



# Review of a new concept of glaucoma pathogenesis based on the glymphatic theory of cerebrospinal fluid circulation

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## Abstract

**General aspects of glaucoma:** Glaucoma is a heterogeneous multi-factorial disease that is one of the main causes of blindness, along with degeneration of retinal ganglion cells and optic nerve atrophy.

**Theories of pathogenesis:** There are three theories of glaucoma pathogenesis: biomechanical, vascular, and biochemical.

**Basic theory of the glymphatic system:** The classical knowledge of cerebrospinal fluid circulation has been revised, and in 2012 a new concept of glial-perivascular – glymphatic perfusion of the brain parenchyma was introduced. Due to experimental and clinical studies, it is approved by many scientists, especially in relation to Alzheimer's disease (AD), in which amyloid pathology is the result of dysfunction of the para-/perivascular transport/cleansing pathways.

**Features of the optic nerve and the cribriform plate:** The cribriform plate forms a barrier at the border of intraocular (IOP) and intracranial (ICP) pressures, thus affecting the para-/periarterial flow of cerebrospinal fluid to the optic nerve and retina, as well as the para-/perivenous cleansing outflow.

**Morphofunctional evidence of an ocular glymphatic system:** The presence of an ocular glymphatic system is confirmed by *in vivo* experiments with the transfer of labeled substances through para-/perivascular structures from the ventricular or subarachnoid space to the optic nerve and by postmortem morphology.

**Clinical evidence for the glymphatic system hypothesis:** There is some clinical, including case-based, and epidemiological evidence for similarities between glaucomatous optic nerve/retinal injuries and AD, since both occur in the form of improper secretion of neurotoxic metabolites, and both are often diagnosed together.

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## Keywords

glaucoma, neurodegeneration, glymphatic system, Virchow-Robin spaces, perivascular spaces.

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## General aspects of glaucoma

Glaucoma is a huge medical, social and economic problem worldwide, as it is one of the main causes of irreversible blindness (Quigley 2006). According to WHO estimates, the number of people who have gone blind as a result of primary glaucoma is 4.5 million (12% of all people who suffer from blindness). Currently, the etiology and pathogenesis of glaucoma remain insufficiently studied for the development of an effective treatment. The controversies and obscure aspects of the disease are reflected in multiple concepts of the problem. Moreover, even the definition of glaucoma was not unified for a long time due to high heterogeneity, because up to 60 eye diseases can lead to glaucomatous damage of the nervous structures of the eye (Nesterov 2008). Despite this, the key feature of glaucoma can be defined as glaucoma optical neuropathy (GON), which occurs as a result of degeneration of the retinal ganglion neurons, followed by optic nerve injury and the appearance of corresponding visual defects (Weinreb 2004).

There are three main forms of primary glaucoma: open-angle, closed-angle, and mixed (Weinreb et al. 2014).

The open-angle form is characterized by preserving the angle of the anterior chamber of the eye, which gives free access of aqueous humor to the drainage zone. Resistance to fluid outflow is found in the trabecula, venous sinus of sclera (Schlemm's canal), collector channels, and intrascleral plexus. This form of glaucoma is accompanied by an increased, and sometimes moderate, IOP. With moderate IOP, normal-pressure glaucoma is identified separately, occurring mainly in people over 35 years of age, as well as in people of Asian ethnic group.

The closed-angle form has a narrow angle of the anterior chamber of the eye due to the closure of the trabecula by the iris root, as a result of which a decrease in the outflow of intraocular fluid and, accordingly, a sharp increase in IOP are observed. This form of glaucoma appears when the iris and cornea join at the periphery of the anterior chamber of the eye, which can be caused by various factors, pushing the iris into the corner of the eye. Primary closed-angle glaucoma occurs in older people, because as a person ages, the lens of the eye continues to grow, so young people do not have a narrowing of the angle of the anterior chamber (AAC) of the eye. In addition to age, the risk factors for narrowing the AAC include ethnicity: Asians and Hindus are at a higher risk, while Africans and Europeans are at a lower risk.

The mixed form manifests as a combination of the narrowing of the AAC and disruption of the permeability of filtration channels for aqueous humor.

In addition to all these forms of primary glaucoma, there are also, though much less frequent, congenital, hypersecretory, low-pressure, and many other forms of secondary glaucoma.

## Aim of study

The aim of this paper is to review the achievements in understanding glaucoma pathology based on the latest morphofunctional concepts of the transport systems of cerebral metabolites.

