Association of primary angle-closure disease in patients with retinal vein occlusion in North Indian population

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Purpose: To determine the association of primary angle-closure disease (PACD) in patients with retinal vein occlusion (RVO) at a tertiary eye care center in North India. Methods: It is a cross-sectional, observational study. Sixty consecutive patients with retinal vein occlusion within a period of one year from a single tertiary eye care center were enrolled. Detailed history, slit-lamp examination of the anterior segment, intraocular pressure measurement by applanation tonometry, gonioscopy and fundus examination were done. Anterior chamber depth and axial length were also measured. Results: Among the 60 patients, 29 were males (48.3%) and 31 females (51.6%). Twenty-seven (45%) of them had central retinal vein occlusion (CRVO) and 33 (55%) had branch retinal vein occlusion (BRVO). Forty percent of patients with RVO had PACD. Relative risk of PACD was 1.71 times in patients with CRVO as compared to BRVO. Risk of glaucoma was 49% more in CRVO than BRVO. Probability of PACD was more in patients of RVO who had diabetes and CAD as comorbidity. Conclusion: The association between PACD and RVO is less known. PACD can be one of the risk factors for the development of RVO. A comprehensive examination and detailed angle evaluation of both of the eyes should be done in all cases of RVO, in addition to investigating for systemic risk factors. However, larger population-based studies would be required to prove it as an independent risk factor.

Key words: Glaucoma, primary angle closure disease, retina, vein occlusion

Glucoma and retinal vascular obstrucitive disease are leading causes of ocular morbidity worldwide and one condition may lead to the other. The association between primary open-angle glaucoma (POAG) and retinal vein occlusion (RVO) has been researched in the past and it has been found that the prevalence of POAG in central retinal vein occlusion (CRVO) is 5.7% to 65.5% and in branch retinal vein occlusion (BRVO) is 6.6% to 15%. Data from various trials including the Beaver Dam Eye Study and the Blue Mountain Eye Study have further supported this relationship between glaucoma and vein occlusion.[8,9] However, the association between primary angle-closure glaucoma (PACG) and RVO has not yet been established conclusively. Few studies done in the past have found the prevalence of PACG with CRVO and BRVO to be 0%–9.9% and 1.72%, respectively. These studies on PACG with RVO have primarily been conducted in the European and African populations where prevalence of PACG is much lower as compared to Asians.

Many factors may be invoked in the pathogenesis of vein occlusion in POAG. As vascular sclerosis is the common risk factor in both the conditions, there may be additional compression of the central retinal vein due to the increase in intraocular pressure (IOP) in POAG, thereby causing RVO.[4,10] Thinning of the retinal nerve fiber layer may also cause loss of structural support for a given retinal artery which collapses over the crossing vein, resulting in blood stasis. The stasis of blood contributes to thrombus formation which may in turn cause RVO.[9,11]

The pathogenesis of RVO in primary angle closure (PAC) is not very clear and so is the direction of association. Some studies suggest that the intermittent rise of pressure in PAC or the chronically high IOP in PACG may be a predisposing factor in eyes susceptible to development of RVO, whereas other studies suggest that vascular engorgement and edema of the posterior segment may result in anterior rotation of the cilio-lenticular diaphragm, thereby closing a previously narrow but open drainage angle in patients with CRVO.[12,13]

The patients with RVO also require frequent pupillary dilatation, and in the presence of an occludable angle, it may lead to acute primary angle closure changes. The fellow eye is also at an increased risk as angle closure is usually bilateral.

Considering the high prevalence of PACG in Asians and the paucity of literature on the subject, this study...
was undertaken to determine the association of primary angle-closure disease (PACD) in RVO.

**Methods**

This is a cross-sectional, observational study conducted at a tertiary eye care institute in North India. This study followed the tenets of the Declaration of Helsinki for research involving human subjects and was approved by the Institutional Review Board. Consecutive patients diagnosed with RVO from May 2014 to April 2015 were enrolled for glaucoma evaluation. Informed consent was obtained from each enrolled patient. Any media opacity precluding view of retina (dense corneal opacity, dense cataract), retinal vein occlusion with associated neovascularization of the iris/angle and eyes with pseudophakia were excluded from the study.

