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Is "normal tension glaucoma" glaucoma? Differences between hypertensive and normotensive glaucoma.

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Abstract

An up-to-date review of the actual new developments in pathogenesis, functional and structural changes in Normotensive Glaucoma (NTG) and the differences between normotensive and Hypertensive Glaucoma (HTG) are presented. The authors point out new facts that distinguish the two diagnostic groups. Antiglaucomatous treatment with prostaglandins and beta blockers is essential to reduce Intra Ocular Pressure (IOP) in HTG. When treating NTG, it is important to preserve blood supply to the posterior pole of the eye, but especially to the anterior optic nerve. Prostaglandins are not appropriate in NTG patients, although their effect on reducing IOP is high. The most suitable are beta blockers (betaxolol and carteol) and brimonidine. It remains an open question whether NTG belongs to the group of open-angle glaucomas. The authors do not share this opinion.

Keywords: Hypertension glaucoma, Normal tension glaucoma, Functional and structure differences, Treatment.

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Abbreviations

BCR: Bicaudate Ratio; CCT: Central Corneal Thickness; CSF-P: Cerebrospinal Fluid Pressure; DWM: Deep White Matter; ERG: Electroretinogram; fMRI: functional Magnetic Resonance Imaging; GCC: Ganglion Cell Complex; HTG: Hypertensive Glaucoma; IOP: Intraocular Pressure; LGN: Lateral Geniculate Nucleus; MRI: Magnetic Resonance Imaging; NTG: Normotensive Glaucoma; OCTA: Optical Coherence Tomography Angiography; OD: Overall Defect; OND: Optic Nerve Diameter; OSD: Optic Nerve Sheath Diameter; PD: Pattern Defect; PERG: Pattern Electroretinogram; POAG: Primary Open-Angle Glaucoma; PVEP: Patter Visual Evoked Potential; PVWM: Periventricular White Matter; RNFL: Nerve Fibre Layer; VD: Vessel Density; VF: Visual Field.

Introduction

Definition of glaucoma

Glaucoma's are defined as a group of progressive optic neuropathies characterised by degeneration of retinal ganglion cells and resulting in changes in the optic nerve head. Loss of ganglion cells is related to the level of intraocular pressure, but other factors may also play a role. Reduction of Intraocular Pressure (IOP) is the only proven method of treating the disease [1].

Even this definition, emphasising damage to the ganglion cells of the retina before its axons, is not complete because it does not indicate damage to the ganglion cells of the subcortical and cortical centres of the brain in hypertensive glaucoma [2].

Current definitions also do not distinguish between Hypertensive Glaucoma (HTG) and Normotensive Glaucomas (NTG). Although high IOP is a risk factor for HTG, its normal value cannot explain the damage to retinal ganglion cell axons in NTG [3].

There is no evidence to date showing that normal IOP is harmful to eyes with NTG or glaucomatous optic neuropathy [4].

Literature Review

Incidence

The prevalence of NTG varies among races. Cho and Kee demonstrated the occurrence of NTG in 52-92% of Primary Open-Angle Glaucoma (POAG) in an Asian population [5].

A South African study by Rotchord et al. showed NTG in 57.1% of POAG [6]. The incidence of NTG was lower in the white population, compared to the Asian and African populations. Klein et al. found POAG in 104 individuals (2.1%) in the Beaver Dam Eye Study, which consisted of 4 926 subjects. Of this number, 33 patients (31.7%) had NTG [7]. A study from northern Italy (Egna-Neumarkt Study) by Bonomi et al. showed the prevalence of POAG in 2% of the population. Of these, 33% were NTG [8].

Pathogenesis of excavation

The pathogenesis of optic nerve disc excavation was

summarized by Hayreh in 1974 as three factors that are most probably responsible for this abnormality:

1) Destruction of nerve tissue in the prelaminar region,

2) Distortion of the lamina cribriformis posteriorly, resulting from retrolaminar fibrosis and the lack of normal posterior lamina support due to its loss,

3) Weakening of the lamina cribriformis.

However, these changes are not only characteristic of glaucomatous optic nerve target atrophy, but also have other (mainly vascular) causes [9].

Destruction of nerve tissue may occur not only in the prelaminar but also in the retrolaminar region. As was shown in the HTG experiment [10], it probably occurs in NTG as well.

Functional and structural changes

The impetus that led us to investigate glaucoma can be traced back to 1989, when we simultaneously measured the Pattern Electroretinogram (PERG) and Pattern Visual Evoked Potentials (PVEP) in a 20-year-old healthy individual. Firstly, at an intraocular pressure of 15 mm Hg and then after increasing it to 40 mm Hg. To our surprise, the transmission of electrical voltage changes was blocked at the level of retinal ganglion cells, while PVEPs changed slightly [2].

