Management of Retinal Vein Occlusion, Who Is Responsible?

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Abstract- Retinal vein occlusion (RVO) is a common retinal vascular occlusive disorder and is associated with a variety of systemic risk factors. The aim of this study was to investigate whether the underlying diseases were evaluated and managed appropriately by ophthalmologists. We performed a study of 1344 patients with retinal vein occlusion (RVO). Patients were evaluated with a questionnaire including ten closed questions to determine whether ophthalmologists evaluated and informed their patients about the underlying systemic diseases. None of the patients' homocysteine levels were measured. Only a small percentage of the patients were asked about the history of thrombotic diseases or family history of thrombotic diseases. We believe that most ophthalmologists are still not entirely convinced of their responsibility of managing the underlying predisposing factors of RVO. Ophthalmologists should either manage or engage other healthcare providers in the management of RVO to guarantee the patient the best care.

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Introduction

Retinal vein occlusion (RVO) is by far the most common retinal vascular occlusive disorder and is usually associated with a visual loss of variable degree (1). CRVO is the second most frequent retinal vascular disease causing visual loss after diabetic retinopathy (2). The clinical manifestations of CRVO are associated with venous congestion, which leads to optic disc swelling, ischemia, widespread intra-retinal hemorrhage, and macular edema (3,4). RVO is a relatively frequent disease that may be associated with many different systemic diseases (5).

Most patients with RVO are middle aged to elderly (1,2), and more than half have relation with cardiovascular disease (CVD) (6,7). Previous reports have revealed an increased risk of RVO in patients with hypertension, (5,8-11) diabetes mellitus, (6,11) dyslipidemia, (1,12) CVD (1,8) and open-angle glaucoma (4,9-11,13). Although RVO is common in elderly, with 51% of cases happening in patients older than 65 years, (12) RVO can also be detected in young adults (14). There is a controversy in literature about the exact risk factors and pathogenesis of RVO in younger patients, most of whom are otherwise healthy. Due to the occurrence of RVO in younger patients, several predisposing risk factors of thrombophilic abnormalities have recently been observed in greater details. Published reports on coagulation abnormalities in RVO patients have reported association of increased risk of RVO with deficiency of protein C, protein S, (15) elevated fibrinogen levels (16), antithrombin III, (9,13) and other possible etiologies include Behcet disease, (12) antiphospholipid syndrome (3,12) and hyperhomocysteinaemia (4,12).

Central retinal vein occlusion (CRVO) was correlated with an increase in mortality (17) compared with controls that attributed statistically to

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cardiovascular disorders. Therefore, RVO presentation should trigger the evaluation of glaucoma and cardiovascular risk factors. Patients with cardiovascular disorders should be treated adequately with referral of patients who are not already being treated by a primary care physician (1,14).

The purpose of this survey was to investigate whether the respective underlying diseases of patients with RVO were evaluated and managed appropriately by ophthalmologists.

Materials and Methods

This cross-sectional study involved patients who were diagnosed and treated for retinal vein occlusion between January 1, 2009, and December 31, 2013 (Table 1). The study was approved by Ethics committee in ophthalmology department review board. The diagnosis of RVO was made based on clinical examination by the treating ophthalmologist. The patients with RVO were evaluated with a questionnaire between 1 and 4 years after their first clinical visit. Fundus photographs, fundus fluorescein angiograms, and written records of patients who were registered and examined at the institution with the diagnosis of RVO were reviewed. The diagnosis of RVO was made based on the following criteria: branch retinal vein compression at an arteriovenous crossing outside the optic disc, cotton wool spots, intra-retinal hemorrhage, upstream venous congestion, edema, and vein-to-vein collaterals with adjacent branch veins in the absence of similar changes in the surrounding venous drainage units. In order to decrease the risk of recall bias, 3 sources (questionnaire, the medical record of hospital admission, and medical record of an office visit) were used for data collection. It was then assessed if the ophthalmologists had ordered cardiovascular or other risk factors work up from the medical notes. It was also assessed if the patients were referred to a physician for the management of the medical condition. Ten closed questions were chosen by the Ophthalmology Board of our university. Questions that had not been used previously were tested cognitively in the context of a complete questionnaire on a sample of patients in the age group specified for the survey. A pilot study was made on the complete baseline questionnaire before being finalized. The questionnaire was designed to determine whether ophthalmologists whether they evaluate background risk factors and cardiovascular work up and inform their patients about the underlying disorder. The patients or their next of kin (who were listed in the medical records) were contacted by phone, and the surveys (the questionnaires) were completed by interview. When the interviewers were not able to establish contact with the patient after 5 times tried over weeks or if the patient was dead and his/her relative could not give adequate data, the patient was excluded from the study. Data was analyzed in SPSS version 11 (SPSS Inc., Chicago, IL, USA). All data were summarized using descriptive statistics (mean [SD], the number of patients per category, etc.).