All the patients diagnosed with RVO by the vitreo-retina specialist were referred to the glaucoma clinic for further evaluation. Demographic information, medical history and ophthalmic history of the patients were recorded. Clinical examination included Snellen’s visual acuity, pupil examination and documentation of RAPD, slit-lamp biomicroscopy (including Van Herick grading and lens status), Goldmann application tonometry (average of three readings) and gonioscopy, optic nerve head (ONH) evaluation and ultrasound A-scan biometry.

Gonioscopy was performed in all cases by a single experienced glaucoma specialist. Posner four-mirror indirect gonio-lens was used in dim illumination using a shortened slit beam that did not fall upon the pupil. Grading of the irido-corneal angle was done as per the Spaeth classification. Mydriatic (tropicamide 1%) drops were used to dilate the pupil. ONH evaluation was done at the slit lamp with a Volk 90 D lens. A-scan ultrasonography using the OcuscanRxp machine was performed for each patient to measure anterior chamber depth (ACD) and axial length (AL) in both eyes.

For the purpose of this study, primary angle-closure disease (PACD) was classified according to the Foster classification.\(^{(16)}\) In two patients with PAC, the disc could not be visualized due to venous occlusion.

**Diagnostic criteria used to diagnose RVO**

Engorgement and dilatation of the involved retinal veins associated with intra-retinal hemorrhages, cotton wool spots, intra-retinal edema, retinal exudates, and macular edema were all the criteria that were used to diagnose RVO. CRVO typically presents with retinal hemorrhages, both flame-shaped and deep blot type, and dilated and tortuous vessels in all the four quadrants, and has a classic “blood and thunder” appearance. In case of BRVO, only a branch of retinal venous system is affected, most common location being the superotemporal quadrant.

The diagnostic criteria for hemiretinal vein occlusion (HRVO) are the same as that for BRVO except the former involves the superior or inferior half of the retina. HRVO was included in the CRVO group.

**Statistical analysis**

For comparing the mean of two continuous variables (such as age, IOP, AL and ACD), t-test was applied, and for categorical variables, Chi-squared and Fisher’s exact tests were applied. The mean of the continuous variables has been reported as mean ± SD. Depending on the expected direction of the parameters in alternative hypothesis, one-tail test was applied instead of the usual two-tailed ones. The strength of the association has been reported in terms of odds ratio. Data entry was done in Microsoft Excel 2013. Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) version 16.

**Results**

**Gender-age profile of the participants**

Sixty patients diagnosed with RVO between 1 May 2014 and 30 April 2015 were enrolled in the study. The participants’ group comprised of 29 males (48%) and 31 females (52%). The average age of the participants was 58.30 ± 14.09 years. The average age of males was 61.62 ± 14.21 years, whereas that of the females was 55.19 ± 13.47 years.

**Ratio of BRVO to CRVO**

Out of 60 patients, 33 had BRVO (55%) and 27 had CRVO (45%), the ratio of BRVO to CRVO being 1.22.

**RVO and PACD**

Twenty-four patients (40%) with RVO had PACD while the rest of the patients (60%) had open angle. When both of the groups of RVO were compared, PACD was seen in 52% of patients with CRVO and in 30% with BRVO. This difference was statistically significant \((P = 0.045, \text{one-tail } z \text{ test})\). Relative risk of PACD was 1.71 times higher in patients with CRVO as compared to BRVO.

**Angle characteristics in patients with RVO are listed in Table 1.**

**RVO and Glaucoma**

The coexistence of RVO and glaucoma was found in 33% of patients. Incidence of glaucoma was more among those with CRVO (41%) as compared to those with BRVO (27%). Stated otherwise, the risk of having glaucoma was 49% more in the CRVOs than in the BRVOs (relative risk = 1.49). However, the statistical significance of the difference could not be established.

Among the subgroups of glaucoma, OAG was seen to be associated more with BRVO than CRVO (67% vs 18%) though a statistical significance of difference could not be established \((P = 0.20)\), whereas PACG was seen to be significantly associated with CRVO than BRVO \((82\% \text{ vs } 33\%) \ (P = 0.02, \text{ Fisher’s exact test})\). Relative risk of PACG in CRVO was found to be 3.67 and that of OAG in BRVO was found to be 2.45 [Table 2].

