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Diabetes a major risk factor for blinding condition of Neovascular Glaucoma: An update on this condition

Dr. Sunil Kumar
MS (ophthalmology), Assistant professor, Department of ophthalmology, Patna Medical College, Patna-800004n information

Dr. Ajay Kumar Sinha
MS (ophthalmology), Assistant professor, Department of ophthalmology, Patna Medical College, Patna-800004n information

Dr Sujata Kumari
Senior resident, Department of ophthalmology, Patna Medical College, Patna-800004
Corresponding author email: kumarisujata606@gmail.com

***Abstract*---**Importance: Neovascular glaucoma (NVG) is a severe form of secondary glaucoma has a varying prevalence of 0.01 to 3.9% of all glaucoma in different regions of world. Majority of them are affected with proliferative diabetic retinopathy. Although NVG overall prevalence is low but it is a dreadful condition led to blindness. If not detected earlier of the disease by latest investigating majors and treated systematically on different stages of the disease along with taking care of the alleviation of different aggravating factors for retinal hypoxia. Objectives: To summarize published evidence on etiopathogenesis, clinical feature, stages of NVG and to provide treatment recommendation on different stages of the NVG for ophthalmologists based on published evidence. Evidence Review: A literature search of PubMed was conducted from January 1, 1974 to June 30, 2022. Publications describing prevalence, etiopathogenesis, clinical staging, investigation and treatment modality were included in the study. Findings: NVG is characterized by development of new vessels on iris and fibrovascular tissue proliferation in the anterior chamber angle with increase in IOP, principally driven by Retinal ischemia and among the commonest causes are proliferative diabetic neuropathy (PDR), central retinal venous occlusion, and ocular ischemic syndrome (OIS). Conclusions and Relevance: Increasing incidence of PDR is responsible for increasing prevalence of disease now a days. Hence in Diabetic retinopathy the regular examination of both anterior and posterior segment should be monitored on regular

basis other than Hypertension and cardiac condition. Newer examination tools like FA and OCT can detect the condition earlier and anti-VEGF application, photocoagulation 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.

***Keywords*---**Neovascular glaucoma, Secondary glaucoma, Rubeosis iridis, Retinal hypoxia, diabetic retinopathy

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), 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] 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.[11] **Table 1,** there are many conditions which mimic the NVG.[11] This review includes an overview of the etiopathogenesis, diagnosis, stages and updated management guideline.

Etiopathogenesis

Out of multiple ocular and systemic causes [12-18]
It could be categorized as common and uncommon causes i.e. Diabetic retinopathy, ischemic central retinal vein occlusion (CRVO) and ocular ischemic

syndrome common whereas uveitis ocular radiation, trauma, Crohn's disease, Bechet's disease along with Other 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) and systemic diseases i.e. cryoglobulinemia and Churg-Strauss syndrome those can cause retinal vascular occlusion could be categorized in uncommon.[12] The ocular ischemic syndrome, mainly unilateral mainly caused by atherosclerosis is a rare condition characterized by chronic ischemia of the anterior and/or posterior segment of the eyes and is primarily caused by the stenosis of the carotid artery has poor prognosis with a mortality rate of 40% within 5 years of onset. Although usually asymptomatic. It occurs in patients with poor collateral circulation between internal and external carotid artery. The major cause of OIS is atherosclerosis, and other common causes include giant cell arteritis, thrombogenesis, Takayasu arteritis, trauma, and different types of diseases involving the carotid arteries. The majority of OIS patients are older males and suffering from more than two systemic diseases, such as systemic arterial hypertension, Diabetes, and Hyperlipidemia.[13]

In a study of 208 patients with NVG. Commonest etiology was CRVO (36.1%), followed by diabetic retinopathy by a narrow margin (32.2%), and other were carotid artery obstructive disease (12.9%). Overall, 97% of eyes with NVG had a disease process that produced extensive retinal ischemia and preceded the onset of iris neovascularization. Patients with NVG, but without an obvious precipitating fundus condition, should be suspected of having severe carotid artery obstructive disease.[14]

The underlying pathogenesis in most cases is posterior segment ischemia, which is most commonly secondary to proliferative diabetic retinopathy or central vein retinal occlusion. The neovascularization process in the eye is driven by the events that alter the homeostatic balance between pro-angiogenic factors, such as the vascular endothelial growth factor and anti-angiogenic factors, such as the pigment-epithelium-derived factor.[15]

