Aspects of the Pathogenesis of Glaucomatous Optic Neuropathy

Jost B Jonas
Professor and Chairman, Department of Ophthalmology, Medical Faculty Mannheim, University of Heidelberg, Germany

Correspondence: Jost B Jonas, Professor and Chairman, Universitäts-Augenklinik, Theodor-Kutzer-Ufer 1-3, 68167 Mannheim Germany, Phone: 49-621-383-2652, e-mail: jost.jonas@augen.ma.uni-heidelberg.de

ABSTRACT

Purpose: To discuss aspects of the pathogenesis of glaucomatous optic neuropathy based on morphologic findings of the glaucomatous optic nerve head and examinations of the cerebrospinal fluid pressure.

Methods and results: Findings were: normal pressure and high intraocular pressure glaucoma eyes can show a similar appearance of the optic nerve head. These features are not found in any (other) vascular optic neuropathy (except for arteritic anterior ischemic optic neuropathy). The translamina cribrosa pressure difference is of importance for the physiology of the optic nerve head. A physiological association exists between arterial blood pressure, cerebrospinal fluid pressure and intraocular pressure. Patients with normal (intraocular) pressure glaucoma had significantly lower cerebrospinal fluid pressure and a higher translamina cribrosa pressure difference when compared to normal subjects.

Conclusions: A low (orbital) cerebrospinal fluid pressure may be associated with normal (intraocular) pressure glaucoma. A low systemic blood pressure, particularly at night, could physiologically be associated with a low cerebrospinal fluid pressure, which leads to an abnormally high translamina cribrosa pressure difference and as such to a similar situation as if the cerebrospinal fluid pressure is normal and the intraocular pressure is elevated. This model could explain why patients with normal (intraocular) pressure glaucoma tend to have a low systemic blood pressure, and why eyes with normal (intraocular) pressure glaucoma and eyes with high-pressure glaucoma, in contrast to eyes with a direct vascular optic neuropathy, show profound similarities in the appearance of the optic nerve head.

Keywords: Cerebrospinal fluid pressure, Intraocular pressure, Translamina cribrosa pressure difference, Transcorneal pressure difference, Glaucoma, Glaucomatous optic neuropathy, Normal pressure glaucoma.

INTRODUCTION

The pathogenesis of the glaucomatous optic neuropathy has not been completely cleared yet, in particular, in view of the observation that patients with glaucoma can markedly differ in the level of intraocular pressure. It is the purpose of this review to discuss some aspects from the morphologic appearance of the optic nerve head which may be of potential interest for the discussion of the pathogenesis of glaucomatous optic nerve damage.

Optic Disk Size

Despite a pronounced variability in optic disk size between individuals, studies have revealed that in nonhighly myopic eyes, neither susceptibility for glaucomatous optic neuropathy nor the risk for progression of glaucomatous optic neuropathy is associated with the optic disk size. In highly myopic eyes, glaucoma susceptibility is increased according to a higher prevalence of glaucomatous optic neuropathy in highly myopic subjects compared with nonhighly myopic subjects. The reason for the increased glaucoma susceptibility in the highly myopic macrodisks may be a stretching and secondary thinning of the lamina cribrosa and a marked thinning of the peripapillary sclera in highly myopic eyes. The thinning of the lamina cribrosa leads to a decreased distance between the intraocular space and the space of the retrobulbar cerebrospinal fluid compartment, so that at a given translamina cribrosa pressure difference between both compartments, the pressure gradient gets steeper due to the reduced distance between both compartments. In addition, changes in the biomechanical properties of the lamina cribrosa tissue may occur due to the myopia induced stretching of the lamina cribrosa, as general and specific aspects of recent research in the biomechanics of the optic nerve head suggest. The thinning of the peripapillary sclera may be an additional biomechanical factor, which by an increased tension in the lamina cribrosa beams may lead to increased glaucoma susceptibility.

