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GLAUCOMA

Trans-lamina cribrosa pressure difference correlated with neuroretinal rim area in glaucoma

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Abstract
Background The aim of this work is to prospectively assess the relationship between trans-laminar cribrosa pressure difference and neuroretinal rim area as morphologic surrogate of glaucomatous optic nerve damage.
Methods The study included 22 patients with high-pressure glaucoma, 13 patients with normal-pressure glaucoma, and 17 subjects with ocular hypertension. All participants underwent a standardized ophthalmologic examination including confocal laser scanning tomography of the optic nerve head and computerized perimetry and a neurologic examination including measurement of the lumbar cerebrospinal fluid (CSF) pressure. The trans-lamina cribrosa pressure difference was calculated as difference of intraocular pressure minus lumbar CSF pressure.
Results Neuroretinal rim area (p=0.006; correlation coefficient r=−0.38) and mean visual field defect (p=0.008; r=0.38) were significantly associated with trans-lamina cribrosa pressure difference. The probability of error was lower (i.e., the p value were lower) and the correlation coefficients were higher for the associations between rim area/visual field defect with trans-lamina cribrosa pressure difference than for the associations between rim area/visual field defect and intraocular pressure or lumbar CSF pressure.
Conclusions The trans-lamina cribrosa pressure difference as the difference of intraocular pressure minus the lumbar CSF pressure was the main pressure parameter associated with the amount of glaucomatous optic nerve damage. This may suggest that the CSF pressure as trans-lamina cribrosa counter pressure against the intraocular pressure may play some role in the pathogenesis of glaucomatous optic neuropathy.

Keywords Cerebrospinal fluid pressure · Trans-lamina cribrosa pressure difference · Neuroretinal rim · Ocular hypertension · Normal-pressure glaucoma · Lamina cribrosa · Intraocular pressure · Blood pressure

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Introduction

Glaucomatous optic neuropathy, one of the three leading causes of blindness worldwide, has usually been considered to be a primarily ocular disease caused by abnormally high intraocular pressure [1]. Changes in the lateral geniculate ganglion detected in recent neuro-pathological studies on patients with glaucoma have been regarded to be secondary to the primarily intraocular disease [2]. Although numerous

studies have shown an association between intraocular pressure and glaucoma [3] (such as the Early Manifest Glaucoma Trial), the concept of elevated intraocular pressure as the primary pathogenic mechanism in glaucoma has not taken into account that what ophthalmologists call "intraocular pressure" is in reality the transcorneal pressure difference between the surrounding air with its atmospheric pressure and the intraocular space with its slightly higher pressure [4, 5]. Instead of the transcorneal pressure difference, the pressure difference between the intraocular space and the retro-lamina cribrosa space may be the primary pressure-related parameter for glaucoma [6–9], since the optic nerve head is located at the junction between the intraocular space and the orbital retrobulbar space. In the orbital retro-lamina cribrosa space, the optic nerve as part of the brain is surrounded by optic nerve meninges and cerebrospinal fluid (CSF). According to experimental studies performed by Morgan and colleagues in dogs [10], the orbital CSF pressure determines the retro lamina cribrosa tissue pressure above a level of about 4 mmHg. With the lamina cribrosa forming the bottom of the optic nerve head, the pressure difference between the intraocular space and the retrobulbar space can be called the trans-lamina cribrosa pressure difference. To test the hypothesis of a low orbital CSF pressure playing part in the pathogenesis of glaucomatous optic neuropathy, and using the lumbar CSF pressure as surrogate for the orbital CSF pressure, we conducted the present study to prospectively assess a potential relationship between the trans-lamina cribrosa pressure difference and the size of the neuroretinal rim. The later is the morphological equivalent of the optic nerve fibers in the optic nerve head and can clinically be measured.

