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Original Research Article

Neovascular Glaucoma: An Update

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Abstract

Background: Neovascular glaucoma (NVG) is a severe secondary and refractory condition accounts for a varying prevalence of 0.01 to5.1% of all glaucoma in different regions of world. This pathological condition which is caused by the new vessels over Iris and followed by growth of a fibrovascular membrane secondary to a local angiogenic stimulus over the trabecular meshwork obstructing aqueous outflow at angle of anterior chamber resulting increased Intraocular pressure (IOP), that 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 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 sight saving to the affected person.

Keywords: Neovascular glaucoma, Rubeosis iridis, Retinal hypoxia, diabetic retinopathy, Central retinal venous occlusion, Ocular ischemic syndrome

Background

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), which results fibrovascular tissue proliferation in the anterior chamber angle causes rise in intraocular pressure (IOP), is principally driven by retinal ischemia and among the common causes 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, thrombotic glaucoma [2]. Later on, in 1963 Weiss and colleagues named it as neovascular glaucoma (NVG) and related the new vessel formation with elevation of intraocular pressure (IOP) [3]. As the name suggest the secondary glaucoma it is due to new vessel formation. The new vessel is formed in response to retinal ischemia or

environment of retinal neural tissue as natural defense attempt due to vascular endothelial growth factors (VEGF)In hospital-based studies the proportion of eyes with NVG among secondary glaucoma was 9-17.4% [4,5]. In one eye or both the eyes at a tertiary eye care center in South India between November 2018 and August 2019 study they found that in all case of NVG main cause by PDR and of those 54.4% of cases presented with rubeosis iridis [6] The prevalence of NVG was found 0.3% of all glaucoma in a hospital-based study in Nigeria [7]. The Data from the European Union estimated that NVG makes up approximately 3.9% of all glaucoma [8]. The prevalence of NVG was 0.01% in the population-based Hooghly River Study in West Bengal, India [9]. The prevalence of NVG among migrant Indians in Singapore was 0.12% [10]. Neovascular glaucoma (NVG) is a secondary, refractory condition that accounts for 0.7–5.1 % of glaucoma in an Asian population [11,12]. It seems from literatures that prevalence of NVG is very low but increasing trend of Proliferative diabetic retinopathy warns the close follow up of this complication as NVG which can ultimately blind the affected eye and complete 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 [13]. Table 1 shows many conditions which may mimic the C/F of NVG which must be differentiated from others [13].

Table 1: Conditions mimicking NVG

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 (NVI) present Neovascularization in angle (NVA) present	± Slit lamp, fundus examination, USG 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, USG B-scan
6	Anterior segment dysgenesis	Corectopia, iris atrophy with prominent blood vessels	Slit lamp, USG B- scan

(AC-Anterior chamber, AS-OCT-Anterior segment- Optical coherence tomography KP-Keratic precipitate, NV- Neovascularization, PVR- Proliferative Vitreoretinopathy, RD-Retinal detachment, UGG-B-Ultrasonography B scanning)

This review includes an overview of the etiopathogenesis, diagnosis, stages and updated management guideline. Etiopathogenesis Out of multiple ocular and systemic causes NVG could be categorized as: [14]

(A) Common causes

- Diabetic retinopathy
- ischemic central retinal vein occlusion (CRVO)
- Ocular ischemic syndrome (OIS)

(B) Uncommon causes

- Uveitis
- Ocular radiation
- Trauma
- Crohn's disease
- Bechet's disease

(C) Miscellaneous retinal conditions

- Coat's disease
- Eales' disease
- Frosted branch angiitis
- Giant cell astrocytoma of the retina
- Peripheral retinal detachment
- X-linked retinoschisis (Rosenfeld *et al*. 1998)

(D) Systemic diseases

- Cryoglobulinemia
- Churg-Strauss syndrome

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

In most of cases of NVG, the underlying pathogenesis is posterior segment ischemia, 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 (PEDF), a potent angiogenic inhibitor [15]. This balance is critical for the regulation of vascular permeability and angiogenesis [16]. 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 balance between VEGF and PEDF lead to neovascularization [17,18].

Retinal hypoxia is frequently present in cases of rubeosis iridis and frequently in proliferative retinopathies [19].

In a study NVG accounted 5.8 % of all glaucoma patients [20].

The NVG is secondary, due to obstruction of the trabecular meshwork (TM) by neo-vascular membrane that develops in response to retinal ischemia [21,22].

OIS is a severe but rare ocular disease caused mainly by carotid artery stenosis [23].

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 [25].
Hence OIS could be non-diagnosed or mis-diagnosed.

A study on NVG is presented with CRVO in 36.1%, PDR in32.2% 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 [26]. 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 [27]. 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 [28]. 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 [29]. 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 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*). decreased cell proliferation via HIF-mediated upregulation of the cyclin-dependent kinase inhibitors *p21* and *p27*.
3. *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.[30]*

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 [31].

