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 condition, 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 retina 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

| 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 balance 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 misdiagnosed 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, bFGF (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 intraocular 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
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                                     | NV at TM                                     |
|                    |                                              |                                              | PAS 1 - 3 quadrant                            | PAS > 3 quadrant                              |

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

Figure 1. Rubeosis iridis.

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 synechiae [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.**

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

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

**Table 4. Stages of NVG and management.**

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

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

References

[1] Coats, G. (1906) Further Cases of Thrombosis of the Central Vein. J. & A. Churchill, London.

[2] Salus, R. (1928) Rubeosis iridis diabetica, eine bisher unbekannte diabetische Irisveränderung. Medizinische Klinik, 7, 256-258.
Weiss, D.I., Shaffer, R.N. and Nehrenberg, T.R. (1963) Neovascular Glaucoma Complicating Carotid-Cavernous Fistula. *Archives of Ophthalmology*, **69**, 304-307. https://doi.org/10.1001/archoph.1963.0096004310007

Ohrt, V. (1971) The Frequency of Rubeosis Iridis in Diabetic Patients. *Acta Ophthalmologica*, **49**, 301-307. https://doi.org/10.1111/j.1755-3768.1971.tb00954.x

Mocanu, C., Barăscu, D., Marinescu, F., Lăcrățeanu, M., Iliuși, F. and Simionescu, C. (2005) Neovascular Glaucoma Retrospective Study. *Oftalmologia* (Bucharest, Romania), **49**, 58-65.

Khayoom, N.S. and Mayuri, T.K. (2020) A Prospective Observational Study to Evaluate the Etiology and Staging of Neovascular Glaucoma. *Indian Journal of Clinical and Experimental Ophthalmology*, **6**, 123-128. https://doi.org/10.18231/j.ijceo.2020.027

Fiebai, B. and Onua, A. (2019) Prevalence, Causes and Management of Neovascular Glaucoma: A 5-Year Review. *Open Journal of Ophthalmology*, **9**, 1-8. https://doi.org/10.4236/ojoph.2019.91001

Wong, T.Y., Chong, E., Wong, W.L., Rosman, M., Aung, T., Loo, J.L., et al. (2008) Prevalence and Causes of Low Vision and Blindness in an Urban Malay Population: The Singapore Malay Eye Study. *Archives of Ophthalmology*, **126**, 1091-1099. https://doi.org/10.1001/archoph.126.8.1091

Narayanaswamy, A., Baskaran, M., Zheng, Y., Lavanya, R., Wu, R., Wong, W.L., Saw, S.M., Cheng, C.Y., Wong, T.Y. and Aung, T. (2013) The Prevalence and Types of Glaucoma in an Urban Indian Population: The Singapore Indian Eye Study. *Investigative Ophthalmology & Visual Science*, **54**, 4621-4627. https://doi.org/10.1167/iovs.13-11950

Wang, B., Atherton, P., Patel, R., Manning, G. and Donnelly, R. (2010) Antiangiogenic Effects and Transcriptional Regulation of Pigment Epithelium-Derived Factor in Diabetic Retinopathy. *Microvascular Research*, **80**, 470-485. https://doi.org/10.1016/j.mvr.2010.02.012

Zhang, S.X., Wang, J.J., Gao, G., Parke, K. and Ma, J.X. (2006) Pigment Epithelium-Derived Factor Downregulates Vascular Endothelial Growth Factor (VEGF) Expression and Inhibits VEGF-VEGF Receptor 2 Binding in Diabetic Retinopathy. *Journal of Molecular Endocrinology*, **37**, 1-12. https://doi.org/10.1677/jme.1.02008

