

Neovascular Glaucoma: An Update on Etiopathogenesis, Diagnostics and Management

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Abstract

Neovascular glaucoma (NVG) is a severe secondary and refractory *severe secondary conditio, that accounts for a varying prevalence between 0.01% to 5.1% of all glaucoma those studied in different regions of the world. **This is a pathological condition, which is caused by the new vessels over iris surface and followed by fibrovascular membrane formation over the trabecular meshwork, secondary to a local angiogenic stimulus. The fibrovascular membrane over trabecular meshwork obstructs the aqueous outflow at an angle of the anterior chamber. ***The obstruction in outflow of the aqueous results increase of intraocular pressure (IOP), within the eyeball. NVG results from a number of ocular and systemic conditions with retinal ischemia leading to anoxia as a mediator in over 95% of cases. Most of them are affected with proliferative diabetic retinopathy (PDR) followed by central retinal venous occlusion (CRVO), and ocular ischemic syndrome (OIS) along with other uncommon causes or all those causes that causes retinal anoxia which led to angiogenic activity in retina and iris of eye. Although NVG overall prevalence is low, but it is a dreadful condition led to blindness. The objective of this review is to provide detailed information on its basic and clinical aspects, to enable us to manage it logically. Here its etiopathogenesis, methods of early diagnosis and management are discussed. It was concluded that if NVG is detected earlier and managed systematically (both medical and surgical) along with an eye on alleviation of different aggravating factors of the retinal hypoxia, it could be a sight-saving measure to the affected person.

Keywords

Neovascular Glaucoma, Rubeosis Iridis, Retinal Hypoxia, Diabetic Retinopathy, Central Retinal Venous Occlusion, Ocular Ischemic Syndrome

1. Introduction

Coats first described rubeosis iridis with central retinal venous occlusion (CRVO) in 1906 [1].

A condition of new vessel development on iris (NVI) and angle (NVA), that is followed by fibrovascular tissue proliferation in the anterior chamber angle, causes a rise in intraocular pressure (IOP) and that is principally driven by retinal ischemia. The common of those conditions which causes retinal ischemia are central retinal venous occlusion, proliferative diabetic neuropathy (PDR) and ocular ischemic syndrome. This condition was called previously by different names such as rubeotic glaucoma, diabetic hemorrhagic glaucoma, congestive glaucoma and thrombotic glaucoma [2]. Later in 1963 Weiss and colleagues named it as neovascular glaucoma (NVG) and also related this neovascularization with the elevation of intraocular pressure (IOP) [3].

As the name suggests that secondary glaucoma is due to new vessel formation of new vessels. This new vessel is formed in response to retinal ischemia or as a natural defense attempt to compensate the hypoxic environment of retinal neural tissue. The vascular endothelial growth factors (VEGF) play a role in the said attempt of defense.

In a hospital-based study, the proportion of eyes with NVG among secondary glaucoma was 9% - 17.4% [4] [5].

In one eye or both at a tertiary eye care center in South India between November 2018 and August 2019 study they found that in all cases of NVG main cause by PDR and of those 54.4% of cases presented with rubeosis iridis [6]. The prevalence of NVG was 0.3% of all glaucoma in a hospital-based study in Nigeria [7].

The prevalence of NVG was 0.01% in the population-based Hooghly River Study in West Bengal, India [8]. The prevalence of NVG among migrant Indians in Singapore was 0.12% [9]. Neovascular glaucoma (NVG) is a secondary, refractory condition that accounts for 0.7% - 5.1% of glaucoma in an Asian population [10] [11]. It seems that the prevalence of NVG is very low but growing trend of proliferative diabetic retinopathy in population warns to have a close follow-up of this complication because NVG can ultimately blind the affected eye in unilateral cases whereas completely blind in bilateral cases, if not detected and treated appropriately by available means. Following the treatment algorithm proposed by Sirisha Senthil, Tanuj *et al.* may be of great help [12].

This review includes an overview of the etiopathogenesis, diagnosis, stages of NVG and its updated management guideline.

