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High Tension Glaucoma and Normal Tension Glaucoma in Brain MRI

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Abstract

Introduction: Functional and structural changes of the central nervous system corresponding to high tension glaucoma (HTG) and normal tension glaucoma (NTG) were studied.

Methods: In four patient groups, 80 eyes in 40 patients were examined. First group of 30 patients had three types of HTG: 10 with primary open angle glaucoma (POAG), 10 with pigmentary glaucoma (PG) and 10 of the monitored patients had pseudoexfoliative glaucoma (PEXG). The last patient group consisted of 10 patients with NTG. Comparison of the visual field, GDx, macular volume, PERG and PVEP was performed with the control group consisting of 40 eyes in 20 healthy subjects of comparable age and refraction.

From the group of patients with HTG and NTG, we further studied functional brain changes using functional magnetic resonance imaging (fMRI). We examined 9 patients with HTG in different stages and 8 NTG patients (stage initial to medium) using fMRI with optical stimulation. Brain activations in both patient groups were compared with group of 8 healthy controls.

Moreover, the size of lateral geniculate nucleus in these patients with HTG and different stages of NTG was compared.

Results: Patients with PG had the highest degree of damage of the optic pathway. In the NTG, however, the ganglion cell layer was relatively normal but significant pathological changes were found in the optic pathway. Restriction in visual cortex activation indicates that the progression of high tension glaucoma corresponded to the functional changes in the cerebral cortex. Similar behavior was not observed in patients with NTG. We also proved the reduction of lateral geniculate nucleus (LGN) in both HTG and NTG.

Conclusion: We conclude that in HTG of varied etiology, the damage occurs in the entire optic pathway. Based on our experience as well the medical literature, we think that HTG and NTG are different diseases and therefore their approach should be different.

Keywords: High tension glaucoma; Normal tension glaucoma; Functional changes; FMRI

Abbreviations: B/W: Black/white; CNS: Central Nervous System; CCT: Central Corneal Thickness; FWHM: Full-width at Half-maximum; FMRI: Functional Magnetic Resonance Imaging; NFI: Nerve Fiber Indicator; HHVF: Homolateral Halves of Visual Field; HTG: High Tension Glaucoma; Hz: Hertz; LHVF: Left Hemifield of Visual Field; LE: Left Eye; LGN: Lateral Geniculate Nucleus; IOP: Intra Ocular Pressure; NTG: Normal Tension Glaucoma; PET: Positron Emission Tomography; PD: Pattern Defect; PERG: Pattern Electroretinogram; PEXG: Pseudo Exfoliative Glaucoma; PG : Pigmentary Glaucoma; POAG: Primary Open Angle Glaucoma; PVEP: Pattern Visual Evoked Potential; RE: Right Eye; RHVF: Right Hemifield of Visual Field; VA: Visual Acuity; YB: Yellow/blue

Introduction

HTG is defined as a chronic progressive neuropathy with excavation and atrophy of the optic nerve and consequent changes in the visual field, primarily due to intraocular pressure. This definition does not reflect current knowledge and should be updated. The current concept of glaucoma can be defined as a disease where progressive loss of retinal ganglion cells and their axons is manifested by changes in the visual field and atrophy and excavation of the optic nerve disc. Nevertheless, even this definition, emphasizing the damage to retinal ganglion cells prior to their axons, is incomplete as it does not include damage to the ganglion cells of sub cortical and cortical centers in the brain.

NTG is known to be different in some aspects from HTG. Apart from intraocular pressure, the differences are related to: the character of visual field changes that extend more to the center and have a more pronounced reduction in sensitivity [1-3], the loss of nerve fibers reaching more into the retinal center and having a focal character [4], larger and deeper excavations, while the lamina cribrosa is thinner [5], vasospasms [6], nocturnal systemic hypotension, reduced ocular pulse amplitude and fluctuations in ocular perfusion pressure [7-10], narrower retinal veins, lately even worse hemorrheologic properties of blood [11,12].

The pathophysiologic mechanism of retinal damage in HTG is not well understood. Epidemiologic studies have shown that elevated intraocular pressure is the most frequent parameter detected in human glaucoma [13]. The pathognomonic retinal change in glaucoma is the loss of ganglion cells. Whether the selective loss of ganglion cells arises as a direct consequence of intraocular pressure, due to pressure-induced ischemia or another mechanism, remains the subject of debate.

