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High Tension Versus Normal Tension Glaucoma. A Comparison of Structural and Functional Examinations

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Abstract

Purpose: The aim of the study was to compare the results of structural and functional examinations in a group of high tension glaucomas of different aetiologies and normal tension glaucoma.

Methods and patients: The authors examined 80 eyes in 40 patients; out of this number 30 patients had high tension glaucoma of three types: ten of the patients had primary open angle glaucoma (POAG), ten of them had pigmentary glaucoma (PG) while ten of the monitored patients had pseudoexfoliative glaucoma (PEXG). Ten patients had normal tension glaucoma (NTG). Results of the examinations of the visual field, GDx, macular volume, PERG and PVEP were compared with the results of the same examinations in the control group consisting of 40 eyes in 20 healthy subjects of comparable age and refraction.

Results: The results were processed using the Kruskal-Wallis test, Changes in the visual field were statistically significant in all the clinical groups compared to the control group (p<0.00-0.02>). Similarly, statistically significant changes were found in the nerve fibre layer (p<0.00-0.00005>) and in the macular volume (p<0.00-0.000281>). While PERG P50-N95 amplitude in the high tension glaucoma was significantly lower (<0.00000-0.000005>), no statistically significant difference was observed in the normal tension glaucoma (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 (p=1.0), while NTG had the statistically highest difference (p=0.000). The amplitudes N70-P100 and P100-N140 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).

Conclusion: Using the examination technique of PERG and PVEP, the authors found that in high tension glaucomas of varied etiology (POAG, PG, PEXG), the damage occurs in the whole 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 normal tension glaucoma, however, the ganglion cell layer was relatively normal but significant pathological changes were found in the optic pathway.

Keywords: High tension glaucomas; Normal tension glaucoma; Nerve fibre layer; Macular volume; PERG, PVEP

Introduction

In high pressure glaucoma, intraocular pressure is the major risk factor involved in the disease development and its progression. The degree of damage to the retinal ganglion cells and their axons depends on its level while in the normal tension glaucoma; it is rather the vascular factors which are involved in the disease progression. Based on these facts, we can assume a different location and extent of damage of the retinal cell structures and the optic pathway.

Purpose

The aim of the study was to compare the structural and functional examination techniques between the high tension glaucoma and normal tension glaucoma groups.

Group of Patients and Methods

Sixty subjects were enrolled in our set and had both eyes examined. The set was divided into 5 groups. The criteria for enrolling in the set were: Age between 23 and 75 years. Only in the pseudoexfoliative glaucoma we had to accept patients up to 75 years of age. Myopic refractive defect less than -6 dioptres and hypermetropic refraction less +3 dioptres. In clinical groups, bilateral glaucoma disease, however, not in advanced stage. Visual acuity was 1.0 without correction, or in refractive defects, with correction. The exclusion factor was a presence of ether an eye disorder or a CNS neurological disorder different than the disease which characterized the different subgroups. We tried to enroll patients with the same stage of disease into the clinical groups. The criterion changes in the visual field. The groups, therefore, had an equal number of eyes to ensure statistical validity of results.

The first group consisted of 40 eyes in 20 healthy subjects (ten women aged between 33 and 50 and ten men aged between 23 and 50 years) with no eye pathology. Their average eye refraction was -0.125 dioptres.

The second group included 20 eyes in 10 subjects with primary open angle glaucoma - POAG (five women aged between 44 and 55 and five men between 44 and 50 years). Their average eye refraction was -0.1 dioptre.

The third group included 20 eyes in ten patients with pigmentary

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glaucoma-PG (three women aged between 50 and 55 and seven men aged between 21 and 49 years). Their average eye refraction was -4.325 dioptres.

The fourth group consisted of 20 eyes in ten patients with pseudoexfoliative glaucoma -PEXG (eight women aged between 59 and 74 and two men aged between 65 and 75 years). The average refraction in both of their eyes was 0.66 dioptres.

The fifth group consisted of 20 eyes in ten patients with normal tension glaucoma-NTG (seven women aged between 44 and 69 and three men aged 46, 49 and 67 years). Their average eye refraction was 0.08 dioptres. Patients had no bleeding or notch in the optic nerve disc. The cup/disc ratio is not shown in the Table. The loss of fibers is indicated by NFI.