2. Etiopathogenesis

There are multiple ocular and systemic causes for NVG. This could be categorized as follows [13]:

- 1) Common causes
 - a) Diabetic retinopathy
 - b) Ischemic central retinal vein occlusion (CRVO)

- c) Ocular ischemic syndrome (OIS)
- 2) Uncommon causes
 - a) Uveitis
 - b) Ocular radiation
 - c) Trauma
 - d) Crohn's disease
 - e) Bechet's disease
- 3) Miscellaneous retinal conditions
 - a) Coat's disease
 - b) Eales' disease
 - c) Frosted branch angiitis
 - d) Giant cell astrocytoma of the retina
 - e) Peripheral retinal detachment
 - f) X-linked retinoschisis (Rosenfeld *et al.* 1998)
- 4) Systemic diseases
 - a) Cryoglobulinemia
 - b) Churg-Strauss syndrome

All those etiologies those can cause retinal vascular occlusion could be categorized in uncommon.

Table 1, there are many conditions those mimic the NVG [12].

Nearly in all cases of NVG posterior segment ischemia is the underlying pathogenesis is, which is most commonly secondary to proliferative diabetic retinopathy (PDR) or central vein retinal occlusion (CRVO) and ocular Ischemic Syndrome (OIS).

It has been shown that the balance between vascular endothelial growth factor (VEGF), a major angiogenic stimulator, and pigment epithelium-derived factor

Table 1. Conditions mimics NVG are summarized below.

S. N	Ocular condition	Differentiating feature	Investigation required
1	Uveitis	Engorged iris blood vessels, KP, AC cells	Slit lamp, uveitis workup, blood test
2	Acute attack of angle closure glaucoma	Shallow AC, Corneal edema but no Neovascularization on iris	Slit lamp, gonioscopy, AS-OCT, fundus, fellow eye examination
3	Intraocular tumors	Neovascularization on iris and in angle	± Slit lamp, fundus examination, B scan, ancillary imaging for Metastasis
4	Carotid-cavernous fistula	Blood in Schlemm's canal	Gonioscopy, imaging studies of brain
5	Long standing Retinal detachment	PVR changes and neovascularization, post R.D surgery—signs of ischemia in anterior segment	Slit lamp, fundus, B scan
6	Anterior segment dysgenesis	Corectopia, iris atrophy with prominent blood vessels	Slit lamp, B scan

AC: Anterior Chamber; AS-OCT: Anterior Segment-Optical Coherence Tomography; KP: Keratic Precipitate; NV: Neovascularization; PVR: Proliferative Vitreoretinopathy; RD: Retinal Detachment; B scan: Ultrasonography B-Scanning.

(PEDF), a potent angiogenic inhibitor [14]. This balance is critical for the regulation of vascular permeability and angiogenesis [15]. It has also been suggested that a critical balance exists between PEDF, endostatin (Bhutto *et al.* 2004, endogenous antiangiogenic agents) and VEGF (angiogenic factors) may counteract the angiogenic potential of VEGF. The homeostatic imbalance between VEGF and PEDF results to neovascularization [16] [17].

Retinal hypoxia is frequently present in cases of rubeosis iridis and frequently in proliferative retinopathies [18].

In a study NVG accounted 5.8% of all glaucoma patients [19].

The NVG is secondary, due to obstruction of the trabecular meshwork (TM) by neo-vascular membrane that develops in response to retinal ischemia [20] [21]. OIS is a severe but rare ocular disease caused mainly by carotid artery stenosis [22]. Undiagnosed or mis diagnosed cases of OIS can lead to irreversible blindness due to NVG [23]. Study suggested that nearly 15% of patients with OIS had ocular symptoms like visual deterioration to periorbital pain and rest 85% complained of constitutional symptoms [24]. Hence OIS could be non-diagnosed or mis-diagnosed. A study on NVG is presented with CRVO in 36.1%, PDR in 32.2% and OIS 12.9% cases. Nearly half of cases were suffering with Systemic arterial hypertension and diabetes mellitus and overall, 97% of eyes had a disease process that produced extensive retinal ischemia and preceded the onset of iris neovascularization [20]. The ocular angiogenesis is a complex pathophysiologic process. The influence of stimulating growth factors is counterbalanced by a number of antiproliferative agents. The net result of these opposing factors on the vascular endothelial cell determines the outcome of angiogenesis homeostasis. Both endogenous and synthetic molecules can regulate ocular angiogenesis [17].

