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Original Research Article

A prospective observational study to evaluate the etiology and staging of neovascular glaucoma

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ABSTRACT

Purpose: To identify the most common cause and the frequent stage of presentation in patients with neovascular glaucoma.

Materials and Methods: The present study is a prospective observational study. 136 eyes of 109 patients having neovascular glaucoma in one eye or both the eyes were included in the study. All patients underwent thorough ocular examination i.e., visual acuity, slit lamp bio-microscopy, intraocular pressure (IOP) measurement by Goldmannapplanation tonometry, gonioscopy with Posner 4 mirror indirect gonioscope and dilated fundus examination. Neovascularization of iris (NVI) was identified in an undilated state, presence of any ectropionuveae, hyphema, anterior chamber reaction, pseudoexfoliative material, keratic precipitates and other signs of uveitis were noted. The number of quadrants of the angle having neovascularization was noted.

Results: The mean age was 57.59 ± 12.6 years, 80.73% were males and 19.26% were females. Mean IOP was 27.14 ± 11.3 mm of Hg. 74 (54.4%) presented in rubeosisiridis stage, 38 (27.9%) in angle closure stage and 24 (17.6%) in open angle stage. 89 (65.4%) had diabetic retinopathy in variable severity, 16 (11.7%) had uveitis and 14 (10.2%) had retinal vein occlusion. Mean IOP angle closure stage was found to be 36.53±16.259 mm of Hg which is significantly higher than the other two stages ($P = 0.000$)

Conclusion: In the present study, it was found that Proliferative diabetic retinopathy is the most common cause and rubeosisiridis is the most common stage of presentation in NVG.

1. Introduction

Neovascular glaucoma (NVG) is a severe form of secondary glaucoma characterized by development of new vessels on iris and formation of fibrovascular tissue in the anterior chamber angle with increase in IOP.[1] NVG was previously known as hemorrhagic glaucoma, congestive glaucoma, thrombotic glaucoma, and rubeotic glaucoma.[2] Weiss and colleagues named it asneovascular glaucoma in 1963.[3]

1.1. Pathogenesis

NVG is a severe form of glaucoma with formation of new blood vessels and obstructing aqueous humor outflow, most commonly due to posterior segment ischemia.[4] It shows the development of a fibrovascular membrane on the anterior surface of the iris and iridocorneal angle.[5] The fibrovascular membrane in the anterior chamber obstructs aqueous outflow in open-angle initially and later it contracts causingsynechial angle-closure which in turn causes high IOP.[4] Usually iris and angle new vessels develop before the intraocular pressure rises.[5]

The formation of new vessels is influenced by imbalance between pro-angiogenic factors (such as, vascular endothelial growth factor-VEGF) and anti-angiogenic factors (such as pigment-epithelium-derived factor).[6] VEGF plays an important role in formation of new vessels in patients with ischemic retinal diseases.[7] VEGF and insulin growth-1 factors are produced by Mueller cells, retinal pigment epithelial cells, retinal capillary pericytes, endothelial cells and ganglion cells.[8]

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Accumulation of Insulin growth-1 factor in aqueous humorcausesrubeosisiridis and later the formation of adhesions between cornea and iris block the aqueous humor drainage.[9] VEGF concentration decreases after the regression of new vessels.[10] The non-pigmented ciliary epithelium is the major site of synthesis of VEGF in patients with NVG.[11] Increased Interleukin-6 was noted in the aqueous of patients with NVG secondary to central retinal vein occlusion.[12] Studies have shown increased levels of basic fibroblast growth factor (bFGF),[13] transforming growth factor-beta1 and beta 2,[14] nitric oxide,[15] endothelin-1[16] and free-radicals such as the superoxide[17] in the aqueous humor of patients with NVG.

Normal iris vessels have nonfenestrated endothelial cells with tight intercellular junctions whereas new vessels are thin walled without muscular layer or supporting tissue. New vessels show basement membrane changes, gaps and fenestrations in the endothelial cells on electron microscopy.[18,19] The new vessels are mostly accompanied by a fibrovascular membrane consisting of proliferating myofibroblasts.[20]

1.2. Causes

Thecommoncauses of NVG are diabetic retinopathy, retinal vein occlusions and carotid artery obstruction. Other causes are uveitis, pars planavitrectomy, irradiation, ocular tumors.[4]

1.3. Clinical course

NVG can be classified into four stages: pre-rubeosis, rubeosis, open angle glaucoma, and angle-closure glaucoma.

