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Neovascular Glaucoma

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Summary: Neovascular glaucoma is an aggressive form of secondary angle-closure glaucoma that can potentially lead to blindness. It is characterized by neovascularization of the iris and the drainage angle. The proliferation of fibrovascular tissue within the drainage angle leads to the formation of peripheral anterior synechiae and an increase in intraocular pressure. Neovascular glaucoma develops as a consequence of ischemia and hypoxia in the posterior segment of the eye. The ischemic retina produces pro-angiogenic factors. The most important factor in the process of neovascularization is vascular endothelial growth factor. The most common underlying causes of neovascular glaucoma are diabetic retinopathy, central retinal vein occlusion, and ocular ischemic syndrome. The course of neovascular glaucoma can be divided into four stages: pre-rubeosis stage, iris rubeosis, secondary open-angle glaucoma, and secondary angle-closure glaucoma. Management of neovascular glaucoma focuses on treating retinal ischemia, controlling neovascularization, and reducing intraocular pressure. The aim of treatment is to prevent vision loss through panretinal photocoagulation, intravitreal and intracameral anti-VEGF injections, and glaucoma treatment, including pharmacological therapy and surgical procedures. It is essential to address the underlying disease.

Key words: neovascular glaucoma, secondary angle-closure glaucoma, neovascularization of the drainage angle, ischemia of the eye.

Introduction

Neovascular glaucoma (NVG) is a severe and potentially blinding form of secondary angle-closure glaucoma. It arises from conditions marked by retinal ischemia, ischemia of the entire ocular globe, or intraocular inflammation. The most common underlying causes include diabetic retinopathy, central retinal vein occlusion (CRVO), branch retinal vein occlusion (BRVO), and ocular ischemic syndrome. The disease is characterized by branching blood vessels on the surface of the iris, the pupillary margin, and the trabecular meshwork, accompanied by the formation of a fibrous membrane [1]. The development of peripheral anterior synechiae in the drainage angle ultimately leads to secondary angle-closure glaucoma.

Rubeosis was first described by Coats in 1906 in a patient with CRVO. The term neovascular glaucoma (NVG) was introduced by Weiss *et al*. in 1963, who linked elevated intraocular pressure (IOP) to the formation of new blood vessels and the proliferation of fibrous tissue [2].

The incidence of NVG is low, ranging from 0.01% to 0.12% in the general population. It accounts for 3.9% of all types of glaucoma and 9–17.4% of all secondary glaucoma cases. The incidence of NVG increases with the prevalence of proliferative diabetic retinopathy [3].

The aim of this paper is to discuss this condition, with emphasis on its pathogenesis, causes, clinical manifestations, and current treatment approaches.

Pathogenesis

A wide range of ocular and systemic conditions can contribute to the development of neovascularization of the iris and the drainage angle. The pathogenesis of neovascular glaucoma is rooted in ischemia and hypoxia of ocular tissues. As a consequence, the balance between pro-angiogenic and anti-angiogenic factors is disrupted, leading to the development of new pathological blood vessels [4]. The most important pro-angiogenic factors include vascular endothelial growth factor (VEGF), insulin-like growth factor 1 (IGF-1), interleukin 6 (IL-6), platelet-derived growth factor (PDGF), hepatocyte growth factor (HGF), and tumor necrosis factor (TNF) [4, 5]. All these factors may represent potential therapeutic targets in the management of neovascular glaucoma; however, further studies are required [6]. In the posterior pole, pro-angiogenic factors induce the development of ischemic proliferative retinopathy. These factors then diffuse with the aqueous humor into the anterior segment, promoting neovascularization of the iris and the drainage angle. Procedures that reduce barriers to the spread of pro-angiogenic factors toward the anterior segment, such as lensectomy or Nd:YAG capsulotomy, increase the risk of developing NVG [5].

VEGF plays a central role in the process of neovascularization. The VEGF family includes VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E, and placental growth factor (PlGF), with VEGF-A being the key mediator in the process of angiogenesis. Each member of the VEGF family binds to one or more receptors: VEGFR1, VEGFR2, and VEGFR3, which belong to the transmembrane tyrosine kinase receptor family [6]. Upon binding to its receptor on the surface of vascular endothelial cells, VEGF triggers activation, proliferation, and migration of endothelial cells, promotes inflammation, facilitates leukocyte adhesion to the endothelial cell surface, increases vascular permeability, and disrupts the blood-retinal barrier [5]. VEGF is produced by various retinal cells (including Müller cells, retinal pigment epithelial cells, ganglion cells, and pericytes) as well as by non-pigmented epithelial cells of the ciliary body [4]. In patients with neovascular glaucoma, the ciliary body serves as a key site of VEGF synthesis, making it a novel therapeutic target in cases where panretinal photocoagulation yields a poor response [6].