## Theories of glaucoma pathogenesis

The pathogenesis of glaucoma raises many questions due to the presence of many contradictory studies that reveal the role of a large number of factors that affect the occurrence and development of glaucomatous processes. In this regard, various theories of pathogenesis were considered, of which there are three main ones: vascular, biomechanical, and biochemical.

In the *vascular theory* of GON, the predominant role in pathogenesis is played by a decrease in the hemoperfusion of the eye, which leads to ischemia of the optic disk and retina. However, all the accumulated information does not give full account of this theory, since there is evidence of both hypertension as a serious risk factor for the development of GON (Bonomi et al. 2000; Yanagi et al. 2011) and hypotension, which strongly affects the development of GON (Graham and Drance 1999; Tokunaga et al. 2004). At the same time, there is a hypothesis stating that the death of ganglion cells occurs as a result of the primary and secondary stroke of the retinal ganglion cells. For example, it is assumed that primary stroke occurs in the axons of ganglion cells at the level of the cribriform plate (Caprioli and Coleman 2010). In them there appear the conditions observed during ischemia-reperfusion and leading to damage to the mitochondria, since the activation of oxidation processes with the release of free radicals occurs (Kyhn et al. 2009). Secondary damage is observed in disorders of autoregulation of the optic nerve circulation and neurovascular interaction (Balaratnasingam et al. 2010). To this day, questions concerning the physiology and pathophysiology of blood circulation of the eye remain open, which directly relates to the understanding of the vascular theory of glaucoma pathogenesis.

The *mechanical theory* suggests that GON may be the result of increased IOP, resulting in high-tension areas that cause displacement and deformation of the cribriform plate, compression of prelaminar tissue, and, as a result, loss of glial cells (Flammer et al. 2002). The reason for an increased IOP is an increase in resistance in the main structures of the eye fluid outflow – in the trabecular reticulum and Schlemm's canal (Zolotarev et al. 2013; Fan et al. 2015). According to (Iomdina et al. 2011), an important role in the development of glaucomatous process is played by distorted elasticity of the fibrous capsule, which occurs due to abnormal acceleration of the aging processes as a result of pathological changes in the metabolism of one of the most important structural proteins of the sclera

– collagen. A number of studies have proven the effect of mechanical deformation of the collagenous structures of the cribriform plate on glaucomatous excavation of the optic nerve. For instance, in experiments on monkeys, it was found that a sharp rise in IOP did not cause changes in the cribriform plate (Blumenthal et al. 2009), whereas a long-term increased IOP leads to an increase in the distensibility of the sclera and to its deformation (Agapova et al. 2001; Pena et al. 2001; Golubnitschaja et al. 2004).

The theory is supported by the conclusions in (Minckler et al. 1978; Levy et al. 1981; Jonas 2014) made as a result of experimental and clinical observations of the dependence of a degree of glaucomatous defects of the visual field, a degree of the displacement of support structures, and electrophysiological indicators on the value of IOP.

Over the past few years, evidence about the possible role of biochemical mechanisms leading to glaucomatous neurodegeneration has been increasing in the literature. It includes the role of the effects of excitatory amino acids, caspases, protein kinases, oxygen free radicals, nitric oxide, and tumor necrosis factor-alpha (Ahmad et al. 2013).

Studying the primary, secondary and terminal products of lipid peroxidation in the aqueous humor and drainage system of the eyes, Grzybowski A et al. (2019) found an increase in their concentrations in patients with glaucoma compared to the norm. Based on this, they made an assumption that the destruction of trabecular tissue in primary open-angle glaucoma (POAG) occurs when two factors are combined: an abnormally high concentration of peroxidants in aqueous humor and a reduced activity of the antioxidant system in the tissues of the trabecula and Schlemm's canal. Violation of the ratio between the formation and removal of lipid peroxidation metabolites in patients with primary glaucoma leads to changes in the permeability of cell membranes and the molecular structure of cells. According to Yu. S. Zavadskaya and G. G. Karzhaubaeva, this is due to a deficiency of tocopherol, one of the leading endogenous antioxidants. The metabolic mechanisms involved in the occurrence and development of glaucoma also include pseudo-exfoliative dystrophy in the anterior segment of the eye and impaired glycosaminoglycans metabolism (Ahmad 2016).