Methods

The clinical investigation included an open-angle glaucoma group and an ocular hypertensive control group. The open-angle glaucoma group was divided into a normal-pressure glaucoma subgroup in which all recorded intraocular pressure measurements were equal to or lower than 21 mmHg; and a high-pressure glaucoma subgroup in which intraocular pressure readings were higher than 21 mmHg. The ocular hypertensive control group included subjects with elevated intraocular pressure higher than 21 mmHg as repeatedly measured by applanation tonometry, with a normal appearance of the optic nerve head and with a normal visual field. The Medical Ethics Committee of the Beijing Tongren Hospital approved the study protocol and all participants provided written informed consent, according to the Declaration of Helsinki. Based on theoretical considerations and findings in the literature [10–20], it was explained to the glaucoma patients that an abnormally low CSF pressure may be involved in the pathogenesis of their disease. These patients were also told that the purpose of the lumbar puncture was primarily for scientific reasons, but that knowledge of an abnormal CSF pressure in their individual situation may also have therapeutic consequences, such as avoidance of systemic carbonic anhydrase inhibitors, since these drugs lower cerebrospinal fluid pressure [21]. Diagnostic criteria for glaucoma were glaucomatous abnormalities of the optic nerve head, such as notches in the neuroretinal rim and localized or segmental loss of the retinal nerve fiber layer [22, 23], and glaucomatous visual field defects as shown by computerized perimetry. The optic nerve head was examined on the optic disc photographs, which were examined in a masked manner by three glaucoma specialists (WN, RR, JBJ) separately, and then in a masked manner by a panel that included all three glaucoma specialists. If one of the examiners was in doubt about the diagnosis, the patient was excluded from the study. Diagnostic criteria for a normal appearance of the optic nerve head in the ocular hypertensive group were a physiological shape of the neuroretinal rim, fulfilling the so-called Inferior-Superior-Nasal-Temporal (ISNT-) rule with the smallest part of the rim located in the temporal 60° of the optic disc [24]; no disc hemorrhages; a normal appearance of the retinal nerve fiber layer, usually with a slightly better detectability in the temporal inferior fundus region, followed by the temporal superior region, the nasal superior region, and finally the nasal inferior region [25]; the lack of wedge-shaped localized retinal nerve fiber layer defects; and a normal appearance of the retinal arteries without signs of localized narrowing and a normal appearance of the arterial diameter [26]. A glaucomatous visual field was defined by an abnormally high mean defect or pattern standard deviation of the computerized visual field examination, with the perimetric defects in spatial correlation to the abnormal morphology of the optic nerve head. The study participants with glaucomatous optic neuropathy underwent a 24-h intraocular pressure profile to substantiate the diagnosis of an elevated intraocular pressure above 21 mmHg. During those profiles, intraocular pressure was measured at 10 am, 2 pm, 6 pm, 10 pm, 2 am, 5 am, and at 7 am. In the normal-pressure glaucoma group, the patients had never used antiglaucomatous medications before, or they had stopped taking any anti-glaucomatous medication for 1 month before the examinations were performed. In the high-pressure glaucoma group, intraocular pressure lowering therapy was not stopped when the intraocular pressure profile was performed. The results of the 24-h diurnal curve were taken to classify the patients into a normal-pressure glaucoma group and into a high-pressure glaucoma group. All ocular hypertensive subjects underwent repeated intraocular pressure measurements, with some subjects participating in 24-h pressure profiles. For the diagnosis of ocular hypertension, at least two intraocular pressure measurements corrected for their dependence on the central corneal thickness

had to be higher than 21 mmHg. The intraocular pressure measurements obtained by Goldmann applanation tonometry were corrected for their dependence on the central corneal thickness according to the study by Kohlhaas and Pillunat [27], with an approximately 1-mmHg correction for every 25-μm deviation from a central corneal thickness of 550 μm. Central corneal thickness was measured for all ocular hypertensive patients by sonography (ultrasonic pachymeter SP-3000, Tomey Co. Nagoya, Japan). The neuroretinal rim area was determined by confocal scanning laser tomography (Heidelberg Retina Tomograph; Heidelberg Engineering, Heidelberg, Germany). The visual field was assessed by computerized perimetry (Humphrey Field Analyzer, Zeiss Meditec AG, Jena, Germany).

All study participants were primarily seen and examined in the Ophthalmic Department and were then referred to the Neurological Department to exclude any neurological disease. Examination there included magnetic resonance imaging of the brain and optic nerve and examination of the cerebrospinal fluid, including a lumbar pressure measurement. All study participants had an unremarkable neurological examination.

Exclusion criteria were any factors or disorders that could influence intracranial pressure, such as pseudotumor cerebri, intracranial tumors, medication (including drugs such as carbonic anhydrase inhibitors), any cranial surgery, or any lumbar puncture before inclusion in this study.