Hypoxia-inducible factor-1 (HIF-1) is a transcriptional activator that functions as a master regulator of cellular and systemic oxygen homeostasis [32]. 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 [33].

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 [34].

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 pericytes, 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
a. 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
2. Other ocular disorders:
   a. Rhegmatogenous retinal detachment
   b. Chronic uveitis c. Retinal-vitreous degeneration
3. 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
4. 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 [35].

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 [36].

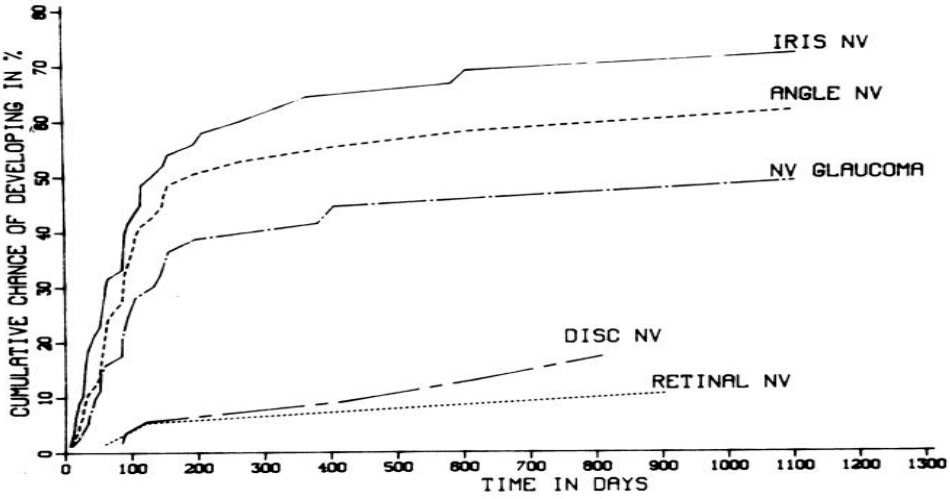

Figure 1: A graphic representation of cumulative chances (in %) of developing various types of ocular NV in ischemic

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)

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 NVI- that begins at pupillary margin or iridectomy margin.

Visible NVA -via Gonioscope – partial or complete closure of angle could be seen.

IOP > 50 mm of Hg with or without corneal edema

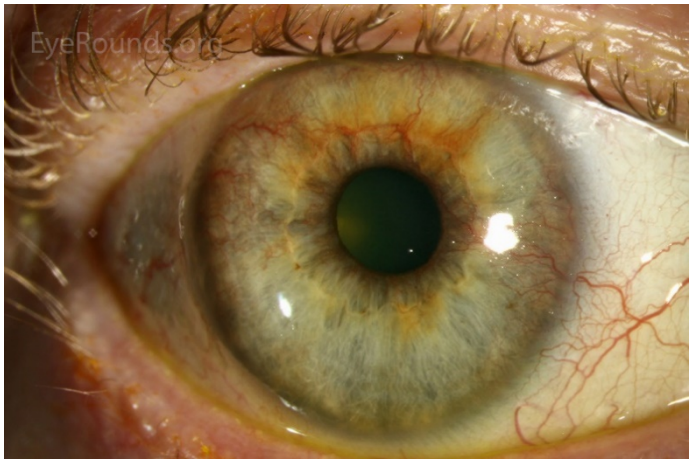

Figure 2: Rubeosis iridis is clearly visible on pupillary margin.

Table 2: Weiss and gold has tries to classify NVI and NVA [37]

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

Table 2 classification and grading of NVG (NV- Neovascularization, NVA- Neovascularization at angle NVI-Neovascularization at iris, TM- Trabecular meshwork, PAS- Peripheral anterior synechia)

Stages of NVG [38]

Pre-rubeotic stage – Clinically NVI invisible but detected at Fluorescein angiography

Rubeotic stage – Clinically visible NVI

Secondary *open* angle glaucoma

Secondary *closed* angle glaucoma

Investigation

Ophthalmic

Slit lamp examination and gonioscopy are essential tools. Very fine new vessels are not visible sometimes in early stage detected by FA [39-41].

Fundus fluorescein angiography is gold standard to detect NVD or NVE and in large fundaus area about 200° of fundus, Indocyanine green angiography helps more to identify vasculature in detail. Most important now a days is optical coherence tomography angiography (OCTA) [42-44].

This imaging technique is based on motion contrast.

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

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

USG-B Scan is used to rule out intraocular tumors or longstanding retinal detachment.

Carotid doppler of retrobulbar vessels specially in Takayasu disease [45] MRI, CT scan, Carotid intraarterial subtraction angiography [46] are used in investigating.

Management

It could be managed by following protocol [13].

Table 3: Shows the outline of management protocol of NVG.