Tissue hypoxia is sensed by molecular switches which regulate synthesis and secretion of growth factors and inflammatory mediators. As a consequence, tissue microenvironment is altered by reprogramming metabolic pathways, angiogenesis, vascular permeability, pH homeostasis to facilitate tissue remodeling. Most cellular responses to hypoxia are associated with a family of transcription factors called hypoxia-inducible factors (HIFs) *i.e.* VEGF, b FGF (basic fibroblast growth factor), TNF (tumor necrosis factor), IGF (insulin growth factor) and PDGF (platelet derived growth factor), are proangiogenic.

HIF induce the expression of a wide range of genes that help cells adapt to a hypoxic environment [25].

The HIF pathway is currently viewed as a master regulator of angiogenesis. HIF modulation could provide therapeutic benefit for neovascular eye diseases.

HIF regulates several hundred genes and vascular endothelial growth factor (VEGF) is one of the primary target genes [26].

The HIF pathway mediates the primary cellular responses to hypoxia, which promotes both short- and long-term adaptation to hypoxia by

1) Rapidly increases O₂ supply: through upregulation of the vasodilatory enzyme inducible nitric oxide synthase (iNOS). Nitric oxide (NO), the enzymatic product of iNOS, relaxes vascular smooth muscle cells, providing a *short-term*

increase in blood flow.

2) O₂ Demand is also lowered: by

i) Increased utilization of glycolysis via induction of glycolytic enzymes, glucose uptake through increased *glucose transporter-1 (GLUT-1)* expression, and inhibition of mitochondrial respiration by upregulation of *pyruvate dehydrogenase kinase (PDK1)*.

ii) Decreased cell proliferation via HIF-mediated upregulation of the cyclin-dependent kinase inhibitors *p21* and *p27*.

Long-term adaptation is achieved primarily through relief of local hypoxia by stimulating angiogenesis. The HIF pathway regulates a host of all those pro-angiogenic genes *VEGF, angiopoietin-1, angiopoietin-2, Tie2, PDGF, bFGF, TNF* [27].

The finding that the endothelial expression of some growth factors, cytokines as well as other genes is influenced by variations in oxygen concentration has obvious physiological implications.

Two main cascades of reactions have been characterized depending on the duration of the oxygen deficiency.

a) *Following acute hypoxia*, endothelial cells become activated and neutrophil adherence is observed. One consequence of this process is the development of a local inflammatory reaction in ischemic organs which is then made worse if reperfusion occurs.

b) *If chronic hypoxic* conditions persist then the expression of growth factors, cytokines and pro-coagulation molecules is increased.

The hypoxic tissue makes sure an increase of adenosine production, which binds to its specific cell receptors and increases the activity of VEGF [28].

Hypoxia-inducible factor-1 (HIF-1) is a transcriptional activator that functions as a master regulator of cellular and systemic oxygen homeostasis [29]. The genes on which HIF acts encode proteins that determine increased tissular oxygen release and mediate the adaptive responses in hypoxia. Activation of this factor is influenced by the intracellular oxygen level and by the transduction pathways of the stimulus of different growth factors. VEGF *increases permeability of vessels* via a nitric oxide synthase/cGMP-dependent pathway that results in vasodilatation and increased flow lead to angiogenesis [30].

The intra ocular VEGF mirrors the elevated vitreous and retinal tissue levels of IGF 1. The elevation of IGF 1 precedes the onset of diabetic proliferative retinopathy, and a positive correlation has been observed between concentrations of IGF 1 in serum or vitreous fluid and extent of neovascularization in diabetic retinopathy [31].

Vascular permeability leads to increased permeability for plasmatic proteins and fibrinogen. The fibrinogen converts to fibrin resulting in a temporary matrix for the new blood vessel. The endothelial cells organize to form the “vascular bud” and express integrins. These cells advance from the main vessel to the angiogenic stimulus. Proliferation of the cells from the “bud” determines the development of the vascular lumen, resulting in a thin capillary wall with few peri-

cytes, but which can start to secrete the basal membrane components. If VEGF is suppressed at this stage the vascular growth stops and lead to the regression of the newly formed vessel.

