Management of Neovascular Glaucoma

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Abstract: Management of NVG remains a therapeutic challenge. The diagnosis of NVG should be made as early as possible if the patient is to be provided the best chance to maintain vision. To achieve this goal, a high index of suspicion, a full ocular examination including undilated gonioscopy, and pupil examination are essential. There are two key aspects to the management of NVG: treatment of the underlying disease process responsible for rubeosis and treatment of the increased IOP. Treatment of rubeosis is directed at the ischemic retina in most cases. Panretinal photocoagulation (PRP) is considered the treatment of choice. However, other modalities such as panretinal cryotherapy, transscleral diode laser retinopexy, and panretinal diathermy have been described. Medical management of NVG consists of IOP-lowering agents, including topical β-adrenergic antagonists, alpha-2 agonists, and topical and oral carbonic anhydrase inhibitors. However, once the angle is synechially closed, medical management becomes unsuccessful and one has to resort to surgical management. Although the ideal surgical procedure has yet to be determined, trabeculectomy with antimetabolite therapy, aqueous shunt implants, and diode laser cyclophotocoagulation are the best current surgical options. Studies have shown VEGF as a key molecule in ocular angiogenesis and direct targeting of VEGF might be another possible therapeutic strategy to treat neovascularization.

Keywords: Neovascular glaucoma, neovascularization of iris, vascular endothelial growth factors, gonioscopy, proliferative diabetic retinopathy, panretinal photocoagulation, trabeculectomy, diode laser cyclophotocoagulation, bevacizumab.

INTRODUCTION

Neovascular glaucoma (NVG) is a serious sequelae of many ocular ischemic conditions, 97% of which are associated with retinal ischemia, the leading causes being central retinal vein occlusion (CRVO) and diabetic retinopathy (DR). Over the past century, our knowledge about NVG has followed an exponential growth curve. It was in 1906 that Coats put our knowledge of NVG on a sound anatomic basis, followed by the works of Salus (1928), Kurz (1937), etc. In 1963 Weiss and colleagues proposed the term NVG, which has since found universal acceptance, while Walton and Grant proposed the term NVI, which was found to be more accurate than rubeosis iridis.

Since the 1960s, there has been a virtual explosion in our knowledge of the pathophysiology of NVG as well as great progress in our ability to treat this disorder. With the elucidation of the major aspects of angiogenesis, we are on the threshold of taking the treatment of NVG to a new level—from treating a disease after its occurrence to its prevention.

PATHOPHYSIOLOGY

Retinal ischemia is the most common and important mechanism in most, if not all, cases that result in the anterior segment changes causing NVG. Only 3% of cases of NVG are caused by inflammation without retinal ischemia.

Ischemia triggers the release of factors that promote new vessel growth. For this process to occur, viable retinal tissue, a low oxygen tension, and venous drainage that allows the accumulation of these factors must be present.

The concept of a diffusible factor that affects the budding of new vessels was proposed initially in 1948. Vascular endothelial growth factor (VEGF), an endothelial cell mitogen, is the best studied and described component of this pathway. Elevated levels of VEGF have been identified in the aqueous humor of patients with rubeosis and NVG. Their level is also higher in patients with diabetic NVG, compared to patients with only proliferative diabetic retinopathy. VEGF is synthesized by several types of retinal cells, but under ischemic conditions, Muller cells are the primary source. Once released, VEGF must reach the iris and the angle for rubeosis to occur. Removal of the lens, especially if the posterior capsule is not left intact, is thus associated with a high incidence of rubeosis.

The growth of fibrovascular tissue over the trabecular meshwork (TM) will initially decrease aqueous outflow. Myofibroblasts, transiently present in new fibrovascular tissue, also proliferate and contract, thereby closing the angle. Corneal endothelial proliferation over the angle also occurs. All these factors result in increased intraocular pressure (IOP).

Multitude of other substances that might be involved in angiogenesis are under investigation. These include insulin-
like growth factors I and II, insulin-like growth factors binding proteins 2 and 3, basic fibroblast growth factor, platelet-derived growth factor, and interleukin 6.

