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Neovascular Glaucoma as a Complication of Diabetic Retinopathy – a Review

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Summary: Neovascular glaucoma is a disease entity marked by pathological angiogenesis within the iris and drainage angle, secondary to retinal ischemia. The clinical course typically progresses through three successive stages: rubeosis iridis, secondary open-angle glaucoma, and, ultimately, secondary angle-closure glaucoma accompanied by significantly elevated intraocular pressure and severe ocular pain. This condition poses a substantial therapeutic challenge, as it most often arises following acute ischemic events – such as central retinal vein occlusion – or during advanced stages of chronic retinal vascular diseases, primarily diabetic retinopathy. Although neovascular glaucoma is a relatively uncommon complication, if left untreated, it can lead to blindness. Preventive strategies focus on managing the underlying disease, as the metabolic disturbances associated with diabetes mellitus contribute to the progression of vascular changes within the eye. Diagnostic management is based on the early detection of neovascularization. Slit-lamp examination, tonometry, gonioscopy, and imaging studies constitute the standard of care. The prognosis is serious, and the range of therapeutic options is broad – from conservative treatment to surgical intervention – allowing for considerable individualization of therapy. Importantly, therapeutic success depends not only on controlling intraocular pressure, but above all on achieving metabolic stabilization of the patient's diabetes.

Key words: neovascular glaucoma, secondary glaucoma, diabetes, diabetic retinopathy.

Introduction

Diabetes mellitus (DM) and its complications are among the most challenging lifestyle-related health conditions of the 21st century. Despite extensive health promotion and preventive efforts, statistics remain concerning, with long-term trends continuing to rise. According to 2024 data from the National Health Fund, an estimated 3.4 million individuals in Poland are affected by DM, including approximately 25,000 children [1, 2]. Of these, nearly 1 million are unaware of their condition. Poor metabolic control of diabetes increases the risk of numerous macrovascular and microvascular complications, one of which is diabetic retinopathy (DR). This microangiopathy affects approximately one in three patients with DM and is among the leading causes of vision loss worldwide in working-age adults [3, 4]. Initially completely asymptomatic, DR may progress over time – particularly in the context of poor metabolic control – leading to increasingly severe retinal complications.

Chronic retinal ischemia induces neovascularization and vascular proliferation, which in very advanced stages can also involve the drainage angle, ultimately contributing to the development of neovascular glaucoma (NVG). This serious and late complication, most commonly associated with advanced proliferative DR, remains a considerable therapeutic challenge.

The aim of this review is to outline the pathophysiology, diagnostic approach, and treatment of NVG in patients with advanced diabetic eye disease.

Epidemiology

The prevalence of NVG in the general population is relatively low, estimated at approximately 0.1%, which accounts for about 4% of all glaucoma types in Europe [5, 6]. Studies have shown an increased risk of this neuropathy in elderly individuals, which is associated with common cardiovascular risk factors, and a slight male predilection for this form of glaucoma [6].

In the course of DM, the earliest signs suggesting the development of NVG typically manifest as rubeosis iridis, most commonly observed in patients with a disease duration exceeding 10 years. Scientific evidence demonstrates a close correlation between the development of NVG and the severity of retinal ischemia; consequently, this form of glaucomatous neuropathy is most frequently seen in patients with proliferative diabetic retinopathy (PDR). According to Senthil et al., iris rubeosis affects between 1% and approximately 17% of diabetic patients, with prevalence rising to nearly 65% among those with established PDR [7]. Although this condition usually occurs unilaterally, in the course of DR the neuropathy typically develops bilaterally [7–9].

It is worth noting that the rising prevalence of DM is likely to lead to an increased incidence of ocular complications, including NVG. Clinical observations suggest that NVG is frequently diagnosed at a late stage, follows an aggressive course, and rapidly leads to loss of visual acuity. In extreme cases, it may even result in the loss of the eye.

Pathophysiology of neovascular glaucoma in diabetes mellitus

Endothelial cells, which line the lumen of blood vessels, play a role in maintaining proper vascular homeostasis through the secretion of various biologically active compounds. Additionally, they are responsible for the processes of angiogenesis [10]. Current evidence indicates that chronic hyperglycemia induces a range of biochemical and molecular changes within cells, leading to endothelial dysfunction and, consequently, the development of angiopathy [10, 11]. Retinal ischemia and hypoxia trigger a cascade of events that lead to the formation of new, structurally and functionally deficient blood vessels, i.e. pathological neovascularization. These hypoxic conditions and perfusion disturbances stimulate increased secretion of proangiogenic factors. The main factor is vascular endothelial growth factor (VEGF), which leads to increased vascular permeability, uncontrolled mitosis of endothelial cells (resulting in the formation of new pathological vessels), and leukocyte adhesion to the endothelium, causing disruption of

the blood-retinal barrier (BRB). This is also accompanied by elevated production of proinflammatory cytokines and the onset of a subclinical inflammatory state [12].