Transforming growth factor beta (TGF-β) and fibroblast growth factor (FGF) stimulate fibroblast proliferation and the formation of a fibrovascular membrane on the surface of the iris and within the drainage angle [7]. As this membrane contracts, peripheral anterior synechiae (PAS) begin to form, gradually reducing the flow of aqueous humor through the trabecular meshwork. The resulting rise in intraocular pressure damages the optic nerve, initially leading to secondary open-angle glaucoma. Progressive closure of the drainage angle by PAS ultimately results in the development of secondary angle-closure glaucoma.

Causes

Various ocular and systemic conditions may contribute to the development of NVG. They are typically associated with exten-

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sive retinal ischemia. In 75% of cases, NVG arises from diabetic retinopathy (DR) (33%), ischemic CRVO, or ocular ischemic syndrome (OIS) (13%) [4].

Approximately 60% of patients with ischemic CRVO will develop neovascularization in the anterior segment within a period ranging from a few weeks to two years [8]. The risk of NVG increases proportionally to the area of the retina affected by ischemia. NVG most commonly develops 8–15 weeks after a CRVO episode, with an average onset at three months, hence the term 'hundred-day glaucoma'. The ischemic form of CRVO is defined as a retinal ischemic area exceeding ten optic disc areas on fluorescein angiography. NVG may also occur in non-ischemic CRVO, particularly when DR or OIS coexist. Neovascularization of the iris (NVI) develops in 10% of non-ischemic cases [5]. The risk of progression from non-ischemic CRVO to the ischemic form is 30% [9].

In diabetic retinopathy, NVI occurs in 1–17% of cases and is considered a sign of advanced disease [4]. NVI is more common in proliferative diabetic retinopathy (PDR), affecting approximately 65% of patients, with glaucoma developing in 5–8% of these cases. The development of NVI in eyes with non-proliferative diabetic retinopathy, without significant retinal ischemia, may suggest the presence of other coexisting conditions. Vitrectomy and lensectomy significantly increase the risk of NVG development, as these procedures facilitate the migration of pro-angiogenic factors toward the anterior segment [5].

The average age at NVG onset in diabetes is significantly lower than in CRVO. The interval between retinal ischemia and the development of NVI and NVG is longer in patients with diabetes than in those with CRVO. NV and NVG associated with diabetes are less aggressive than those observed in CRVO [5].

Other causes of NVG include retinal ischemic conditions such as central retinal artery occlusion (CRAO), persistent retinal detachment, and Coats disease; systemic diseases like giant cell arteritis and Takayasu arteritis; ocular inflammatory conditions including endophthalmitis, chronic uveitis, and retinal vasculitis; intraocular tumors such as choroidal melanoma, retinoblastoma, and metastatic lesions; and ophthalmic procedures (cataract surgery, vitrectomy, and radiotherapy) [4].

Clinical course

Neovascular glaucoma clinically presents with conjunctival hyperemia, ocular pain, reduced visual acuity, and elevated IOP. In its early stages, the condition may be asymptomatic.

The first sign of NVG, visible during slit-lamp examination, is neovascularization of the iris. NVI most commonly begins at the pupillary margin and appears as small, fine, tortuous, and irregular tufts of blood vessels. In some cases, NVI may originate on the surface or periphery of the iris, as well as at the edge of an Nd:YAG iridotomy. New pathological vessels should be differentiated from normal iris vessels, which form a radial vascular pattern connecting the major and minor arterial circles of the iris [10]. Once NVI is identified, gonioscopy should be performed to assess for neovascularization of the angle (NVA). NVA appears as fine blood vessels crossing the scleral spur and proliferating over the trabecular meshwork. In rare cases, NVA may develop without concurrent NVI, or even precede its onset. It is important to consider this in the context of CRVO, where in 10% of cases neovascularization may first appear in the drainage angle and only later involve the iris [6]. Among other reasons, this is why gonioscopy should always be performed. To visualize leakage from vessels at the pupillary margin before it becomes clinically apparent during slit-lamp examination, fluorescein angiography is recommended during the prerubeosis stage [4]. In advanced cases, contraction of the fibrovascular membrane on the surface of the iris may lead to eversion of the iris pigment epithelium (ectropion uveae) (Fig. 1, 2) [11].