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A great deal of information about damage to retinal ganglion cells and their axons was provided by the work of Naskar et al. [14]. The authors presumed that changes at the level of ganglion cells occurred earlier than changes in their axons and concluded that in the experimental model of glaucoma, the apoptosis of retinal ganglion cells arose due to the blockade of axoplasmatic transport.

We had doubts about damage affecting only the axons of retinal ganglion cells in HTG previously in 1987, when we simultaneously measured the Pattern Electroretinogram (PERG) and the Pattern Visual Evoked Potential (PVEP) (Figure 1). We examined the healthy eyes of a 20-year-old man with an Intraocular Pressure (IOP) of 15 mmHg. Subsequently, we increased the IOP to 40 mmHg and repeated the examination. To our surprise, neurotransmission at the level of ganglion cells became blocked, while the PVEP changed only slightly. Based on our findings, we concluded that initial changes will be at the level of the ganglion cells and not their axons. For a long time, we could not find an explanation for the inability of ganglion cells to respond. Recently, with the help of work by Shou et al. [15] on shrinkage of ganglion cells after increased IOP in animal models, we have reached a better understanding. Ganglion cells, before undergoing apoptosis, defend themselves by shrinking and becoming unresponsive.

Assuming a link between HTG and NTG, we would expect ganglion cells in NTG to react similarly.

However, our previous work, in which we compared functional and structural changes in different types of HTG and NTG, does not support such a link [16]. Therefore, if the entire visual pathway is damaged by HTG, then changes must occur at both the LGN level and in the visual cortex in human glaucoma. This hypothesis has been experimentally confirmed by numerous works on LGN [17-22] and the visual cortex [18,19,23]. Similar changes as in experimental glaucoma were also identified at both levels in human glaucoma [24,25]. Using functional Magnetic Resonance Imaging (fMRI) we demonstrated changes in the visual cortex of hypertensive glaucoma patients (Lešťák 2011) and also a correlation between visual field changes in high tension glaucoma and changes in BOLD signal in functional magnetic resonance of the visual cortex. We presumed that in the case of NTG, no changes will be detected in the visual cortex. The presumption was supported by the results of PERG and PVEP, where the response of ganglion cells of the retina was relatively normal, and changes were found mainly in the visual pathway [16]. In this present study, we also tested the hypothesis that in HTG there is also a change in visual cortex activation under color stimulation unlike in NTG where changes in activation have not been detected [26,27].

Methods

Group of patients and methods

Sixty subjects were included in our study and had both eyes examined. To be enrolled, patients had to have a visual acuity of 1, with a refraction defect less than -5 diopters of myopia or + 3 diopters of hypermetropia. None of them had any ocular or neurological disorders other than glaucoma. There were 4 groups of 10 patients according to the type of glaucoma. Thirty patients had three types of HTG: primary open angle glaucoma (POAG), pigmentary glaucoma (PG) or pseudoexfoliative glaucoma (PEXG) and another 10 patients had NTG. The control group was composed by 20 healthy subjects of comparable age and refraction. The characteristics regarding sex, age and refraction are listed in (Table 1).

All subjects underwent comprehensive eye examinations, including biomicroscopy, gonioscopy, daytime IOP curve, perimetry, GDx NFI, PERG and PVEP. Best corrected visual acuity was 1, IOP after Corneal Central Thickness (CCT) correction was under 18 mmHg, with treatment in those patients with HTG. Examination of the visual field was made using a Medmont M700 device with a fast threshold glaucoma program. The degree of change was determined using the index - pattern defect - PD (dB). Measurement of the nerve fiber layer was done with the GDx - VCC device (laser polarimeter with a corneal and lens compensator). The NFI (nerve fiber indicator) parameter was evaluated. Measurement of the macular volume - MV was performed using an OCT Stratus device; results are presented in volume units (mm^3).

Pattern electroretinogram - PERG and visual evoked potentials - PVEP, were performed using a Retiscan (Roland Consult, Germany).