In the pre-rubeosis stage, iris new vessels or the angle new vessels are not detectable. Iris fluorescein angiography is useful in detecting occult neovascularization.

In the rubeosis stage, new vessels appear on the iris usually at the papillary margin. The angle is spared of new vessels and the intraocular pressure is normal.

In the third or open-angle glaucoma stage, new vessels start invading the iris stroma and the angle. Gonioscopy shows open angle and the intraocular pressure may be elevatedor normal.

In the final stage or angle-closure glaucoma stage, the new vessels become more prominent forming a fibrovascular membrane resulting in total synechial closure of the angle.

1.4. Justification of study

We, the authors wanted to know the most common cause and stage of presentation of NVG in our setup. So the present study was taken up.

2. Aims and objectives of the study

To identify the most common cause and the most frequent stage of presentation of the patient in neovascular glaucoma.

3. Materials and Methods

The present study is a prospective observational study, 136 eyes of 109 patients who underwent ophthalmological examination and diagnosed as having neovascular glaucoma in one eye or both the eyes at a tertiary eye care center in South India between November 2018 and August 2019 were included in the study. Patients were explained about the study and informed consent for the same was obtained. Relevant detailed medical and ocular history were obtained from all the patients.

All patients underwent thorough ocular examination i.e., visual acuity, slit lamp bio-microscopy, intraocular pressure (IOP) measurement by Goldmannapplanation tonometry, gonioscopy with Posner 4 mirror indirect gonioscope and dilated fundus examination with +90 D lens. Neovascularization of iris (NVI) was identified as tuft of new vessels on iris mostly at the pupillary margin in an undilated state, presence of ectropionuveae, hyphema was noted [Figures 1, 2 and 3] A single tonometer used throughout the study and IOP was measured by a single person throughout the study. Indirect ophthalmoscopy or B-Scan was done in eyes with hazy media due to corneal edema and/or dense cataract.

Gonioscopy was done to identify new vessels and to grade the angle As open or closed. The number of quadrants with new vessels in the angle were noted.

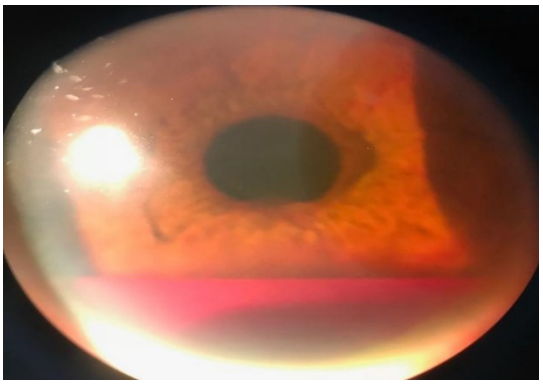

Fig. 1: NVI with ectropion uveae and hyphema

3.1. Statistical analysis

The data collected was entered in excel sheet and is analyzed using SPSS version 20.0. Descriptive variables were given with frequency (percentage) or mean (standard deviation). The association of various variables like Cause of NVG with stage of NVG and stage of NVG with IOP were analyzed

