Chapter 15

Neovascular Glaucoma

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Additional information is available at the end of the chapter

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1. Introduction

Iris neovascularization and angle closure glaucoma are serious complications of a number of diseases affecting the eye. Pathologic intraocular neovascularization can be potentially blinding if not detected and treated promptly.

The first report of neovascular glaucoma was made in 1871. It was described as a condition in which the eye developed progressive neovascularization of the iris and lens, elevated intraocular pressure and blindness. First called hemorrhagic glaucoma because of its association with bleeding of the anterior chamber, it has also been called congestive glaucoma, rubeotic glaucoma and diabetic hemorrhagic glaucoma.

During the first descriptions of this type of glaucoma, only clinical findings were mentioned, but in 1906, Coats, described the histological findings of new vessels on the iris of an eye with a history of central retinal vein occlusion. In 1928, Salus, described new vessels on the irises of diabetic patients. In 1937, with the introduction of clinical gonioscopy, the new vessels found in the angle and the histological findings were correlated, explaining the mechanism of angle closure, and in 1963, Weiss and colleagues, proposed the term neovascular glaucoma, which includes the real cause of the rise in intraocular pressure.

2. Etiology

There are many systemic disease and ocular conditions that cause neovascular glaucoma, but they all share a common etiology, which is retinal ischemia, and hypoxia that triggers a

pro-angiogenic cascade that finally causes the growth of defective vessels with altered permeability. There are three common causes of NVG: Proliferative diabetic retinopathy, central retinal vein occlusion and ocular ischemic syndrome.

2.1. Common causes

2.1.1. Proliferative diabetic retinopathy

Neovascular Glaucoma is a late manifestation of proliferative diabetic retinopathy (PDR), although it may occur due to ischemia, before neovascularization of the retina or optic disc are present, the most common presentation is in association with PDR. The time of progression from iris neovascularization (IN) to neovascular glaucoma (NVG) is not well established because in some cases it progresses very rapidly, in others it might remain stable for years or even regress with treatment.

The reported rate of IN is 1-10% among all diabetics and about 64% among patients with PDR. Prevalence of NVG in DM is 2%, but it increases to 21% in PDR where the frequency of IN can be as high as 65%. All of these risk factors plus activation of the inflammation cascade by ocular surgery makes the incidence of NVG, rise to 80%, in eyes after pars plana vitrectomy.

NVG is caused more frequently by diabetes than by retinal vein occlusions in Mexico. The proportion is precisely the opposite as that reported in a classic work (Brown et al. 1984). We found that 114 out of 134 (85%) patients operated with an Ahmed valve for NVG during a 22-month period were diabetic (Albis-Donado et al. 2012).

2.1.2. Central retinal vein occlusion

One third of the central retinal vein occlusion (CRVO) cases are ischemic at presentation, the remaining two thirds are non-ischemic, but with a conversion to ischemic rate of about 10%. NVG is a frequent complication of ischemic central retinal vein occlusion. The larger the area of capillary non-perfusion, the greater the risk of developing NVG, especially during the first 18 months.

In general, the development of NVG in CRVO depends upon the severity and extent of the ischemia, for example, hemi retinal vein occlusion or branch retinal vein occlusion have a lower risk of developing NVG and in either case, only if ischemic. Studies have indicated that at least half of the retina must be ischemic for NVG to develop.

In cases in which the ischemic subtype was not defined, the incidence of NVG at 6 months after the CRVO was 50%. In cases of non-ischemic CRVO, the incidence of NVG was approximately 1% eight to fifteen months after the event. NVG incidence in ischemic CRVO ranged from 23% to 60%, but it has been reported to be as high as 80% over a period of 12 to 15 months.

2.1.3. Ocular ischemic syndrome

Ocular ischemic syndrome is caused by reduced blood flow to the eye, which produces anterior and posterior segment ischemia, resulting in the development of iris and angle neovascularization. This is caused by severe carotid artery occlusion (greater than 90%), occlusive disease of the aortic arch or the ophthalmic artery, and less frequently when the ciliary arteries are involved.

2.2. Uncommon causes

2.2.1. Ocular tumors

The development of NVG has been reported in several ocular tumors such as melanoma, choroidal hemangioma, retinoblastoma, malignant lymphoma and some metastatic tumors. Radiation retinopathy after the treatment of certain tumors has been associated with the development of NVG because irradiation causes retinal capillary non-perfusion and retinal ischemia.

2.2.2. Uveitis

NVG has been reported in both anterior and posterior uveitis. It is thought that inflammation and its related Inflammatory factors may directly cause neovascularization on the iris, angle and retina.

Diseases Associated With Retinal Neovascularization
Diabetes mellitus*
Age-related macular degeneration*
Retinopathy of prematurity*
Central retinal vein occlusion* Branch retinal vein occlusion*
Sickle cell disease*
Systemic lupus erythematosus
Eales' disease
Multiple sclerosis
Distal large artery occlusion
Takayasu's disease
Carotid artery obstruction
Coats' disease
Tumors
Retinal detachment
*Most frequently associated with retinal neovascularization

Table 1. Diseases associated with retinal neovascularization

Diseases Associated With Iris Neovascularization	
Vascular disorders	
Central retinal vein occlusion*	Central retinal artery occlusion
Branch retinal vein occlusion	Carotid occlusive disease
Takayasu's disease	Giant cell arteritis
Cartotid artery ligation	Carotid-cavernous fistula
Leber ciliary aneurysms	Retinopathy of prematurity
Sturge-Weber disease with choroidal hemangioma	
Ocular diseases	
Neovascular glaucoma*	Uveitis
Endophthalmitis	Vogt-Koyanagi syndrome
Retinal detachment	Persistent hyperplastic vitreous
Coats' disease	Eales' disease
Pseudoexfoliation of the lens capsule	
Sympathetic ophthalmia	Surgery and radiation therapy
Retinal detachment surgery	Vitrectomy
Laser coreoplasty	Cataract extraction
Radiation Trauma	
Systemic diseases	
Diabetes mellitus*	Norrie's disease
Sickle cell disease	Neurofibromatosis
Lupus erythematosus	Marfan's syndrome
Neoplastic diseases	
Retinoblastoma*	Melanoma of the choroid
Melanoma of the iris	Metastatic carcinoma
Reticulum cell sarcoma of ciliary body	
*Most frequently associated with iris neovascularization	