Cerebrospinal fluid pressure was measured by an experienced neurologist under local anesthesia in a standardized manner at 2 pm in a lateral decubitus position, with the patient's neck bent in full flexion and the knees bent in full flexion up to the chest [28]. A standard spinal needle (20-gauge needle, 90-mm length) was inserted between lumbar vertebrae L3/L4 or L4/L5 and pushed in until a decrease in resistance indicated that the needle had passed the dura mater. The stylet from the spinal needle was withdrawn, a manometer was connected to the needle, and the opening pressure of the CSF was measured. The neurologists performing the lumbar CSF pressure measurement were masked to the ophthalmologic findings. Taking the lumbar spinal fluid pressure measurement as surrogate for pressure in the orbital CSF space, the trans-lamina cribrosa pressure difference was calculated as intraocular pressure minus CSF pressure. For that calculation, the intraocular pressure measurement was obtained on the same day when the lumbar puncture was performed. Due to the physiologic variation of the intraocular pressure, the pressure value measured in some of the ocular hypertensive subjects at the day of the examination and then used for the statistical analysis was lower than 21 mmHg.

Statistical analysis was performed using SPSS (SPSS for Windows, version 17.0, SPSS, Chicago, IL); data are presented as mean ± standard deviation. General parameters of the study groups (Table 1) and the outcome parameters (intraocular pressure, CSF pressure and their difference) (Table 2) were compared applying Student's t test for unpaired samples or a nonparametric test (Mann–Whitney test). Linear regression was used to investigate the associations of the dependent variable "neuroretinal rim area" with the continuous or categorical independent variables, such as age, intraocular pressure, CSF pressure, and trans-lamina cribrosa pressure difference. All p values were two-sided and were considered statistically significant when the values were less than 0.05. Finally, a multivariate analysis was carried out to assess which of the pressure parameters (trans-lamina cribrosa pressure difference, CSF pressure, intraocular pressure) was best correlated with neuroretinal rim area.

Results

The study included 35 patients with open-angle glaucoma differentiated into 13 patients with normal-pressure glaucoma and 22 patients with high-pressure glaucoma, and 17 subjects with ocular hypertension (Table 1). In the glaucoma patients, the mean visual field defect as measured by computerized perimetry was 11.3±8.7 dB (median: 7.6 dB). The study groups did not vary significantly in gender, systolic and diastolic blood pressure, body height or body mass index (Table 1). The ocular hypertensive subjects were significantly (p=0.02) younger than the patients of the glaucoma group. The central corneal thickness measured in the ocular hypertensive group 581±27 μm and was significantly (p<0.001) higher than the mean central corneal thickness (546±31 μm) measured in the glaucoma group.

Intraocular pressure measured on the same day when the lumbar CSF puncture was performed did not differ significantly between both groups, if its dependence on central corneal thickness was taken into account (Table 1). The lumbar CSF pressure was significantly higher (p<0.001) in the ocular hypertensive group (Table 1). Consequently, the trans-lamina cribrosa pressure difference was significantly (p<0.001) lower in the ocular hypertensive control group than in the glaucoma group (Table 1). The neuroretinal rim area as surrogate for the amount of optic nerve fibers was significantly (p=0.001) smaller in the glaucoma group than in the ocular hypertensive group (Table 1).

Trans-lamina cribrosa pressure difference was not significantly associated with age in the total study group (p=0.59) and assessed separately in the glaucoma group (p=0.94) and in the ocular hypertensive group (p= 0.46). In a similar manner, neuroretinal rim area was statistically independent of age in the total study group (p= 0.57 for the right eye; p=0.06 for the left eye) and assessed separately within the in the glaucoma group (p= 0.61 for the right eye; p=0.14 for the left eye) and in the

Table 1 Composition of the ocular hypertensive study group and the group with primary open-angle glaucoma (mean ± standard deviation)