It took quite a long time to find an explanation in the experimental work of Shou et al., who demonstrated in an animal model the shrinkage of retinal ganglion cells after increasing IOP [11]. Ganglion cells undergo shrinkage before apoptosis is triggered and stop responding. If the high IOP lasts for a critical period of time, when the energy potential of the cell is used up, the shrinkage goes into apoptosis.

In experimental glaucoma, ERG changes (up to 50% decrease in amplitudes) preceded changes in the retinal nerve fibre layer [12].

These findings, like those of other authors [13-16] prompted us to use electrophysiological methods (PERG and PVEP) to determine the level and depth of damage in different types of HTG and NTG.

We included 80 eyes of 40 patients. 10 patients had chronic simple open-angle glaucoma, 10 had pigmentary glaucoma, 10 had pseudoexfoliative glaucoma, and 10 had NTG. We compared the results of PERG and PVEP in these patients with those of 20 healthy subjects of comparable age and refraction.

From the results of these examinations, we concluded in our work that HTG damages the entire visual pathway, in contrast to NTG, where we found a relatively normal retinal ganglion cell response, but significant changes in the visual pathway [17].

These findings inspired us to further investigate the visual cortex, using functional Magnetic Resonance Imaging (fMRI). If they were correct, then it can be assumed that the visual cortex activity examined by fMRI would be lower in HTG as opposed to NTG.

We first compared the sum of sensitivities in the homolateral halves of the visual fields (fast threshold program in the range 0-22 degrees) in 8 HTG patients of different degrees with the results of contralateral visual cortex activity by fMRI.

Statistical results showed a moderately strong correlation between changes in visual fields and brain activity. We demonstrated that, in HTG, disease progression correlates with functional changes in the visual cortex [18].

Similar measurements and statistical processing in NTG of different degrees of progression showed no correlation between changes in visual fields and changes in visual cortex. We concluded that HTG behaves differently from NTG [18].

Since HTG primarily involves damage to the ganglion cells of the retina, it is obvious that these patients must also have impaired color recognition. Therefore, in the following work, we sought to determine whether fMRI activity changes with different stimulation. We used both black-white and yellow-blue stimulation as paradigms. We compared the measured values in HTG patients (different stages) with those of healthy subjects. The results were surprising. We found that the difference in the number of activated voxels was 59% in HTG patients using black-white versus yellow-blue stimulation. In the control group, it was only 2% [18].

If HTGs were pathogenetically the same group as NTG, then the fMRI findings after colour stimulation would be similar. Similar measurements were performed in NTG.

The mean difference in the number of activated voxels between black-white and blue-yellow stimulation was 6% in NTG patients. In healthy subjects, this difference was equal to 2%. We have also demonstrated with this experiment that HTGs behave pathogenetically differently from NTG [18].

If ganglion cells are damaged diffusely throughout the retina (with more damage to magnocellular cells), then the changes in the fields of view must also be different for NTG. It is known from the literature that NTG has perimetric changes mainly in the centre and that these defects have a deeper decrease in sensitivity [19-21].

To confirm these findings, we examined the visual field with a glaucoma fast threshold program, using the Medmont M700 in 25 HTG and 25 NTG patients. Both groups had approximately the same changes in visual fields. In all of them, we observed the Pattern Defect (PD) and Overall Defect (OD) of the visual field. Statistical analysis showed that PD was statistically greater than OD (P=0.0001) in NTG patients. Conversely, patients with

HTG had statistically higher OD values compared to PD (P=0.000). This finding also confirmed the above findings of differences in visual field changes in both groups [17].

In relation to the visual field, we were interested in whether there was a correlation between the "Ganglion Cell Complex" (GCC) and the Nerve Fibre Layer (RNFL) in the same altitudinal retinal half with the sum of the sensitivities of the other half of the visual field (0-22 degrees) of the same eye in the HTG group (50 eyes, 25 patients) and the NTG group (50 eyes, 25 patients). Pearson's correlation coefficient was used to assess the relationship between the selected parameters. Comparing GCC and sensitivity in the hemifields of vision, we found a moderate correlation only in NTG patients. We observed a similar correlation between RNFL and visual field, except for RNFL in the upper half of the retina and the lower hemifield (r=0.3, P=0.1). We found no statistically significant correlation for HTG [22].

Focal retinal nerve fibre layer damage in NTG was also evidenced by Optical Coherence Tomography Angiography (OCTA), which showed that vessel density maps of superficial and deep retinal layers were significantly reduced at the 7 and 11 o´clock positions around the optic disc [23].