Table 2. Diseases Associated With Iris Neovascularization

3. Prevalence and incidence

Overall incidence and prevalence of NVG has not been accurately reported, a retrospective study has shown a prevalence rate of 3.9%. The most common conditions associated with NVG are central retinal vein occlusion (CRVO), proliferative diabetic retinopathy (PDR),

and other conditions such as ocular ischemic syndrome and tumors. Approximately 36% of NVG occurs after CRVO, 32% with PDR, and 13% occurs after carotid artery obstruction. Given that the underlying etiology of developing NVG is some form of retinal ischemia, it is more prevalent in elderly patients who have cardiovascular risk factors such as hypertension and diabetes, and may be more aggressive in those with obstructive sleep apnea syndrome (Shiba et al. 2009 and Shiba et al. 2011).

4. Physiopathology

Salus first observed abnormal vessels in the iris in 1928, calling the condition rubeosis iridis. Neovascularization of the iris (INV) is often followed by NVG, with its associated blindness and pain. (Laatikainen, 1979). The most common conditions that develop NVG as a complication of the disease are Diabetic Retinopathy (DR) and Central Retinal Vein Occlusion (CRVO), both having retinal hypoxia and ischemia as main contributory factor. (Al-Shamsi HN, Dueker DK, et, al. 2009)

Retinal hypoxia-ischemia increases the production of multiple factors: Vascular endothelial grow factor, nitric oxide, inflammatory cytokines, free radicals and accumulation of intracellular glutamate. (Charanjit Kaur et, al. 2008). The mechanism for reaching the critical level of retinal hypoxia-ischemia is different between DR and CRVO, because the first may need years to reach the level of VEGF that can develop INV and NVG, but CRVO could reach that level in only a few weeks.

4.1. Physiopathology of central retinal vein occlusion

Green made the most relevant histopathology study, in our opinion, in 1981. This study showed the natural history and characteristic evolution of thrombi in CRVO. First there is adherence of the thrombus to an area of the vein wall without its endothelium.

Inflammatory cell infiltration becomes prominent as a secondary factor. In early thrombosis, neutrophils may be seen clinging to the wall of the vein. After several weeks, a variable degree of lymphocyte infiltration was present in almost half of their cases. The infiltrate was seen in three places: around the vein (periphlebitis), in the wall of the vein (phlebitis) and/or in the occluded area. Endothelial-cell proliferation is an integral part of the process of organization and recanalization of the thrombus, and it occurs after several days.

In some of the eyes with an interval of a year or more between CRVO and the histologic study, a thick-walled vein with a single channel was present. They believe that these cases represent an old thrombus that now has a single or a main channel of recanalization. (Green, et al.1981)

Rubeosis iridis and NVG had a high prevalence in Green's study, reaching 82.8%. Other authors had previously described the high incidence of rubeosis iridis in CRVO, associated with clinical risk factors such as visual acuity less than 6/60 (20/200), more than 10 cotton-wool spots and/or severe retinal oedema seen by ophthalmoscopy. Some fluorescein angiog-

raphy findings were also described, such as: severe capillary occlusion, prolonged arteriovenous transit time (over 20 seconds), posterior pole or peripheral severe large or small diameter vessel leakage. (Stephen H. Sinclair, Evangelos S. Gragoudas,1979). All these features are signs of hypoxia-ischemia and enhance the production of multiple vascular growth factors, the most important being vascular endothelial growth factor (VEGF).

4.2. Physiopathology of diabetic retinopathy

DR is widely regarded as a microvascular complication of diabetes. Clinically, DR can be classified into non-proliferative DR (NPDR) and proliferative DR (PDR) (Cheung et al., 2010. Remya Robinson, Veluchamy A. Et, al. 2012). In contrast to CRVO, the establishment of hypoxia-ischemia is slow. The transition between subsequent events caused by retinal hypoxia-ischemia in DR is reflected in the clinical classification. The most important factor that causes almost all vascular complications in diabetes mellitus is chronic hyperglycemia, although chronic hypoxia-reperfusion events may play an important role (Shiba et al. 2011).

The pathogenesis of the development of DR is complex and the exact mechanisms by which hyperglycemia initiates the vascular or neuronal alterations in DR have not been completely determined (Curtis et al., 2009; Villarroel et al., 2010; Remya Robinson, Veluchamy A. Et, al. 2012). Chronic hyperglycemia thickens the endothelial basement membrane of the capillaries and produces endothelial damage. Damaged endothelium can't be replaced properly because of perycite disfunction. Pericytes provide vascular stability and control endothelial proliferation, they are essential for the maturation of the developing vasculature.(Hans-Peter Hammes et, al. 2002).

Cellular damage could be caused by several mechanisms such as increased flux through the polyol pathway, production of advanced glycation end-products, increased oxidative stress and activation of the protein kinase C pathway, but many of these potential mechanisms remain as hypotheses. Chronic inflammatory response and the expression of vasoactive factors and cytokines may also play an important role in the pathogenesis of DR. (Remya Robinson, Veluchamy A. Et, al. 2012) In both CRVO and DR a hypoxic-ischemic retinal environment enhances the production of vascular proliferation factors, such as VEGF, in a dose-dependent manner, and the resultant rubeosis iridis is related to the degree of retinopathy, especially in proliferative diabetic retinopathy. (Francesco Bandello, Rosario Brancato, et, al. 1994)

4.3. Vascular Endothelial Growth Factor (VEGF)

One of the most important molecules involved in the pathogenesis of NVG is VEGF. This molecule is an endothelial cell specific angiogenic and vasopermeable factor (Lloyd Paul Aiello, Robert L Avery, et, al. 1994) and a molecule of convergence of various physiopathological mechanisms in both diseases.