The causes which can determine secondary NVG is listed here as:

1) Vascular ocular diseases: Thrombosis of the central retinal vein or its branches

a. PDR b. CRVO c. Coats disease d. Eales disease e. Retinal hemangioma f. PPHV g. ROP

2) Extra-ocular vascular diseases: Carotid occlusive diseases

a. Carotid-cavernous fistula b. Ligation of the carotid artery c. Giant cell arteritis (Horton arteritis) d. Takayasu disease

3) Other ocular disorders:

a. Rhegmatogenous retinal detachment b. Chronic uveitis c. Retinal-vitreous degeneration

4) Ocular Neoplasia:

a. Iris: melanoma, hemangioma, metastatic lesions

b. Ciliary body: melanoma

c. Choroid: melanoma; Conjunctiva: squamous cell carcinoma

d. Retina: retinoblastoma, large cell lymphoma

5) After surgery involving: Cataract; Vitrectomy; Surgery for retinal detachment.

Newly formed blood vessels move over the anterior chamber angle towards the ciliary body and the scleral spur and then towards the trabecular meshwork which becomes reddish. In stages NVG could be described as pre glaucoma or rubeosis iridis followed by open angle and later closed angle glaucoma [32].

The cumulative risk in NV in ischemic CRVO is illustrated in **Figure 1**. That shows that the risk of developing NVG in eyes with ischemic CRVO reaches a maximum of about 45% in aggregate over several years—the maximum risk being during the first 7 - 8 months and only 20% of all eyes with CRVO are of the ischemic type. The risk of an eye with CRVO developing NVG is not 100% but about 9% - 10%. However, if an ischemic CRVO is identified, one should have a high index of suspicion for development of NVG [13].

3. Clinical Features

Symptoms:

A chronic red, painful eye that often has significant vision loss. It could be asymptomatic in the early stages, if IOP rise is gradual and the corneal endothelial count is good, especially in young individuals.

Signs:

The first sign of iris NV is leakage of intravenously injected sodium fluorescein from vessels at the pupillary margin. The leakage can be detected even when the iris is apparently normal on slit-lamp examination.

The following features are clinically seen:

- Visible neovascularization of the iris (NVI) begins at pupillary margin or

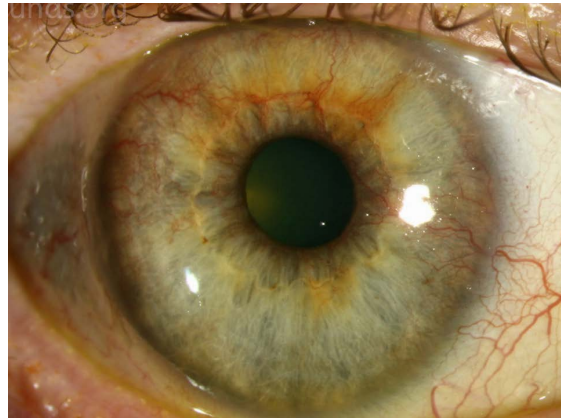


Figure 1. Rubeosis iridis.

Table 2. Grading of NVI and NVA.

Neovascularization	Grade 1	Grade 2	Grade 3	Grade 4
NVI	NV at pupillary zone < 2 quadrant	NV at pupillary zone > 2 quadrant	NV at ciliary zone/ectropion uveae 1 - 3 quadrant	NV at pupillary zone > 3 quadrant
NVA	NV cross SS and branches over TM < 2 quadrant	Angle vessels cross SS and branches over TM > 2 quadrant	NV at TM PAS 1 - 3 quadrant	NV at TM PAS > 3 quadrant

NV: Neovascularization; NVA: Neovascularization at Angle; NVI: Neovascularization at Iris; TM: Trabecular Meshwork; PAS: Peripheral Anterior Synechia.

iridectomy margin.

- Visible neovascularization of angle (NVA).
- IOP > 50 mmHg with or without corneal edema
- Gonioscopically, NVA with partial or complete closure of the angle.

Table 2, Weiss and gold has classified NVI and NVA [33].

Figure 2, Hayyeh *et al.* had studied the chances of NVI, NVA, NVGMR, Disc NV and Retinal NV in case of CRVO with duration of disease [13].

Stages of NVG:

NVG can be divided into different stages as follows [13]:

- 1) Pre-rubeotic stage—NVI is not visible clinically but detected at Fluorescein angiography (FA)
- 2) Rubeosis iridis stage
- 3) Secondary open angle glaucoma
- 4) Secondary closed angle glaucoma

4. Investigation

Ophthalmic:

Slit lamp examination and gonioscopy are essential tools. Very fine new vessels are not visible sometimes in early stage detected by FA [34] [35] [36].