**CLINICAL MANIFESTATIONS**

Although there is a certain amount of overlap, it is convenient to divide NVG into the following three stages:

1. Rubeosis iridis.
2. Secondary open-angle glaucoma.

**Early Stage (Rubeosis Iridis)**

The first visible signs of incipient NVG are tiny tufts of new vessels at the pupillary margin. Unless one maintains a high index of suspicion and looks carefully under high magnification at the slit lamp, it is easy to overlook these vessels, especially in darkly pigmented irises. If a contact gonioscopy is used at the initial examination, even light pressure on the lens is sufficient to collapse these neovascular tufts and render them clinically invisible. The new vessels grow radially over the surface of the iris in an irregular meandering manner towards the angle, sometimes joining dilated blood vessels at the collarette. At this stage, the IOP is normal and the new vessels may regress either spontaneously or with treatment. However, neovascularization of the angle (NVA) can occur with or without neovascularization of the iris (NVI), so a careful gonioscopy is a must in all eyes at high-risk for NVG, even in the absence of pupillary and iris involvement.

As NVI would begin where the greatest aqueous tissue contact occurs, it is important to examine the other passageways for aqueous to enter the AC bypassing the pupil (e.g. the presence of a peripheral iridotomy).

**Weiss and Gold Classification**

As proposed by Weiss and Gold:

- **Iris Grade 1**: Fine surface neovascularization of the pupillary zone of the iris, involving less than 2 quadrants (Fig. 1).
- **Anterior Chamber Angle Grade 1**: Fine neovascular twigs cross scleral spur and ramify on trabecular meshwork, involving less than 2 quadrants.
- **Iris Grade 2**: Surface neovascularization of the pupillary zone of the iris, involving more than 2 quadrants.
- **Anterior Chamber Angle Grade 2**: Neovascular twigs cross scleral spur and ramify on trabecular meshwork, involving more than 2 quadrants.

**Iris Grade 3**: In addition to neovascularization of the pupillary zone, neovascularization of the ciliary zone of the iris and/or ectropion uveae involving 1 to 3 quadrants (Fig. 2).

**Anterior Chamber Angle Grade 3**: In addition to neovascularization of trabecular meshwork, peripheral anterior synechiae (PAS) involving 1 to 3 quadrants (Fig. 3).

**Iris Grade 4**: Neovascularization of the ciliary zone of the iris and/or ectropion uveae involving 3+ quadrants.

**Anterior Chamber Angle Grade 4**: PAS involving 3+ quadrants (Fig. 4).
Early Stage (Secondary Open-angle Glaucoma)

The new vessels continue to grow across the iris surface and join the circumferential ciliary body artery. When these new vessels reach the angle, they cross the ciliary body band and scleral spur on to the TM. Until NVA covers a significant portion of the TM, the IOP may be completely normal. A fibrovascular membrane, which is invisible on gonioscopy, accompanies NVA and may block enough of the TM to raise the IOP and cause a secondary form of open-angle glaucoma.

Advanced Stage

The fibrovascular membrane has a tendency to contract causing peripheral anterior synechiae (PAS). As these PAS coalesce, synechial angle closure occurs.

In the prototypic picture of NVG, the diagnosis is difficult to miss. The main clinical features are:

- Severely reduced visual acuity, often at the CF- to HM-level. The extremely poor vision is due to an edematous cornea and the primary disorder underlying the NVG
- Congestion of the globe and pain.
- Very high IOP (around 60 mm Hg or higher), but in some cases, such as carotid artery obstructive disease, it may be normal or even subnormal.
- Corneal edema, but if the patient is young and the endothelium is healthy, the cornea may remain clear with an IOP as high as 60 mm Hg.
- Aqueous flare due to leakage of proteins from the new iris vessels.
- Severe rubeosis iridis.
- Distortion of the pupil and ectropion uveae due to radial contraction of fibrovascular tissue are late changes. As a corollary, when one sees ectropion uveae in NVG, one can presume that there is synechial angle closure in the same meridian.
- Gonioscopy shows synechial angle closure with inability to see any of the angle structures posterior to Schwalbe line. The picture of a smooth zippered-up line of iridocorneal adhesion is pathognomonic.