n	Ocular hypertensive study group 17	Primary open-angle glaucoma 35	*p* value
Age (years)	33±15	45±16	0.02
Females/males	4/13	11/24	0.75 (n.s.)
Systolic Blood Pressure (mmHg)	117±16	117±13	0.90 (n.s.)
Diastolic Blood Pressure (mmHg)	77±9	75±7	0.33 (n.s.)
Body height (cm)	170±7	170±7	0.92 (n.s.)
Body weight (kg)	69±11	66±11	0.42 (n.s.)
Body mass index	24±3	23±3	0.30 (n.s.)
Central corneal thickness (μm)	581±27	546±31	<0.001
Intraocular pressure (mmHg) (uncorrected) (right eye)	24±3	21±5	0.03
Intraocular pressure corrected for central corneal thickness (mmHg) (right eye)	22±3	21±5	0.37 (n.s.)
Intraocular pressure (mmHg) (uncorrected) (left eye)	24±4	21±5	0.01
Intraocular pressure corrected for central corneal thickness (mmHg) (left eye)	23±4	21±5	0.14 (n.s.)
Lumbar cerebrospinal fluid pressure (mmHg)	16±3	11±3	<0.001
Trans-lamina cribrosa pressure difference (mmHg) (right eye)	6±2	11±5	<0.001
Trans-lamina cribrosa pressure difference (mmHg) (left eye)	7±3	10±5	0.006
Neuroretinal rim area (mm^2) (right eye)	1.6±0.3	1.2±0.4	0.001
Neuroretinal rim area (mm^2) (left eye)	1.7±0.3	1.3±0.4	<0.001

n.s. statistically not significant

p value: statistical significance of the difference between the groups (Student's *t* test for unpaired samples)

ocular hypertensive group (p=0.49 for the right eye; p= 0.83 for the left eye).

Correlating the trans-lamina cribrosa pressure difference with the neuroretinal rim area resulted in a significant association between both parameters for the right eyes and for the left eyes (Table 2) (Fig. 1). In a similar manner, the trans-lamina cribrosa pressure difference was significantly associated with mean visual field defect as measured by computerized perimetry. Comparing the associations between neuroretinal rim area and mean visual field defect on

Table 2 Associations between neuroretinal rim area, visual field defect, and cerebrospinal fluid pressure data in subjects with ocular hypertension or primary open-angle glaucoma

	Correlation coefficient	*p* value
Neuroretinal rim area		
Correlated with (right eye):		
Intraocular pressure (corrected)	−0.16	0.27
Lumbar cerebrospinal fluid pressure	0.24	0.09
Trans-lamina cribrosa pressure difference	−0.32	0.02
Correlated with (left eye):		
Intraocular pressure (corrected)	−0.17	0.24
Lumbar cerebrospinal fluid pressure	0.28	0.04
Trans-lamina cribrosa pressure difference	−0.38	0.006
Mean visual field defect		
Correlated with (right eye):		
Intraocular pressure (corrected)	0.19	0.20
Lumbar cerebrospinal fluid pressure	−0.33	0.02
Trans-lamina cribrosa pressure difference	0.41	0.003
Correlated with (left eye):		
Intraocular pressure (corrected)	0.10	0.49
Lumbar cerebrospinal fluid pressure	−0.38	0.008
Trans-lamina cribrosa pressure difference	0.38	0.007

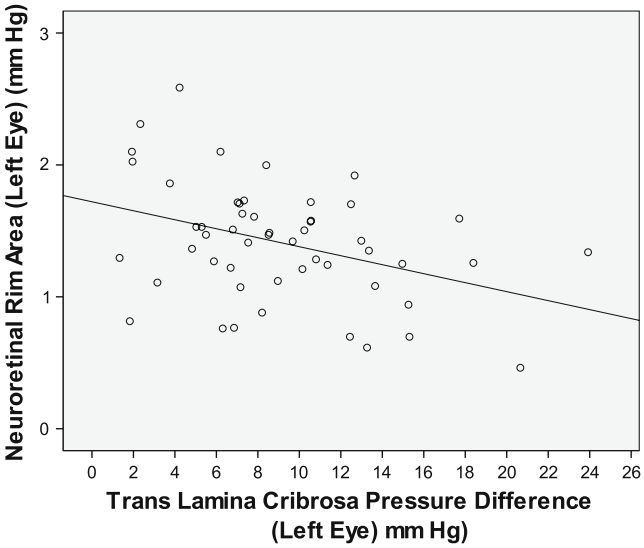

Fig. 1 Scatterplot showing distribution of the trans-lamina cribrosa pressure difference (defined as difference of intraocular pressure reading minus lumbar cerebrospinal fluid pressure) and the area of the neuroretinal rim of the optic nerve head as surrogate of the amount of glaucomatous optic nerve damage in ocular hypertensive subjects and patients with chronic open-angle glaucoma. The correlation was statistically significant ($p<0.001$; $r=-0.38$; equation of the regression line: neuroretinal rim area (mm^2) = -0.03 × trans-lamina cribrosa pressure difference (mmHg)+1.72)

one side, and intraocular pressure, lumbar CSF pressure and trans-lamina cribrosa pressure difference on the other side with each other, revealed that the probability of error was considerably lower (i.e., the p value were lower) and the correlation coefficients were higher for the associations between neuroretinal rim area/visual field defect with trans-lamina cribrosa pressure difference than for the associations between neuroretinal rim area/visual field defect and intraocular pressure or lumbar CSF pressure (Table 2).