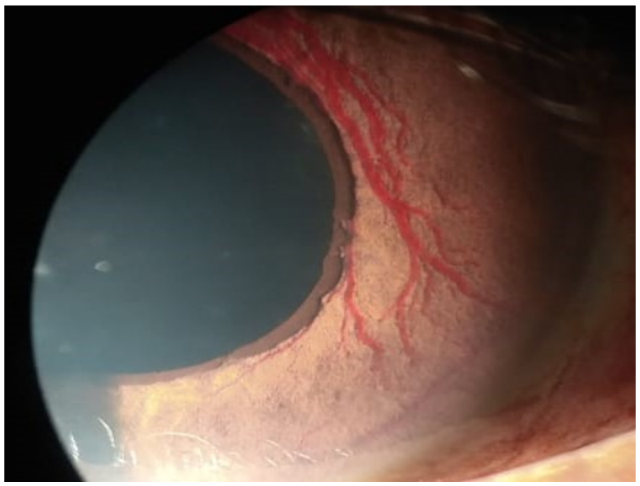

Fig. 2: Neovascularization of iris with ectropion uveae

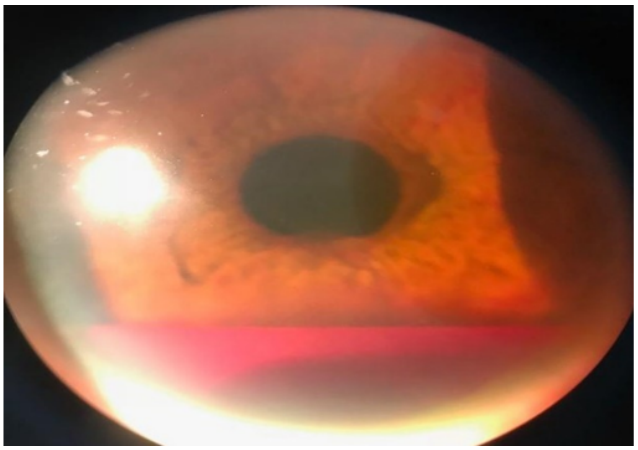

Fig. 3: VI with ectropion uveae and hyphema

using appropriate parametric and non-parametric tests like chi-square test (p-value) and ANOVA- test.

4. Results

The present study was conducted in 136 eyes of 109 patients out of which 82 patients had either eye involvement and 27 patients had both eyes involvement. All Patients were aged between 14–84 years with a mean of 57.59 ± 12.6 years. Out of 109 patients, 88 (80.73%) were males and 21 (19.26%) were females.

4.1. IOP and gonioscopy

The range of intraocular pressure (IOP) was 2-76 mm of Hg with mean of 27.14 ± 11.3 mm of Hg. IOP of 2 mm of Hg was noted in 4 patients out of which 2 had chronic retinal detachment, 1 had chronic uveitis and 1 had vitreous haemorrhage with combined rhegmatogenous and tractional retinal detachment. IOP of 76 mm of Hg was noted in 1 case which had proliferative diabetic retinopathy. IOP < 10 mm of Hg IOP was noted in 27 out of 136 eyes of which 3 had chronic uveitis, 5 had retinal detachment, 17 had diabetic retinopathy in variable severity, 1 had central retinal vein occlusion and 1 underwent parsplanavitrectomy. >50 mm of Hg IOP was noted in 12 eyes out of which 4 had CRVO, 3 had PDR, 2 had PDR and VH, 2 had chronic uveitis and 1 had chronic pseudoexfoliative glaucoma.

On gonioscopic examination, most of the cases i.e., 74 (54.4%) had only rubeosisiridis without involvement of the angle, 27 (19.9%), 15 (11%), 8 (5.9%), 12 (8.8%) had neovascularization of angle (NVA) in one, two, three and four quadrants respectively. 4 cases had hyphema.

In the present study, most of the patients i.e., 74 (54.4%) presented in rubeosisiridis stage, 38 (27.9%) in angle closure stage and 24 (17.6%) in open angle stage [Table 1]. The number of eyes and the respective stage of NVG is plotted in the graph [Figure 4]

Table 1: Stage of NVG

Stage of NVG	n	%
Angle closure stage	38	27.9
Open angle stage	24	17.6
Rubeosisiridis	74	54.4
Total	136	100.0

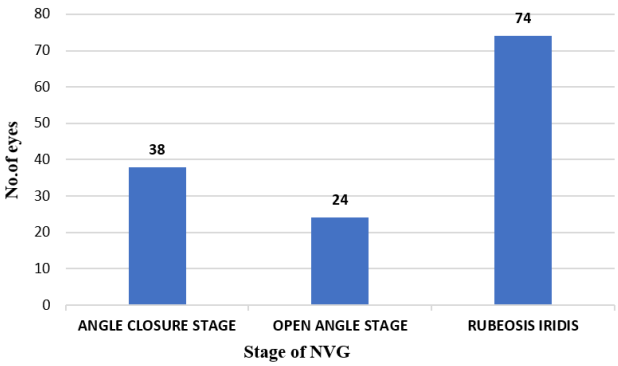

Fig. 4: Number of eyes in each stage of NVG

Table 2: Causes of NVG

Cause	**n**	**%**
Chronic RRD	2	1.5
DR	89	65.4
Glaucoma	14	10.3
Inflammation	16	11.8
S/P PPV	1	.7
Vein occlusion	14	10.3
Total	136	100.0