VEGF incorporates five ligands (A, B, C, D & Placenta Growth Factor) that bind to three receptor tyrosine kinases (VEGFR-1 to 3). The founding member and the most characterized member is VEGF-A, for its angiogenic and permeability effects. VEGF-A binds to VEGFR-1 and 2, which may explain the properties of each regarding vascular permeability, angiogenesis, and survival. (Will Whitmire, Mohammed MH Al-Gayyar, et, al. 2011).

In the retina, VEGF-A is produced by retinal pigment epithelium (RPE), endothelial cells, pericytes, astrocytes, Muller cells, amacrine, and ganglion cells. (Will Whitmire, Mohammed MH Al-Gayyar, et, al. 2011).

There is a high level of VEGF in the anterior chamber of patients with ischemic CRVO and PDR. A close temporal correlation between aqueous VEGF levels and the degree of iris neovascularization has been demonstrated. (Sohan Singh Hayreh. 2007. Ciro Costagliola, Ugo Cipollone, et, al. 2008)

VEGF enhances the development of new abnormal vessels in the iris (INV) and the associated growth of fibrovascular tissue causes the formation of anterior synechiae and angle closure, which mechanically blocks aqueous humour outflow through the trabecular meshwork and increases intraocular pressure. (Ciro Costagliola, Ugo Cipollone, et, al. 2008)

A histopathological staging of eyes with neovascular glaucoma, according to the formation and extension of fibrovascular tissue in the anterior chamber angle and on the iris surface, has divided the condition into four stages. (Table 3, Figure 1)(Nomura T, Furukawa H, et, al. 1976).

Stage	Characteristics
1	Fibrovascular tissue occurs in the trabecular meshwork. Angle is open.
2	Fibrovascular tissue extends from the trabecular meshwork into the anterior chamber: peripheral anterior synechiae develop because of shrinkage of the fibrovascular tissue within the angle.
3	Fibrovascular tissue spreads on the anterior surface of the iris.
4	A single layer of endothelial cells develops on the surface of the fibrovascular membrane overlying the iris.

Table 3. Histopathological staging of neovascular glaucoma. (Nomura T, Furukawa H, et, al. 1976).

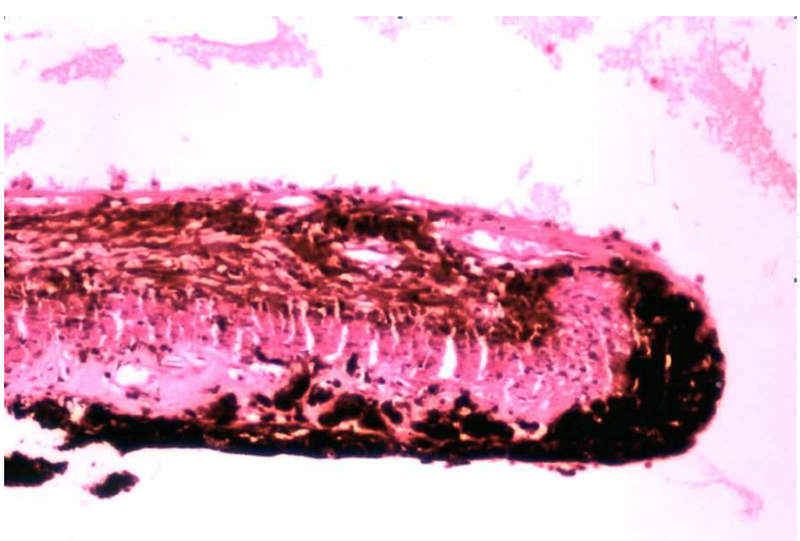

Figure 1. Fibrovascular tissue spreads on the anterior surface of the iris. The tissue pulls the posterior epithelial pigment of the iris over the pupil, causing ectropion uveae. Photography from Pathology Service, Asociación Para Evitar la Ceguera en México.

4.4. Physiopathology of optic nerve damage

VEGF, the main protein in the pathogenesis of NVG, plays a nonvascular and neuroprotective role in adult normal retinas. VEGF-A neutralization can cause neuroretinal cell apoptosis and loss of retinal function without affecting the normal vasculature of the retina. Treatment with VEGF-B protects retinal ganglion cells (RGC) in various models of neurotoxicity. This neuroprotective effect of VEGF-B was attributed to inhibition of pro-apoptotic proteins like p53 and caspases. The detrimental effects in environments with excessive VEGF-A, as happens in PDR, might be explained by excessive levels of peroxynitrite that can inhibit the VEGF-mediated survival signal via tyrosine nitration and subsequent inhibition of key survival proteins in retinal cells. (Will Whitmire, Mohammed MH Al-Gayyar, et, al. 2011).

Ischemia of the optic nerve head is the main reason of optic nerve damage in NVG. As the IOP rises the perfusion pressure decreases, worsening the ischemic condition of the optic nerve and retinal ganglion cells. (Ciro Costagliola, Ugo Cipollone, et, al. 2008).

5. Clinical manifestations and classifications

NVG could be underestimated in early stages of the disease, because there are very few signs that may be easily missed in a routine ophthalmologic exam. It's very important to identify patients who are at risk of developing NVG, specially those that have PDR or ischemic CRVO.

5.1. Early manifestations of neovascular glaucoma

INV could be seen like fine vessels at the pupillary margin in early stages, in fact INV starts in most cases at this level (Figure 2). In a small number of patients, neovascularization could start at the angle, making gonioscopy with an undilated pupil mandatory to all patients at risk of NVG. Careful gonioscopy is essential to detect early angle NV and early anterior synechiae. Other early signs often seen in NVG are flare, and sometimes a few cells, which may erroneously be diagnosed as a sign of uveitis.(Will Whitmire, Mohammed MH Al-Gayyar, et, al. 2011).