Results

A total of 1344 patients were diagnosed to have RVO during the study period. Patients' ages ranged from 27 to 90 years with a mean age of 65.9 years. 81.1% of cases were older than 60 years (P=0.013). There were more women (56.2%) than men (43.8%) (P=0.14) in the study (Table 1).

Table1. Baseline demographic features of the enrolled patients

Parameters	Number of patients (%)			*P*.value
	CRVO*	BRVO**	Total	
Number of patients	495 (36.8%)	849(63.2%)	1344 (100%)	0.32
Male (%): Female (%)	256(51.8%): 239(48.2%)	333(39.3%): 516(61.7%)	589(43.8%):755(56.2%)	0.14
Mean age (year)	63.4	67.3	65.9	0.24
Age range (No.)	27-84	31-90	27-90	0.16
0-60	96(19.4%)	158(18.6%)	254(18.9%)	0.09
60+	399(80.6%)	691(81.4%)	1090(81.1%)	0.11
Total	495(100%)	849(100%)	1344(100%)	0.21

* CRVO: Central retinal vein occlusion
** BRVO: Branch retinal vein occlusion

Right, eyes (46.7%) and left eyes (37.5%) were nearly equally affected. Both eyes were involved in 15.8% of subjects. BRVO was more common (63.2%) than CRVO (36.8%) (P=0.32). The supratemporal branch was involved in most BRVO subjects (63.3%) and macula was involved in only 2.1 % of the subjects

(Table 2).

4% of patients were checked for blood pressure by their ophthalmologists (Table 3). Information pertaining to comorbid conditions and RVO risk factors was not uniformly documented in the medical records. None of the patients' homocysteine levels were measured. Full blood count, urea, and electrolytes evaluation were scheduled to be performed as an outpatient procedure in 8.4% of patients older than 60 years old (Table 3). Only a small percentage of the patients were asking about the history of thrombotic diseases (4%) or family history of thrombotic diseases (1%). (Table 3) A total of 9.5% of patients have referred patients to internists or cardiologists for hypertension and cardiovascular work up. Of the patients who visited the hospital, only 8.3% were informed about underlying disease (Table 3).

Table 2. Pattern of retinal vein occlusion-diagnosis/laterality by subjects

Pattern		Bilateral eyes	Left eye	Right eye	Total
BRVO*	Superotemporal	90(10.6%)	240(28.3%)	208(24.5%)	537(63.2%)
	Inferotemporal	34(4%)	93(10.9%)	109(12.9%)	236(27.8%)
	Hemiretinal	4 (0.5%)	21(2.5%)	15(1.8%)	41(4.8%)
	Macular	5(0.6%)	0(0.0%)	13(1.5%)	18(2.1%)
	Inferonasal	5(0.6%)	4(0.5%)	8(0.9%)	17(2%)
	Total	138(16.2%)	358(42.2%)	353(41.6%)	849(100%)
CRVO**	Non-ischaemic	38(7.7%)	47(9.5%)	196(39.6%)	281(56.8%)
	Ischaemic	37(7.5%)	99(20%)	78(15.8%)	214(43.2%)
	Total	75(15.2%)	146(29.5%)	274(55.3%)	495(100%)
Total RVO*** (%)		213(15.8%)	504(37.5%)	627(46.7%)	1344(100%)