Fundus fluorescein angiography is gold standard to detect NVD or NVE and in large fundus area of about 200° of fundus, Indocyanine green angiography (IGA)

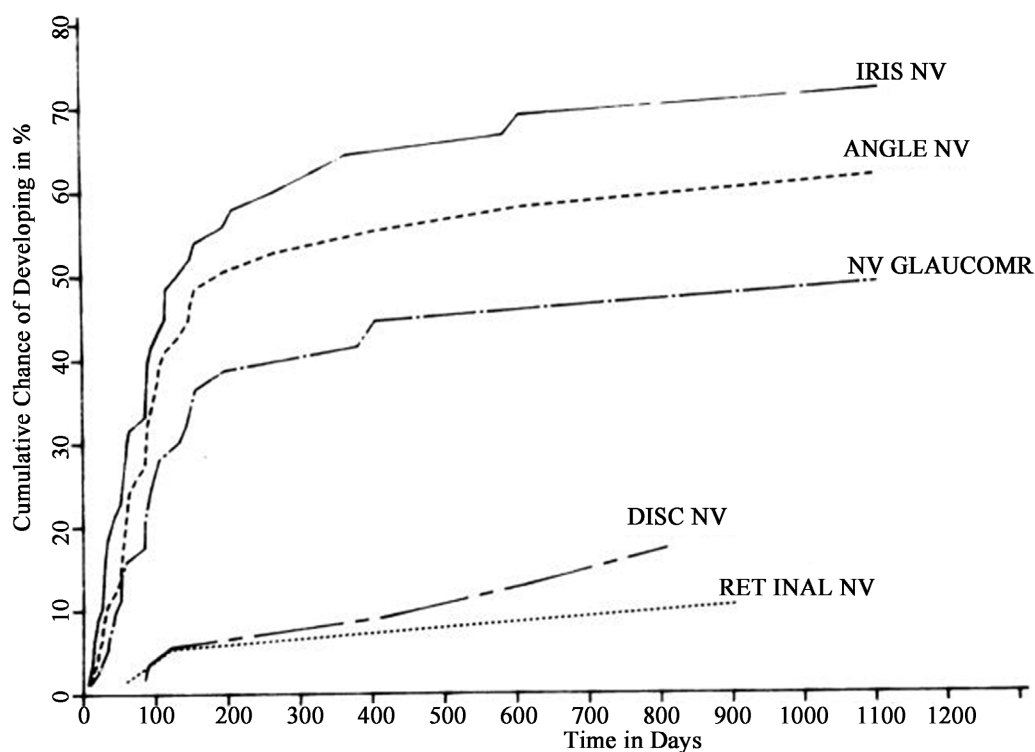


Figure 2. A graphic representation of cumulative chances (in %) of developing various types of ocular NV in ischemic CRVO in relation to time from onset of the disease (in days). (Reproduced from Hayreh *et al.* 1983).

helps more to identify vasculature in detail.

Nowadays, optical coherence tomography angiography (OCTA) became most important noninvasive investigation [37] [38].

This imaging technique is based on motion contrast.

This noninvasive widefield imaging has been used to image the iris vasculature and detect NVI.

In comparison to FA, OCTA is 79% to 100% sensitive and 96% to 97% specific.

B scan is used to rule out intraocular tumors or longstanding retinal detachment.

Carotid doppler of retrobulbar vessels specially in Takayasu disease [39] MRI, CT scan, Carotid intraarterial subtraction angiography [40] are used in investigating.

5. Management

It could be managed by following protocol [12]. **Table 3** shows the outline of management protocol of NVG.

Treatment of NVG:

Treatment principles

- 1) Treatment of retinal ischemia that reduces stimulus for NV
 - a) Intravitreal anti-VEGF agents to suppress iris and angle NV
 - b) Pan retinal photocoagulation (PRP)
- 2) Treatment of underlying systemic disease to improve retinal blood flow

3) Control of IOP
 4) Control of inflammation
 The current treatment of choice is PRP [41] [42] [43] [44].
 PRP is indicated not only in initial rubeosis but also in late stages of NVG with gonio synechia [43].
 Total 1200 - 1600 burns of around 500 µm and one spot apart in 1 to 3 session

Table 3. Outline of management protocol of NVG.