5.2. Late manifestations of neovascular glaucoma

Late manifestations of NVG appear when the disease is well established and the IOP is elevated. These include mid-peripheral neovascularization of the iris (Figure 3), neovascularization of the trabecular meshwork when the angle is still open, fibrovascular membrane over the iris and angle, peripheral anterior synechiaes, progressive angle closure and ectropion uvea.

5.3. Fluorescein iris angiogram classification

Fluorescein iris angiogram could help differentiate normal iris vessels from INV. The vascular abnormalities revealed by fluorescein angiography of the iris are: dilated leaking vessels around the pupil, irregular or slow filling of the radial arteries, superficial arborizing neovascularization, usually starting in the angle; and dilatation and leakage of the radial vessels, particularly the arteries. (Leila Laatikainen, 1979). On the basis of angiographic findings, diabetic iridopathy was divided in 4 grades (Table 4).

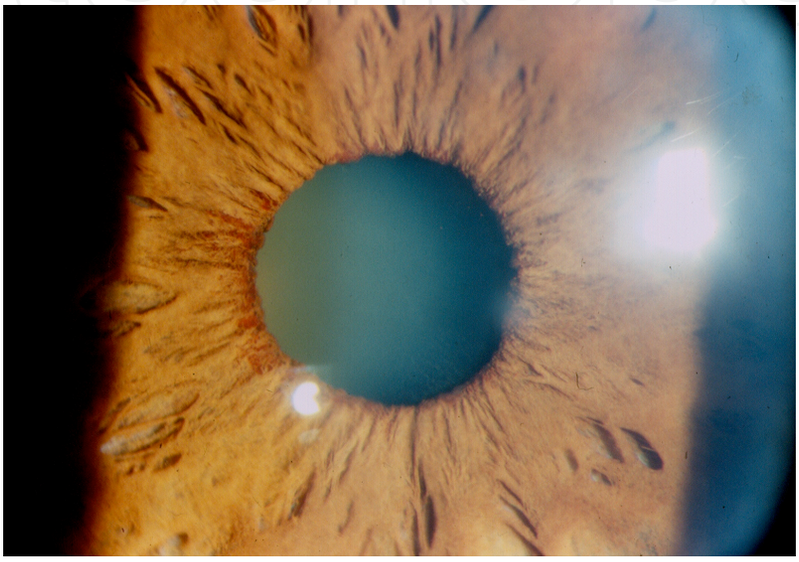

Figure 2. Early rubeosis at the pupillary margin. Photography from the Glaucoma Service, Asociación Para Evitar la Ceguera en México.

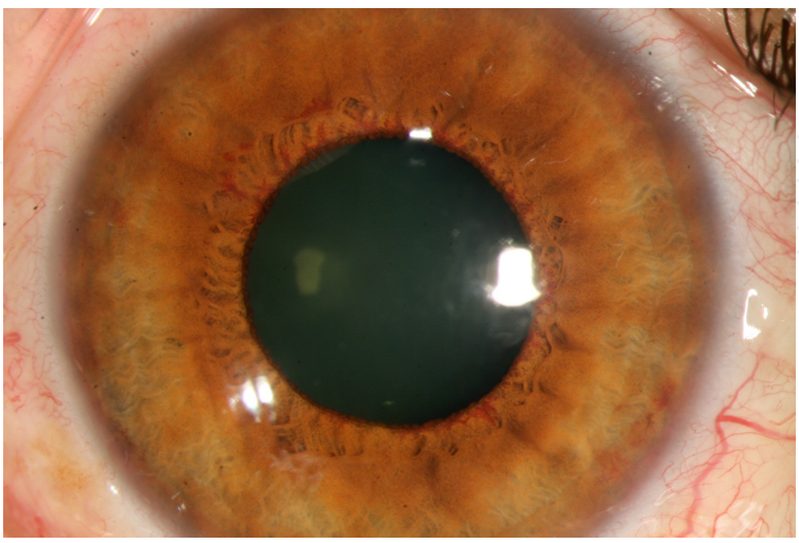

Figure 3. Late rubeosis with mid-peripheral neovascularization of the iris. Photography from the Glaucoma Service, Asociación Para Evitar la Ceguera en México.

Grade	Findings
1	Peripupillary vessel dilatations, Dilated leaking capillaries around the pupil, Irregularities in the filling of radial vessels
2	Early neovascularization of the angle (gonioscopy) Arborizing superficial, early, new vessels Filling of vessels in the early arterial phase and leakage of fluorescein
3	Prominent rubeosis with or without NVG Prominent arborizing new vessels grown out of the angle, covering a larger iris surface Filling of new vessels in early arterial phase Generalized marked leakage
4	Florid rubeosis Complete angle closure New vessels covering the entire iris surface Eversion of the pigmented border of the pupil

Table 4. Classification of rubeosis iridis in diabetic eye disease. (Leila Laatikainen, 1979).

In preproliferative and proliferative DR, iris fluorescein angiogram detection of iris neovessels has a reported sensitivity of 56% and a specificity of 100%. (Francesco Bandello, Rosario Brancato. 1994).

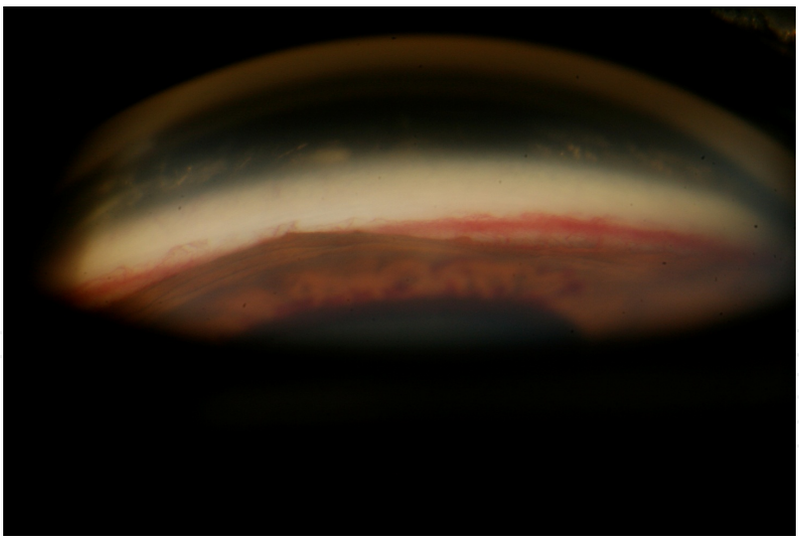

Figure 4. Neovascularization of the trabecular meshwork and anterior peripheral synechiae. Photography from the Glaucoma Service, Asociación Para Evitar la Ceguera en México.