## Main concept of the glymphatic system (GLS)

Since the study by Brinker, Morrison, and Kling (Brinker et al. 2014), which provided a detailed description of new ideas in molecular and cellular biology, as well as neuroimaging studies that indicate that the physiology of cerebrospinal fluid (CSF) is much more complex than previously thought, the classical theory of CSF circulation has become more complex, and a new hypothesis has been proposed regarding CSF hydrodynamics. Recent research on the biology of CSF has revealed the importance of the so-called "glymphatic system" in elimination of potentially

neurotoxic products, including amyloid- $\beta$ . The glymphatic system was first described by Iliff (Iliff et al. 2012), who first identified a brain-wide network of paravascular channels in mice, which they called the "glymphatic" pathway, through which most of the subarachnoid cerebrospinal fluid recycles through the brain's parenchyma, facilitating the clearance of interstitial solutes, including amyloid- $\beta$  (A $\beta$ ), from the brain. Although the glymphatic concept is also called into question and more research is needed to confirm its functional significance, one of its consequences is that glymphatic pathway dysfunction may contribute to insufficient A $\beta$  clearance in the pre-clinical stages of Alzheimer's disease (AD) (Yang et al. 2013). It is believed that AD is caused by an imbalance between the production and excretion of A $\beta$ , leading to the accumulation of this protein in the brain (Dadas et al. 2016; Lobzin et al. 2018). New research in the physiology of CSF circulation may also open up new possibilities in understanding other neurodegenerative diseases in which defective accumulation of neurotoxic deposits contributes to the development of the disease.

## Features of the optic nerve and ocular cribriform plate from the glymphatic system point of view

The optic nerve, the white matter tract of the central nervous system (CNS), is surrounded by all three meninges and cerebrospinal fluid in the subarachnoid space (SAP) with a pressure equivalent to IOP (Wostyn et al. 2015, 2017). The movement of CSF on the outer side of the optic nerve has been studied quite fully. When tracers are introduced into the cisterna magna or lateral ventricles, they are found in or around the optic nerve itself. Thus, in addition to IOP, the optic nerve is affected by ICP (Wostyn et al. 2017). The cribriform plate is a cribriform structure at the back of the sclera that allows for the passage of RGC axons and central retinal vessels. It separates these two areas under pressure and forms a pressure barrier between the high-pressure area of the intraocular space and the low-pressure area of the retrobulbar space of CSF. The forces acting on the optic disk are influenced by both IOP and ICP. The difference between rear-facing IOP and front-facing ICP passing through the cribriform plate is known as the pressure difference of the cribriform plate. The pressure drop in the area of the cribriform plate increases with an increase in IOP or a decrease in ICP (Wostyn et al. 2017).

## Morphological and functional criteria of the intraocular glymphatic system

In 2015, researchers from England (Denniston and Keane 2015) and a research group from Antwerp University

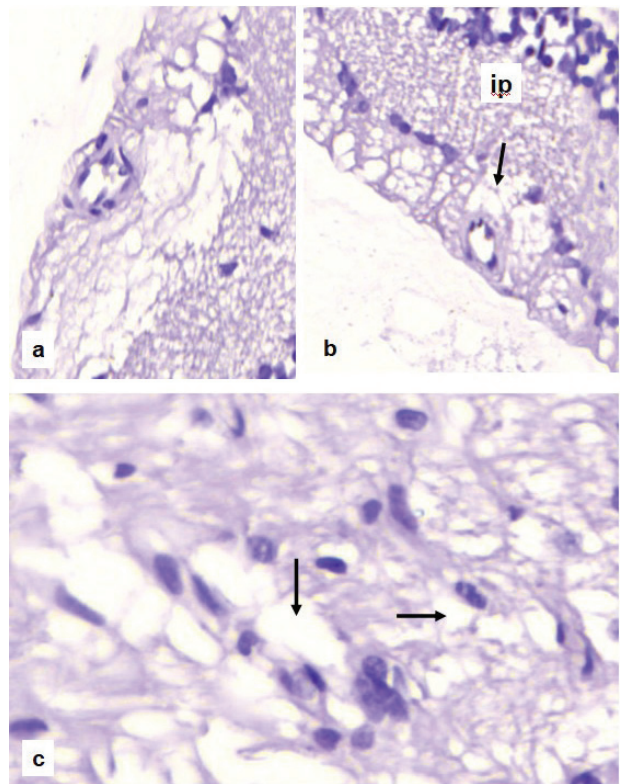
Hospital (Wostyn et al. 2015) independently hypothesized the existence of a paravascular transport system in the retina and optic nerve, similar to the described glymphatic system in the brain. Two years later, the latter (Wostyn et al. 2017) published a comprehensive review of the recent studies which supports the hypothesis that there is a "glymphatic system" in the eye and optic nerve, similar to the described "glymphatic system" in the brain. In their opinion, clarification of the glymphatic clearance pathway in the eye may provide a new unifying hypothesis for glaucoma, which may include many aspects of vascular, biomechanical, and biochemical theories of the disease.