Functional MRI

A subset of 9 patients with different stages of high-tension glaucoma (3 females aged 41-65 and 6 males aged 40-73) and 8 patients with normotensive glaucoma (6 females aged 53-

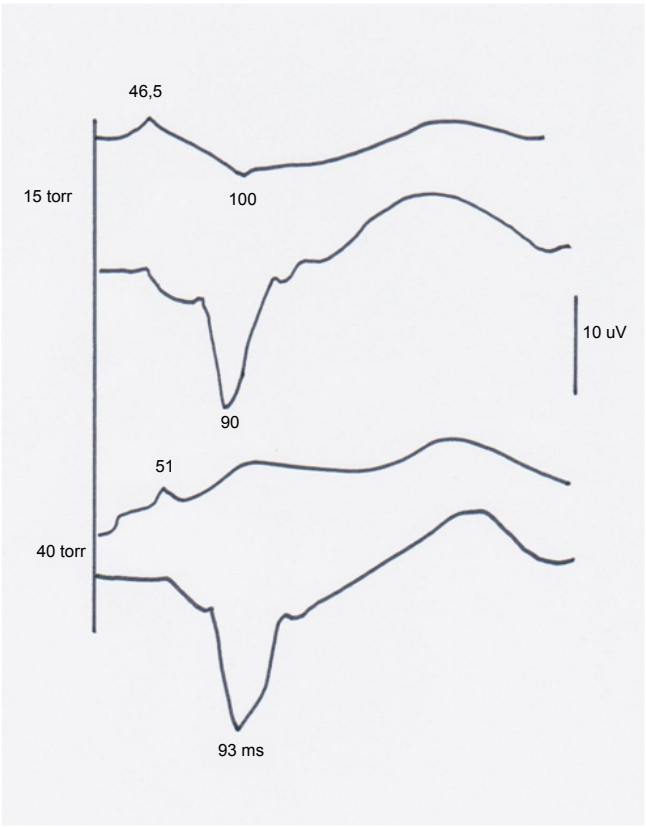

Figure 1: Simultaneous PERG and PVEP measurement of normal IOP (top) and after an increase in IOP to 40 mmHg (below).

Group	Sex (M/F)	Age (mean/range)	Refraction (mean/range)
POAG	5/5	47/44-55	-0.1/-3.25-+1
PG	3/7	45/21-55	-4.325/-1.5-6.25
PEXG	8/2	65/59-75	0.66/-2.5-+1.5
NTG	7/3	55/44-69	0.08/-2.5-+1.5
control	10/10	40/23-50	-1.12/-2.75-+2.25

Table 1: Patient demographic data.

70 and 2 males aged 40 and 52 years) were further studied using fMRI (3 females aged 41-65 and 6 males aged 40-73). The sum of sensitivities in the homolateral halves of the visual fields (ranging from 0-22 degrees) was compared to the extent of fMRI contralateral activity of the visual cortex. This group was compared with a group of eight healthy subjects (3 females aged 23-46 and 5 males aged 23-65).

Functional MRI examinations were carried out on a Philips Achieva 3T TX MR system (Philips Healthcare, Eidhoven, Netherlands) operating with a magnetic field strength of 3 Tesla using the BOLD method. A standard 32-channel SENSE head RF coil was used for scanning. For measuring fMRI with the BOLD technique, the gradient-echo EPI sequence was used with the following parameters: TE=30 ms, TR=3 s, flip angle of 90°. The measured volume contained 39 continuous 2mm-thick slices. The voxel size measured was 2 × 2 × 2 mm (FOV=208 × 208 mm, matrix 104 × 104, SENSE factor 1.8).

Optical stimulation was provided by a black/white and yellow/blue checkerboard alternated with its negative image with a frequency of 2 Hz (BW and YB stimulation). Both measurements consisted of a sequence of five 30-second active phase periods and five resting periods of the same length (10 dynamic scans). During the resting phase of each fMRI scan, a static crosshair situated in the center of the visible field was projected. In total, every measurement included 100 dynamics and took 5 minutes.

The obtained data were processed using SPM8 software and general linear model (GLM). During the pre-process, the data were motion corrected (realignment) and corrected for time-shift of individual slices (slice timing), and then smoothed with a Gaussian filter with FWHM 6 × 6 × 6 mm and finally standardized into the MNI_152 space. For statistics on the level of individual subjects, a GLM with canonical Hemodynamic Response Function (HRF) applied to the block scheme of stimulation was used. Statistical maps were thresholded at p=0.05 with FWE correction. The difference in the number of activated voxels when using the BW or YB stimulations was tested by a t-test.

Statistical group maps of BW>YB and BW<YB differences for patients and controls were also calculated and thresholded at the uncorrected threshold of p=0.001.

Lateral geniculate nucleus

The last part of this study deals with the size of the lateral geniculate nucleus in HTG and NTG patients. We assumed that the damage to the axons of retinal ganglion cells results in degeneration of LGN ganglion cells [28].