5.4. Clinical classifications

A clinical grading system was also proposed in order to guide pan-retinal photocoagulation therapy, and to select patients who will respond well to the treatment. (Table 5) (Teich SA,

Walsh JB, 1981). This classification is no longer used in our glaucoma service, because treatment has changed with the use of antiangiogenic drugs.

Grade	
0	Absence of iris neovascularization
1	Neovascularization of the pupillary zone less than 2 quadrants
2	Neovascularization of the pupillary zone more than 2 quadrants
3	Neovascularization of the pupillary zone more than 2 quadrants + ectropion uvea or less than 2 quadrants at iris ciliary zone
4	Ectropion uvea and more than 3 quadrants of neovascularization at the iris ciliary zone

Table 5. Clinical grading system of Iris Neovascularization. (Teich SA, Walsh JB, 1981).

In order to differentiate patients for specific treatments, we classify NVG patients in three stages, depending on the characteristics of the angle, the iris and IOP, since the advent of anti-angiogenics and their rapid onset of action has made the amount of iris neovascularization irrelevant in the absence of angle closure. (Castaneda-Díez, García-Aguirre, 2010.)

Grade	Characteristics
1	Early Iris or angle neovascularization with open angle and normal IOP
2	Clinically evident Iris or angle neovascularization with open angle and IOP between 20 and 30 mmHg.
3	Prominent iris and/or angle neovascularization with angle closure, ectropion uvea and IOP over 30 mmHg.

Table 6. Clinical classification of Neovascular Glaucoma. (Castaneda-Díez, García-Aguirre, 2010.)

6. Medical and surgical treatment of neovascular glaucoma

The management of neovascular glaucoma is summarized in figure 5, and depends on whether the angle is open or closed, and whether media are clear or not in order to correctly visualize the retina. Management can be divided in:

Measures to decrease the amount of VEGF produced by the retina, or its effects: Pan-retinal photocoagulation, antiangiogenic drugs and/or pars-plana vitrectomy.

Measures to control intraocular pressure: Medications to reduce intraocular pressure and/or filtering procedures.

6.1. Pan-retinal photocoagulation

Neovascular glaucoma is best treated with prevention. Since retinal ischemia (and VEGF production) is the main predisposing factor for the development of rubeosis iridis, angle neovascularization and NVG, laser photocoagulation to the areas of retinal ischemia continues

to be one of the mainstays of treatment, and should be performed promptly in patients with NVG that have media clear enough for the treatment to be delivered.

The rationale behind pan-retinal photocoagulation (PRP) is to preserve central vision, if possible, by sacrificing peripheral vision. Retinal ablation is thought to reduce the metabolic needs of the hypoxic retina by reducing the total amount of functional retina, so remaining retinal circulation is sufficient to prevent further production of vessel growth factors by the non-ablated retinal tissue.

For the treatment to be applied correctly, a fluorescein angiogram is necessary, in order to determine the presence of areas of retinal non-perfusion and retinal neovascularization. Treatment is applied under pharmacologic mydriasis, using a wide-field contact lens (such as the Super-Quad or Mainster lenses). The parameters for retinal photocoagulation used in the ETDRS are preferred (ETDRS, 1987: A spot diameter of 500 μm, 100 msec duration and enough power to produce a gray-whitish burn on the retina, with a separation between spots of 250 μm), and the whole treatment is delivered in one session, if possible, in order to ablate the largest area of retina possible.

If there are concerns regarding possible complications of an excessive photocoagulation, such as serous retinal detachment or choroidal detachment, reduced fluence parameters may be used (spot diameter of 500 μm, 20 msec duration and power enough to produce a gray-whitish burn on the retina), which have proven to be effective, (Muqit MM, 2011) and to cause less discomfort to the patient (Alvarez-Verduzco O, Garcia-Aguirre G, 2010). These reduced fluence parameters may be used with the Pattern Scan Laser (PaScaL photocoagulator, OptiMedica) (Velez-Montoya R, Guerrero-Naranjo JL, 2010), or with a standard 532 nm laser (Alvarez-Verduzco O, Garcia-Aguirre G, 2010).

PRP has proven to be effective for the prevention of neovascular glaucoma secondary to diabetic retinopathy (The Diabetic Retinopathy Study Research Group, 1976) and central retinal vein occlusion, (Central Vein Occlusion Study Group, 1996) which are the most frequent causal entities. Some concerns have been raised, however, regarding the efficacy of this treatment in central retinal vein occlusion (Hayreh SS, 2007).

The timing of PRP is critical, regarding final visual acuity and NVG prevention. It takes about 4 weeks for PRP to show regression of anterior segment neovascularization (ASNV), and this is thought to depend on the pre-existing levels of vitreous growth factors, mainly vascular endothelial growth factor (VEGF). Once PRP stops the hypoxic retina from producing additional growth factors, existing VEGF and other factors remain in the vitreous for a period during which additional vessel growth may still occur under their influence.

To further complicate matters, a PRP treatment may need 2 or 3 sessions in order to be complete (2000 to 2500 shots), and these sessions are frequently done 2 to 4 weeks apart to avoid excessive inflammation. The period between sessions before a full-treatment has been given is also a period during which further VEGF production may be taking place, especially in the most hypoxic retinas.