**Ocular parameters**

Mean IOP was significantly higher in the PACD group than in the open angle group \((P = 0.028, \text{one-tail } t \text{-test})\). The mean

| Table 1: Angle characteristics in patients with RVO |
|-----------------|-----------------|-----------------|
|                  | BRVO  | CRVO  | Total |
| Open angle (no glaucoma) | 17    | 11    | 28    |
| OAG              | 6     | 2     | 8     |
| PACG             | 3     | 9     | 12    |
| PAC              | 7     | 3     | 10    |
| PACS             | 0     | 2     | 2     |
| Total            | 33    | 27    | 60    |
IOP in the fellow eyes of PACD and open angle group was not significantly different ($P = 0.2375$, one-tail $t$-test) [Table 3].

Mean AL of the diseased eye in the PACD group was significantly smaller than in the open angle group ($P = 0.023$, one-tail $t$-test). It was observed that in the fellow eye too, the mean AL was significantly lower in the PACD group than in the open angle group ($P = 0.029$, one-tail $t$-test) [Table 3].

ACD of the diseased eye was expectedly lower in the PACD group as compared to that in the open angle group. The difference was significant with a $P$ value of 0.000 (one tail $t$-test). ACD of the fellow eyes too was significantly smaller in the PACD group than in the open angle group ($P = 0.0005$, one-tail $t$-test) [Table 3].

## Comorbidity

Ten of the 60 participants (17%) had a history of diabetes. Odds ratio of PACD in RVO with and without any history of diabetes was equal to 1 and thus ruled out the possibility of any association of diabetes with RVO and PACD [Table 4, Part I]. However, the coexistence of diabetes with CRVO portrayed a completely different picture. Odds of occludable angle in the presence of diabetes along with CRVO was estimated to be 4.8 [Table 4, Part II] though the significance of association could not be established ($P = 0.186$, Fisher’s exact test).

Eight of the 60 RVO patients had coronary artery disease (CAD). Odds ratio of occludable angles with and without the coexistence of CAD with RVO was estimated to be 2.89 [Table 5, Part I]. The ratio increased slightly (from 2.89 to 3.27) when the co-existence of CAD was seen only with CRVO (BRVOs excluded) [Table 5, Part II]. However, in none of the situations was the association statistically significant.

## Discussion

The prevalence of angle closure shows much wider variations than for open angle glaucoma worldwide.[17] Among primary glaucomas, POAG seems to have a close association with

### Table 2: RVO and glaucoma

| Glaucoma Type | BRVO | CRVO | Total |
|---------------|------|------|-------|
| OAG           | 6 (67%) | 2 (18%) | 8     |
| PACG          | 3 (33%) | 9 (82%) | 12    |
| # Glaucoma identified | 9 (100%) | 11 (100%) | 20    |
| # Participants | 33   | 27   | 60    |

### Table 3: Ocular parameters in PACD and open angle group

| Ocular Parameters | PACD | Open Angle | Difference | $P$ (2-tailed, $t$-test) | $P$ (1-tail, $t$-test) |
|-------------------|------|------------|------------|--------------------------|-------------------------|
| IOP               | 20.17±9.24 | 15.94±6.01 | 4.230      | 0.056                    | 0.026                   |
| Fellow eye        | 15.00±5.41 | 16.03±5.43 | −1.030     | 0.475                    | 0.238                   |
| AL                | 22.75±0.99 | 23.29±1.02 | −0.544     | 0.046                    | 0.023                   |
| Fellow eye        | 22.78±1.04 | 23.31±1.04 | −0.534     | 0.057                    | 0.029                   |
| ACD               | 2.86±0.24  | 3.38±0.31  | −0.517     | 0.000                    | 0.000                   |
| Fellow eye        | 3.06±0.49  | 3.42±0.34  | −0.359     | 0.001                    | 0.001                   |

### Table 4: Coexistence of diabetes and RVO

|                | All RVO Cases | CRVO |
|----------------|---------------|------|
|                | History of Diabetes | No History of Diabetes | Total |
| Open angles    | 6 | 30 | 36 |
| Occludable angles | 4 | 20 | 24 |
| Total          | 10 | 50 | 60 |
| Odds ratio     | 1.0 |   | 4.8 |

### Table 5: Coexistence of CAD and RVO

|                | All RVO Cases | CRVO |
|----------------|---------------|------|
|                | History of CAD | No History of CAD | Total |
| Open angles    | 3 | 33 | 36 |
| Occludable angles | 5 | 19 | 24 |
| Total          | 8 | 52 | 60 |
| Odds ratio     | 2.89 |   | 3.27 |
RVO, as reported in existing literature.\cite{3,4} At present, there is paucity of data on the association between PACD and RVO. Primary angle closure disease is highly prevalent in Asians, so it is possible that the prevalence rates may be higher than in the Caucasians.