The size of the lateral geniculate nucleus was studied in another subset of patients selected from the entire group which included 18 patients, 9 with HTG (3 women and 6 men aged 41-71 years, mean 49.3) and 9 with NTG (6 women and 3 men aged 28-74 years, mean 60.1). The control group consisted of 9 healthy subjects (4 women and 5 men, aged 24-66 years, mean 43.7). None of them had any neurological disease and structural brain imaging using MRI was normal in all subjects. The sum of sensitivity in the right halves of the visual fields (RH VF) of each individual was compared with the left LGN, and vice versa (LH VF *vs*. R LGN).

The LGN size achieved by MRI studies was performed on a 3-Tesla MRI scanner (Philips Achieva TX series release 3.2.1.1) using eight-channel sense head coil. Multiple sequences were applied: sagittal 3D T1 TFE (TR / TE 8/3, 8, 160-170 slices, voxel size of 1 × 1 × 1 mm^3, FOV 240 × 240 mm, Sense factor of 1.7, NSA 1), axial T2 TSE (TR/TE 3000/80, 28 to 30 slices, 4 mm gap, slice thickness 1 mm, FOV 240 × 240 mm, TSE factor 15, voxel size of 0.57 × 0, 74 × 4 mm^3, NSA 1), coronal and axial PDW TSE (TR/TE 3000/12, 50 slices, 2 mm slice-thickness, gap 0, FOV 120 × 120 mm, TSE factor 7, voxel size of 0.7 × 0, 89 × 2 mm^3, NSA 3). Axial T2W and sagittal T1W 3D TFE images of the brain were obtained for optimal spatial orientation and to rule out any incidental abnormalities along the visual pathways. LGN images were acquired in the coronal and transversal plane, 2mm proton-density weighted, giving a bright signal intensity by low signal intensity of white matter tracts. In all subjects, each LGN was visible.

Image analysis was performed by one neuro-radiologist, who was able to access coronal and axial PDW images of the LGN only. MR image data were analyzed using Extended MR Workspace (Philips, version R2.6.3.1). LGN height was obtained by drawing a perpendicular line from the apex of the convexity to the base of the nucleus. Other diameters of the LGN were obtained in the axial PDW plane in two perpendicular drawings [28].

The measured values were subjected to statistical analysis using Wilcoxon´s test and Spearman's rank correlation coefficient.

Results

Ophthalmological examination

Changes in the visual field were statistically significant in all the clinical groups compared to the control group (p=0.02). Similarly, statistically significant changes were found in the nerve fiber layer (p=0.00005) and in the macular volume (p=0.000281), while PERG P50-N95 amplitude in the HTG was significantly lower (p=0.000005). No statistically significant difference was observed in the NTG (p=0.463). PERG N95 latencies were statistically significantly prolonged in POAG and PG (p=0.000025 and 0.000128, respectively); no difference was observed in PEXG, while NTG had the highest difference (p=0.000). The amplitudes N70-P100 and P100-N140 PVEP were pathological in all of the glaucoma types; when comparing individual groups, the greatest difference was observed for PG (p=0.000) and NTG (p=0.000).

fMRI

The mean value of the difference in number of activated voxels when using the BW vs. YB stimulation was 59% for the patients with HTG, while for the healthy controls it was only 2%. While the BW-YB difference between the control group and the patients was given by the statistically significant 1606 voxels (p=0.039), no difference was found for YB-BW (p=0.18). This supports the hypothesis that in advanced stages of glaucoma, functional changes occurred also in the cerebral cortex. The color vision defect in patients with HTG was more significant than we had expected (28). An example of a patient with HTG is illustrated in (Figure 2 BW stimulation) and (Figure 3YB stimulation). This situation is also demonstrated in group statistic maps of BW>YB difference in Figure 4 (paired t-test).

Different situation occurred in the case of patients with NTG. The mean value of the difference in the number of activated voxels when using the BW vs. YB stimulation was only 6% for these patients (2% for the controls). Both the BW-YB and the YB-BW differences between the control group and the patients were not significant values: 318 voxels (p=0.098) and 23 voxels (p=0.799), respectively. We did not detect any corresponding functional changes in the cerebral cortex. Similarly to healthy individuals, we did not find significant differences in activation using BW and YB stimulation. An example of a patient with NTG is shown in BW stimulation (Figure 5) and YB stimulation (Figure 6).

Lateral geniculate nucleus

The LGN reduction dependence on the stage of changes in the visual fields was not statistically significant, in HTG for the right half of the visual fields (RH VF) and the left LGN r=0.3255, p=0.3926, and for the left half of the visual field (LH VF) and the right LGN r=0.0033, p=0.9934. Similarly, in NTG, a statistically significant correlation between RH VF and L LGN (r=0.0496, p=0.1745) and between LH VF and R LGN (r=0.5399, p=0.1335) was not found as well.