Neuroretinal Rim

In contrast to glaucoma, all vascular optic neuropathies (except for arteritic anterior ischemic optic neuropathy) do not show a loss of neuroretinal rim, which keeps its physiological shape despite loosing retinal ganglion cell axons. Similar findings were reported for monkeys after an experimental central retinal artery occlusion. The discrepancy in the loss of neuroretinal rim in all types of glaucoma, including normal pressure glaucoma in contrast to the preserved rim in the vascular optic neuropathies, the normal color of the remaining rim in glaucoma in contrast to the pale color of the existing rim in eyes with a...
vascular optic nerve damage, the finding that the loss in neurorretinal rim in normal pressure glaucoma is related to the height of the intraocular pressure, the finding that the location of the deepest part of the optic cup in normal pressure glaucoma spatially correlates with the location of the most marked perimetric loss, and the finding that lowering of intraocular pressure is therapeutically helpful in normal pressure glaucoma may point against a primarily vascular pathogenesis in normal pressure glaucoma.

Parapapillary Atrophy

Beta zone of parapapillary atrophy can be found in all types of the chronic open-angle glaucomas, including normal pressure glaucoma. In contrast, none of the vascular optic neuropathies, including arteritic anterior ischemic optic neuropathy show an enlargement of beta zone or an increased frequency of beta zone. Optic Disk Hemorrhages

Hospital-based studies have shown that eyes with normal pressure glaucoma have significantly more often and more disk hemorrhages than eyes with high-pressure glaucoma. They also showed that the size of the hemorrhage is larger in eyes with normal pressure glaucoma than in eyes with high-pressure glaucoma. It has been discussed that the difference in the frequency of detected disk hemorrhages between high-pressure and normal pressure glaucoma patient groups was due to the difference in intraocular pressure between high-pressure and normal pressure glaucoma. Assuming that the size of the leaking part in the vessel wall is similar in both glaucoma groups, then the amount of blood leaking out of the vessel into the adjacent tissue depends on the transmural pressure difference. The latter is the difference between the blood pressure in the vessel and the pressure in the surrounding space, i.e., the intraocular pressure. Taking into account the lower intraocular pressure in the normal pressure glaucoma eyes than in the high-pressure glaucoma eyes, just the difference in intraocular pressure between both glaucoma groups may be reason enough for larger disk hemorrhages which take a longer time to be absorbed and have a higher chance to be detected by ophthalmoscopy.

Thinning of the Retinal Arteries

Thinning of the retinal arteries (arterioles) in a diffuse manner and in a localized manner have been described to occur in eyes with glaucoma, and that the amount and location of the reduction in the arteriolar diameter correlate with the amount and location of glaucomatous optic nerve damage. The retinal arteriolar caliber reduction has been found in eyes with normal pressure as well as in eyes in high-pressure glaucoma. Since, however, the localized and generalized thinning of the retinal arterioles can be found in any type of optic nerve damage, the reduction in the arteriolar diameters is neither pathognomonic for glaucoma in general nor for normal pressure glaucoma in particular, but may at least partially be a secondary phenomenon due to the loss of retinal tissue and the consequently reduced demand for blood supply.

Phenotyping of the Chronic Open-Angle Glaucomas according to the Morphology of the Optic Nerve Head

Analyzing the morphology of the optic nerve for differences between subgroups of chronic open-angle glaucoma may lead to various phenotypes, such as the highly myopic type of (primary) open-glaucoma, and the age-related atrophic type of open-angle glaucoma. The juvenile high-pressure glaucoma type is characterized by a relatively young age of the patients (usually less than 40 years at the time of the first diagnosis), with a steep and deep cupping, a relatively small parapapillary atrophy (beta zone), and a apparently diffuse loss of retinal nerve fiber layer. At a close look, however, there are multiple small localized retinal nerve fiber layer defects which can mimic a diffuse loss. The so called focal type of normal pressure glaucoma may typically be found more in females than in males with an age of about 45 to 65 years; the patients tend to have a low arterial blood pressure and to report some vasospastic symptoms. The optic disk can show a relatively deep and steep cupping, rim notches, disk hemorrhages, marked localized retinal nerve fiber layer defects, and parapapillary atrophy. The location of the deepest part of the optic cup in normal pressure glaucoma spatially correlated with the location of the most marked perimetric loss. In selected examples, there was a strikingly similar appearance in the appearance of the optic nerve head between eyes with open-angle glaucoma and high intraocular pressure and eyes with normal intraocular pressure. Correspondingly, monkey experiments performed by Hayreh have shown that monkeys with experimental high-pressure glaucoma develop localized retinal nerve fiber layer defects, what formerly was believed to be typical for normal pressure glaucoma.