4.2. Chronic RD

Chronic Rhegmatogenous Retinal Detachment, DR – Diabetic retinopathy, Glaucoma – pseudoexfoliative glaucoma (PXG) and absolute glaucoma, Inflammation – Chronic uveitis, Vasculitis and Eales disease, S/P PPV – status post parsplanavitrectomy, Vein occlusion – central retinal vein occlusion and branch retinal vein occlusion.

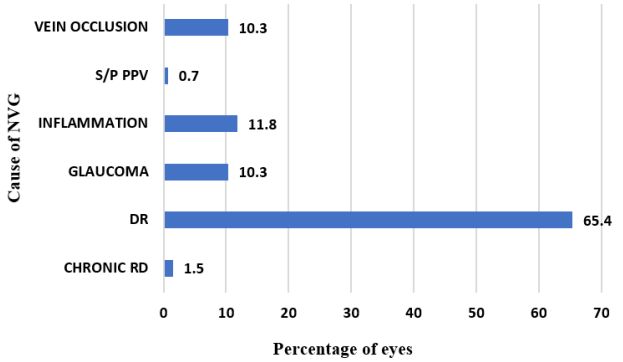

Fig. 5: Causes of NVG

Out of 136 eyes, 89 (65.4%) had diabetic retinopathy in variable severity, 16 (11.8%) had inflammatory etiology, 14 (10.3%) had retinal vein occlusion and 14 (10.3%) had glaucoma (PXG and absolute glaucoma) [Table 2]. The percentage of eyes and the respective cause of NVG is plotted in the graph [Figure 5]. 27 patients had bilateral involvement, of which 26 had bilateral diabetic retinopathy in variable severity and 1 patient had bilateral absolute glaucoma.

Table 3: Mean IOP in three stages of NVG

Stage of NVG	Mean IOP (mm of Hg)
Angle closure stage	36.53±16.259
Rubeosis iridis	23.65±15.857
Open angle stage	23.08±18.472

Compares the mean IOP in different stages of NVG. Mean IOP in Angle closure stage is significantly higher than the mean IOP in other two stages (P = 0.000). Whereas there is no statistically significant difference between the mean IOP in rubeosisiridis stage and open angle stage (P = 0.988).

81 eyes (59.5%) had IOP $<$ 30 mm of Hg of which 51 were in rubeosisiridis stage. 55 eyes (40.4%) had IOP $>$ 30 mm of Hg of which 25 were in angle closure stage. IOP $<$ 30mm of Hg was found mostly in rubeosisiridis stage and $>$ 30 mm of Hg was found in angle closure stage.

On assessing the Cause of NVG in relation to stage of NVG (P= 0.107), 89 eyes (65.4%) had diabetic retinopathy in variable severity, of these 49, 22 and 18 were in rubeosisiridis, angle closure and open angle stage respectively. 9 had severe NPDR and all 9 were in rubeosisiridis stage. 22 had vitreous haemorrhage out of which 10, 10 and 6 were in rubeosisiridis, angle closure and open angle stage respectively. One had vitreous haemorrhage with combined rhegmatogenous and tractional retinal detachment, presented in rubeosisiridis stage.

5. Discussion

Neovascular glaucoma (NVG) is a form of secondary glaucoma characterized by formation of new vessels and proliferation of fibrovascular tissue on iris and in the angle. Slit lamp examination can reveal new vessels on iris, ciliary injection, corneal edema due to increase in IOP, anterior chamber reaction and ectropion uvea due to contraction of the fibrovascular membrane on the iris. Rubeosis can be missed in early stages as it can't be seen unless the iris is examined under high magnification in undilated stage. New vessels on iris usually appear before the appearance of new vessels in angle but in rare conditions like ischemic central retinal vein occlusion, new vessels in the angle are seen without involvement of the iris. Therefore, it is very important to perform gonioscopy even though new vesselsare not present on iris. Initially, the anterior chamber angle is open on gonioscopy but later, new vessels appear in the angle andin the final stages, due to formation of fibrovascularmembrane and tissue contraction synechiae can occur leading to synechial angle closure.[4,21]

136 eyes of 109 patients were included in the present study out of which 82 patients had either eye involvement and 27 patients had both eyes involvement.

