Normotensive glaucoma

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This article provides an updated overview of the structural and functional changes in normotensive glaucoma and its variations from hypertensive glaucoma. The authors point out the less familiar facts in which both diagnostic groups differ.

Key words: normotensive glaucoma, structural and functional changes, variations from hypertensive glaucoma

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INTRODUCTION

Glaucoma is still defined as a chronic progressive neuropathy with excavation and atrophy of the optic disc and subsequent changes in the visual field. However, this formulation does not capture current knowledge and must be corrected. In a more updated conception, glaucoma may be defined as a disease where progressive loss of retinal ganglion cells and their axons is manifested in changes in the visual field, with atrophy and excavation of the optic disc. But even this definition, emphasising damage of retinal ganglion cells ahead of their axons, is not comprehensive, because it does not simultaneously refer to the damage of ganglion cells in the subcortical and cortical centres of the brain. The current definitions do not differ between hypertensive (HTG) and normotensive glaucoma (NTG).

In comparison with HTG, NTG differs in several aspects: in addition to the level of intraocular pressure, there are changes in the visual field damaging the more central part and having deeper sensitivity effects in NTG patients^{1,2}; nerve fibres are damaged more significantly in the central retinal part and damage has a more focal character³; excavation is usually wider and deeper⁴; vasospasms occur in NTG patients⁵; there are night systemic hypotension, reduction of the ocular pulse amplitudes and fluctuations of the eye perfusion pressure⁶⁻⁸, narrow retinal veins and even deprived haemorheological blood characteristics^{9,10}, among others.

Many ophthalmologists still believe that the acquired excavation of the optic nerve papilla is a consequence of the fact that the intraocular pressure is higher than the eye perfusion pressure, which causes damage to nerve fibres in the retinal ganglion cells and leads to excavation occurrence and worsening. Pathogenesis of the optic disc excavation was summarised by Hayreh in 1974 (ref.¹¹) as three factors that are probably the most responsible for this abnormality:

- 1) Destruction of the nerve tissue in the prelaminar area;
- 2) Distortion of lamina cribiformis rearwards that occurs due to retrolaminar fibrosis and a lack of normal support in the back part of the lamina due to its loss;
- 3) Weakening of lamina cribiformis.

These changes, however, are not characteristic only for optic disc glaucoma atrophy, but also have other (mainly vascular) causes.

BRIEF OVERVIEW

In an experimental glaucoma, changes in ERG (the amplitudes drop by up to 50 %) preceded changes in the retinal nerve fibre layers¹².

This fact, as well as the conclusions of other authors¹³⁻¹⁵ led us to use electro-physiological methods (PERG and PVEP) to determine the level and depth of damage in various types of hypertensive glaucoma and NTG.

We included 80 eyes of 40 patients in the group. 10 patients suffered from chronic simple open-angle glaucoma (POAG), 10 from pigment glaucoma (PG), 10 from pseudo-exfoliative glaucoma (PEXG), and 10 from NTG. Results of the visual field examinations, GDx, macular volume, pattern electroretinogram (PERG), and pattern visual evoked potential (PVEP) performed in these patients were compared with the results of 20 healthy individuals of comparable age and refraction.

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 ($P<0.0001$). 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 ($P<0.0001$) and NTG ($P<0.0001$). For further information about used data see citation.

Based on these examinations, we came to the conclusion that, unlike NTG, hypertensive glaucoma damages the entire visual path. In NTG we found a relatively normal response of the retinal ganglion cells but with significant changes in the visual path¹⁶.

These findings inspired us to perform further examination of the visual cortex with the use of functional magnetic resonance. If these findings were correct, we could anticipate that activity of the visual cortex examined by means of functional magnetic resonance (fMR) would be lower in HTG than in NTG.

Firstly, we compared the sum of sensitivities in homolateral halves of the visual fields (fast threshold program on the Medmont M700 device in the range of 0-22 degrees) in eight patients with various degrees of HTG, with the results of collateral activity of the optic cortex by means of fMR.

We evaluated the obtained data concerning HTG with the use of the Non-Parametric Spearman's Correlation Coefficient that showed a moderately strong correlation between changes in the visual fields and the brain activity. $R=0.667$ ($P<0.05$), $R=0.767$ ($P<0.016$) respectively. We provided evidence that in HTG the disease progression corresponds to the changes in the visual cortex.

In NTG, the correlation coefficient showed no correlation between changes in the visual fields and changes in the optic cortex in NTG. $R=-0.270$ ($P=0.558$), $R=-0.071$ ($P=0.879$) respectively. We concluded that HGT behaves differently from NTG.

