A Study of the Relation between Ocular Axial Length and Central Retinal Vein Occlusion at a Tertiary Care Hospital in Mumbai

ABSTRACT

Aim: This study aims to assess the association between the ocular axial length (AL) and the pathogenesis of central retinal vein occlusion (CRVO) at a tertiary care hospital. **Methods:** This study included patients of unilateral CRVO. Informed consent was obtained, followed by comprehensive history taking, ophthalmic evaluation, systemic investigations as per protocol, and ocular investigations including OCT/FFA, depending on the requirement of the patient and duration of disease. Fifteen women and 15 men with a mean age of 64.98 years were selected. ALs of the affected (study group) and unaffected eye (control group) were measured by A-scan ultrasonography (US). **Results:** The mean AL of affected eyes in males was 23.0267 mm and that in unaffected eyes was 23.191 mm ($P = 0.000$). The mean AL of affected eyes in females was 23.0131 mm and that in unaffected eyes was 23.030 mm ($P = 0.000$). The ALs of affected eyes were shorter than those of unaffected eyes ($P = 0.000$). These differences were statistically significant. The Cronbach's α found is 0.925, which suggests a strong correlation between AL and CRVO. A comparison was also made between the ALs and CRVO based on the gender, and no statistical difference was found. **Conclusion:** Our study confirms the existence of shorter ALs in the affected eye of patients of CRVO on comparison with the unaffected eye. It also confirms that this difference is statistically significant in the total population and in each gender.

Key words: Community health, health-care management, non-communicable disease

INTRODUCTION

Central retinal vein occlusion (CRVO) is a sight-threatening condition, which is the second most common cause of retinal vasculopathy after diabetic retinopathy. It is a common cause of unilateral visual loss.

The etiopathogenesis of this condition is still a matter of debate. It is said to involve a cascade of events, beginning with local atherosclerotic changes of the central retinal artery impinging on the vein. Alternatively, hemodynamic changes predisposing to thrombus formation have been implicated in precipitating venous occlusion. This, in turn, results in elevation of venous and capillary pressure, stagnation of blood flow, and retinal hypoxia, leading to variable degrees of vision loss.[1]

The impact of systemic comorbidities such as hypertension, cardiovascular disease, arteriosclerosis, diabetes, hypertriglyceridemia, and hypercholesterolemia has been apportioned due significance in literature.[2-5] In addition, certain local factors have also been implicated, such as chronic open-angle glaucoma causing elevated intraocular pressure.[6]

While ocular biometric measurements have been suspected to influence the development of this condition, their presumed impact still remains inconclusive and controversial. It has been proposed that eyes with shorter axial lengths (ALs) demonstrate crowding of the retinal artery, vein, and optic nerve fibers, due to narrower fenestrations in the lamina cribrosa and a shorter scleral canal. Due to shorter AL, a small lamina cribrosa, and also narrow scleral canal, a relative mechanical blockage in

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the vein may be precipitated. This blockage was thought to cause thrombus formation by causing turbulence of blood flow in the vein. Hence, these patients may potentially be at a greater risk of developing local obstructions, giving rise to CRVO.[7-9] Brown *et al*. have also conjectured that eyes with a shorter AL might be predisposed to crowding in the lamina cribrosa.[10] In our study, we aim to scrutinize this association and determine its significance, if any.

CRVO is characterized by diminution of vision that may be caused due to macular edema, vitreous hemorrhage, macular ischemia, optic neuropathy, tractional, or even combined retinal detachment. Due to the increased intravenous pressure, the fundus characteristically shows superficial and deep intraretinal hemorrhages in all four quadrants of the retina associated with variable degrees of retinal venous engorgement and tortuosity, optic disc swelling, cotton wool

spots, and optic nerve edema. Congestion of the capillary bed may result in cystoid macular edema[11] [Figure 1].

However, this may resolve in up to 30% of patients in the non-ischemic subtype of CRVO.[11] Overtime, the obstruction may be bypassed due to collateralization, that is, retina-retina and retina-choroid anastomosis. This leads to resolution of clinical signs such as hemorrhages, cotton wool spots, and disc edema.[12] Such patients with resolved or treated macular edema were included in our study for comparison of ALs [Figure 2].