* BRVO: Branch retinal vein occlusion
** CRVO: Central retinal vein occlusion
***RVO: Retinal vein occlusion

Table 3. Characteristic of survey respondents

	Age<50		Age>50		Total
	CRVO	BRVO	CRVO	BRVO	
1. Evaluation of blood pressure (by Ophthalmologists)	0.9%	1.1%	2.1%	2.4%	4%
2. Evaluation of lipid profile	0.6%	1%	2.9%	3.2%	5%
3. Evaluation of full blood count, Urea and electrolytes	1.2%	0%	6.1%	2.3%	7%
4. Evaluation of fasting serum glucose and Haemoglobolin A1C	0.4%	2%	2.2%	3.1%	4.8
5. Evaluation of homocysteine level	0%	0%	0%	0%	0%
6. Taking a history of thrombotic diseases	3.5%	0%	2.1%	2%	4%
7. Taking a family history of thrombosis diseases	1.8%	0%	0.8%	0%	1%
8. Referring patients to internists or cardiologists for assessment and management of cardiovascular diseases	8.7%	0%	3.5%	6.1%	9.5%
9. Informing patients about underlying disease	4.9 %	2.1%	8.6%	0%	8.3%
10. Evaluation of hyperecoagulable states (Function of Protein C and Protein S level, Anti thrombin III level, Antiphospholipid antibodies level, Factor V Leiden mutation)	0.7%	0.5%	0.5%	0%	0.6%

Discussion

Our survey of 1344 women and men with a mean age of 65.9 years suggests that individuals with RVO may be under evaluated and undertreated in our institution. Less than 5% of the patients had blood pressure measurements, and only a few patients were asked to undergo screening tests for systemic risk factors such as a hyperlipidemia, diabetes mellitus, atherosclerotic vascular disease as baseline investigations (full blood count, urea and electrolytes, fasting serum glucose and lipids, hemoglobin A1C, homocysteine levels); although studies clearly show that baseline investigations should be performed for all patients older than 50 years with an RVO (5,18-20). Dursun *et al.*, revealed increased neutrophil levels and decreased lymphocyte levels in patients with RVO and concluded that higher neutrophil/lymphocyte ratio

(NLR) was associated with the development of RVO. In researchers opinion, the NLR may be used as a predictive tool for identifying risk for RVO (21).

The latest meta-analysis of risk factors in RVO conducted by Kolar reconfirmed the role of hypertension, arteriosclerosis, diabetes mellitus, hyperlipidemia, vascular cerebral stroke, blood hyperviscosity, and thrombophilia and evidenced that a strong risk factor for RVO is the metabolic syndrome (hypertension, diabetes mellitus, and hyperlipidemia) (22).

It is important to recognize that RVO may be the first indication of hypertension and atherosclerosis (18,19,23). Various systemic diseases that cause atherosclerosis have been associated with RVO, and there is an excess of cardiovascular morbidity and mortality on long term follow-up (19,20). These results agree with previous long-term investigations where two-thirds of the deaths in patients presented with RVO were due to cardiovascular disease, and the incidence of mortality from myocardial infarction was twice the expected level. (11,18). In addition RVO patients have a greater prevalence of stroke than similarly aged people without RVO (5,19). The results from the most recent nationwide population-based study conducted by Shih *et al.*, suggest that before the diagnosis of RVO, patients showed increased risks for hypertension, dyslipidemia, diabetes, liver diseases, renal diseases, and cerebrovascular diseases. After the diagnosis of RVO, patients were at greater risk of developing diabetes, peripheral artery disease, and major adverse cardiovascular events. Researchers have demonstrated a bidirectional association between the risk of comorbidities and the diagnosis of RVO in an elderly population (24).

RVO in young patients may be an early marker of potentially treatable, controllable and life-threatening medical conditions (25).

A principle step in the management of RVO is to inform the patients that they have the atherosclerotic vascular disease. The patients with RVO should be investigated for the risk factors, and appropriate referral should be made to the treating primary care physician. Assessment of patients with retinal vein occlusion should include a detailed history taking, clinical evaluation and laboratory investigations to check for the presence of cardiovascular risk factors (25).