As damage of all types of retinal ganglion cells occurs primarily in HTG, it is clear that a colour-vision deficiency must also occur in these patients. This fact has been known since 1883, when it was evidenced by Bull and subsequently confirmed by other authors who specified the defect in the yellow-blue area and also found evidence of its progression with the progressing HTG. In another work, we therefore strived to find whether the fMR activity changes with the use of different stimulation. As a paradigm, we used black and white as well as yellow and blue stimulation that has to date not been quoted in any other work. We examined eight patients with HTG (various stages) and compared the results with the results of eight healthy persons. The results were surprising. We found that the difference in the number of activated voxels reached 59% in the patients with HTG when using black and white versus yellow and blue stimulation. And it amounted to only 2% in the control group. While the difference between black and white and yellow and blue stimulation reached statistically significant 1606

voxels ($P=0.039$), no difference was detected in the control group ($P=0.18$). We thereby provided evidence that in HTG the fMR activity decrease is higher when using colour paradigms than when using black and white paradigms. If HTGs pathogenetically belonged to the same group as NTGs, the fMR finding would also be similar after the colour simulation.

To confirm this hypothesis, we examined eight NTG patients and compared the results with the results of eight healthy persons. The average number of activated voxels after black and white stimulation reached 7 626 in NTG patients. It amounted to 7 462 in the control group. The average number of activated voxels after blue and yellow stimulation reached 5 650 in NTGs and 6 353 in the control group. However, the difference was not statistically significant. The average value of the difference in the number of activated voxels between black and white and blue and yellow stimulation was 6% in NTG patients. In healthy persons this difference amounted to 2%. Also in this experiment we demonstrated that HTG behaves pathogenetically differently from NTG (ref.¹⁷).

We were also interested in the structural results of the peripheral part of the visual path. Structural examination of the peripheral part of the visual path also showed interesting results. To evaluate the size of corpus geniculatum laterale (CGL) in HTGs and NTGs, we examined (Philips Achieva TX series) a group of 9 HTG patients and 9 NTG patients. The diagnosis was established, based on a complex ophthalmological examination that was supplemented with a visual field examination with the use of a fast threshold program and the Medmont M700 device. The sum of sensitivities in the homolateral halves of the vision fields (in the extent from 0 to 22 degrees) was compared to the size of contralateral CGL. We compared the measurement results with a group of 9 healthy people and submitted them to a statistical analysis with the use of the Wilcoxon test and the Spearman's rank correlation coefficient.

We detected CGL reduction in both HTGs and NTGs ($P=0.0000$). The CGL reduction was not statistically dependent on the advance of changes in the visual fields in HTGs for the right halves of visual fields (RH VF) and the left CGL, and left halves of visual fields (LHVF) and the right CGL. Similarly to in the NTGs, we did not find any statistically significant difference between RH VF and the left CGL and between LHVF and the right CGL.

Abnormally low cerebrospinal pressure (cerebrospinal fluid pressure CSF-P) is currently discussed in NTGs, which may have a similar effect on the orbital retrobulbar area in the pathogenesis of the disease to the effect of increased intraocular pressure on lamina cribiformis. Vasospasm, night systemic hypotension, decrease of the eye pulse amplitude and fluctuation of the eye perfusion pressure, narrow retinal veins and deterioration of rheological blood characteristics are commonly described in patients with NTG and may be related to lower intracranial pressure. A relationship between the blood flow and the intracranial pressure is also well known from the bibliography.

The aim of our study was to learn whether magnetic resonance (MR) could provide evidence of changes in the front part of the visual path in NTG patients with regard to the optic nerve diameter (OND), optic nerve sheath diameter (OSD) and the size of chiasma in comparison with the control group. The study included 16 NTG patients. All patients underwent a complete eye examination and examination of the front part of their visual paths. The MR examination comprised T2 coronary sequence and SS_H (Single Shot) technique with fat suppression. We determined OND and OSD in the direction of 4, 8, 16 and 20 mm from the rear pole of the eye. We compared the results with a group of 12 healthy people. The statistical analysis (pair t-test) did not provide evidence of any differences in the measured values between both optic nerves in NTGs and in the control group. When comparing the averages of NTG patients and the control group (two-sample t-test), we found that the values differ for certain variables. However, this difference could again only have been coincidental. In all cases when the values showed statistically significant differences, the values in NTG patients were lower than in the control group.

Our results showed differences in the measured values, and these differences did not appear statistically significant, with the exception of the optic chiasma width that was statistically significant. In our opinion, the length of chiasma for NTG is much more important than for OSD or OND.

We believe that the main cause of excavation in NTG patients is not the translaminal pressure gradient, but the retrolaminar loss of axons of the retinal ganglion cells, that is most probably a result of a haemodynamic defect.

As provided above, NTG is related with vasospasms, night system hypotension, reduction of the eye pulse amplitude and the eye perfusion pressure fluctuation. On the basis of this information, we defined a hypothesis that ischaemic changes may occur in the brain of NTG patients that could be more extensive than in HTG patients. Therefore, the aim of further research was to determine whether there is a correlation between changes in the visual fields and degenerative lesions in HTG and NTG patients and whether these changes are equal in both groups.