Causes of NVG

Relatively frequent causes include:

- Central retinal vein occlusion
- Proliferative diabetic retinopathy
- Carotid artery occlusive disease.

Less frequent causes include:

- Branch retinal vein occlusion
- Central retinal artery occlusion (CRAO)
- Intraocular tumor
- Chronic retinal detachment
- Chronic or severe ocular inflammation
- Ocular ischemic syndrome/Carotid insufficiency
- Anterior segment ischemia (e.g. previous extraocular muscle surgery)
- Sickle cell retinopathy
- Retinopathy of prematurity.

Fluorescein Studies

Iris fluorescein angiography (FA) shows leakage from damaged iris vessels long before new vessels can be detected.
on slit lamp examination. This is due to the production of VEGF, which is also a potent vasopermeability factor – 50,000 times more potent than histamine.17

In pathologic states, fluorescein leakage occurs throughout the iris and persists and increases with time, unlike in the benign forms of capillary incompetence (e.g. pseudoexfoliation). In one study, NVI could be detected in 37% of eyes before the subsequent development of clinically visible new vessels19 (Fig. 5).

In most eyes with NVI, a high index of suspicion with diligent observation makes iris FA unnecessary. But if extensive capillary dropout is noted in fundus angiography in eyes with DR or CRVO, and NVI is not clinically detectable, iris FA should be performed at the same time.

**MANAGEMENT**

There are two key aspects to the management of NVG: treatment of the underlying disease process responsible for rubeosis and treatment of the increased IOP.

**Treatment of Underlying Disease**

**Panretinal Photocoagulation (PRP)**

*Early stage therapy:* The critical aspect is early detection of NVI. Once NVI is discovered, and there is little or no angle involvement, the mainstay in early therapy is PRP. The mechanism by which PRP works is unclear. Since the outer photoreceptor-retinal pigment epithelium complex accounts for the majority of total retinal oxygen consumption, PRP may decrease retinal oxygen demand by destroying this outer layer. This may allow choroidal oxygen to diffuse into the inner retina, decreasing not only inner retinal hypoxia, but also reducing the stimulus for release of angiogenic factors. There is ample documentation that PRP decreases ocular VEGF levels and subsequent regression of the NVI in CRVO20 and PDR.21 However, the results of PRP in CRAO are not as impressive as in CRVO and PDR.22

Striga and coworkers emphasized the need for adequate treatment with PRP.23 Treatment with 1,200 to 1,600 spots resulted in regression of NVI in a significantly higher percentage of eyes, compared with those that received fewer spots. Ohnishi and colleagues24 documented regression of rubeosis in 68% of patients and normalization of IOP in 42% of patients treated with PRP. There is also a higher success rate for glaucoma filtering procedures when PRP is performed.25

*Late stage therapy:* When synechial angle closure has already occurred, it is considered the late stage and the management of glaucoma becomes difficult. If possible, PRP should still be performed to eliminate the stimulus for new vessel formation; otherwise, filtration surgery is more likely to fail. Regression of NVI can occur within days to weeks of completed PRP. At least 1 week and preferably 3 to 4 weeks should elapse between completed PRP and filtration surgery.

