hypertension was more prevalent with an elevated systolic and diastolic blood pressures comparing to controls. Majority of RVO patients 340 (60%) suffered from systemic hypertension. Simultaneous comorbidities were revealed in 11.3% of cases (52 patients), with 2 diseases in 8.9% (41 patients) and 3 diseases in 2.4% (11 patients) respectively.

Two component comorbidity was manifested by systemic hypertension in all cases combined with diabetes mellitus, or kidney disease, or stroke.

Three component comorbidity was presented by systemic hypertension combined with diabetes and stroke, or diabetes and kidney disease respectively.

In conclusion, in the subgroup of RVO patients with multiple systemic conditions the main association was systemic hypertension.

Hypercoagulability represented by elevated prothrombin ratio has shown a close association with age and RVO, evidencing higher risk of vasoocclusion in older persons with hypercoagulability. It was found that higher blood pressure: systolic blood pressure (OR, 8.49; 95% CI, 4.81 to 15.13) and diastolic blood pressure (OR, 9.37; 95% CI, 6.34 to 13.89); prothrombin ratio (OR, 4.0; 95% CI, 2.17 to 7.7) after adjusting for age and sex, plays a significant role in the development of RVO.

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).

The current study extends the earlier data by examining the association of RVO with systemic hypertension duration. Assessing an impact of systemic hypertension duration on RVO frequency it was evidenced direct relationship indicating increased cases of RVO in patients suffering from systemic hypertension 5-10 years and more

obvious impact in case of longer duration more than 10 years (Figure 1).

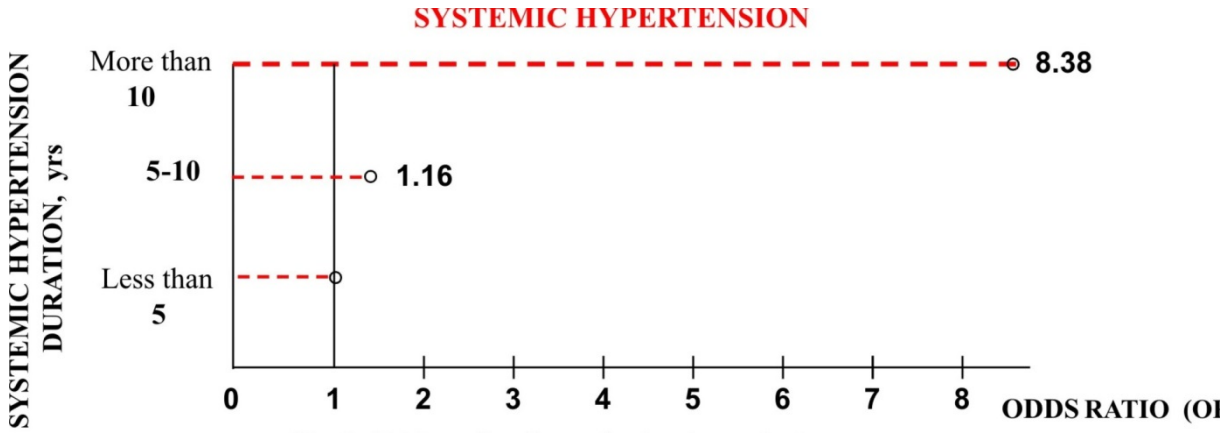

Figure 1: Odds ratio for retinal vein occlusion in systemic hypertension.

Discussion

A large body of evidence suggests that systemic conditions like hypertension, arteriosclerosis, diabetes mellitus, hyperlipidemia, vascular cerebral stroke, blood hyper viscosity, and thrombophilia have been associated with vasooclusion of the retinal vein [8,10]. It is recognized that hypertension is the trigger factor in the development of RVO, and that RVO often provide the first indications of an undiagnosed hypertension [8].

Our findings are consistent with previous data suggested cardiovascular risk profile for persons with CRVO [16-34].

The strong association between hypertension and RVO was evidenced by Goldacre et al. and is consistent with previous studies [35]. In particular, a systematic review of 21 studies (comprising 2916 cases of any form of RVO, and 28 646 controls) generated a pooled OR of 3.5 (95% CI 2.5 to 5.1). As in a previous studies [18,28,36] 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 five-fold increase in risk of RVO. In previously conducted clinic-based studies [14-19] with control groups, systemic hypertension was significantly more common in patients with retinal vein occlusion than in controls.

The latest study of patients through America conducted by Stem et al. evidenced that individuals with end-organ damage from hypertension had a 92% (hazard risk (HR) 1.92; 95% CI, 1.52-2.42) increased risk of CRVO and confirms that hypertension and vascular diseases are important risk factors for CRVO [37]. Assessment of risk factors in patients younger than 60 years also found hypertension association with CRVO in 23% of cases and arterial hypertension and hypercholesterolemia (46.2% and 38.5%, respectively in case of BRVO). Findings from the study of Korean patients confirm the strong association of hypertension with BRVO. Population-based study in Japan [18] found that after adjustment for age and sex systolic and diastolic blood pressures, hypertension, and hematocrit were significantly associated with RVO. In multivariate analysis, age (per 10 years; odds ratio [OR], 1.47; 95% confidence interval [CI], 1.04-2.08), hypertension (OR, 4.25; 95% CI, 1.82-9.94), and hematocrit (per 10%; OR, 3.09; 95% CI, 1.10-1.22) remained independently significant risk factors for RVO. A hospital-based case-control study conducted in Nepal also confirmed a hypertension as a risk factor for RVO [37-41].

The general consensus is that retinal vein occlusion represents an ocular comorbidity in systemic hypertension, but data about specific impact of selectively elevated systolic and diastolic blood pressures and also duration of hypertension on frequency of retinal vein occlusion is not available.

Conclusions

The study emphasized the need for enhanced collaboration between specialties to ensure appropriate management of patients with systemic hypertension and ocular comorbidity in order to prevent occurrence of retinal vein occlusion.

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