Bhutto, I.A., McLeod, D., Hasegawa, T., Kim, S.Y., Merges, C., Tong, P. and Lutty, G.A. (2006) Pigment Epithelium-Derived Factor (PEDF) and Vascular Endothelial Growth Factor (VEGF) in Aged Human Choroid and Eyes with Age-Related Macular Degeneration. *Experimental Eye Research*, **82**, 99-110. https://doi.org/10.1016/j.exer.2005.05.007
[17] Casey, R. and Li, W.W. (1997) Factors Controlling Ocular Angiogenesis (Review). *American Journal of Ophthalmology, 124*, 521-529. https://doi.org/10.1016/S0002-9394(14)70868-2

[18] Rehák, J. (1992) Rubeosis Iridis and Neovascular Glaucoma: I. Etiopathogenesis and Treatment—The Present State of the Problem. *Acta Universitatis Palackianae Olomucensis Facultatis Medicae, 134*, 101-103.

[19] Liao, N., Li, C., Jiang, H., Fang, A., Zhou, S. and Wang, Q. (2016) Neovascular Glaucoma: A Retrospective Review from a Tertiary Center in China. *BMC Ophthalmology, 16*, Article No. 14. https://doi.org/10.1186/s12886-016-0190-8

[20] Brown, G.C., Magargal, L.E., Schachat, A. and Shah, H. (1984) Neovascular Glaucoma. Etiologic Considerations. *Ophthalmology, 91*, 315-320. https://doi.org/10.1016/S0161-6420(84)34293-2

[21] Sivak-Callcott, J.A., O'Day, D.M., Gass, J.D. and Tsai, J.C. (2001) Evidence-Based Recommendations for the Diagnosis and Treatment of Neovascular Glaucoma. *Ophthalmology, 108*, 1767-1776. https://doi.org/10.1016/S0161-6420(01)00775-8

[22] Gavrilenko, A.V., Kuklin, A.V. and Kiseleva, T.N. (2013) Efficacy of Carotid Endarterectomy in Patients with Stenosis of Carotid Arteries and Acute Vision Impairment. *Angiologia i Sosudistaia Khirurgiia, 19*, 106-112.

[23] Knox, D.L. (1969) Ocular Aspects of Cervical Vascular Disease. *Survey of Ophthalmology, 13*, 245-262.

[24] Luo, J., Yan, Z., Jia, Y. and Luo, R. (2018) Clinical Analysis of 42 Cases of Ocular Ischemic Syndrome. *Journal of Ophthalmology, 2018*, Article ID: 2606147. https://doi.org/10.1155/2018/2606147

[25] Mitroshina, E.V., Savuk, M.O., Ponimaskin, E. and Vedunova, M.V. (2021) Hypoxia-Inducible Factor (HIF) in Ischemic Stroke and Neurodegenerative Disease. *Frontiers in Cell and Developmental Biology, 9*, Article ID: 703084. https://doi.org/10.3389/fcell.2021.703084

[26] Ramakrishnan, S., Anand, V. and Roy, S. (2014) Vascular Endothelial Growth Factor Signaling in Hypoxia and Inflammation. *Journal of Neuroimmune Pharmacology, 9*, 142-160. https://doi.org/10.1007/s11481-014-9531-7

[27] Krock, B.L., Skuli, N. and Simon, M.C. (2011) Hypoxia-Induced Angiogenesis: Good and Evil. *Genes Cancer, 2*, 1117-1133. https://doi.org/10.1077/19476019111423654

[28] Michiels, C., Arnould, T. and Remacle, J. (2000) Endothelial Cell Responses to Hypoxia: Initiation of a Cascade of Cellular Interactions. *Biochimica et Biophysica Acta (BBA)—Molecular Cell Research, 1497*, 1-10. https://doi.org/10.1016/S0167-4889(00)00041-0

[29] Zagórska, A. and Dulak, J. (2004) HIF-1: The Knowns and Unknowns of Hypoxia Sensing. *Acta Biochimica Polonica, 51*, 563-585. https://doi.org/10.18388/abp.2004_3545