44.8% of patients were in the age group of 60 – 80 years which is comparable to the study done by Vasconcelloset al.[22] in which 46.16 % of the patients were between 60 and 79 years of age.

In the present study, 106 (77.9%) had hypoxic and ischemic changes in retina like diabetic retinopathy, vein occlusion, chronic retinal detachment and S/P PPV and 16 (11.8%) had inflammatory diseases like uveitis, vasculitis and eales disease. It is comparable to the study done by Vancea PP et al.[23]which states that 81% had NVG secondary to ischemic retinal changes and in another study done by Haefliger IO et al.[24] they found that the majority (97%) of cases are associated with hypoxia and retinal ischemia. The remaining 3% cases are secondary to inflammatory diseases like chronic uveitis and intraocular neoplasms.

The commonest causes of NVG are Proliferative Diabetic Retinopathy (PDR) and central retinal vein occlusion.[4] In our study 63 (46.4%) cases had PDR, 16 (11.8%) had uveitis and 14 (10.2%) had retinal vein occlusion and hence PDR is the most common cause of NVG in the present study. The formation of new vessels is influenced by imbalance between pro-angiogenic factors (such as, vascular endothelial growth factor-VEGF)

and anti-angiogenic factors (such as pigment-epithelium-derived factor). Studies have shown that increased levels of VEGF and decreased levels of PEDF was found in the vitreous of patients with proliferative diabetic retinopathy.[25,26]

In the present study one case who underwent pars planavitrectomy had developed NVG. Surgical intervention like pars planavitrectomy for PDR increases the incidence of rubeosis iridis.[27] Retinal hypoxia is frequently seen in proliferative retinopathies. A portion of oxygen from the aqueous humor diffuses posteriorly towards the hypoxic retina causing the iris hypoxia. This explains the risk of rubeosis after surgery like vitrectomywhere oxygen reaches the ischemic retina faster leading severe iris hypoxia.[28]

In our study 9 cases (6.6%) had NVG due to pseudoexfoliative material on iris. Studies found that pseudoexfoliative material gets deposited adjacent to the endothelial wall and causes thinning of the basement membrane, endothelial wall fenestration and reduction of lumen of the vessel thus causing iris hypoxia and ischemia leading to neovascularization.[29,30]

In the present study 2 (1.5%) had developed NVG due to chronic retinal detachment. Studies described NVG can develop rarely due to ischemia caused by chronic RD.[31,32]

In our study, most of the cases presented in rubeosisiridis stage followed by angle closure stage and open angle stage. 74 eyes (54.4%) were in rubeosisiridis stage, 38 eyes (27.9%) were in angle closure stage and 24 eyes (17.6%) were in open angle stage.

In Rubeosisiridis stage most of the patients present with normal IOP and are usually asymptomatic. IOP begins to rise in Open angle glaucoma stage. In Angle closure glaucoma stage, IOP usually raises very high even up to 60 mmHg. Rubeosismay be severe with hyphema, anterior chamber reaction, conjunctival congestion and corneal edema.[33] In the present study, the mean IOP in angle closure stage was found to be 36.53 ± 16.259 mm of Hg which is significantly higher than the other two stages ($P = 0.000$). Four cases had hyphema and all 4 were in angle closure stage.

6. Conclusion

Neovascular glaucoma is a severe form of secondary glaucoma most commonly because of diseases causing retinal ischemia. So, early diagnosis and prompt treatment of the underlying retinal pathology can prevent neovascular glaucoma. In the present study, it was found that Proliferative diabetic retinopathy is the most common cause and rubeosisiridis is the most frequent stage of presentation in NVG.

7. Source of Funding

None.

8. Conflict of Interest

None.

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