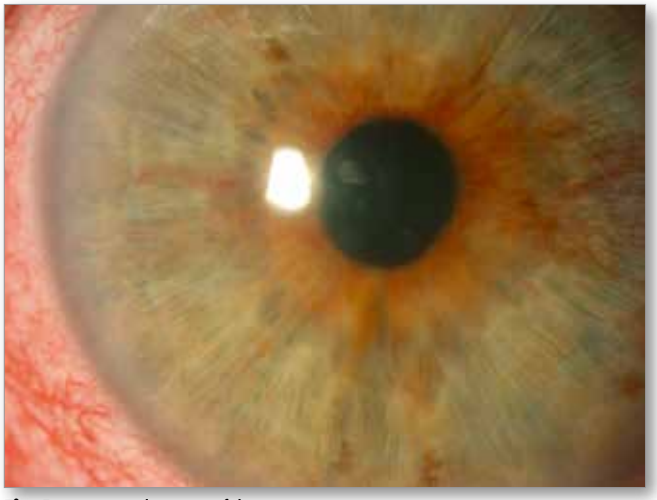

Fig. 1. Neovascularisation of the iris.

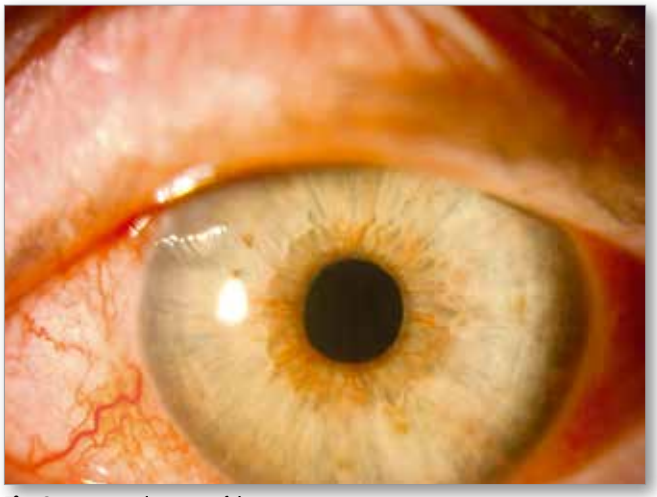

Fig. 2. Neovascularisation of the iris.

The IOP is elevated – often exceeding 50 mmHg – and resistant to treatment. It may cause ocular pain, headache, nausea, and vomiting. Elevated IOP often leads to corneal edema, which can prevent gonioscopic examination.

Visual acuity in patients with NVG is frequently very poor, limited to counting fingers or light perception.

Slit-lamp examination may reveal hemorrhage or inflammatory reaction in the anterior chamber. Inflammation in the anterior

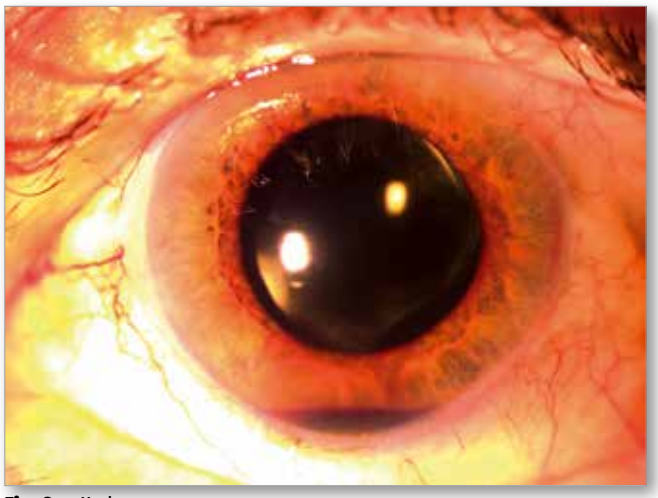

Fig. 3. Hyphema.

chamber must be differentiated from uveitis. Slit-lamp examination also reveals conjunctival injection, corneal edema, rubeosis, ectropion uveae, and an abnormal pupillary light reflex (RAPD – relative afferent pupillary defect) (Fig. 3) [6].

Fundus examination often identifies the underlying cause of NVG: diabetic retinopathy, CRVO/BRVO, ocular ischemic syndrome, or persistent retinal detachment.

Clinically, the course of NVG can be divided into four stages.