[30] Mayhan, W.G. (1999) VEGF Increases Permeability of the Blood-Brain Barrier via a Nitric Oxide Synthase/cGMP-Dependent Pathway. *American Journal of Physiology, 276*, C1148-C1153. https://doi.org/10.1152/ajpcell.1999.276.5.C1148

[31] Santhan Gopal, K.S. (2011) Increased Levels of Vascular Endothelial Growth Factor in Aqueous Humor of Patients with Diabetic Retinopathy: Is It the Whole Truth? *Indian Journal of Ophthalmology, 59*, 405-406. https://doi.org/10.4103/0301-4738.83629

[32] Barac, I.R., Pop, M.D., Gheorghe, A.I. and Taban, C. (2015) Neovascular Secondary
Glaucoma, Etiology and Pathogenesis. *Romanian Journal of Ophthalmology*, **59**, 24-28.

[33] Weiss, D. and Gold, D. (1978) Neofibrovascularization of Iris and Anterior Chamber Angle: A Clinical Classification. *Annals of Ophthalmology*, **10**, 488-491.

[34] Brancato, R., Bandello, F. and Lattanzio, R. (1997) Iris Fluorescein Angiography in Clinical Practice. *Survey of Ophthalmology*, **42**, 41-70. https://doi.org/10.1016/S0039-6257(97)84042-8

[35] Parodi, M.B., Bondel, E., Russo, D. and Ravalico, G. (1996) Iris Indocyanine Green Videoangiography in Diabetic Iridopathy. *British Journal of Ophthalmology*, **80**, 416-419. https://doi.org/10.1136/bjo.80.5.416

[36] Li, Z.Q., Zhou, X.X., Lin, S., Li, J.L. and Wu, J.G. (2013) Angiography Reveals Early Hiding Iris Neovascularization after Ischemic CRVO. *International Journal of Ophthalmology*, **6**, 253-254.

[37] Hwang, T.S., Hagag, A.M., Wang, J., Zhang, M., Smith, A., Wilson, D.J., et al. (2018) Automated Quantification of Nonperfusion Areas in 3 Vascular Plexuses with Optical Coherence Tomography Angiography in Eyes of Patients with Diabetes. *JAMA Ophthalmology*, **136**, 929-926. https://doi.org/10.1001/jamaophthalmol.2018.2257

[38] Spaide, R.F., Klancnik, J.M. and Cooney, M.J. (1974) Retinal Vascular Layers Imag ed by Fluorescein Angiography and Optical Coherence Tomography Angiography. *JAMA Ophthalmology*, **133**, 45-50. https://doi.org/10.1016/0002-9394(74)90338-9

[39] Matos, K.T.F., et al. (2014) Retinal Angiography and Colour Doppler of Retrobulbar Vessels in Takayasu Arteritis. *Canadian Journal of Ophthalmology*, **49**, 80-86. https://doi.org/10.1016/j.jcjo.2013.09.014

[40] Dubey, S. and Pegu, J. (2009) Management of Neovascular Glaucoma. *Journal of Current Glaucoma Practice*, **3**, 27-34. https://doi.org/10.5005/jp-journals-10008-1062

[41] Laatikainen, L. (1977) Preliminary Report on Effect of Retinal Panphotocoagulation on Rubeosis Iridis and Neovascular Glaucoma. *British Journal of Ophthalmology*, **61**, 278-284. https://doi.org/10.1136/bjo.61.4.278

[42] Murphy, R.P. and Egbert, P.R. (1979) Regression of Iris Neovascularization Following Panretinal Photocoagulation. *Archives of Ophthalmology*, **97**, 700-702. https://doi.org/10.1001/archopht.1979.01020010352013

[43] Rodrigues, G.B., Abe, R.Y., Zangalli, C., et al. (2016) Neovascular Glaucoma: A Review. *International Journal of Retina and Vitreous*, **2**, Article No. 26. https://doi.org/10.1186/s40942-016-0051-x