We divided the patients into two groups. The HTG group comprised 5 women and 6 men (with the average age of 60.7). The NTG group of patients comprised 11 women and 6 men (with the average age of 63.1). The control group comprised 9 women and 2 men (with the average age of 61.7). We performed the perimeter examination of all subjects with the use of the Medmont M700 device and the fast threshold program. We evaluated the pattern defect (PD). No HTG patient suffered from a pseudo-foliate glaucoma. We performed the MR examination with the use of the Philips Achieva 3T device, TX with the 32-channel SENSE RF head coil. To quantify T2 hyperintensive lesions of the white brain matter and to determine the degree of brain atrophy with measurement of the bicaudate ratio (BCR), we used transversal T2 TSE, a slice of 4 mm, TR 3000 ms, TE 80 ms. We obtained the white brain matter lesions with the use of axial T2 se-

quences using the Fazekas scale. For the Fazekas scale, we divided the white matter of both brain hemispheres into periventricular (PVWM) and deep white matter (DWM); we determined the lesion degree for each of them based on the size and merging of the lesions. To do so, we used the scale from 0 to 3, where 0 meant no finding and 3 was defined as indirect periventricular extension of T2 hyper-signal in the deep layers of the white matter in PVWM, and 3 was also defined as large confluent areas in DWM.

We did not detect any difference in BCR in either the HTG group or the NTG group. We detected statistically significant changes in BCR that correlated with changes in the visual fields. Higher amounts of PD were related to a greater brain atrophy (BCR). We did not detect any similar relation in PVWM and DWM. We detected a significant change in PVWM and DWM between NTGs, HTGs and the control group. We found the most advanced changes in HTG patients.

If ganglia cells are damaged diffusely over the entire retina in HTGs, the changes in visual fields must also be different in NTGs. It is known from the bibliography that NTG shows perimeter changes especially in the centre and these defects have manifested a greater decrease of sensitivity. To gain confirmation of the aforesaid conclusions, we examined the visual field with the fast threshold program with the use of the Medmont M700 device in 25 HTG patients (with the average age of 62.8) and 25 NTG patients (with the average age of 62.5). Both groups suffered from approximately similar changes in their visual fields. No patient suffered from any other than an ophthalmologic or neurological disease. In all patients we monitored the pattern defect (PD) and the overall defect (OD) of the visual field. Subsequently, we compared PD and OD in both groups. The statistical analysis (pair t-test) showed that PD is statistically greater than OD ($P=0.0001$) in NTG patients. On the contrary, HTG patients showed statistically higher OD values in comparison with PD ($P=0.000$). Also, this conclusion confirmed the aforementioned findings of different changes in the visual fields of both groups.

In relation to the layer of retinal ganglion cells and their axons, we wanted to find whether there is a correlation between the ganglion cell complex (GCC) and the layer of nerve fibres (RNFL) in the same altitudinal half of retina with contralateral sum of sensitivities of a half of the visual pole of the same eye. These investigations were carried out in both the HTG group and the NTG group. The HTG group comprised 25 patients, of which there were 12 women (with the average age of 53.25) and 13 men (with the average age of 60.38). The second NTG group consisted of 17 women (with the average age of 55.35) and 8 men (with the average age of 55.5). The inclusion criteria comprised: visual acuity of at least 1.0 after a possible correction lower than ± 3 dioptres. Approximately similar changes in the visual fields in all patients, while it concerned a beginning glaucoma disease. The patients did not suffer from any other eye or neurological disease. As concerns NTG patients, the diagnosis was confirmed by means of an electro-physiological examination. The GCC layer width was measured with the use of

SD-OCT RTVue -100. RNFL was similarly measured. We examined the visual field with the fast glaucoma threshold program, with the use of the Medmont M700 device. By comparing GCC and sensitivities in hemipoles of the visual fields, we detected a strong correlation only in NTG patients. We detected a similar correlation between RNFL and the visual field, except for RNFL in the upper half of the retina and lower hemipole ($r=0.3$, $P=0.1$). We did not detect any statistically significant correlation in HTG patients¹⁸.

CONCLUSION

This summary comprises new information on NTG confirming its differences from HTG. Therefore, the therapeutic approach to these diagnostic groups should also be different.

Search strategy and selection criteria

In our research strategy we focused on the evaluation of NTG studies including own new conclusions on this topic.

The data were gathered from PubMed using the PubMed Advanced Search from 1991–2016; quotation number 16 is available from: doi:10.4172/2155-9570.S5-006 in full length.

ABBREVIATION

BCR, bicaudate ratio; CGL, corpus geniculatum laterale; CSF-P, cerebrospinal fluid pressure; DWM, deep white matter; fMRI, functional magnetic resonance imaging; GCC, ganglion cell complex; HTG, hypertensive glaucoma; NTG, normotensive glaucoma; MRI, magnetic resonance imaging; OD, overall defect; OND, optic nerve diameter; OSD, optic nerve sheath diameter; PD, pattern defect; PERG, pattern electroretinogram; PEXG, pseudo-exfoliative glaucoma; PG, pigment glaucoma; POAG, open-angle glaucoma; PVEP, pattern visual evoked potential; PVWM, periventricular white matter; RH VF, right halves of visual fields; LH VF, left halves of visual fields; RNFL, layer of nerve fibres; SSh, Single Shot.

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