The pathomechanism of NVG development is illustrated in the figure below (Fig. 1).

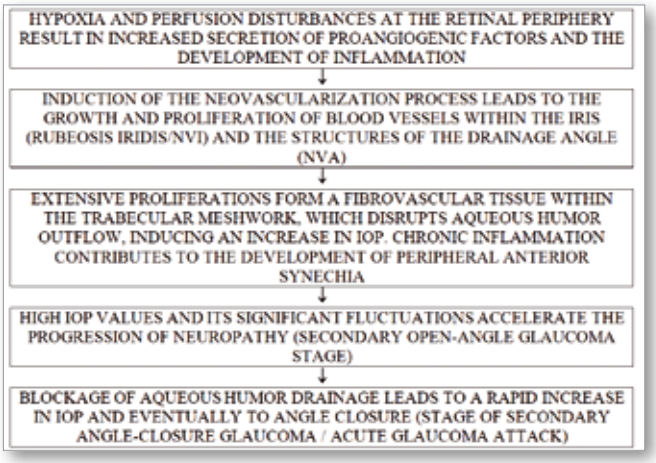

Fig. 1. The pathomechanism of NVG development.

Clinical characteristics

Based on clinical features and histopathological findings, neovascular glaucoma can be characterized by three successive stages.

Rubeosis iridis (neovascularization of the iris, NVI) represents the initial stage of the condition and is often asymptomatic, as intraocular pressure (IOP) values may still fall within the upper limits of normal.

Slit-lamp examination of the anterior segment under high magnification allows visualization of fine vascular tufts, initially appearing at the pupillary margin (Fig. 2). As neovascularization progresses, new vessels proliferate radially across the surface of the iris toward the drainage angle, a process detectable through gonioscopy (Neovascularization of the Angle – NVA) (Fig. 3). Fundus examination reveals advanced changes indicative of PDR, primarily areas of peripheral retinal non-perfusion, as confirmed by fluorescein angiography.

At this stage, the prognosis is favorable provided appropriate treatment is initiated promptly. Interestingly, clinical observations indicate that pathological vessels may also regress spontaneously.

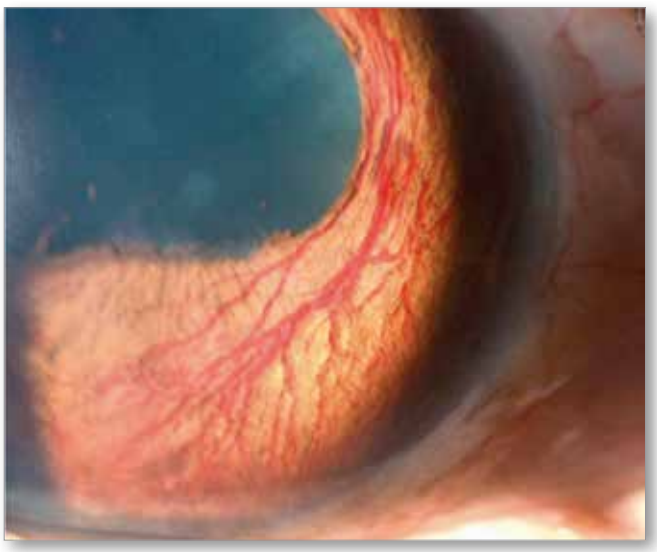

Fig. 2. Rubeosis iridis [Pagoulatos D, Georgakopoulos C. Rubeosis iridis. Pan Afr Med J. 2017 Nov 29;28:279. doi: 10.11604/pamj.2017.28.279.13717. PMID: 29881517; PMCID: PMC5989268.]

Further progression of neovascularization within the drainage angle increases resistance in the trabecular meshwork, contributing to elevated IOP and, subsequently, to the development of open-angle glaucoma. The course may be initially asymptomatic.