6.2. Antiangiogenic drugs

As stated above, VEGF is the main molecule responsible for the development of neovascularization, and therefore neovascular glaucoma. Pan-retinal photocoagulation is very effective for long-term suppression of VEGF, but the decline of such levels tends to take place gradually after treatment, which in theory could leave a time window for the disease to progress. Besides, the need of clear media for PRP treatment of most, if not all, the hypoxic retina may also increase the time before those VEGF levels begin to decrease. To address this problem, anti-VEGF drugs have proven to be of great value.

Since their appearance, both bevacizumab and later ranibizumab (Avastin and Lucentis, Genentech-Roche, South San Francisco, CA) have been used as adjuvants for the treatment of neovascular glaucoma. Injection of a single dose in most cases results in brisk disappearance of iris and/or angle neovascularization (Kahook MY, 2006).

The administration of bevacizumab has been shown to dramatically reduce VEGF levels in the aqueous humor after intracameral injection (Sasamoto Y, 2012) and to reduce edema, fibrin deposition, inflammation and vascular congestion in trabecular meshwork specimens obtained during trabeculectomy performed after intravitreal injection.(Yoshida N, 2011) Several studies have found intravitreal bevacizumab to be of great value as an adjunct to the treatment of neovascular glaucoma of diverse etiologies, causing prompt regression of anterior segment neovascularization (ASNV), and better control of intraocular pressure.(Ehlers JP, 2008. Wakabayashi T, 2008. Yazdani S, 2009. Beutel J. 2010) Good results have also been obtained with ranibizumab (Caujolle JP, 2012), although there are fewer studies in the literature describing the use of this drug.

These agents have also been used for reducing fibrosis in failed filtering blebs (Kahook MY, 2006b) and even for wound modulation in primary trabeculectomies (Horsley et al, 2010) and Ahmed valve implants (Rojo-Arnao, Albis-Donado et al, 2011). A similar trend has been observed with Ranibizumab, a drug designed for intraocular delivery, with an expanding range of on- and off-label indications (Kumar et al, 2012, Mota et al. 2012, Desai et al. 2012, Auila JS, 2012), especially since a potentially deleterious accumulation of Bevacizumab in retinal pigment epithelial cells (Deissler at al. 2012) and approval of Ranibizumab in Europe (and more recently by the FDA) for diabetic macular edema have recently further increased its use despite a greater cost per dose.

As with any procedure, there are complications that have been reported with the use of anti-VEGF drugs. Most of the adverse effects are the ones expected with any intraocular injection, such as subconjunctival hemorrhage, lens damage, or endophthalmitis (Gordon-Angelozzi M, 2009). Other complications, however, are not related to the procedure but to the effect of the drug itself, such as a decrease in the electroretinogram response (Wittström E, 2012), central retinal artery occlusion in eyes with ocular ischemic syndrome (Higashide T, 2012), abrupt angle closure (Canut MI, 2011), or induction of tractional retinal detachment in eyes with abundant retinal neovascular proliferations (Torres-Soriano M, 2009. Arevalo JF, 2008), and should therefore be used with caution in patients at risk.

When anti-angiogenics are used before angle-closure has happened, ASNV regression will prevent IOP elevation, it may revert IOP elevation associated with angle neovessels or at least make it amenable to be medically controlled, and, subsequently, it can also prevent angle-closure and a more aggressive IOP elevation. During this period the media may clear enough for PRP to be completed or initiated.

6.3. Medical management of glaucoma

Once IOP is elevated in NVG cases medical therapy with aqueous production suppressors should be initiated. Topical beta-blockers, topical and oral carbonic anhydrase inhibitors and alpha-2-adrenergic agonists are used, whereas prostaglandin analogues, should not be used because they increase inflammation and may not even lower IOP, unless ASNV has regressed and has a low chance of reappearing, although the exact IOP lowering and safety profile in these patients is still in controversy.

Topical corticosteroids are used concurrently to treat associated inflammation, and may actually help to prevent further angle closure during the initial phase. Atropine may also be used for its cycloplegic effect, but in addition to increasing uveoscleral outflow and maybe lower IOP, it may also help prevent miotic pupillary block, stabilize the blood-aqueous barrier and facilitate posterior segment visualization and treatment. Pilocarpine and other anticholinergic agents are contra-indicated, as they increase inflammation, cause miosis, worsen synechial angle closure and decrease uveoscleral outflow.

In most cases of NVG in closed angle-phases, medical therapy may not be enough to control IOP and prevent visual loss. (Kurt Spiteri Cornish. 2011). If angle-closure has already happened an Ahmed valve-implant is recommended. It may also be needed for around 15% of open-angle phase NVG that remain with elevated IOP, despite anti-angiogenic therapy and adequate PRP. The immediate effect of previously administered intra-vitreous anti-angiogenics during surgery is a reduced tendency for bleeding at the time of tube insertion. On the long term a tendency for better IOP control has been reported (Desai et al. 2012).

6.4. Surgical management of neovascular glaucoma

6.4.1. Tube-shunt surgery

Glaucoma implants have made it possible to save many eyes with NVG from becoming blind, painful eyes. They have also made it possible to preserve useful vision, specially when IOP can be controlled from the day surgery is performed. Using non-valved implants (such as Barveldt or Molteno setons) requires the use of hypotony prevention strategies that have included a two-stage operation, tying off the tube with an absorbable suture or the use of a suture threaded inside the tube.

The idea is to let fibrous tissue grow around the implant, forming a semi-permeable barrier that will eventually absorb excess aqueous. Depending on the chosen strategy, the opening of the implant can be programmed for a couple of weeks in the future for the removable su-

ture or the second stage procedure, or it may happen on its own 3 to 6 weeks later for the absorbable suture.

Since many eyes might still have elevated IOP during this period, damage to the optic nerve may become so advanced as to make the eye legally or even fully blind. A metanalysis comparing restrictive and non-restrictive implants has shown that the mean rate of decrease in visual acuity tends to be lower for the Ahmed valve (19 to 24%) as compared to the other devices (27 to 33%, Hong et al. 2005, Albis-Donado 2009). IOP control from day one and subsequent better visual results have made the Ahmed valve the implant of choice in our hospital for NVG.