**Endophotocoagulation**

It is an effective method of performing intraoperative PRP. It is useful in situations in which it is not possible to perform preoperative PRP, and intraocular surgery (cataract extraction or vitrectomy) must be performed. It can be just as effective as standard photocoagulation, and is now used extensively, especially during vitrectomy.26

**Panretinal Cryotherapy (PRC)**

It is indicated in cases in which the cornea, lens or vitreous is too hazy to allow adequate PRP. A total of 32 to 54 applications is commonly employed under direct visualization until –70ºC is achieved, approximately 5 to 10 seconds, depending on the probe (usually 2.5 mm is used). In a large series, 27 eyes with NVG (9 of which had previous PRP) were treated, and 55% had stabilization or improvement in vision, 55% had reduction of IOP, and 70% had stabilization or regression of NVI after 12 months.27
The pitfall is that PRC produces significantly more inflammation and blood retinal barrier breakdown than does PRP, as shown by vitreous fluorophotometry. Potential complications include traction and exudative retinal detachment (RD) and vitreous hemorrhage.

**Goniophotocoagulation (GP)**

Direct treatment of NVI before development of NVG has been investigated by researchers with mixed results. It was believed that there might be cases in which it might be beneficial before the definitive effect of PRP can manifest itself.

One study evaluated preoperative goniophotocoagulation on the success of filtration surgery, but found no beneficial effect.\(^{28}\) In a limited number of patients in whom it was not possible to perform PRP, GP alone has not proved to be beneficial in preventing synechial angle closure, and, at times, has caused increased inflammation and seemingly more rapid progression of angle NVA. The role of GP in the treatment of NVG is unclear.

**Role of Anti-VEGF Agents**

**Intravitreal Bevacizumab**

Though preoperative PRP has been known to increase surgical success by arresting the stimulus for new vessel growth, its administration may be limited by commonly associated ocular conditions such as poor pupillary dilatation, corneal edema, cataract or vitreous hemorrhage. Also, PRP takes 2 to 3 weeks to have an effect on iris neovascularization. These limitations have given rise to the need for an alternative therapy for the management of patients in whom immediate surgical intervention is required to lower the IOP, or in whom PRP is precluded.

Intravitreal Bevacizumab (IVB) have been shown to cause a dramatic and rapid response in resolution of vascular leakage in age-related macular degeneration and PDR. IVB have likewise been shown to cause marked and rapid regression of anterior segment neovascularization in NVG. It is believed that it might provide “a period of grace paving the way for a more safe and early surgical intervention in the management of NVG till the definitive effect of PRP can manifest.”

Bevacizumab is applied in the dose of 1.25 mg/0.05 ml intravitreally and 0.25 mg/0.02 ml intracameraly.\(^{29}\) Marked regression of iris neovascularization has been noted within a median of 8 days (range 1 to 10 days) in various case reports.\(^{30}\) Although the long-term effectivity is unknown, even a transient effect could be of benefit in the preoperative preparation of filtering surgery for NVG (Fig. 6).

**Treatment of Elevated IOP**

**Medical Therapy**

In the secondary open-angle glaucoma stage, all the standard antiglaucoma medications will be effective to some degree in lowering the IOP, but until PRP is performed, the angle can relentlessly close. With extensive synechial angle closure, any of the medications acting on the aqueous outflow (e.g. pilocarpine, adrenergic agents) are useless and contraindicated as they increase hyperemia and inflammation. Medications that decrease aqueous production, such as topical \(\beta\)-blockers and carbonic anhydrase inhibitors, are beneficial, but do not lower the IOP to a normal range in the face of a closed angle. Prostaglandins may not be very effective in these eyes since the presence of synechiae limits the flow of aqueous via the uveoscleral pathway. Osmotic agents can be used intermittently to clear the cornea enough for treatment or diagnosis.

The two other medication that are of the greatest benefit clinically along with antiglaucoma medications are topical atropine 1% twice per day to decrease ocular congestion, and topical steroids 4 times per day to decrease ocular inflammation.
Conventional Surgery

Trabeculectomy

Filtration surgery in NVG should be reserved in eyes that have potential for useful vision and when the extent of the PAS is >180º. It should be performed only when the eye is quiet; otherwise, intraoperative and postoperative hemorrhages are likely to occur. Also, the presence of active neovascularization may lead to late bleb failure through conjunctival scarring at the filtration site. Using standard filtration techniques with preoperative PRP, surgical success (IOP less than 25 mm Hg on one medication or less) has been reported as 67% 28 and 77%.31