<table>
<tr><th colspan="3">Neovascular glaucoma</th></tr>
<tr><td colspan="2">IOP is raised above normal limit</td><td>IOP is within normal limit</td></tr>
<tr><td colspan="2">No PL</td><td rowspan="7">Management of etiological conditions</td></tr>
<tr><td>With pain</td><td>Without pain</td></tr>
<tr><td>Cycloplegic
Cyclophotocoagulation
Evisceration - finally</td><td>wait and watch</td></tr>
<tr><td colspan="2">PL present</td></tr>
<tr><td>Media is clear</td><td>Media is not clear</td></tr>
<tr><td>Cycloplegic
Steroid
IOP control</td><td>Corneal edema, cataract, Vitreous hemorrhage and Tractional Retinal Detachment raised with IOP in conditions like</td></tr>
<tr><td>Control of IOP either Medical or surgical</td><td>Control of IOP either Medical or surgical</td><td>IOP is not lowered further</td></tr>
</table>

Table 3: outline on management of NVG- Neovascular glaucoma, PL- vision as perception of light, IOP- intra ocular pressure

Treatment of NVG

Treatment of retinal ischemia that reduces stimulus for Neovascularization

Intravitreal anti-VEGF agents to suppress iris and angle NV

1. Pan retinal photocoagulation (PRP)

Treatment principles

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 [47,50].

PRP is indicated not only in initial rubeosis but also in late stages of NVG with gonio synechiae [49].

Total 1200–1600 burns of around 500 µm and one spot apart in 1 to 3 session size and one spot apart. Ideally, it is completed in 1–3 sessions in a week period.

Now a days there is increase 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 [51,52].

In table 5, an outline of treatment guideline of NVG at different stages has been described.

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.[53] and further in extreme case with vitrectomy, anti-VEGF injection, PRP, and endo-cyclo-photocoagulation.

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

Medical Management

Anti-glaucoma medication: beta-lockers and carbonic anhydrase (oral and topical) is mainstay and alpha-2 agonists, which lower aqueous production [13].

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.

VGEF 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 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 [54].

Surgical management

Due to more risk of failure, the surgical management is challenging [55,61].

Hence surgery is only attempted when IOP is uncontrolled by conservative means and extensive PAS is formed after reducing inflammation for better surgical results [50,52,53]. Common surgical interference used 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 Bearveletdt, Molteno device although reduce 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 [62-69].

Cyclophotocoagulation (CPC) using diode laser reduces IOP by decreasing aqueous production. But due to multiple complications of CPC even phthisis bulbi, it is kept as reserve If all other medical and surgical means fail. Endo cyclophotocoagulation with pars plana vitrectomy and PRP has better results [70,71].

If secondary to OIS, it should be treated by multidisciplinary approach (cardiology and vascular surgery for carotid arteries imaging and carotid endarterectomy if indicated) [72].

To outline the principle of NVG management it should be as follows: [73]

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

B. Treatment of the retinal ischemia

1. By PRP or intravitreal injections of anti-VEGF agents.
2. By controlling IOP (medically and surgically).
3. By controlling inflammation (using topical corticosteroid drops).
4. Mydriatics (using topical atropine drops)

Table 4: Stages of NVG and management

Age	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- Intra ocular pressure, NVA- Neovascularization at angle, NVI- Neovascularization at iris, PAS Peripheral anterior synechia, Trabecular meshwork, SS-Scleral spur, VEGF-Vascular Endothelial Growth Factor)

Table 5: Outlines the treatment paradigm of NVG [25-30]

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 Intra ocular pressure NVA + + + ±	Yes	Yes	Yes	±
III	Angle closed	Elevated Intra ocular pressure NVA + + + ±	Yes	Yes	Yes	Yes

(IOP=Intraocular pressure, NVA=New vessels angle, NVI=New vessels at iris, NVG=Neovascular glaucoma, VEGF=Vascular endothelial growth factor)

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. Conclusions. 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.[74]

NVG has a guarded prognosis that depend on three factors

a. prevention of secondary factors

b. early detection and proper treatment according to stage of glaucoma

c. intense follow up.

Conclusion

NVG is a dreadful condition with guarded prognosis. Prevention of secondary factors causing retinal hypoxia, early detection and intense follow up by appropriate medical and surgical managements should be undertaken on stages of NVG based on a defined principle. Diabetic is a principal cause of NVG and it is on global increase. Increasing incidence of PDR is responsible for increasing prevalence of disease now days. 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 treated earlier can definitely decrease the prevalence of NVG. In cases secondary to ocular ischemic syndrome (OIS), a multidisciplinary approach is required.

Newer examination tools like FA and scanning device (OCT) can detect the condition earlier and newer treatment modalities i.e. anti-VEGF application, photocoagulation of retina (PRP) can get rid of disease or deaccelerate the progress of disease along with control of elevated intra ocular pressure (IOP) by taking care of retinal hypoxia can avoid blindness due to NVG.

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