[44] Tasman, W., Magargal, L.E. and Augsburger, J.J. (1980) Effects of Argon Laser Photocoagulation on Rubeosis Iridis and Angle Neovascularization. *Ophthalmology*, **87**, 400-402. https://doi.org/10.1016/S0161-6420(80)35225-1

[45] Horsley, M.B. and Kahook, M.Y. (2010) Anti-VEGF Therapy for Glaucoma. *Current Opinion in Ophthalmology*, **21**, 112-117. https://doi.org/10.1097/ICU.0b013e3283360aad

[46] Grisanti, S., Biester, S., Peters, S., Tatar, O., Ziemssen, F., Bartz-Schmidt, K.U., et al. (2006) Intracameral Bevacizumab Foriris Rubeosis. *American Journal of Ophthalmology*, **142**, 158-160. https://doi.org/10.1016/j.ajo.2006.02.045

[47] Hsieh, M.C., Yeh, P.T., Yang, C.M. and Yang, C.H. (2014) Anterior Retinal Cryotherapy and Intravitreal Injection of Bevacizumab in the Treatment of Nonclearing Vitreous Hemorrhage in Proliferative Diabetic Retinopathy. *Journal of Ocular Pharmacology and Therapeutics*, **30**, 353-358. https://doi.org/10.1089/jop.2013.0104
[48] Grant, W.M. (1974) Management of Neovascular Glaucoma. Symposium on Ocular Therapy, 7, 36-61.

[49] Higashide, T., Ohkubo, S. and Sugiyama, K. (2015) Long-Term Outcomes and Prognostic Factors of Trabeculectomy Following Intraocular Bevacizumab Injection for Neovascular Glaucoma. PLOS ONE, 10, e0135766. https://doi.org/10.1371/journal.pone.0135766

[50] Saito, Y., Higashide, T., Takeda, H., Ohkubo, S. and Sugiyama, K. (2010) Beneficial Effects of Preoperative Intravitreal Bevacizumab on Trabeculectomy Outcomes in Neovascular Glaucoma. Acta Ophthalmologica, 88, 96-102. https://doi.org/10.1111/j.1755-3768.2009.01648.x

[51] Takihara, Y., Inatani, M., Fukushima, M., Iwao, K., Iwao, M. and Tanihara, H. (2009) Trabeculectomy with Mitomycin C for Neovascular Glaucoma: Prognostic Factors for Surgical Failure. American Journal of Ophthalmology, 147, 912-918.e911. https://doi.org/10.1016/j.ajo.2008.11.015

[52] Olmos, L.C. and Lee, R.K. (2011) Medical and Surgical Treatment of Neovascular Glaucoma. International Ophthalmology Clinics, 51, 27-36. https://doi.org/10.1097/IIO.0b013e31821e5960

[53] Nakatake, S., Yoshida, S., Nakao, S., Arita, R., Yasuda, M., Kita, T., et al. (2014) Hyphema Is a Risk Factor for Failure of Trabeculectomy in Neovascular Glaucoma: A Retrospective Analysis. BMC Ophthalmology, 14, Article No. 55. https://doi.org/10.1186/1471-2415-14-55

[54] Mackensen, G. and Harms, H. (1988) Chirurgie der Glaukome. In: Mackensen, G., et al., Eds., Augenärztliche Operationen, Springer, Berlin, 807-930. https://doi.org/10.1007/978-3-642-72939-3_15

[55] Christakis, P.G., Kalenak, J.W., Tsai, J.C., Zurakowski, D., Kammer, J.A., Harasymowycz, P.J., et al. (2016) The Ahmed versus Baerveldt Study: Five-Year Treatment Outcomes. Ophthalmology, 123, 2093-2102. https://doi.org/10.1016/j.ophtha.2016.06.035

[56] Netland, P.A., Ishida, K. and Boyle, J.W. (2010) The Ahmed Glaucoma Valve in Patients with and without Neovascular Glaucoma. Journal of Glaucoma, 19, 581-586. https://doi.org/10.1097/JJG.0b013e3181ca77f7

[57] Netland, P.A. (2009) The Ahmed Glaucoma Valve in Neovascular Glaucoma (An AOS Thesis). Transactions of the American Ophthalmological Society, 107, 325-342.