We found a reduction of LGN in both HTG and NTG patients (p=0.0000). We also found median duration dependence in HTG treatment in the reduction of the LGN. R=-0.4908, p=0.179 for the right LGN and r =-0.7743, p=0.0143 for the left LGN.

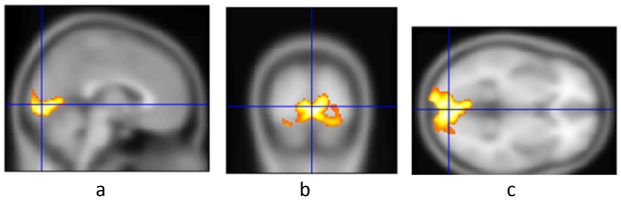

Figure 2: A male patient, 41 years old, POA glaucoma, FMRI after BW stimulation. Sagittal (a), coronal (b), and transversal section (c).

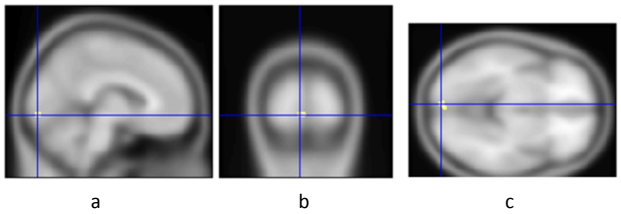

Figure 3: The same patient as in Figure 2, FMRI after YB stimulation, a significant decrease in activity in the visual cortex. Sagittal (a), coronal (b), and transversal section (c).

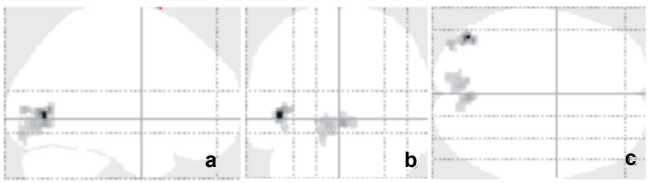

Figure 4: The group statistic map of the difference between BW and YB stimulation (BW>YB). Sagittal (a), coronal (b), and transversal MIP projection (c).

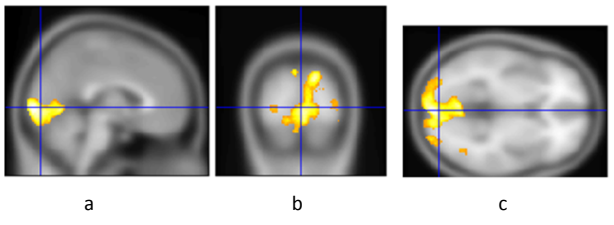

Figure 5: A female patient, 61 years old, normal tension glaucoma, FMRI after B/W stimulation. Sagittal (a), coronal (b), transversal section (c).

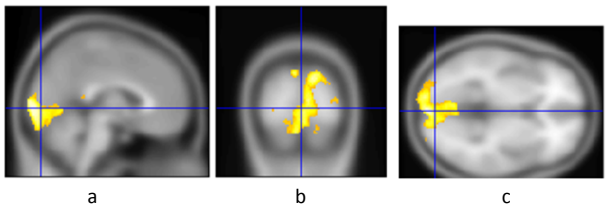

Figure 6: The same patient as in Figure 4, FMRI after B/Y stimulation. The activity in the visual cortex is almost without changes compared to B/W stimulation. Sagittal (a), coronal (b), and transversal section (c).

Discussion

Our results show that in HTG of various etiologies (POAG, PG or PEXG), the damage occurs in the entire optic pathway (from the retinal ganglion cells up to the centers of vision in the brain). Patients with PG had the highest degree of damage of the optic pathway. In the NTG group, however, the ganglion cell layer was relatively normal but significant pathological changes were found in the optic pathway.

Structural changes of the entire optical path in HTG are also verified by the histological findings [24]. This also reflects changes of PERG and PVEP [29,30]. Our results are in good agreement with these results. We still don't know why the decrease of VEP amplitude is more pronounced in PG then in other glaucoma with an open angle. To our best knowledge, the explanation cannot be found in literature because the relevant data comparing VEP in various types of glaucoma have yet to be published. Zhong et al. [31] compared VEP in HTG and NTG patients but they did not find any statistical difference either in latency or amplitudes.