Neovascular glaucoma		
IOP is raised above normal limit		IOP is within normal limit
No PL		
With pain		Management of etiological conditions
Without pain		
1. Cycloplegic 2. Cyclophotocoagulation 3. Evisceration finally	wait and watch	
PL present		
Media is clear		IOP is not lowered further
Media is not clear		
1. Cycloplegic 2. Steroid 3. IOP control	Corneal edema, cataract, Vitreous hemorrhage and Tractional Retinal Detachment raised with IOP in conditions like	
Control of IOP either Medical or surgical		Control of IOP either Medical or surgical

NVG: Neovascular Glaucoma; PL: vision as Perception of Light; IOP: Intraocular pressure.

Table 4. Stages of NVG and management.

Stage	Description	Ocular feature	Treatment			
			PRP	Anti VEGF	Anti-glaucoma medicine	Glaucoma Filtration Surgery
I	Pre-glaucoma/ Rubeosis iridis	NVI++- At pupillary margin than runs irregularly and cross SS to TM IOP normal	Yes	Yes	No	NO
II	Angle open	Development of fibrovascular membrane on iris and angle NVI+++ NVA± IOP Elevated	Yes	Yes	Yes	±
III	Angle closed	Contracture of fibrovascular membrane on iris, pulls the iris over T M and form PAS NVI+++ with ectropion uveae NVA+++± but not visible due to synechia IOP Elevated	Yes	Yes	Yes	Yes

IOP: Intraocular pressure; NVA: Neovascularization at Angle; NVI: Neovascularization at Iris; PAS: Peripheral Anterior Synechia; TM: Trabecular Meshwork; SS: Scleral Spur; VEGF: Vascular Endothelial Growth Facto.

size and one spot apart. Ideally, it is completed in 1 - 3 sessions in a week period.

Nowadays, there is an increasing trend from PRP only in pre-glaucoma stage to combination of anti-VEGF injections, antiglaucoma medications, and glaucoma filtration surgery based on the disease progression and angle configuration. The treatment paradigm is changing with the introduction of anti-VEGF agents [45] [46]. **Table 4**, treatment protocol has been described as per the stages of neovascular glaucoma [12].

In **Table 5**, an outline of treatment guideline of NVG at different stages has been described [25]-[30].

Anterior-retinal cryotherapy (ARC) is another management when adequate PRP is difficult to manage due to hazy media and in advance cases it can be combined with intravitreal anti-VEGF injection.

Combined treatment of ARC and intravitreal bevacizumab (IVB) is associated with more rapid clearing of VH in eyes with PDR compared with IVB alone [47], and further in extreme case with vitrectomy, anti-VEGF injection, PRP, and endocyclo photocoagulation.

NVG with the primary pathology of PDR was reported to be less aggressive than ischemic CRVO.

Medical Management:

Anti-glaucoma medication: beta-blockers and carbonic anhydrase (oral and topical) is mainstay and alpha-2 agonists, which lower aqueous production [12].

Prostaglandin analog (PGA) is used in extreme cases as it increases inflammation and the same with miotics that worsen the synechia post inflammation.

Topical steroid and cycloplegics play a supportive role.

VEGF inhibitors inhibit NVI and NVA lead to lower IOP. Induce rapid involution of NVI and allows time for action of PRP.

Management of neovascular glaucoma should include prophylactic ablation of ischemic retina in the high-risk patients who are identified by fluorescein angiography. Early neovascularization of the filtration angle should be recognized by frequent gonioscopy and treated by repeated gonio-photocoagulation until the new vessels become inactive This should be combined with retinal ablation The established angle closure case should be treated by cyclocryopexy, Diamox and

Table 5. Management guideline based on stages of NVG.