In our study, we evaluated 60 patients of which 55% had BRVO and 45% had CRVO, the ratio of BRVO to CRVO being 1.22. This ratio seemed to be low as compared to other population prevalence studies where BRVO was seen to occur six to seven times more commonly than CRVO. This observation might be an indication of higher prevalence of CRVO in the Indian population as compared to other countries, or it may also be possible that the place of study being a tertiary care hospital received more CRVO referral cases.

Forty percent of these patients had PACD. Fifty-two percent of these patients were in the CRVO group whereas 30% were in the BRVO group, which is much higher than reported in literature till date. One of the prospective studies by D. Calugaru et al.,\cite{18} reported 21% of patients of CRVO/HRVO with narrow drainage angle. In another retrospective case series by Michaelides et al.,\cite{19} 14 out of 19 subjects (74%) had RVO and primary angle closure at the same clinical visit.

Strong association was seen between types of RVO and subgroups of glaucoma.\cite{26} PACG was seen to be associated in 33% CRVO and 9% BRVO patients. This is much higher than what was reported by Vannas and Tarkkanen in their study. They found only 5.6% CRVO and 1.7% BRVO patients to have associated PACG.\cite{27}

Mean IOP in PACD group was higher than the open angle group ($P=0.056$). Verhoeff, Salzmann, have postulated that the increased IOP compresses and collapses the wall of the CRV, leading to intimal proliferation in the vein, which could be the primary cause of CRVO.\cite{20}

Axial length of the eyes with PACD in patients with RVO was significantly lower than those with open angle.\cite{21,22,23} The relationship between RVO and AL has been studied by various workers worldwide. Debate exists over the significance of AL in the development of RVO. Aritürk et al.,\cite{24} Tsai et al.,\cite{25} and Brown MM et al.\cite{26} have shown that smaller axial length can be a local risk factor, in the causation of retinal vein occlusion.

ACD of the diseased eye as well as the fellow eye was expectedly lower in the PACD group as compared to the open angle group. D. Çalışgur et al.\cite{14} also found ACD to be significantly lower in patients with narrow drainage angle compared to those with open angle configuration. In a recent study by Shiu-Chen Wu et al.,\cite{27} 24/25 (95%) of eyes with CRVO were found to have a significantly shallower ACD than the unaffected eyes, but there was a considerable overlap between the mean ACD of the two groups (range: 1.66–3.19 mm in the diseased eyes and 1.71–3.22 mm in the unaffected eyes) suggesting that a larger sample size is required to prove the same. We did not come across any patient with asymmetric anterior chamber depth in between the eyes.

Risk of having PACD was more in patients of RVO who had diabetes and CAD as comorbidity. PACD was present in both the diseased as well as the fellow eyes in the majority of the patients in our study. Thus, we propose that PACD may lead to RVO and not the reverse, though the reverse can also occur at times due to uveal effusion. All patients with narrow angles underwent peripheral laser iridotomy. This resulted in widening of the drainage angle except in the areas of peripheral anterior synchiae in all patients, ruling out both plateau iris and uveal effusion. Clinically, none of the patients had any documented choroidal effusion, as examined by the vitreo-retina specialist. We did not do Anterior segment optical coherence tomography (AS-OCT) or ultrasound biomicroscopy (UBM) to rule out these conditions. However, it is recommended to do UBM to objectively rule out angle closure due to uveal effusion.

There are some limitations to our study. Though we have the largest series, of 60 patients, till date, a larger prospective study can be planned to find out the association between PACD and RVO. Choroidal thickness measurement with a spectral domain OCT will provide more objective evaluation to rule out any subtle uveal effusion that can be present due to RVO.

Conclusion

The association between PACD and RVO is less known. PACD can be one of the risk factors for development of RVO. A comprehensive examination and detailed angle evaluation of both eyes should be done in all cases of RVO, in addition to investigating for systemic risk factors. However, larger population-based studies would be required to prove it as an independent risk factor.

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Conflicts of interest

There are no conflicts of interest.