METHODS

The study was conducted at the department of ophthalmology at a tertiary care center and medical college in the time period

Figure 1: Fundus photo of a 64-year-old male hypertensive patient with CRVO in OS. The typical features of hemorrhages in all quadrants, macular edema, swollen optic disc, and engorged tortuous veins are seen

Figure 2: Fundus photo of the same patient, taken 4 months after initiation of treatment with injection of an intravitreal anti-VEGF agent. There is resolution of disc edema and macular edema, along with reduction in the number of hemorrhages in all quadrants

between November 2016 and May 2018. Ethical clearance was obtained from the Institutional Review Board. Patients presenting as diagnosed cases of unilateral CRVO or with clinical findings suggestive of unilateral CRVO (such as vision loss and ophthalmoscopic findings of retinal hemorrhages in all four quadrants, cotton wool spots, and optic disc edema) with a normal contralateral eye, were selected after obtaining informed consent. Cases that could potentially interfere with AL measurements by A-scan ultrasonography (US) or give inaccurate results (e.g., aphakia, severe macular edema, corneal scars, etc.) were excluded from the study.

A detailed presenting, past, systemic, and family history was obtained. This was followed by a detailed ophthalmic evaluation, including baseline visual acuity assessment, slit lamp examination, and dilated indirect ophthalmoscopic examination using a 20D lens. Systemic investigations as per protocol were performed, including complete hemogram, blood sugars, glycosylated hemoglobin, coagulation profile, lipid profile, kidney function tests, and serum homocysteine levels. Ocular investigations included OCT/FFA or both, depending on the requirement of the patient and duration of disease. They were also used to definitively exclude patients who were diagnosed to have macular edema.

Fifteen women (50%) and 15 men (50%) with a mean age of 64.98 years were thus included in our study. ALs of the affected eye (study group) and unaffected eye (control group) were measured by A-scan US. Six consecutive measurements were obtained by the manual direct contact technique. Patients were instructed to fixate on a small red light within the center of the probe tip and high quality, consistent measurements were taken as optimum AL values. All measurements were done by the same person to minimize errors.

Obtained data were tabulated in a spreadsheet, using Microsoft Excel 2016. The difference in the mean ALs of the affected (study group) and unaffected eyes (control group) was evaluated using the paired t-test. Intergroup comparisons between genders were made using the unpaired t-test. These were subjected to statistical analysis using SPSS software (version 18 for Windows; SPSS Inc., Chicago, IL, USA). Statistical analyses were performed using test of association, and Cronbach's alpha was calculated. Statistical significance was set at $P < 0.05$.

RESULTS

Our study included 15 males and 15 females. The mean age was 60.23 ± 4.73 years. The right eye was affected in 18 patients and the left eye in 20 patients. The mean AL of affected eyes in males was 23.0267 mm and that in unaffected eyes was 23.191 mm. This difference was found to be statistically significant ($P = 0.000$). The mean AL of affected eyes in females was 23.0131 mm and that in unaffected eyes was 23.030 mm. This difference was found to be statistically significant ($P = 0.000$). The AL of affected eyes was shorter

than that of unaffected eyes ($P = 0.000$). The Cronbach's α found is 0.925 which suggests a strong correlation between AL and CRVO [Table 1 and Figure 3]. A comparison was also made between the ALs and CRVO based on the gender and found no statistical difference [Table 2].

DISCUSSION

CRVO remains a common cause of unilateral visual loss. Although it was originally described over 150 years ago by Richard Liebreich, variable terminology has been used to describe CRVO. Liebreich in 1855 first labeled CRVO as "retinal apoplexy."[13] Hayreh coined the terms "venous stasis retinopathy" for the milder degrees of CRVO and "hemorrhagic retinopathy" for the more severe forms of the disease.[14] After so many years of investigation, the exact etiopathogenesis CRVO has still not been clarified. However, we do know that there are a variety of factors that can disturb ocular circulation and eventually lead to retinal vein occlusion.