Use of Antifibrotic Agents

With its introduction, the chances of a successful filtration surgery have been significantly increased when combined with retinal ablation procedures. Studies have shown variable results when standard filtering surgery with antifibrotic agents had been done for NVG. One study had a reported success rate of 68% with 5-FU at 3 years.32

In a study33 of 35 eyes who had undergone trabeculectomy with Mitomycin C for NVG due to diabetic retinopathy, the complications encountered in the early postoperative period were hyphema (34.3%), shallow AC (20.0%), and vitreous hemorrhage (22.9%). In another study,34 out of 15 eyes one patient developed hyphema, while another had shallow anterior chamber. One eye also had endocapsular hematoma.

Valve Implant Surgery

When conventional surgery fails or is not possible because of excessive conjunctival scarring, insertion of a drainage device may be indicated.

Mermoud and coworkers35 used Molteno implants in 60 eyes with NVG. They reported a success rate of 62% at one year, but only 10% at five years. In this study, eyes with NVG secondary to central retinal vein occlusion had a worse prognosis compared with eyes with NVG due to diabetic retinopathy.

Sidoti and colleagues,36 using Baerveldt implants in 36 eyes, reported a success rate of close to 80% at one year, but only 56% at 18 months.

The largest reported series of valve implant surgery uses the Krupin-Denver valve.37 To date, 79 eyes with NVG have been operated on, with 67% success in controlling IOP (< 24 mm Hg), with a mean follow-up of 23 months.

Thus, the long-term results of implant surgery are not encouraging. Obstruction of the internal fistula is frequent in NVG by intraocular blood and fibrovascular membranes, which can be treated by combination of the argon and Nd:YAG lasers to pull and cut the iris or membrane away from the opening.

Ciliodesstructive Procedures

In end-stage NVG, when there is total synechial angle closure and no useful vision remaining, there is no indication for surgical intervention, and control of pain becomes the primary therapeutic aim. Ciliodesstructive procedures were widely used before the advent of the antifibrotic agents and the anti-VEGF agents in the management of NVG. Although they may be highly effective in lowering IOP, the visual results are disappointing, especially with cyclocryotherapy (CCT). Sympathetic ophthalmia, RD, anterior segment ischemia, and phthisis have all been reported with cyclocryotherapy.38 Direct laser cyclophotocoagulation seems to have a better control and titration of the ciliary processes destroyed and a lower complication rate, but the percentage of patients with NVG who lose total vision remains high, with long-term vision loss of 46.6% as reported by Shields and Shields.39

Transscleral Cyclophotocoagulation is another method. There is less elevation of IOP in the immediate postoperative period, along with less inflammation and pain than after CCT. With the contact system, there is a report of 140 eyes treated, 45 of which had NVG. An IOP less than 19 mm Hg was achieved in 40% of the eyes with NVG. It was also noted that 50% of the serious complications were in eyes with NVG, including one eye with phthisis and one with traction RD.40

CONCLUSION

Neovascular glaucoma still remains a therapeutic challenge. Despite many advances in the treatment of NVG, visual prognosis remains poor. Early detection of neovascularization and prophylactic treatment with PRP directed at the ischemic retina are key elements in preventing a visually devastating outcome of this disease. Once IOP becomes elevated, successful management of the disease may be extremely difficult. Although the ideal surgical
procedure has yet to be determined, trabeculectomy with antimetabolite therapy, aqueous shunt implants, and diode laser cyclophotocoagulation are the best surgical options. Current research on ocular angiogenesis and the advent of new pharmacological agents with activity against vascular endothelial growth factors have increased our treatment options for combating this serious disease. Bevacizumab may be a valuable addition in the treatment of NVG by hastening the resolution of anterior segment neovascularization and thereby improving the results of glaucoma surgeries.

REFERENCES


“If you think you can, you can. And if you think you can’t, you’re right.”

—Henry Ford