Stage	Description	Ocular feature	Treatment			
			PRP	Anti VEGF	Anti-glaucoma medicine	Glaucoma Filtration Surgery
I	Pre-glaucoma	NVI++-	Yes	Yes	No	NO
II	Angle open	Elevated Intraocular pressure NVA+++±	Yes	Yes	Yes	±
III	Angle closed	Elevated Intraocular pressure NVA+++±	Yes	Yes	Yes	Yes

NVA = New vessels angle, NVI = New vessels at iris, NVG = Neovascular glaucoma, VEGF = Vascular endothelial growth factor.

carefully monitored beta blocking agent The use of implanted silicone rubber tubes may also be attempted A blind painful eye may be treated by Dexamethasone and Atropine drops coupled with cyclocryopexy as necessary With these regimes enucleation of an eye could be avoided [48].

Surgical Management:

Surgical management is challenging due to more risk of failure [49]-[54].

Hence, surgery is only attempted when IOP become uncontrolled by all conservative means and extensive PAS is formed after reducing inflammation to achieve better surgical results [44] [46] [47]. The commonly surgical interference is used such as filtration surgery (trabeculectomy), Glaucoma drainage device (GDDs) and cyclodestructive procedure. Traditional trabeculectomy results in severe inflammation and hyphema increases the chance of failure. Mitomycin c application increase the success rate significantly which may decrease by times.

Success rate of GDs (valved—Ahmed Glaucoma valve or non-valved like Bear-veletdt, Molteno device). Those values although reduces IOP immediately and chance of hypotony are lesser but success rate is lower than in other indications and don't make much difference either valved or non-valved, either treated with prior anti-VEGF or PRP [55]-[62].

Cyclophotocoagulation (CPC) using diode laser reduces IOP by decreasing aqueous production. But due to multiple complications of CPC even phthisis bulbi, it is kept reserve. If all other medical and surgical means fail. Endo cyclophotocoagulation with pars plana vitrectomy and PRP has better results [63] [64].

If secondary to OIS, it should be treated by multidisciplinary approach (cardiology and vascular surgery for carotid arteries imaging and carotid endarterectomy if indicated) [65].

To outline the principle of NVG management it should be as follows [66]:

Identifying and managing the etiological factor (diabetes, carotid artery obstruction, or other causes those causing retinal ischemia (hypoxia).

a) Treatment of the retinal ischemia by doing pan-retinal photocoagulation or intravitreal injections of anti-VEGF agents.

b) Control of intraocular pressure by both medically and surgically.

c) Control of inflammation by using topical corticosteroid eye drops.

d) Cycloplegia by use of mydriatics like topical atropine eye drops.

Prognosis:

Angle closure had the greatest impact on final IOP. Greater than 90% of patients treated with trabeculectomy with mitomycin C (LEC) had persistent declines in IOP (≤ 21 mmHg). Stand-alone and combination anti-VEGF therapies were not associated with improved long-term prognosis of IOP.

Angle closure was found to have the greatest effect on NVG-IOP prognosis. When target IOP values are not obtained after adequate PRP with or without anti-VEGF, early LEC may improve the prognosis of IOP [67].

The prognosis of NVG depends on three factors:

a) Prevention of secondary factors

- b) Early detection and proper treatment according to stage of glaucoma
- c) Intense follow up.

6. Conclusions

NVG is a dreadful condition with a guarded prognosis. Prevention of secondary factors causing retinal hypoxia, early detection and intense follow up and by undertaking appropriate medical and surgical management according to stages of NVG, based on a defined principle. Diabetic is a principal cause of NVG, incidence of which is increasing globally. The increasing incidence of PDR is responsible for the increasing prevalence of the NVG. Early detection of both anterior for rubeosis iridis (NVI) and neovascularization in angle (NVA) and posterior segment for diabetic retinopathy (PDR) should be monitored on regular basis other than Hypertension and cardiac condition to check CRVO. If detected and treated earlier may definitely decrease the prevalence of NVG.

In cases secondary to ocular ischemic syndrome (OIS), a multidisciplinary approach is required.

Newer examination tools like FA, OCTA, Carotid doppler of retrobulbar vessels, CT scan, Carotid intraarterial subtraction angiography can detect the condition earlier and newer treatment modalities *i.e.* anti-VEGF application, photocoagulation of retina (PRP) can get rid or deaccelerate the progress of disease along with control of elevated intraocular pressure (IOP) by taking care of retinal hypoxia can avoid blindness due to NVG.

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3) We also acknowledge the picture of rubeosis iridis collected from web search on <https://medicine.uiowa.edu/eye/>.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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