As far as functional changes of the visual cortex found using fMRI is concerned, there are only several publications. There has been little interest in brain fMRI in glaucoma and in both previous studies changes in the visual cortex in human glaucoma were reported [32,33]. In this present study, we observed not only damage to the central nervous system in HTG patients with various changes in the visual field, but also functional changes in the visual cortex in response to changes in visual fields. Apart from our previous work [34], investigation of visual cortex activity in NTG has not been described in the literature. We demonstrated that in the patients with NTG there were no corresponding functional changes in the cerebral cortex, unlike in those with HTG, where the advanced stage of glaucoma changes were associated with lower activation of the visual cortex. We assume that NTG has a different pathogenetic behavior than the HTG.

It must be emphasized that the results of neural activity changes using fMRI is not direct evidence of neurodegeneration LGN in glaucoma patients or the visual cortex. We believe that, specifically in HTG, changes in BOLD activity are evidence of decreased oxygen utilization due to the reduced number of surviving ganglion cells in the visual cortex of the brain. Previous structural studies support this assumption as well [35].

Gupta et al. [24] described in greater detail the pathophysiology of glaucoma along the afferent direction, from the eye to the superficial layers of the primary visual cortex. They reported a case of advanced

human glaucoma with changes in the visual fields demonstrating the presence of central neural degeneration at multiple levels of the visual system. Pathological findings in the optic nerves, posterolateral part of the LGN and visual cortex below the sulcus calcarinus correlated with clinical findings as well.

Boucard et al. [35] arrived at similar results after the examination of eight glaucoma patients in comparison with twelve age-matched healthy subjects. They acquired high-resolution anatomic images of the visual cortex by magnetic resonance imaging. A comparison of the gray matter between patients and the control group revealed density reduction in the approximate retinal lesion projection zones in visual cortex. The authors concluded the study by stating that long-term cortical deprivation, due to retinal lesions acquired later in life, was associated with a specific retinotopical neuronal degeneration of the visual cortex.

On the other hand, the collected NTG data showed a weak indirect correlation between changes in the field of vision and changes in the visual cortex, R= -0.270 (p=0.558), R=-0.071 (p=0.879), respectively. The obtained HTG data subjected to statistical analysis (non-parametric Spearman's rank correlation coefficient) showed a medium-grade correlation between the visual field changes and the changes in the visual cortex, R=0.667 (p<0.05), R=0.767 (p<0.016), respectively. This leads to the conclusion that the progression of HTG corresponds to the functional changes in the cerebral cortex.

The reason that changes in ganglion cells, the LGN and visual cortex occur can be explained by the principle of transneuronal degeneration of the visual system [36]. Besides Walerian degeneration, feedback mechanisms of the visual cortex and the cortex itself may also participate in the process of degeneration. Excessive flushing or blockage of resorbed glutamate induces apoptosis of retinal ganglion cells. The same neurotransmitter can be found in the LGN and visual cortex, therefore higher values may also damage the ganglion cells of these structures. In NTG, there is no direct damage to retinal ganglion cells, and ganglion cells of visual cortex stay relatively normal. Damage to axons of the frontal part of visual pathway by potential ischemic processes involves damage of the LGN.

We did not detect any structural abnormalities in the brain of HTG patients or in controls by MRI. In three NTG patients with the largest visual field changes, we found nonspecific gliotic foci probably of vascular etiology. Focal neurological findings were normal in all of these subjects. Ong et al. [33] and Stroman et al. [37] found by means of MRI similar changes of cerebral strokes of ischemic etiology giving possible ground for normotensive glaucoma.

Limitation of the Study

The principal limitation of our study is low number of subjects in each of the studied groups (8 subjects in each group). Unfortunately, it is not easy to include patients with various types of glaucoma into a scientific study and this fact is also confirmed by other authors with an even lower number of studied patients [32,38].

Conclusion

In this present study, we outlined differences between HTG and NTG diagnostic groups.

By means of functional MRI, we were able to demonstrate differences in the level of visual path damage. In HTG, it is the damage of the entire visual path (beginning with ganglia cells of the retina and ending in the brain visual cortex). In the case of NTG, retinal cells remain relatively normal but the visual path is altered. With fMRI, we ascertained a restriction in visual cortex activation indicating that the progression of high tension glaucoma corresponded to the functional changes in the cerebral cortex. Similar behavior was not observed in patients with NTG. We also established that there is a reduction of lateral geniculate nucleus in both high tension and normal tension glaucoma

We believe that our results will contribute to the confirmation of the fundamental difference of both diagnostic groups.

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