References

1. Hitchings RA, Spaeth GL. Chronic retinal vein occlusion in glaucoma. Br J Ophthalmol 1976;60:694-9.
2. Dryden RM. Central retinal vein occlusions and chronic simple glaucoma. Arch Ophthalmol 1965;73:659-63.
3. Becker B, Post LT. Retinal vein occlusion: Clinical and experimental observations. Am J Ophthalmol 1951;34:677-86.
4. Verhoeff HF. The effect of chronic glaucoma on the central retinal vessels. Arch Ophthalmol 1913;42:145.
5. Eye Disease Case-Control Study Group. Risk factors for branch retinal vein occlusion. Am J Ophthalmol 1993;116:286-96.
6. Klein R, Klein BE, Moss SE, Meuer SM. The epidemiology of retinal vein occlusion. Ophthalmology 2004;111:133-41.
7. Cugati S, Wang JJ, Rochtchina E, Mitchell P. Ten-year incidence of retinal vein occlusion in an older population: The Blue mountains eye study. Arch Ophthalmol 2006;124:726-32.
8. Vannas S. Glaucoma due to thrombosis of the central vein of the retina. Ophthalmologica 1961;142:266-82.
9. Vannas S, Tarkkanen A. Retinal vein occlusion and glaucoma: Tonographic study of the incidence of glaucoma and of its prognostic significance. Br J Ophthalmol 1960;44:583-9.
10. Posner A. Central retinal vein thrombosis in angle closure glaucoma. Eye Ear Nose Throat Mon 1958;37:777-8.
11. Hayreh SS, Zimmerman MB, Beri M, Podhajsky P. Intraocular pressure abnormalities associated with central and hemisentral retinal vein occlusion. Ophthalmology 2004;111:133-41.
12. Phelps CD. Angle-closure glaucoma secondary to ciliary body
swelling. Arch Ophthalmol 1974;92:287-90.

13. Grant WM. Shallowing of the anterior chamber following occlusion of the central retinal vein. Am J Ophthalmol 1973;75:384-9.

14. Quigley HA, Broman AT. The number of people with glaucoma worldwide in 2010 and 2020. Br J Ophthalmol 2006;90:262-7.

15. Wong TY, Loon SC, Saw SM. The epidemiology of age related eye diseases in Asia. Br J Ophthalmol 2006;90:506-11.

16. Foster PJ, Buhrmann R, Quigley HA, Johnson GJ. The definition and classification of glaucoma in prevalence surveys. Br J Ophthalmol 2002;86:238-42.

17. George R, Ramesh SV, Vijaya L. Glaucoma in India: Estimated burden of disease. J Glaucoma 2010;19:391-7.

18. Călugăru D, Călugăru M. Gonioscopic findings in patients with acute central/hemicentral retinal vein occlusions. Rev Med Chir Soc Med Nat Iasi 2014;118:407-16.

19. Michaelides M, Foster PJ. Retinal vein occlusion and angle closure: A retrospective case series. J Glaucoma 2010;19:643-9.

20. Silver DM, Quigley HA. Aqueous flow through the iris–lens channel: Estimates of differential pressure between the anterior and posterior chambers. J Glaucoma 2004;13:100-7.

21. Salzmann M. Glaukom und Netz hautzirkulation. In: Streiff EB, editor. Bibliotheca ophthalmologica. Vol. 15. Berlin: Karger; 1933.

22. George R, Paul PG, Baskaran M, Ramesh SV, Raja P, Arvind H, et al. Ocular biometry in occludable angles and angle closure glaucoma: A population based survey. Br J Ophthalmol 2003;87:399-402.

23. Ritch R, Shields B, Krupin T. The Glaucomas. 2nd ed. Vol 2. St Louis: Mosby; 1996.

24. Aritürk N, Oge Y, Erkan D, Süllü Y, Mohajerý F. Relation between retinal vein occlusions and axial length. Br J Ophthalmol 1996;80:633-6.

25. Tsai SC, Chen HY, Chen CY. Relationship between retinal vein occlusion and axial length. Kaolisiung J Med Sci 2003;19:453-6.

26. Brown MM, Brown GC, Menduke H. Central retinal vein obstruction and axial length. Ophthalmic Surg 1990;21:623-4.

27. Wu SC, Lee YS, Wu WC, Chang SH. Anterior chamber depth and angle-closure glaucoma after central retinal vein occlusion. BMC Ophthalmol 2016;16:68.