Our simpler surgical technique, without the use of a scleral graft patch, has been routinely used for the past 19 years and has been described elsewhere (Gil-Carrasco et al.1998, Albis-Donado, 2006, Albis-Donado et al. 2010). In brief, a fornix-based conjunctival flap is made in the designated quadrant, and then the valve is primed with BSS and fixated 8 to 10 mm behind the limbus with 7-0 silk. A scleral tunnel initiated 3-4 mm from the limbus is constructed using a 22 or 23 G needle, bent as a "Z" to avoid obstruction from the eyelids, brow or lid speculum.

The needle is passed bevel-up under the episclera, in a tangential direction; at the limbus the direction is abruptly changed to make the tunnel parallel to the iris, attempting to enter through the trabecular meshwork. The tube is then trimmed to create a 30-45º bevel and inserted through the tunnel into the anterior chamber, leaving the tip at least 2 mm from the limbus. The conjunctiva is closed using the same 7-0 silk in cooperating adults. Post-operative regimen includes steroid drops in a reducing dose for 3 months, antibiotic drops for 2 weeks, and a cycloplegic for the first month.

The most common complications after an Ahmed valve implant in NVG are hyphema (up to 45% without bevacizumab, and reduced to about 8% with an injection 1 day before the implant), and flat anterior chamber (around 32%, especially in phakic eyes, Albis-Donado et al, 2012).

In the long term the most common complication is elevation of IOP during the so termed hypertensive phase, but that might become permanent, both are thought to occur due to fibrosis around the plate. A tendency for lower rates of IOP elevation with the use of antiangiogenic drugs has been reported (Ehlers JP, 2008. Wakabayashi T, 2008. Yazdani S, 2009. Beutel J. 2010, Rojo-Arnao et al, 2011, Caujolle JP, 2012).

Removal of the fibrous tissue around the implant, adjuvant aqueous suppressants and massage might also be of value for the long-term of IOP control.

6.4.2. Pars plana vitrectomy

A significant proportion of eyes with neovascular glaucoma have significant media opacities that preclude adequate panretinal photocoagulation. In such cases, vitreoretinal surgery plays an important role in its management, since it allows to clear the media opacities, to repair the damaged posterior segment and/or to deliver laser treatment via endophotocoa-

gulation probes. For this reason, several studies have been conducted to explore the usefulness of posterior segment procedures for the treatment of neovascular glaucoma, most of the time performed in conjunction with filtering surgery.

One of the earliest studies was published in 1982 by Sinclair et al, who performed pars plana vitrectomy and lensectomy, and an sclerectomy in 14 eyes with neovascular glaucoma, with poor results. After six months, 64% of eyes had maintained or improved visual acuity, 7% had decreased visual acuity, and 28% lost light perception. This procedure had several complications, including fibrinous vitritis (71%), suprachoroidal hemorrhage (14%), endophthalmitis (7%), retinal detachment (7%) and phthisis bulbi (14%).

Several years later, in 1991, Lloyd et al reported the results of a study in which pars plana vitrectomy and a pars plana Molteno implant were performed in 10 eyes, achieving control of intraocular pressure (21 mmHg or less) in 6 of them. However, three eyes developed vitreous hemorrhage, three developed retinal detachment and two lost light perception.

In 1993, Gandham et al published a study of 20 eyes with glaucoma of difficult management (8 out of which had neovascular glaucoma), that underwent pars plana vitrectomy, and placement of a Molteno or Schocket implant. In six out of the eight eyes (75%), an intraocular pressure of 22 mmHg or less was achieved.

In 1995, Luttrull and Avery reported 22 eyes in which pars plana vitrectomy and a pars plana Molteno implant placement were performed. As an additional procedure, either a ligature of the implant tube with absorbable suture or perfluropropane gas tamponade were performed, in order to avoid postoperative hypotony. With this procedure, an intraocular pressure of 21 mmHg or less was achieved in all eyes, and stabilization or improvement of visual acuity was achieved in 86% of eyes. Among the postoperative complications, retinal detachement was observed in two eyes, and loss of light perception in one eye.

More recently, Faghihi et al in 2007 published their experience in 18 eyes with neovascular glaucoma that underwent pars plana vitrectomy and pars plana Ahmed valve implant. An intraocular pressure of 21 or less was achieved in 13 eyes (72.2%). Light perception was lost in two eyes and two evolved to phthisis bulbi.

In these four studies, the justification to introduce the tube through the pars plana into the vitreous cavity instead of the anterior chamber was to avoid complications such as hyphema or blockage of the tube by a fibrovascular membrane.

6.4.3. Cycloablation

The main goal in the struggle with neovascular glaucoma in blind eyes is to control intraocular pressure (IOP) and pain. (A Janićijević-Petrović M, 2012). In one prospective study the average value of IOP and eyeball pain intensity was significantly lower after cyclocryocoagulation. Cyclocryocoagulation could be a good method in the treatment of uncontrolled elevated IOP and pain of progressive NVG resistant to medical and surgical treatment, but does not have any effect on the improvement of sight in these patients. (Kovacić Z, Ivanisević M, 2004)