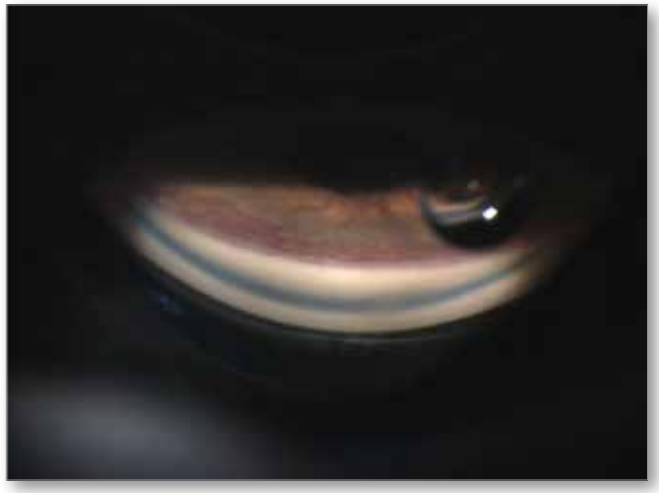

Fig. 3. Neovascularization of the drainage angle visualized by gonioscopy. [https://eyewiki.org/File:Neovascularization_of_the_Angle.jpg]

As the disease progresses, fine blood vessels extend through the ciliary body and scleral spur, branching deep into the trabecular meshwork. This leads to the formation of a fibrovascular membrane which, contracting in a "zipper-like" manner, completely closes the drainage angle, causing a significant rise in IOP. It leads to severe eye pain accompanied by corneal edema, which significantly impairs visual acuity. Notably, in young individuals or those with a high endothelial cell count, the corneal tissue may compensate for elevated IOP over an extended period without developing edema. Following drainage angle closure, patients report photophobia and the presence of rainbow-colored halos around light sources. Additionally, some individuals experience severe headache, nausea, or vomiting. IOP values may reach as high as 60–80 mmHg. On palpation, the eyeball feels "hard as a rock".

Slit-lamp examination of the anterior segment of the eye reveals conjunctival hyperemia, microcystic corneal edema, and a pupil that reacts poorly or not at all to light [5]. Furthermore, biomicroscopy reveals a shallow anterior chamber and a Tyndall effect of the aqueous humor due to the presence of erythrocytes and inflammatory cells. This is an acute condition; therefore, any patient presenting with symptoms suggestive of acute angle closure should be urgently referred to the emergency department to initiate prompt IOP-lowering treatment.

Diagnostic work-up

Key diagnostic components of NVG include thorough slit-lamp examination, tonometry, and gonioscopy. Among these, gonioscopy is the most diagnostically valuable modality, as it enables visualization of the drainage angle structures and the presence of neovascularization. Another important step in the diagnostic process is fluorescein angiography (FA), which makes it possible to visualize extensive areas of non-perfusion in the peripheral retina. Pathological changes can also be demonstrated using optical coherence tomography (OCT). Furthermore, this examination also allows assessment of the anterior chamber angle structures (Anterior Segment Optical Coherence Tomography – AS-OCT), as well as analysis of RNFL (Retinal Nerve Fiber Layer) thickness, evaluation of the optic nerve head, and assessment of the GCC (Ganglion Cell Complex), i.e., the thickness of the ganglion cell layer. This non-invasive examination, performed periodically, may serve as a reliable tool for monitoring and assessing the rate of pro-

gression of glaucomatous neuropathy, as well as for analyzing the retinal response to the implemented treatment [6–8].

Differentiation

Neovascular glaucoma occurring in the course of DM should always be differentiated from other conditions that result in neovascularization of the drainage angle.

These include central retinal vein occlusion (CRVO), which – particularly in its ischemic form – is associated with a high risk of neovascularization, and ocular ischemic syndrome (OIS), which develops due to pathology within the internal carotid arteries leading to ischemia of the entire eye [7].

Among other, far less common causes of this neuropathy are central retinal artery occlusion, intraocular tumors, chronic retinal detachment, proliferative vitreoretinopathy (PVR), retinopathy of prematurity (ROP), and immunologically mediated conditions such as uveitis or endophthalmitis [13].

Therapeutic management

Management of the underlying disease – alongside strict control of blood glucose, blood pressure, and lipid levels – constitutes an integral part of the overall therapeutic process. Clinical experience shows that effective collaboration between the diabetologist and the ophthalmologist enhances patient awareness of the condition's specific nature and, consequently, ensures better treatment compliance. Nevertheless, patients should be informed that neovascular glaucoma developing in the course of DM is a serious complication, often difficult to treat, with therapeutic outcomes that are frequently unpredictable, resulting in an uncertain prognosis. According to the study by Tang et al., the failure rate for both conservative and surgical treatment approaches reaches as high as 62.8% [9].

Local and ophthalmic treatment

The complex pathomechanism of neovascular glaucoma necessitates the implementation of combination therapy, which is usually carried out in several stages.