[58] Yalvac, I., Eksioglu, U., Satana, B. and Duman, S. (2007) Long-Term Results of Ahmed Glaucoma Valve and Molteno Implant in Neovascular Glaucoma. Eye, 21, 65-70. https://doi.org/10.1038/sj.eye.6702125

[59] Kang, J.Y., Nam, K.Y., Lee, S.J. and Lee, S.U. (2014) The Effect of Intravitreal Bevacizumab Injection before Ahmed Valve Implantation in Patients with Neovascular Glaucoma. International Ophthalmology, 34, 793-799. https://doi.org/10.1007/s10792-013-9875-7

[60] Sahyoun, M., Azar, G., Khoueir, Z., Antoun, J., Kourie, H., Nehme, J., et al. (2015) Long-Term Results of Ahmed Glaucoma Valve in Association with Intravitreal Bevacizumab in Neovascular Glaucoma. Journal of Glaucoma, 24, 383-388. https://doi.org/10.1097/IJG.0000000000000234

[61] Arcieri, E.S., Paula, J.S., Jorge, R., Barella, K.A., Arcieri, R.S., Secches, D.J., et al. (2015) Efficacy and Safety of Intravitreal Bevacizumab in Eyes with Neovascular Glaucoma Undergoing Ahmed Glaucoma Valve Implantation: 2-Year Follow-Up. Acta Ophthalmologica, 93, e1-e6. https://doi.org/10.1111/aos.12493

[62] Kolomeyer, A.M., Seery, C.W., Emami-Naeimi, P., Zarbin, M.A., Fechtner, R.D.
and Bhagat, N. (2015) Combined Pars Plana Vitrectomy and Pars Plana Baerveldt Tube Placement in Eyes with Neovascular Glaucoma. *Retina*, 35, 17-28. https://doi.org/10.1097/IAE.0000000000000235

[63] Bloom, P.A., Tsai, J.C., Sharma, K., Miller, M.H., Rice, N.S., Hitchings, R.A., et al. (1997) "Cyclodiode": Trans-Scleral Diode Laser Cyclophotocoagulation in the Treatment of Advanced Refractory Glaucoma. *Ophthalmology*, 104, 1508-1520. https://doi.org/10.1016/S0161-6420(97)30109-2

[64] Marra, K.V., Wagley, S., Omar, A., Kinoshita, T., Kovacs, K.D., Silva, P., et al. (2015) Case-Matched Comparison of Vitrectomy, Peripheral Retinal Endolaser, and Endocyclophotocoagulation versus Standard Care in Neovascular Glaucoma. *Retina*, 35, 1072-1083. https://doi.org/10.1097/IAE.0000000000000449

[65] Terelak-Borys, B., Skonieczna, K. and Grabska-Liberek, I. (2012) Ocular Ischemic Syndrome—A Systematic Review. *Medical Science Monitor*, 18, RA138-RA144. https://doi.org/10.12659/MSM.883260

[66] Mishra, C. and Meyer, J.J. (2022) Neovascular Glaucoma. In: StatPearls [Internet], StatPearls Publishing, Treasure Island. https://www.ncbi.nlm.nih.gov/books/NBK576393

[67] Nakano, S., Nakamuro, T., Yokoyama, K., Kiyosaki, K. and Kubota, T. (2016) Prognostic Factor Analysis of Intraocular Pressure with Neovascular Glaucoma. *Journal of Ophthalmology*, 7, Article ID: 1205895. https://doi.org/10.1155/2016/1205895