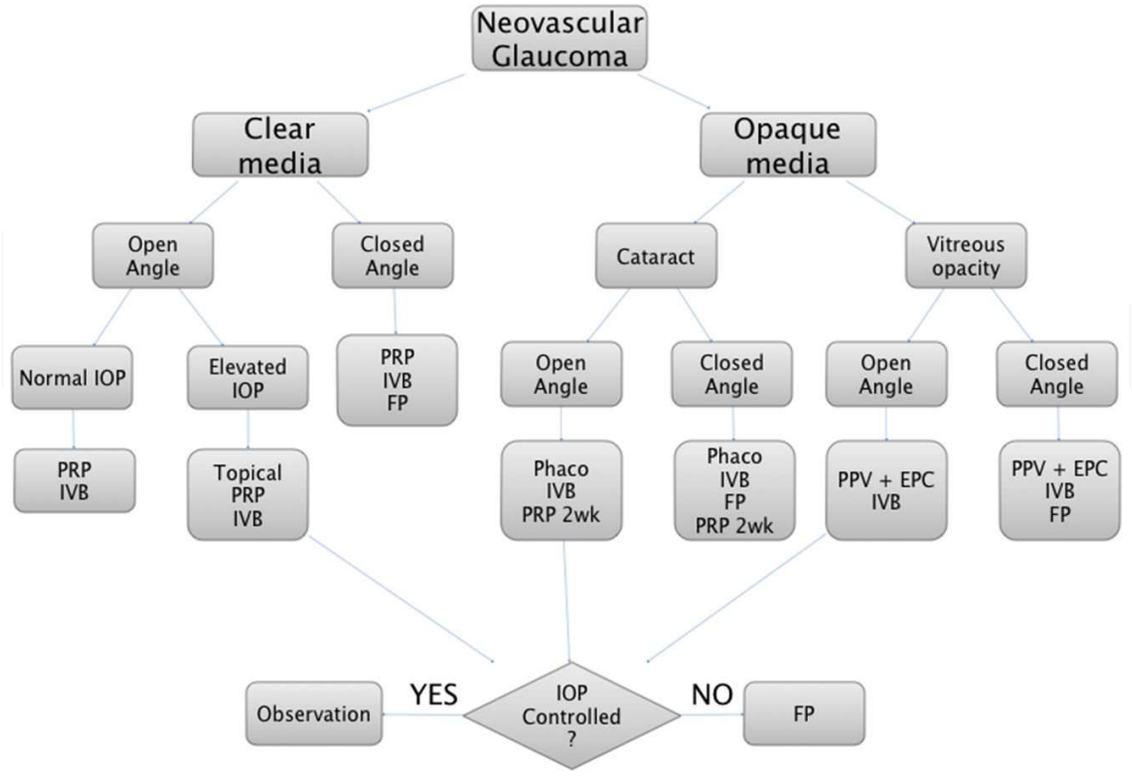

Figure 5. Management of Neovascular Glaucoma. IOP: Intraocular pressure; PRP: Panretinal photocoagulation; IVB: Intravitreal bevacizumab; Topical IOP lowering drugs; FP: Filtering procedure (Ahmed valve); PRP 2wk: Panretinal photocoagulation 2 weeks after the procedure PPV+EPC: Pars plana vitrectomy and endophotocoagulation.

7. Conclusions

The physiopathology of NVG involves various biochemical and biological mechanisms that result in the presence of abnormal vessels that lead to the clinical forms of the disease. This natural history can be modified and steered into a more appropriate and less devastating behavior, depending on the sagacity of the physician and the commitment that the patient has to his/her own condition.

One fundamental aspect of NVG management is the treatment of the underlying condition that caused it. Uncontrolled diabetes, systemic hypertension, vascular diseases, and even primary open angle glaucoma are all modifiable factors that may reduce the incidence of NVG. Periodic ophthalmology visits for patients at risk should be part of their primary care, especially since the prevalence of these systemic conditions seems to be on the rise.

What used to be a condition that was a synonym for irreversible, painful blindness is now expected to be controllable to a degree compatible with useful vision, but through a challenging course of treatment.

Three strategies for preserving vision have increasingly improved the visual prognosis in NVG patients. First was the advent of Panretinal Photocoagulation, when done on time prevented or treated the worst cases of NVG.

The second strategy, and probably the most pivotal turning point, was the arrival of Ahmed valves, permitting control of IOP from day 1, and, in conjunction with PRP, preserving useful vision for the first time without the frequent failures of trabeculectomies. In our initial series (Gil-Carrasco et al. 1997) 137 NVG eyes had a preoperative IOP of 36.7 (SD 11.2) and it lowered to 13.7 (SD 3.4), around 80% were successful at 12 months. Shunt devices have gained in popularity for the management of NVG.

The third and newest strategy has been the incorporation of anti-angiogenic agents from the beginning of this century. Our group performed a prospective study on the use of 2.5 mg of intravitreal Bevacizumab plus PRP in 36 patients who had rubeosis iridis (group A), NVG in open-angle phase (Group B) or NVG with at least 180 degrees of angle closure (Group C).

At 1 week all eyes had regression of all visible anterior segment neovascularization. Additionally in group B, survival of adequate IOP control using only topical medications, without progressing to closed-angle phase, was 90% at 3 months, 81% at 6 months, and 70.9% at 9, 12 and 18 months. All eyes in group C had an Ahmed valve implant (AVI) within 96 hours of the intravitreal injection without serious complications, observing only scant intraoperative bleeding in one eye and a 1 mm hyphema in 2 other eyes on the first postoperative day. Kaplan-Meier analysis of group C showed survival of post-AVI IOP control, without further interventions, of 100% at 6 months, 85.7% at 9,12 and 18 months of follow-up. Survival rate for neovessel-free anterior segment was 75%, 57.7% and 62.5% at 18 months in groups A, B and C, respectively.

We concluded that Preoperative intravitreal Bevacizumab has an important role as an adjuvant to pan-retinal photocoagulation in neovessels regression, controlling IOP and avoiding angle-closure in open-angle NVG, and for reducing bleeding after Ahmed Valve implantation.

A recent review of 912 Ahmed valve implants without a patch, followed for up to 16 years at our hospital found a 49% success rate for avoiding blindness and maintaining IOP under 21 mmHg. There were 363 NVG cases (39.8%), by far the most frequent indication for Ahmed valve implants and most of them associated with diabetic retinopathy (Gil-Carrasco et al. 2012).

The combination of Ahmed valve implants, anti-angiogenics and full PRP, plus topical anti-glaucoma medications as needed, has become the spearhead in the management of neovascular glaucoma at our institution. New surgical approaches for NVG and a better understanding of the disease offer an encouraging perspective for the visual prognosis of these patients.

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