The risk factors need to be appropriately treated so as to avoid delayed complications including mortality. Appropriate education to the patients regarding the underlying condition can improve their awareness about the management of the underlying disease.

It seems that current management options do not address the underlying predisposing factors of RVO. Instead, they focus on treating ocular complications, such as traction retinal detachment from neovascularization, macular edema, and vitreous hemorrhage.

Pathogenesis of RVO is a multifactorial process, and there is no single factor causes RVO, therefore, the management of RVO involves a multidisciplinary approach between the ophthalmologist and the general physician (26).

Following a diagnosis of RVO, the United Kingdom Royal College of Ophthalmologists recommends that treatment of risks known to be associated with all types of RVO is necessary. It is the responsibility of the ophthalmological team to ensure that medical evaluations and management are initiated on the diagnosis of RVO. This ensures that the risk of occurrence of new occlusions, or the recurrence of RVO are reduced (27).

It is expected that the ophthalmic team will evaluate, or arrange for such assessment, of the patient for common risk factors of hyperlipidemia and systemic hypertension. A referral would be expected to the appropriate physician for optimal management. Patients should also be referred to the appropriate specialists in the relevant field for evaluation and treatment of the rarer risk factors (27).

Hypertension and Cardiovascular Disease are more prevalent in patients with BRVO than in those with CRVO. More than 64% of RVO patients more than 50 years are hypertensive, and it is a predominant finding in recurrent RVO (88%) (28).

According to United Kingdom Royal College of Ophthalmology Interim guidelines for management of retinal vein occlusion, examination of Full blood count, ESR or plasma viscosity, urea, electrolytes, creatinine, random blood glucose, random cholesterol, HDL cholesterol, Plasma protein electrophoresis, and ECG suggested in all patients with RVO. When tests for these common predisposing factors are negative, consideration should be given to ordering additional investigations in young patients to detect abnormalities of the thrombolytic system, especially in patients with a history of thrombosis or a family history of thrombosis or in those with bilateral RVO (27). In addition Rehak *et al*., recommended medical investigation of a new patient with RVO must include as a first line, examination of blood pressure, glucose levels and lipid profile because RVO may be a presentation of significant vascular

morbidity (29). Hyperlipidemia and Hypercholesterolemia are the risk factor for RVO in patients under 50-year-old. It is also detected in up to 50% of older patients. It was revealed that up to71.4% of all patients investigated with RVO do have hypercholesterolemia (28).

Younger patients (less than 50 years of age) with BRVO usually have underlying systemic conditions such as hypertension or hyperlipidemia which should be treated appropriately (27,30).

Those with CRVO present a particular problem in evaluation and treatment. Many of these patients will have no identifiable underlying cause despite extensive evaluation including the specialized investigations like Thrombophilia screen, Anti-cardiolipin antibody, lupus anticoagulant, C-reactive protein, and Serum ACE (13,27).

Initiating a comprehensive treatment of patients with RVO may significantly reduce the incidence, recurrences and severity of subsequent complications and is necessary to manage the predisposing factors that could lead to systemic events (31).

Obviously, it seems that the most ophthalmologists in this study are still not entirely convinced of their responsibility and the importance of managing the underlying predisposing factors after RVO. In addition, availability of both time and resources is restricted for ophthalmologists, and in a busy clinic, the possibility of under treatment of the underlying cause will increase; therefore, ophthalmologists should engage other healthcare providers and the hospitals in setting up RVO service programs, that they help coordinate this care for their patients, and that they contribute to financing the coordination program resources.

Study limitations include the retrospective nature of this study and the recall bias which the authors tried to reduce by reviewing of patients' medical record. Nevertheless, this is, to date, the first study that evaluates the management of RVO by ophthalmologists and some useful clinical information can be gained from this study.

The current findings suggest that a majority of patients with RVO is caused by highly prevalent atherosclerosis risk factors that can be measured in routine baseline investigations. Along with a review of the articles, a practical approach for the treatment of RVO is required, which requires collaboration between the ophthalmologists and heath care providers. We suggest extensive investigation for systemic diseases in RVO cases because management and follow-up can prevent morbidity and mortality.

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