The questions arose, why despite marked differences in intraocular pressure between eyes with high-pressure glaucoma and eyes with normal pressure glaucoma, both glaucoma subtypes could have a sometimes strikingly similar optic nerve head appearance, and how one may explain the marked differences in the optic nerve head appearance between eyes with normal pressure glaucoma and eyes with any (other) vascular optic neuropathy, if normal pressure glaucoma was supposed to have a (partially) vascular pathogenesis. In was suggested that one may consider looking beyond the lamina cribrosa. The bottom of the optic cup on the inner surface of the optic nerve head is formed by the lamina cribrosa. On its outer surface, the lamina cribrosa faces the anterior region of the optic nerve. The main functions of the lamina cribrosa are to allow the retinal ganglion cell axons and the central retinal vein to leave the eye; to allow the central retinal artery to enter the intraocular space; and to stabilize the intraocular pressure by forming a barrier between the intraocular space and the...
extraocular space. Due to the barrier function, the lamina cribrosa prevents a major leakage of aqueous humor from the intravitreal space into the retrobulbar cerebrospinal fluid space surrounding the retrobulbar part of the optic nerve. Since the lamina cribrosa forms the border between the intraocular space with a higher pressure and the retrobulbar space with a lower pressure, a pressure gradient exists across the lamina cribrosa as difference of intraocular pressure minus pressure in the retrobulbar cerebrospinal fluid space. This translamina cribrosa pressure gradient is of importance for ocular diseases in which the pressure on one or on both sides of the lamina cribrosa is either abnormally high and/or abnormally low. \(^\text{32-43}\) An abnormal pressure gradient influences the physiology of the optic nerve fibers with their orthograde and retrograde axoplasmic flow. \(^\text{44-46}\) Also for glaucomatous optic nerve damage, one may discuss that not the transcorneal pressure difference (which usually has been called (intraocular pressure) but the translamina cribrosa pressure difference and the translamina cribrosa pressure gradient may be important. \(^\text{47}\)