All the monitored eyes were examined using the following methods:

1. Determination of refraction by adding the spherical and cylindrical refractions. Patients with high hypermetropic refractions over +3 dioptres not enrolled in the set due to potential PERG abnormalities. Also, we did not enroll patients with higher myopia over -6 dioptres due to possible distortion of the macular volume results;
2. Examination of the visual field using the Medmont M700 device with a fast threshold glaucoma program. The degree of change was determined using the index - pattern defect - PD (dB);
3. Measurement of the nerve fibre layer with the GDx – VCC device (laser polarimeter with a corneal and lens compensator); the NFI (nerve fiber indicator) parameter was evaluated;
4. Measurement of the macular volume - MV using the OCT Stratus device; results are presented in volume units (mm^3);
5. Examination of the pattern electroretinogram - PERG and visual evoked potentials – PVEP, using the Retiscan device made by Roland Consult according to the ISCEV methodology. The stimulating board size was 30x38 cm for both the PERG and PVEP; the size of the squares was 1.7 cm. The distance of the stimulating board from the eye was 30 cm and the eye was corrected to this distance if necessary. Contrast of the black and white squares was 99% for PERG and 97% for PVEP. Reversal rate was 4.02 Hz for PERG and 1.827 Hz for PVEP.

The PERG voltage was detected using corneal DTL electrodes. The skin dish-shaped electrodes were placed 1 cm laterally from the outer corner of the eye. We evaluated the P50 and N95 latencies (ms) and the P50 – N95 amplitudes (uV). In the PVEP (Fz-Oz electrodes) we evaluated the P100 latency and the N70-P100 and P100-N140 amplitudes (uV).

Statistical Analysis

The statistical analysis was aimed at establishing possible differences between the groups. Testing of the differences between the control group (1) and the POAG (2), PG (3), PEXG (4) and NTG (5) groups involved independent sampling of data. In most cases, the data did not meet the normality requirement. Therefore, the non-parametric Kruskal-Wallis test was used which tests the null hypothesis that there is no evidential difference between the groups being compared against the alternative hypothesis stating that there is a significant difference between them. If the significance value of the Kruskal-Wallis test is lower than 0.05 (5%), there are statistically significant differences between the groups being compared at the reliability level of 5%.

Results

The data obtained for the visual field (PD - dB), nerve fiber layer (NFI), macular volume (MV - mm^3), PERG P50 latency (ms), PERG N95 latency (ms), PERG P50-N95 amplitudes (uV), PVEP P100 latency (ms), PVEP N70-P100 amplitude (uV) and for PVEP P100-N140 amplitude (uV) in the groups are presented in Table 1.

Changes in the visual fields were statistically significant in all of the clinical groups when compared to the control group (p<0.00-0.02>). Similarly, statistically significant changes were observed in the nerve fiber layer (p<0.00-0.00005>) as well as in the macular volume (p<0.00-0.000281>).

The PERGP50 latency did not show statistically significant difference against the control group (p<0.2-1.000>). There were statistically significant differences between PEXG and POAG, and PEXG and PG (p=0.01848 and p=0.020, respectively). The PERG N95 latencies differed as well. They were statistically significantly

	control group		POAG		PG		PEXG		NTG	
	mean	st.dev.	mean	st.dev.	mean	st.dev.	mean	st.dev.	mean	st.dev.
VF-PD	2.06	0.42	3.12	1.03	2.74	0.78	4.40	3.71	5.18	3.13
NFI-GDX	13.61	2.85	39.06	8.10	33.61	15.19	30.81	11.13	41.36	14.97
MV	7.27	0.19	6.81	0.22	6.84	0.54	6.69	0.31	6.85	0.27
P50 PERG	50.29	1.56	50.71	1.46	47.81	11.02	48.16	2.88	50.41	3.08
N95 PERG	95.26	1.59	99.81	5.62	99.96	6.52	95.06	3.92	103.41	7.24
P50-N95 PERG	14.80	2.51	9.84	2.17	9.80	3.07	9.33	2.100	12.69	2.75
P-100 PVEP	104.99	5.96	102.11	8.65	116.66	9.92	111.51	9.21	109.66	8.96
N70-P100 PVEP	12.22	3.22	7.06	1.18	5.43	2.102	7.33	2.95	4.84	2.39
P100-N140 PVEP	14.65	4.74	7.07	1.57	5.38	2.136	8.75	4.38	5.34	1.67

VF-PD (fisual field-pattern defect),
NFI (nerve fiber indicator)
MV (macular volume)
P50 PERG (latency P 50 PERG)
N95 PERG (latency P95 PERG)
P50-N95 PERG (amplitude PERG)
P-100 PVEP (latency P-100 PVEP)
N70-P100 PVEP (amplitude PVEP)
P100-N140 (amplitude PVEP)

Table 1: Summary data of examined parameters.

prolonged for PGOA and PG (p=0.000025 and 0.000128, respectively). No difference was found for PEXG (p=1.0) and the highest statistical difference was for NTG (p=0.000).