Advancing age has been considered an important systemic risk factor. The mean age for CRVO is 69.6 years. Rogers et al. performed a meta-analysis, which showed a 0.27/1000 prevalence of CRVOs in 40–49 years old, 0.69/1000 in 50–59 years old, 1.67/1000 in 60–69 years old, 2.87/1000 in 70–79 years old, and 5.44/1000 in those above the age of 80 years. It was found to be 20 times more prevalent in the population above 80 years than those between 40 and 49 years old.[15]

A longitudinal analysis has shown that both complicated and uncomplicated hypertension places the patient at an increased risk for the genesis of CRVO, even before other systemic complications of hypertension are evident. Stem et al. proposed that diseases caused by atherosclerosis such as peripheral artery disease and stroke, are associated with an increased risk of CRVO. Patients of CRVO are considered to be at a higher risk for developing stroke and ischemic heart disease. They have also reported that complicated diabetes mellitus increases the risk of CRVO, whereas uncomplicated diabetes mellitus does not have much bearing on the condition. Hyperlipidemia, being an established risk factor for the development of atherosclerosis, is also considered a systemic risk factor for CRVO.[16]

The role of inflammatory disorders was primarily considered in some subtypes of CRVO, especially in the younger patients. Although their role has not been confirmed as yet, anecdotal clinical cases that were treated with high-dose corticosteroids and intensive immunosuppressant agents and finally preserved their vision suggest their significance.[17] Some cases have been linked to thrombophilic or hypofibrinolytic states, including factor V and factor II mutations and the deficiency in anticoagulant proteins such as protein C, protein S, and antithrombin III. Other thrombophilic abnormalities, such as factor XII deficiency and hyperhomocystinemia, have also been reported.[18] The role of B-vitamins, namely, folic acid and Vitamin B6 and B12, as independent risk factors for arterial and venous thrombotic events, is also considered. The association between low folic acid levels and the occurrence of RVO had been demonstrated in a meta-analysis.[19] It was postulated by Sodi et al. that post-methionine hyperhomocysteinemia, elevated factor VIII, and reduced plasma levels of B6 and folic acid were more frequent in the patients with CRVO.[20]

Medications such as diuretics, sympathomimetics, oral contraceptives, and antipsychotics have also been thought to play a role. Any drug that may precipitate hemoconcentration, thrombophilia, or dehydration may lead to CRVO.[21] In our study, we have controlled the effect of systemic predispositions to CRVO, by including contralateral, unaffected eyes of the same patient for comparison. On our intergroup comparisons, we could not find a statistically significant difference ($P = 0.32$) affirming that the gender did not have an influence on the presence of CRVO. Therefore, a combination of all these factors such as local anatomical susceptibility, vessel wall changes, hemorrhagic, and thrombotic tendencies may all culminate in retinal vein occlusion.

In the previous studies conducted, A-scan US and partial coherence laser interferometry have been used to measure the AL in eyes with CRVO. Since A-scan US measures AL from the anterior cornea to the internal limiting membrane, the significantly shorter ALs reported in these studies in affected eyes as compared to control eyes, were attributed to complications from RVO (such as macular edema). Occlusion in retinal vein, leading to macular edema, was proposed to have a confounding effect on AL.[22] As we used A scan to measure the AL in our study, this factor was controlled by including only those cases with no macular edema or treated/resolved macular edema. Hence, we reported the true AL.

The role of AL in CRVO patients still remains controversial. Some studies did not find differences in AL in eyes with CRVO, while others found significantly shorter AL in the affected eyes of patients with CRVO. The AL of affected eyes in our study was shorter than that of unaffected eyes.

Table 1: Comparison of axial lengths of affected and unaffected eyes of patients of CRVO included in our study

	Affected	Unaffected	Difference	P value	α (correlation)
	Mean±SD	Mean±SD			
Gender					
Male	23.0267±0.959	23.191±1.050	−0.1643±0.09	0.000**	0.978
Female	23.0131±0.677	23.030±0.645	−0.016±0.612	0.000**	0.925