A multivariate was then conducted and included the neuroretinal rim area as the dependent parameter and the trans-lamina cribrosa pressure difference, the CSF pressure and the intraocular pressure as dependent parameters. The analysis revealed that the rim area remained to be significantly associated with the trans-lamina cribrosa pressure difference ($p=0.041$; unstandardized coefficient B: -0.13; 95% confidence intervals (CI): -0.26, -0.01). The association between rim area with intraocular pressure ($p=0.10$; unstandardized coefficient B: 0.10; 95% confidence intervals (CI): -0.02, 0.22) and CSF pressure ($p=0.29$; unstandardized coefficient B: -0.07; 95% confidence intervals (CI): -0.20, 0.06) was no longer statistically significant.

Discussion

The results suggest that the trans-lamina cribrosa pressure difference as compared to the intraocular pressure ("transcorneal pressure difference") was significantly better correlated with the neuroretinal rim area and with the visual field loss as surrogates of the amount of glaucomatous optic nerve damage. This may suggest that the CSF pressure as trans-lamina cribrosa counter pressure against the intraocular pressure may play some role in the pathogenesis of glaucomatous optic neuropathy.

The findings of our study agree with previous investigations. More than 30 years ago, Volkov pointed out that the CSF pressure could pathogenetically be associated with glaucomatous optic neuropathy [11]. In an experimental study, Yablonski et al. decreased the intracranial pressure in cats to 5 cm H_2O below the atmospheric pressure by cannulation of the cerebral cisterna magna [12]. The intraocular pressure of one eye was reduced to slightly above atmospheric pressure by cannulation of the anterior chamber. After 3 weeks, the optic nerve heads of the eyes in which intraocular pressure was unaltered showed typical features of glaucomatous optic neuropathy. In contrast, in the eyes in which the intraocular pressure was also lowered, no changes were detected. Recent experimental and clinical studies additionally supported the hypothesis that an abnormally low CSF pressure can lead to glaucomatous optic nerve damage [6–8, 10–20, 29]. These investigations showed that the optic disc appearance in patients with normal-(intraocular)pressure glaucoma could be strikingly similar to the optic nerve head morphology in glaucoma patients with high intraocular pressure [14]. This may imply that for both patient groups, a similar pathomechanism could be postulated, i.e., an elevated trans-lamina cribrosa pressure difference either due to an abnormally high intraocular pressure or due to an abnormally low CSF pressure. Correspondingly, Chang and Singh reported that the prevalence of glaucoma in patients with normal-pressure hydrocephalus was significantly ($p=0.02$) higher than in a control group (18.1 vs. 5.6%) [19]. Consequently, Berdahl and colleagues found in a retrospective review of 31,787 medical records that the CSF pressure was lower in a group of 28 patients with open-angle glaucoma than in a control group of 49 non-glaucomatous patients [17]. In an even larger parallel study of a similar design, Berdahl and colleagues retrospectively examined the charts of 62,468 patients who had a lumbar puncture between 1985 and 2007 [18]. They analyzed 57 subjects with primary open-angle glaucoma (including 11 subjects with normal-tension glaucoma), 27 subjects with ocular hypertension, and 105 control subjects. The CSF pressure was significantly ($p<0.0001$) lower in the primary open-angle glaucoma than in the age-matched non-glaucomatous control group (9.1±0.77 mmHg vs. 11.8±0.71 mmHg). The subjects with normal-tension glaucoma also had a lower CSF pressure than did the control subjects (8.7±1.16 mmHg vs. 11.8±0.71 mmHg; $p<0.01$). Furthermore, the CSF pressure was

higher in the ocular hypertension group than in age-matched control subjects (12.6±0.85 mmHg vs. 10.6± 0.81 mmHg; $p<0.05$).