## Clinical evidence and applied aspects of the glymphatic system hypothesis

Many clinical and epidemiological data show that there is a similarity between glaucomatous optical neuropathy and Alzheimer's disease, for which the pathogenetic role of glymphatic clearance disorders is almost postulated (Dadas et al. 2016, Lobzin et al. 2018).

Several studies have found an increased prevalence of patients with AD. In their study in a nursing home in Germany, Bayer et al. (2002) studied 112 patients with AD and 116 patients in the control group. The prevalence of POAG was 25.9% in patients with AD and 5.2% in the control group. In a Japanese study, Tamura H et al. (2006) found a prevalence of POAG in 23.8% of 172 patients with AD, which was significantly higher than 9.9% among 176 patients in the control group. This prevalence of glaucoma among patients with AD, combined with multiple similarities between the two diseases, raised the question of whether AD and glaucoma may have a common pathogenesis (Bizrah et al. 2011). It is important to note that the concentration of A $\beta$  increases with a chronic increase in IOP in animals with experimentally induced ocular hypertension, which causes the death of retinal ganglion cells (Ito et al. 2012). Glymphatic pathway dysfunction as a potential mechanistic link between AD and glaucoma is an important hypothesis, as it may explain the comorbidity of these two disorders. The results showed that in glaucoma, there is an IOP-sensitive increase in A $\beta$ . McKinnon et al. (2002) reported that the retinal ganglion cells of rats subjected to a chronic increase in IOP showed caspase-3-mediated abnormal processing of the  $\beta$ -amyloid precursor (APP) with an increased A $\beta$  expression. This suggests a new hypothesis of ganglion cell death in glaucoma involving chronic A $\beta$  neurotoxicity that mimics AD at the molecular level (Mancino et al. 2018).

Increasing evidence indicates that intracranial pressure is lower in patients with POAG compared to non-glaucomatous control groups. In addition, ICP has been reported to be lower at normal tension compared to the high-tension



**Figure 1.** Changes in the optic disk area in simulated hypertensive retinopathy: **a, b** – marked enlargement and edema of the periarterial spaces; **c** – enlargement of the perivenular space (vertical arrow) and a decrease in interstitium in the optic nerve. Stained with hematoxylin-eosin. Scanned slide. Magnification of  $\times 400$  (according to unpublished data). These results may reflect an overloaded state of perivascular structures and, on the other hand, serve as our own evidence that intraretinal glymphatic structures are associated with passages for fluid transport within the optic nerve.

sion form of POAG (Berdahl and Allingham 2010). If ICP is too low, the flow of fluid from the paravascular spaces in the optic nerve to the paravascular spaces in the retina may decrease or stop, considering that this paravascular flow must cross the IOP-ICP pressure barrier. There are also specific cases indicating the role of cerebral para/perivascular (Virchow-Robin) spaces as an indicator of glymphatic clearance dysfunction in primary open-angle glaucoma (Wostyn et al. 2016).

In an experimental study of retinal ischemia-reperfusion, a simulated mechanical pressure of up to 110 mm Hg was reproduced in the anterior chamber of the eye for 30 minutes (Peresytkina et al. 2017), as a result of which we found pronounced microcirculatory disorders and destructive neuronal changes with the highest vulnerability of the retinal ganglion layer. In addition, there were obvious changes in paravascular structures near the cribriform plate and inside the optic nerve (unpublished data). Periarterial spaces were extremely enlarged and edematous. Internal structure of the optic nerve with a marked weakening of the interstitial and perivenular edematous space (Fig. 1).

## Conclusion

The theory of transport and clearance of the brain parenchyma has a lot of evidence that makes it possible to apply it to the nutritional and cleansing mechanisms in the optic nerve and retina. The existence of the glymphatic pathways of the optic nerve and retina is confirmed by the structural similarity between the meninges and optic neural brain complexes, the coexistence of pathologies associated with glymphatic system dysfunction

on (AD, glaucoma) and experimental data. Further studies of the morphofunctional basis of the paravascular system of the eye and its changes in simulated glaucoma are important and promising for advancing the understanding of glaucoma pathology and developing an appropriate therapy.

## Conflict of interests

The authors declare no conflict of interests.

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