1. **Prerubeosis stage** – neovascularization of the iris and the drainage angle is not yet visible. IOP remains within normal limits. Ophthalmic examination may help identify the underlying cause of retinal ischemia, such as diabetic retinopathy, CRVO, BRVO, and OIS. Fluorescein angiography reveals leakage from vessels at the pupillary margin. Intervention at this stage offers the greatest chance of preventing the development of NVG [7].
2. **Iris rubeosis stage** – new pathological blood vessels first appear at the pupillary margin and then spread across the surface of the iris. Neovascularization may also be present in the drainage angle. Gonioscopy reveals new vessels crossing the scleral spur, while the angle remains open. IOP remains within normal limits [7].
3. **Secondary open-angle glaucoma stage** – the development of a fibrovascular membrane on the surface of the iris and within the drainage angle reduces aqueous humor outflow through the trabecular meshwork, leading to elevated IOP and optic nerve damage [7].
4. **Secondary closed-angle glaucoma stage** – contraction of the fibrovascular membrane leads to the formation of peripheral anterior synechiae, which close the drainage angle. IOP is often markedly elevated, typically ranging from 50 to 70 mmHg (Fig. 4, 5) [7].

Fig. 4. Neovascularisation of the angle.

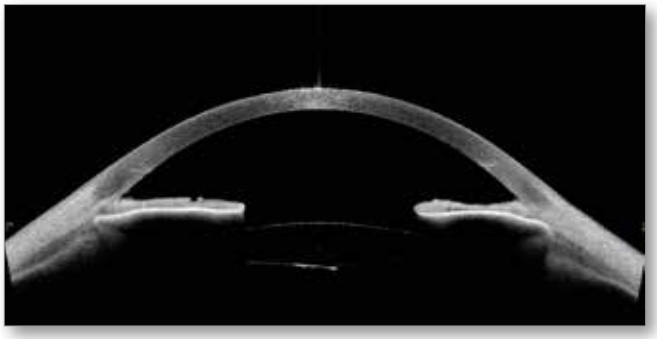

Fig. 5. AS-OCT neovasularistaion of the angle.

Treatment

Treatment of neovascular glaucoma is challenging and requires collaboration between a retinal specialist and a glaucoma specialist. Management must address the following aspects:

1. treatment of the ischemic retina: panretinal photocoagulation and intravitreal injections of anti-VEGF agents;
2. control of IOP: topical and systemic IOP-lowering medications, surgical procedures;
3. control of inflammation;
4. treatment of the underlying disease.

Panretinal photocoagulation (PRP)

PRP is the primary treatment for diagnosed retinal ischemia and should be performed as soon as possible. In cases of NVG, 1200–1600 burns are recommended, each with a spot size of 500 μm. Treatment should be administered over 1–3 sessions, spaced 5–7 days apart [4]. The purpose of PRP is to eliminate ischemic regions of the retina, which decreases retinal oxygen demand and inhibits the production of VEGF, IL-6, and other pro-angiogenic factors. If fundus visualization is poor, cryotherapy or vitrectomy with endolaser should be considered. These procedures may be combined with intravitreal anti-VEGF injections. In patients with elevated intraocular pressure, IOP-lowering medications should be continued after PRP until pressure normalizes due to regression of neovascularization [6].

Anti-VEGF agents

Anti-VEGF agents used in the treatment of neovascular glaucoma (NVG) include bevacizumab, ranibizumab, aflibercept, brolucizumab, and conbercept. They induce rapid regression of neovascularization in the anterior segment and lower IOP, often within a few days. However, their effect is only temporary, typically lasting 4–6 weeks. Moreover, anti-VEGF agents do not act on the fibrovascular membrane that occludes the drainage angle [6]. Due to these limitations, anti-VEGF therapy should be combined with panretinal photocoagulation and surgical interventions.

Bevacizumab (Avastin)

Bevacizumab is a recombinant human monoclonal antibody. It inhibits neovascularization by inactivating all biologically active isoforms of VEGF-A [6]. Studies have shown significant regression of NVI, NVA, as well as IOP reduction as early as one week after bevacizumab injection administered either into the vitreous chamber or the anterior chamber [12]. Unfortunately, the effect of the drug is short-lived.

Ranibizumab (Lucentis)

Ranibizumab is a fragment of a recombinant humanized monoclonal antibody that binds and inhibits VEGF-A. It is a Fab fragment, unlike bevacizumab, which is a full-length antibody [6]. Studies have demonstrated a beneficial effect on intraocular pressure reduction when ranibizumab therapy is combined with trabeculectomy [13].

Aflibercept (Eylea)

Aflibercept, also known as VEGF-TRAP, is a recombinant fusion protein. It consists of the Fc fragment of human IgG1 and the extracellular domains of human VEGFR-1 and VEGFR-2. Aflibercept binds VEGF-A, VEGF-B, and PlGF with greater affinity than their native receptors [14].

Brolucizumab (Beovu)

Brolucizumab is a humanized single-chain variable fragment (scFv) of a monoclonal antibody. It strongly binds all isoforms of VEGF-A. Its small molecular weight allows for faster penetration

into the retina compared to other anti-VEGF agents. Determining brolucizumab's efficacy in the treatment of NVG requires further studies [6, 7].