For the high pressure glaucomas, the PERGP50-N95 amplitude was significantly lower when compared to the control group (<0.00000-0.000005>). No statistically significant difference was found for the normal tension glaucoma (p=0.463). Statistically significant difference was also found between NTG and POAG and PEXG (p=0.041 and p=0.000071, respectively).

The PVEPP100 latency was statistically significantly prolonged for PG and PEXG against the control group (p=0.000387 and p=0.0188 respectively). Variability was also shown between NTG and POAG (p=0.004496), between PEXG and POAG (p=0.000034) and PG and POAG (p=0.000001).

The N70-P100 amplitudes also differed**.** They were pathological for all the glaucomas when compared to the control group (p<0.000011-0.000012>), however the highest difference against the other groups was found for PG (p=0.000) and NTG (p=0.000). It was similar for the P100-N140 amplitudes. They were pathological for all the glaucomas when compared to the control group (p<0.000002-0.000362>), however the highest difference against the other groups was found for PG (p=0.000) and NTG (p=0.000).

Discussion

Many ophthalmologists still believe that acquired excavation (cupping) of the optic nerve disc is a result of intraocular pressure being higher than the ocular perfusion pressure. Expert reports provide some important information on the issues of disc excavation.

The size of the optic nerve disc and its excavation in healthy individuals was described by Jonas et al. [1] in 319 persons (457 discs). The authors specify its horizontal diameter to be 1.76 +/- 0.31 mm and vertical diameter 1.92 +/- 0.29 mm. The disc shape was slightly vertically oval. The horizontal diameter of the cupping was 0.83 +/- 0.58 mm and its vertical diameter was 0.77 +/- 0.55 mm. The ratio between the diameter of the cupping to the disc (cup-to-disc ratio) c/d was 0.39 +/- 0.28 horizontally and 0.34 +/- 0.25 vertically. In 93.2 % of the discs, horizontal diameter exceeded their vertical diameter. In Czech literature, the size of the neuroretinal rim in relation to age was investigated by Máliš et al. [2] who examined 116 healthy eyes (116 persons). They found that in the third decade its size dropped whereby the c/d ratio increased by 9.74 %, in the fourth decade by 10.01%, in the fifth by 11.47%, in the sixth by 13.48% and in the seventh decade the c/d ratio increased by 17.55%.

The development of cupping of the optic nerve disc was summarized by Hayreh in 1974 [3] into three factors most likely responsible for this abnormality. The first one involves the destruction of neural tissue in the prelaminar region, while the second factor considers a backward bowing of the lamina cribrosa which is due to retrolaminar fibrosis and absence of the normal support of the lamina cribrosa posteriorly due to its disappearance. Weakened lamina cribrosa is the third factor. Interestingly, these changes are not only characteristic of the glaucoma changes of the disc but also of other, mainly vascular, changes.

We should also mention the study by Azuara-Blanco et al. [4] who measured the cupping of the disc in ten emmetropic and ten myopic persons (with normal IOP) using HRT. After increasing the intraocular pressure to 35.4, or 34.4 mm Hg using a suction cap, the cupping of the disc widened.

Nowadays, the changes in the field of vision are no longer used as diagnostic techniques of the early damage to axons of the retinal ganglion cells. The loss of up to 25-35% of retinal ganglion cells in glaucoma is associated with statistically significant changes in static automatic perimetry [5]. To assess the degree of defects in the visual field, we used the pattern defect method which characterizes the pathology of changes in the visual field. Our results indicate statistically significant differences in all the clinical groups compared to the control group.

It was found that changes in the nerve fiber layer precede perimetric changes by up to 6 years [6]. To examine the nerve fiber layer we used a GDx laser polarimeter with corneal compensator. The sensitivity of this examination ranges between 72 and 82% while its specificity is 56 - 82% [7]. As with the pattern defect, we observed statistically significant differences in all the clinical groups as compared to the control group.