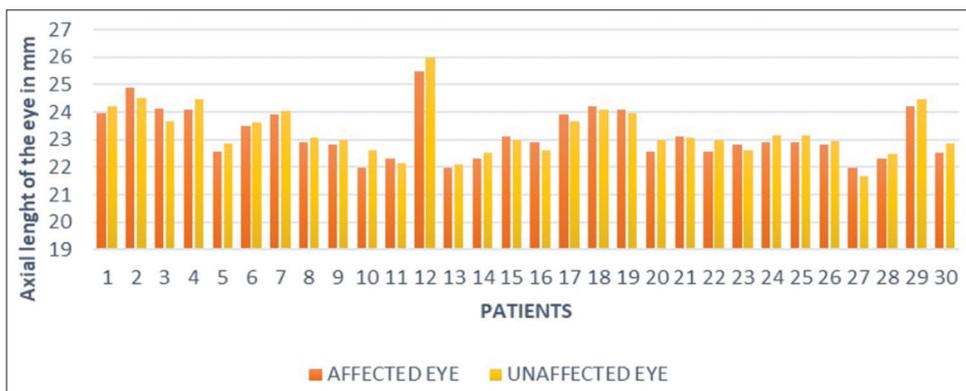CRVO: Central retinal vein occlusion

Figure 3: Comparison between axial lengths of affected and unaffected eyes in our study

Table 2: Comparison between axial lengths and CRVO based on gender

	Gender	Number of patients	Mean±SD	F value	P value
Affected	Males	14	23.0267±0.95941		
	Females	13	23.0131±0.67754	1.021	0.322
Unaffected	Males	14	23.1917±1.05004		
	Females	13	23.0308±0.64539	1.980	0.172

CRVO: Central retinal vein occlusion

This difference was statistically significant ($P = 0.000$). The Cronbach's α was found to be 0.925, which suggests a strong correlation between AL and CRVO.

Some studies did not record a significant difference in ALs in eyes affected by CRVO. A study conducted in the year 1998 assessed whether AL and refraction are risk factors for retinal vein occlusion. They compared eyes with CRVO with control eyes, eyes with branch retinal vein occlusion (BRVO) with control eyes, and eyes with CRVO with eyes with BRVO. The authors did not find any influence of AL on the occlusion of retinal veins.[23]

Another study group in the year 1998 performed a prospective study to elucidate the predisposing role of AL and hyperopia in retinal vein occlusions. The AL of affected eyes was compared to fellow eyes and control eyes in each subgroup of patients with retinal vein occlusion. No statistical difference was noted for any subgroup ($P > 0.05$). The authors concluded that AL and hyperopia may not be risk factors in retinal vein occlusions.[24]

Another group conducted a study to evaluate the association of AL and posterior segment length with CRVO using optical coherence interferometry. Patients with macular edema were excluded. Although the affected eyes were found to have shorter AL (23.26 mm vs. 23.33 mm), the difference was not significant.[25]

At the other end of the spectrum, some studies demonstrated significantly shorter ALs in the eyes that were affected by CRVO. A study in the year 1996 confirmed that the ALs in CRVO and BRVO were significantly shorter than in the controls. This significant difference may be a risk factor in the development of CRVO and BRVO.[26] Another study demonstrated a significantly shorter AL in eyes with CRVO and not in those with BRVO. They, therefore, concluded that the shorter AL could be an additional predisposing factor in the pathogenesis of CRVO.[27] Yet, another study group proposed that the ALs of affected eyes in retinal vein occlusion patients tend to be shorter than those of unaffected eyes, especially in BRVO patients.[28]

The inconsistency in the past data may to some extent be attributed to the different demographic characteristics of patients of CRVO and normal subjects, which have largely been controlled in our study. They may also be due partly to the use of different statistical methods for comparison among studies. Furthermore, statistical methods may vary based on the sample size and study design. However, there seems to be general agreement among several of these studies, including the present one, that ALs of eyes with CRVO are generally shorter than those of unaffected eyes.

CONCLUSION

Our study confirms the existence of shorter ALs in the affected eye of patients of CRVO on comparison with the unaffected eye and also confirms that this difference is statistically significant in the total population and in each gender. By comparing this data with age- and gender-matched control population, the significance of this association can further be confirmed. This anatomic predisposition could then be useful to identify and monitor patients at risk of developing CRVO, with an emphasis on control of other modifiable systemic predisposing factors.

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