According to the guidelines of the Polish Ophthalmological Society and the European Society of Ophthalmology, the first stage involves prompt panretinal photocoagulation (PRP), which should be performed as soon as the diagnosis is confirmed. This is a causal treatment that inhibits the progression of neovascularization mainly by eliminating angiogenic stimuli through the destruction of non-perfused areas. If PRP cannot be performed immediately due to media opacity or significant inflammation, treatment should begin with anti-VEGF injections (e.g., aflibercept, bevacizumab) [14]. The therapeutic effects – including regression of NVI and NVA, and a reduction in IOP – are typically seen within 4 to 7 days. However, this is not a reason to forgo PRP. A retrospective study evaluating the efficacy of bevacizumab in patients with varying stages of NVG – 56% of whom had proliferative diabetic retinopathy (PDR) – demonstrated that combining intravitreal injections with panretinal photocoagulation (PRP) yielded better outcomes than injection therapy alone [15].

At the same time, it is essential to initiate treatment aimed at lowering IOP, which helps to halt or slow the progression of glaucomatous neuropathy. Therapeutic options include β-adrenergic receptor antagonists, α2-adrenergic receptor agonists, or carbonic anhydrase inhibitors. The dosing regimen and general principles of pharmacotherapy are the same as in standard glaucoma treatment, except for the two points outlined below. Prostaglandin analogues should be strictly avoided (or used with particular caution), as they may exacerbate the inflammation. Moreover, the use of miotics (e.g., pilocarpine) is contraindicated, as their mechanism of action increases vascular permeability and may disrupt the blood–aqueous barrier, thereby exacerbating the inflammatory response [14]. Nevertheless, hypotensive treatment remains symptomatic in nature, and its effectiveness is typically short-lived in cases of progressive neovascularization within the drainage angle. Ultimately, when pharmacotherapy proves insufficient, surgical intervention to lower IOP becomes necessary. The most effective treatment for this group of patients is a procedure that involves the destruction of the ciliary body. The most commonly performed procedures include cyclophotodestruction (Transscleral Cyclophotocoagulation – TSCPC) and cyclocryotherapy. These interventions result in the destruction of the ciliary body, leading to a significant reduction in aqueous humor production and, consequently, a decrease in IOP and relief from pain. Another available method is trabeculectomy with the use of antimetabolites. However, according to current reports, this approach shows a low success rate in this form of glaucoma [5]. In some patients, a seton procedure may also be considered [14].

In topical treatment, mydriatic agents (cycloplegics) are also used, and initially, short-term topical corticosteroid therapy can be introduced to reduce the inflammatory process and for analgesic purposes in cases of persistently elevated IOP [14].

In cases of complete vision loss accompanied by severe pain resulting from markedly IOP, one of the available and clinically validated pain-relief methods is retrobulbar ethanol injection. A case series described by Akhtar et al. demonstrated that ethanol injections are an effective method of pain management in patients with absolute glaucoma. The patients included in the study remained pain-free for 12 months following the injection, and no adverse effects of the method were observed [16]. In extreme cases of very advanced NVG, when analgesic treatment options have been exhausted, enucleation or evisceration remains the only solution to preserve the patient's quality of life [7, 17]. However, these procedures are not without complications. According to the literature, some patients may experience phantom eye pain following globe removal [18, 19]. In a study conducted by Rasmussen et al., this type of pain was present in 23% of the 173 participants, with as many as 31% reporting daily severe discomfort [18].

Prognosis

Preservation of good visual acuity depends on the stage at which NVG is diagnosed and the timing of treatment initiation. Nevertheless, in the context of diabetes, achieving proper metabolic control plays a key role, as the risk of blindness in advanced cases is substantial without effective antidiabetic therapy.

Conclusions

- NVG represents a late manifestation of diabetic retinopathy and is characterized by a severe course and poor prognosis. Strict glycemic control is of critical importance, as the cornerstone of treatment for this form of secondary glaucoma is management of the underlying disease.
- Gonioscopy is the primary examination used to assess the drainage angle, detect neovascularization within the trabecular meshwork, and identify peripheral anterior synechiae. Failure to include this assessment in the diagnostic process is an oversight.
- According to current knowledge, the most effective causal treatment remains panretinal photocoagulation in combination with intravitreal injections of anti-VEGF inhibitors. This therapy acts through multiple mechanisms to inhibit the progression of neovascularization, primarily by suppressing angiogenic stimuli.
- Prevention, as well as early detection of the underlying disease (Diabetic Retinopathy – DR) with timely initiation of appropriate treatment, is the only effective method to prevent secondary neuropathy.

- In patients with very poor compliance and advanced PDR, frequent and regular check-ups are necessary to ensure that any NVG diagnosis is made "early", i.e., at the stage of iris rubeosis.
- In cases of secondary angle-closure glaucoma, where the prognosis for maintaining vision is very poor, the primary treatment goal is to preserve the patient's quality of life through effective pain management.

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