The concept of an existing factor that spreads and stimulates the forming of new blood vessels was stated in 1948. From the original description, iris neovascularization and that of the anterior chamber have been described in a multitude of diseases, the majority (97%) being associated with changes that involve hypoxia and retinal ischemia. The rest of 3% are represented by inflammatory diseases - chronic uveitis and intraocular neoplasms. Retinal hypoxia is frequently present in cases of rubeosis iridis and frequently in proliferative retinopathies.[16]

It is possible that a part of the oxygen from the aqueous humor diffuses posterior towards the hypoxic retina, thus resulting the iris hypoxia, through a compensatory mechanism. Therefore, this might explain the high risk of rubeosis in cases of neovascular glaucoma after surgery like vitrectomy and intracapsular lens extraction, in which the oxygen can better reach the ischemic retina through diffusion and lead to a quick and severe iris hypoxia. The endothelial vascular cells respond to a tissular hypoxia and secrete proangiogenic factors like: VEGF (vascular endothelial growth factor), b FGF (basic fibroblast growth factor), TNF

(tumor necrosis factor), IGF (insulin growth factor) and PDGF (platelet derived growth factor).

All these processes stimulate a chain reaction characterized by the activation, proliferation and migration of the endothelial cells that have one outcome: the formation of new blood vessels that are fragile and permeable. The formation of new blood vessels happens through branching from the existing vessels. The hypoxic tissue makes sure an increase of adenosine production, which binds to its specific cell receptors and increases the activity of VEGF. The hypoxia induction factor (HIF-1) is the primary regulator of oxygen homeostasis.

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 induces the production of NO (nitric oxide), resulting in vasodilatation and increased blood flow which precedes angiogenesis. VEGF also has a role in increasing the vascular permeability.

The angiogenesis process starts with the forming of small gaps between the endothelial cells of the capillary walls, which 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” will determine 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.

Increased levels of VEGF have been found in the aqueous humor of patients with neovascular glaucoma, particularly in diabetic patients. Regarding the ocular structures, it seems that the formation of new blood vessels is determined by the balance between the angiogenic factor VEGF and the antiangiogenic factor PEDF (pigment epithelium - derived factor). PEDF is frequently secreted and has a strong inhibitory angiogenic effect as well as a neuroprotective effect. From the causes that can determine secondary neovascular glaucoma, the following has been listed:

1. Vascular ocular diseases: - Thrombosis of the central retinal vein or its branches
 a. Diabetic retinopathy b. Obstruction of the central retinal artery c. Coats disease d. Eales disease e. Retinal hemangioma f. Primary hyperplastic persistent vitreous g. Retinopathy of prematurity.
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 [17]

Clinical Features

Symptoms: a chronic red, painful eye that often has significant vision loss. It could be asymptomatic in the early stages,[18] 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) and neovascularization of angle (NVA). NVI usually begins at pupillary margin or iridectomy margin
- IOP> 50 mmHg with or without corneal edema
- Gonioscopically, NVA with partial or complete closure of the angle.

Fig 1 – Rubeosis iridis
Table 2, Weiss and gold has tries to classify NVI and NVA [19]
NVG can be divided into different stages as follows [20]

1. Pre-rubeotic stage – NVI is not visible clinically but detected at Fluorescein angiography
2. Rubeosis iridis stage
3. Secondary open angle glaucoma
4. 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. [21-23]
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)[24-26]
This imaging technique is based on motion contrast.[27-28]
This noninvasive widefield imaging has been used to image the iris vasculature and detect NVI.[29]
In comparison to FA, OCTA is 79 to 100 % sensitive and 96 to 97 % specific.[30-32]

USG-B Scan is used to rule out intraocular tumors or lon standin retinal detachment.
Carotid doppler of retrobulbar vessels,[33] MRI, CT scan, Carotid intraarterial subtraction angiography [34] are used in investigating.

Management

It could be managed by following protocol.[11] **Table 3** shows the outline of management protocol of NVG.

Treatment of NVG

Treatment principles

1. Treatment of retinal ischemia that reduces stimulus for Neovascularization
   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. [35-37]
PRP is indicated not only in initial rubeosis but also in late stages of NVG with gonio synechiae.[38] 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. [39-43] In table 5, an outline of treatment guideline of NVG at different stages has been described. [28-33]

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 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.[12]

Medical Management

Anti-glaucoma medication: beta-lockers and carbonic anhydrase is mainstay. 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. [44-49]

Surgical management

Due to more risk of failure, the surgical management is challenging. [50-51]
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. [54-55] Mitomycin c application increase the success rate significantly which may decrease by times. [51-53] 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. [56-63] 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.[64] Endo cyclophotocoagulation with pars plana vitrectomy and PRP has better results.[65] NVG secondary to OIS is should be treated by multidisciplinary approach (cardiology and vascular surgery for carotid arteries imaging and carotid endarterectomy if indicated).[66]

Table 4, Stages of NVG and management
Table 5: Outlines the treatment paradigm of NVG.