The degeneration of the retinal ganglion cell axons and also of the cells themselves results in the reduction of thickness of the whole retina. Because of the highest concentration of ganglion cells in the macula, it is appropriate to measure the retinal volume right in this region. To measure the macular volume in the exactly specified range we used an examination with OCT Stratus. Our results published in a different study [8] are similar to those found in literature [9]. For the macular volume, as well, we found statistically significant differences in all the clinical groups as compared to the control group.

The significance of electrophysiological examinations in glaucoma has been recognized since it became evident that the pattern ERG also reflects the response of retinal ganglion cells [10]. In the experimental glaucoma, the ERG changes (drop in amplitudes by up to 50%) preceded changes in the nerve fibers layer [11]. This fact, as well as other findings, [12-14] made us employ the electrophysiological techniques (PERG) to determine the level and layer of changes in the different glaucoma groups. PVEPs characterize the state of the whole visual pathway. This is why we used the PERG and PVEP in our study as an identifier of the visual pathway changes. The PERG P50 latency did not show statistically significant difference between the clinical groups as compared to the control group. There are differences between PEXG and POAG, and PEXG and PG. We conclude that this difference can be caused by minor structural as well as functional changes in the pseudoexfoliation glaucoma. The N95 latency showed statistically significant differences in POAG, PG and NTG when compared to the control group. The largest difference was between the NTG and the control group. This suggests a damage of the retinal ganglion cell axons. Due to minimal structural and function changes the PEXG glaucoma did not show any difference against the control group. There were, however, differences between PEXG and POAG and PG. The P50-N95 amplitude showed statistically significant difference between POG, PG and PEXG when compared to the control group. In NTG, no statistically significant deviation from normal values was observed. It suggests relatively intact retinal ganglion cells. There were statistically significant differences between NTG and POAG as well as between NTG and PEXG. The PVEP P100 latency showed statistically significant difference between PG and PEXG when compared to the control group. Furthermore, a difference between NTG and all the high tension glaucomas was found. The PVEP N70-P100 amplitude and similarly the P100-N140 amplitude showed statistically significant differences between the clinical groups when compared to the control group. The largest difference was found between the NTG and the control group.

Based on our results from PERG a PVEP examinations, we can conclude that the high tension glaucomas (POAG, PG, PEXG) differ

from the NTG, the ganglion cell response being altered in the high tension glaucomas, while in the NTG it is relatively within the norm. In NTG, there is an abnormality in the PERG N95 latency which indicates mainly a damage of the retinal ganglion cell axons. PVEP demonstrates damage of the whole visual pathway in all the analyzed clinical groups. We found the largest differences in the PG and NTG.

Based on these findings we established that the normal tension glaucoma has a different pathogenesis of changes in the optic nerve disc and also the changes in visual fields as compared to high tension glaucomas. We can only speculate that the origin of the changes is other than the intraocular pressure. In high tension glaucomas it was shown experimentally that the first changes appear at the level of ganglion cells and later in their axons [15]. If the normal tension glaucoma was the same etiology, a decrease in response of the retinal ganglion cells would be expected. That is, however, not what we observed.

We could not compare our results with other authors, as there are virtually no similar studies available in the literature that monitoring simultaneously both the PERG and PVEP.

An uncertainty remains in how to proceed with the diagnostic/therapeutic procedure in the NTG patients with visual field changes, in which the ocular origin of the optic nerve disc excavation has been ruled out. Based on our own experience, we can recommend that these patients are referred to a neurologist for a consultation examination; the neurologist will decide whether further examination using imaging techniques (e.g. CT, MRA) is necessary. In addition to the neurological examination, in cooperation with a neurologist, we indicated a sonographic examination of the brain blood vessels using the brain MR and MRA in five of our patients from the NTG group who had the largest visual field changes. There were no focal neurological findings in the examined patients. In all these patients, foci of nonspecific gliosis were found with most probable CNS vascular etiology. We continue monitoring these patients. Stroman et al. [16] arrived at similar results; they found that ischemia of small cerebral vessels is more common in NTG and it potentially reflects an indirect vascular damage of the optic nerve.

Conclusion

Using the examination technique of PERG and PVEP, the authors found that in high tension glaucomas of varied etiology (POAG, PG, PEXG), the damage occurs in the whole 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 normal tension glaucoma, however, the ganglion cell layer was relatively normal but significant pathological changes were found in the optic pathway.

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