Several aspects may be addressed in the discussion of the potential role the orbital CSF pressure may play in the pathogenesis of glaucomatous optic neuropathy. First, a recent study in dogs by Morgan and colleagues showed that if the orbital CSF pressure is reduced to zero, the remaining retro-lamina cribrosa tissue pressure was 3.7±0.2 mm Hg [10]. If the CSF pressure was higher than that value, the trans-lamina cribrosa pressure gradient was strongly correlated to the difference between intraocular pressure and CSF pressure. This may suggest that the retro lamina cribrosa tissue pressure cannot be reduced to zero, even if the passage of CSF from the brain to the orbit is completely blocked. In this case, a remaining optic nerve tissue pressure behind the lamina cribrosa will be about 4 mmHg. Second, conditions associated with an elevated orbital tissue pressure, such as thyroid ophthalmopathy [30], may be expected to have a lower glaucoma prevalence. Up to now, however, studies including patients with thyroid ophthalmopathy were not focused on the prevalence or reduced rate of progression of glaucoma. In a similar manner, one may postulate that any condition with an increased intracranial pressure may be protective against glaucomatous optic neuropathy. As a corollary, brain diseases with an abnormally low CSF pressure, such as chronic liquorrhea, may have an increased prevalence of glaucoma.

Potential limitations of our study should be mentioned. First, it has remained unclear whether the lumbar CSF pressure is directly related to the CSF pressure in the orbit around the optic nerve. One has to clearly keep in mind that it is the difference between the retro-lamina tissue pressure and the intraocular pressure that determines the pressure difference across the lamina cribrosa, which was really the aim of our study in its attempt to show a relationship between trans-lamina pressure difference and glaucoma. We measured, however, the difference between the intraocular pressure determined in a sitting position and the CSF pressure measured in the left lateral decubitus position, and called it the "trans-lamina pressure difference". In a recent study on patients with communicating hydrocephalus, Lenfeldt and colleagues demonstrated that lumbar CSF pressure measurements correlated excellently to intracranial CSF pressure measurements in patients with communicating CSF systems, with a regression coefficient of 0.98 [31]. A study by Magnaes and colleagues showed that the CSF pressure at eye level (which is at the same level as the occipital prominence when sitting or standing) was on average between 0 and −10 mmHg [32]. The same patients had a lumbar CSF pressures of 4–14 mmHg in the left lateral decubitus position. The study suggested that on average the intracranial CSF pressure at eye level falls by an average of 14 mmHg as a subject changes its position from the left lateral decubitus posture to the sitting or standing posture. Second, one clearly has to state that our study has to be considered to be a pilot study. In view of many arguments against the hypothesis of a low CSF pressure as one of several pathogenic factor for glaucomatous optic neuropathy, as pointed out and summarized by Hayreh and others [33, 34], one has to await further proof. Third, the group of subjects with ocular hypertension was taken as the control group although the eyes were not normal but instead had ocular hypertension. In addition, the ocular hypertensive group was younger than the two other groups. The younger age may have been a confounding factor in the statistical analysis. The statistical analysis showed, however, that the trans-lamina cribrosa pressure difference and neuroretinal rim area were not significantly associated with age, neither in the total study group nor assessed separately in the glaucoma group and in the ocular hypertensive group. One may infer, therefore, that the younger age of subjects of the ocular hypertensive group may not have markedly influenced the results and conclusions of our study. Fourth, the anti-glaucomatous therapy for the normal-pressure glaucoma patients was stopped before the 24-h pressure profile was performed, while the patients of the high-pressure glaucoma group continued taking their anti-glaucomatous medications. Since, however, the high-pressure glaucoma patients were usually on long-term treatment (in contrast to the normal-pressure glaucoma patients, most of whom were not treatment before inclusion into the study) the intraocular pressure of the high-pressure glaucoma patients under treatment as compared to stopping the therapy may have represented more accurately the preceding pressure values under which the optic nerve damage developed and the neuroretinal rim was lost. In conclusion, the trans-lamina cribrosa pressure difference as difference of intraocular pressure minus between lumbar CSF pressure was the main pressure parameter associated with the amount of glaucomatous optic nerve damage in our study. This shows the importance the CSF pressure as counter pressure against the intraocular pressure across the lamina cribrosa of the optic nerve head has for the pathogenesis of glaucomatous optic neuropathy. Through the CSF pressure, glaucoma is not only an ocular disorder but a cerebral disease.

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