Prognosis

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.[67]

Conclusion

NVG is a dreadful condition. Prevention of secondary factors causing retinal hypoxia should be on top priority and thereafter early detection followed by appropriate medical and surgical managements should be undertaken on stages of NVG based on a principle. In cases secondary to ocular ischemic syndrome (OIS), a multidisciplinary approach is required. With new scanning devices and FA the early detection of NVI is possible. Hence NVG could be prevented in early stages and similarly with advent of Anti VEGF and with help of PRP could be managed in early stages too. Diabetic is an principle cause of NVG and it is on global increase.[68] Therefore early detection of PDR , treatment of PDR and follow up for NVI can definitely decrease the prevalence of NVG.

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we also acknowledge the picture of rubeosis iridis collected from web search on https://webeye.ophth.uiowa.edu/eyeforum/atlas/pages/NVI/eyerounds.org

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Table document

Table 1: Conditions mimics NVG are summarized below.[11]

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, 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,

Table 2: Weiss and gold has tries to classify NVI and NVA [19]

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

Table 3: Outline of management protocol of NVG

<table>
<tr><td colspan="3">Neovascular glaucoma</td></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></td></tr>
<tr><td>With pain</td><td>Without pain</td><td rowspan="4">Management of etiological conditions</td></tr>
<tr><td>1. Cycloplegic
2. Cyclophotocoagulation
3. 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>1. Cycloplegic
2. Steroid
3. IOP control</td><td>Corneal edema, cataract, Vitreous hemorrhage and Tractional Retinal Detachment raised with IOP in conditions like</td><td></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>

NVG- Neovascular glaucoma, PL- vision as perception of light, IOP- intra ocular pressur

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- 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

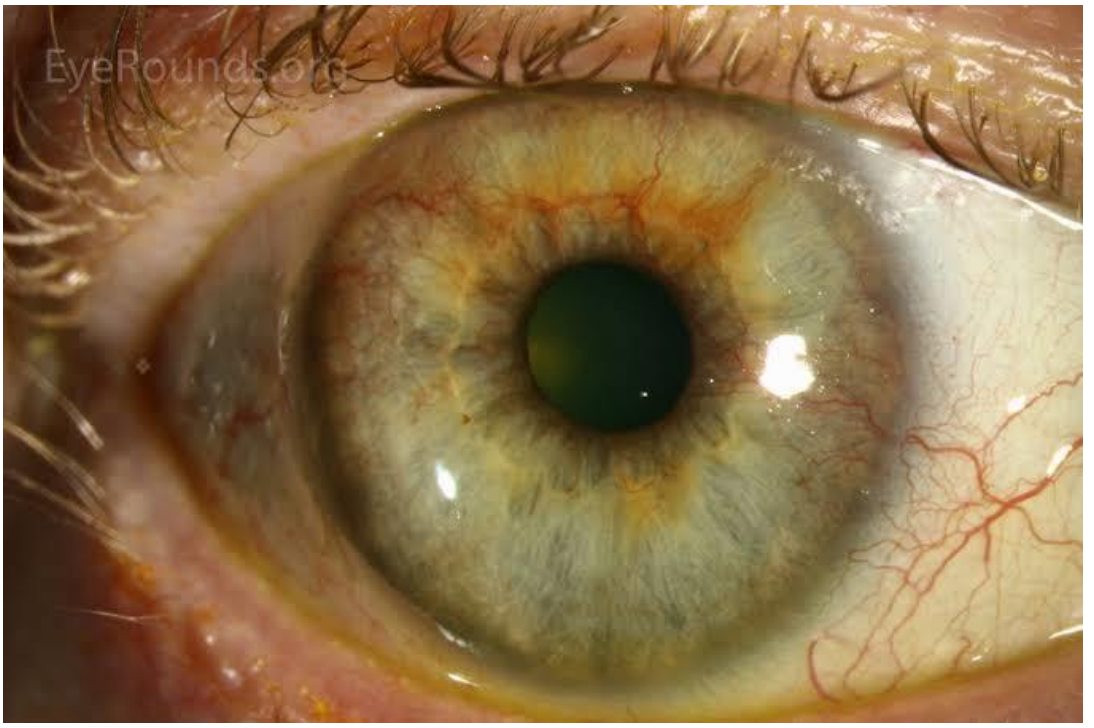

Fig 1. Rubeiosis iridis