IOP-lowering medications

Both topical and systemic agents are used in the treatment of NVG. Topical medications that reduce aqueous humor production include carbonic anhydrase inhibitors, beta-blockers, and alpha-2 agonists. Prostaglandin analogues and anticholinergic agents (e.g., pilocarpine) are generally not recommended in NVG, as they may exacerbate inflammation [6]. Prostaglandin analogues may be considered when IOP cannot be controlled with other medications; however, their effectiveness in NVG remains limited. Anticholinergic agents may predispose patients to the formation of posterior synechiae and reduce aqueous outflow due to anterior displacement of the iris-lens diaphragm [15]. Hyperosmotic agents such as mannitol and glycerol may be used for short-term IOP reduction.

Surgical treatment

Surgical methods used in the treatment of NVG include trabeculectomy, glaucoma drainage devices (GDDs), cyclophotocoagulation (CPC), and vitrectomy combined with endolaser. Approximately 50% of eyes affected by NVG require surgical intervention to achieve adequate IOP control [16].

Trabeculectomy

Trabeculectomy involves creating an artificial filtration fistula connecting the anterior chamber to the subconjunctival space. This establishes an additional outflow pathway for aqueous humor. Unfortunately, in cases of NVG, trabeculectomy is associated with a high failure rate, primarily due to intensified healing processes within the fistula and its subsequent closure [6, 7]. The effectiveness of the procedure may be improved through the use of antimetabolites (MMC – mitomycin C, 5-FU – 5-fluorouracil), anti-VEGF injections, and panretinal photocoagulation. Mitomycin C (MMC) has been shown to increase surgical success rates from 62.6% to 81.2% within the first year. Unfortunately, efficacy declines gradually over time, reaching 51.3% after five years [17, 18]. Preoperative bevacizumab injection reduces the risk of anterior chamber bleeding and improves postoperative outcomes [6].

Glaucoma drainage devices (GDDs)

GDDs are used when trabeculectomy proves ineffective or carries a high risk of failure due to conjunctival scarring and inflammation. GDDs can be divided into two categories: valved (e.g., Ahmed Glaucoma Valve – AGV) and non-valved (e.g., Baerveldt, Molteno). In NVG, valved systems are generally preferred. They provide rapid IOP reduction and carry a lower risk of hypotony and iris damage [6]. However, the effectiveness of GDDs is lower in NVG compared to other types of glaucoma [4].

Combining Ahmed valve implantation with anti-VEGF injections has a beneficial effect on postoperative IOP control. This approach improves surgical success, reduces the need for postoperative antiglaucoma drops, lowers VEGF concentration in aqueous humor, and decreases the risk of anterior chamber bleeding. Studies have shown comparable efficacy between trabeculectomy with mitomycin C and anti-VEGF injection (55%) and Ahmed valve implantation (60%) two years postoperatively (Fig. 6) [19].

Fig. 6. Ahmed glaucoma valve and double trabeculektomy.

Cyclophotocoagulation (CPC)

CPC is used in the management of treatment-resistant NVG when other surgical and pharmacological methods fail to adequately lower IOP. It works by reducing aqueous humor production through destruction of the ciliary body's secretory epithelium using a diode laser. Two types of CPC are distinguished: transscleral and endoscopic. The reported efficacy of CPC is 75% at three months and 66% at six months. Complications of the procedure may include anterior chamber bleeding, chronic iritis, corneal edema, and ocular atrophy [4, 7].

Prognosis

Prognosis in NVG remains uncertain. Prevention, early detection, and timely intervention in the initial stages are crucial. Equally important is the management of the underlying disease. Unfortunately, NVG is often resistant to all forms of therapy, leading to irreversible vision loss. In addition, persistently elevated IOP causes chronic ocular pain. In such cases, enucleation or evisceration of the affected eye may need to be considered.

Conclusions

NVG is a relatively rare form of glaucoma, yet it warrants attention due to its potentially severe course and resistance to treatment, which may result in irreversible blindness and chronic ocular pain. NVG arises as a consequence of ocular ischemia (CRVO, PDR, OIS) which triggers neovascularization in the anterior segment of the eye. Progressive closure of the drainage angle by peripheral anterior synechiae leads to elevated IOP and subsequent optic nerve damage. Effective management of the underlying condition, control of IOP, PRP, and anti-angiogenic therapy are essential components of NVG management. The introduction of anti-VEGF agents into ophthalmology has significantly improved patient prognosis; however their therapeutic effects are short-lived. When pharmacological therapy fails to achieve sufficient IOP reduction, surgical intervention becomes necessary.

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