The translamina cribrosa pressure gradient depends on the pressure difference and the distance between the intracoroidal compartment and the retrobulbar fluid filled compartment. The distance between both compartments markedly depends on the thickness of the lamina cribrosa. Consequently, the thinning of the lamina cribrosa in highly myopic eyes may be one of the reasons, why the glaucoma susceptibility is increased in highly myopic eyes. \(^\text{3,4}\) In addition, histomorphometric studies have shown that in nonhighly glaucomatous myopic eyes, the lamina cribrosa gets thinner in an advanced stage of the disease. \(^\text{48}\) This glaucoma related thinning of the lamina cribrosa may be one of the reasons why the risk for further glaucoma progression in eyes with advanced glaucoma is increased. \(^\text{49,50}\) More than 30 years ago, Volkov pointed out that a low cerebrospinal fluid pressure could pathogenetically be associated with glaucomatous optic neuropathy. \(^\text{51}\) The same idea had already earlier been expressed by Szymansky and Wladyczko. \(^\text{52}\) In a similar manner, Yablonsky, Ritch and Pokorny observed marked glaucomatous changes in normotensive eyes of cats in which the intracranial pressure was reduced to 5 cm H\(_2\)O below the atmospheric pressure, while artificially hypotensive eyes did not show such changes. \(^\text{53}\) Consequently, Berdahl et al found in a retrospective chart review that the mean cerebrospinal fluid pressure was significantly higher in the nonglaucomatous patients than in open-angle glaucoma patients, and that ocular hypertensive subjects had significantly higher cerebrospinal fluid pressure. \(^\text{54,55}\) In a similar manner in a recent prospective study, the lumbar cerebrospinal fluid pressure was significantly lower in the normal-intraocular pressure glaucoma group (9.5 ± 2.2 mm Hg) than in a high-intraocular pressure glaucoma group (11.7 ± 2.7 mm Hg) or a control group (12.9 ± 1.9 mm Hg). \(^\text{56}\) The translamina cribrosa pressure difference was significantly (\(p < 0.001\)) higher in the normal-intraocular pressure glaucoma group (6.6 ± 3.6 mm Hg) and the high-intraocular pressure glaucoma group (12.5 ± 4.1 mm Hg) than in the control group (1.4 ± 1.7 mm Hg). In multivariate analysis, the amount of glaucomatous visual field loss was mainly associated with the translamina cribrosa pressure difference (\(p = 0.005\)) while intraocular pressure and cerebrospinal fluid pressure as single parameters were not significantly (\(p > 0.50\)) associated with perimetric loss. In the control group, cerebrospinal fluid pressure was significantly correlated with both systolic blood pressure (\(p = 0.04\)) and intraocular pressure (\(p < 0.001\)). Since the intraocular pressure is physiologically associated with blood pressure, \(^\text{57,58}\) the translamina cribrosa pressure difference was not significantly (\(p = 0.97\)) related with the blood pressure. In a parallel study, the cerebrospinal fluid pressure was significantly (\(p < 0.001\)) higher in a ocular hypertensive group of 17 patients (16.0 ± 2.5 mm Hg) than in the control group (12.9 ± 1.9 mm Hg). \(^\text{59}\) The correlation between all three pressure parameters, i.e. cerebrospinal fluid pressure, blood pressure and intraocular pressure may suggest a systemic mechanism simultaneously influencing all three of them. It may explain why arterial hypertension, although associated with elevated intraocular pressure, was not associated with glaucoma in population-based studies. One may assume that the elevation in intraocular pressure was compensated by the increase in cerebrospinal fluid pressure, so that the translamina cribrosa pressure difference remained unchanged. This assumption was supported by the study of Ren et al, \(^\text{56}\) in which the translamina cribrosa pressure difference was not significantly (\(p = 0.97\)) related to blood pressure. The correlation between the cerebrospinal fluid pressure and arterial blood pressure supports clinical observations that patients with normal-pressure glaucoma tend to have low blood pressure. \(^\text{60-64}\) It was the reason to postulate a vasogenic pathogenesis of normal-pressure glaucoma. If, however, a low blood pressure is associated with a low cerebrospinal fluid pressure, a barotraumatic pathomechanism in normal-pressure glaucoma with an elevated translamina cribrosa pressure gradient may become likely. In a parallel manner, the translamina cribrosa pressure difference was not significantly associated with the arterial blood pressure. \(^\text{59}\) If one considers the translamina cribrosa pressure difference being the driving force for optic nerve damage in glaucoma, the lack of an association between the translamina cribrosa pressure difference and the systemic arterial blood pressure may contradict that a vascular insufficiency in the optic nerve head may play a major primary role in the pathogenesis of glaucomatous optic nerve fiber loss. \(^\text{60-64}\)

**CONCLUSION**

A primary vasogenic pathogenesis of glaucomatous optic neuropathy may be contradicted by the morphology of the optic nerve head, since normal pressure glaucoma eyes and high intraocular pressure glaucoma eyes can show a similar appearance of the optic nerve head. These features are not found in any (other) vascular optic neuropathy (except for arteritic anterior ischemic optic neuropathy). Other factors, which may be taken into account are: (1) The translamina cribrosa pressure...
difference (instead of the transcorneal pressure difference, i.e. the so called intraocular pressure) is of importance for the physiology of the optic nerve head; (2) a physiologic association exists between arterial blood pressure, cerebrospinal fluid pressure and intraocular pressure; and (3) patients with normal (intraocular) pressure glaucoma had significantly lower cerebrospinal fluid pressure and a higher lamina cribrosa pressure difference when compared to normal subjects. One may, therefore, discuss that a low (orbital) cerebrospinal fluid pressure may be associated with normal (intraocular) pressure glaucoma. A low systemic blood pressure, particularly at night, could physiologically be associated with a low cerebrospinal fluid pressure, which leads to an abnormally high lamina cribrosa pressure difference and as such to a similar situation as if the cerebrospinal fluid pressure is normal and the intraocular pressure is elevated. This model could explain why patients with normal (intraocular) pressure glaucoma tend to have a low systemic blood pressure, and why eyes with normal (intraocular) pressure glaucoma and eyes with high-pressure glaucoma, in contrast to eyes with a direct vascular optic nerve damage. A low systemic blood pressure, particularly at night, may be associated with normal (intraocular) pressure glaucoma and patients with therapeutically reduced intraocular pressures. Am J Ophthalmol 1998;126:487-97.