Therefore, in the following work, we focused on Vessel Density (VD) and field of view sensitivity in both HTG and NTG. The cohort consisted of 20 HTG patients. VD was measured using the Avanti RTVue XR from Optovue. The Visual Field (VF) was examined with a rapid threshold glaucoma program, using a Medmont M700 instrument. The sum of sensitivities in apostilbes was evaluated in the range of 0-22 degrees of visual field. The visual field sensitivity results were then compared with the VD of the same eye. Comparison of VF and VD of all peripapillary vessels and VD of small vessels showed a strong correlation (r=0.65 and 0.64, respectively). A similarly strong correlation was observed by comparing VF and VD of all vessels of the whole image and VD of small vessels of the whole image (r=0.65 and r=0.64, respectively). The measurements confirmed to us that all vessels are largely involved in the changes in the visual field in HTG [24].

We followed a similar procedure with NTG. The cohort also consisted of 20 patients with NTG. The correlation coefficient between VF and VD of all peripapillary vessels and VD of small peripapillary vessels showed a moderate correlation (r=0.54, r=0.55). The correlation coefficient between field of view and VD of all vessels of the whole image showed a moderate correlation (r=0.52), and VD of small vessels of the whole image showed a very weak correlation (r=0.23). Our findings confirmed that the peripapillary vascular component is mainly involved in the changes in the fields of view in NTG [25].

Because the pathology of the development of the optic nerve target excavation is, in our opinion, different in NTG than in HTG, we disagreed with the results of some authors on the thickness of the eye envelope. The aim of the next study was to determine whether there is a difference in Central Corneal Thickness (CCT) between HTG and NTG patients. Subsequently, it was to compare prostaglandin application corrected CCT (CCT correction) in both types of glaucoma. We included 50 patients with HTG (100 eyes) and 50 patients with NTG (100 eyes). Antiglaucomatous drugs, if indicated, had been taken by the patients for at least the last 5 years. Statistical evaluation showed that, in the case of both CCT and CCT correction, the values were lower in the NTG group than in the HTG group. In the case of CCT, the difference was not statistically significant (NTG 554.9+-35.7 vs. HTG 561.4+=32.7, P=0.181). In the case of CCT correction, the difference was larger, but not statistically significant (NTG 550.8+-35 vs. HTG 559.6+-33.1, P=0.06). We did not demonstrate a difference in CCT between HTG and NTG in this work [26].

Currently, abnormally low cerebrospinal fluid pressure (CSF-P) is much discussed in NTG, which may have a similar effect on the retrobulbar region of the eye as elevated intraocular pressure has on the lamina cribriformis in the pathogenesis of the disease [27-29].

Vasospasm, nocturnal systemic hypotension, decreased ocular pulse amplitude and ocular perfusion pressure fluctuations, narrow retinal veins, and impaired blood rheology are commonly described in patients with NTG and may be associated with lower intracranial pressure. A relationship between blood flow fluctuations and intracranial pressure is also known from the literature.

In our next study, the aim was to determine whether MRI can demonstrate changes in the anterior visual pathway in NTG patients, with respect to Optic Nerve Diameter (OND), Optic nerve Sheath Diameter (OSD), and chiasm size, compared with controls. The study included 16 patients with NTG. Using structural MRI, we determined OND and OSD at 4, 8, 16, and 20 mm from the posterior pole of the eye. We compared the results with a group of 12 healthy controls. Statistical analysis showed no differences in the measured values between the two optic nerves in NTG and the control group. When comparing the means between the NTG patients and the control group, we found that the values differed for certain variables. However, this difference could have been purely coincidental. In all cases where the values showed statistically significant differences, the values were lower in the NTG patients than in the control group.

Our results showed differences in the measured values, but these differences were not statistically significant, except for the width of the optic chiasm. According to us, the width of the chiasm is more important for NTG than OSD or OND [17].

We hypothesise that the main cause of excavation in NTG patients is not the translaminar pressure gradient, but the retrolaminar loss of retinal ganglion cell axons, which is most probably the result of a haemodynamic disturbance.

In a previous study, we also found a smaller value of chiasma width in NTG. Therefore, the aim of our further work was to determine whether this value is the same in HTG and NTG patients, and whether there is a correlation between the progress of the two diagnostic groups. The cohort consisted of 9 patients with HTG and 9 patients with NTG. The visual field was examined with a rapid threshold program on a Medmont M700 instrument. The sum of the sensitivities from both visual fields in the range of 0-22 degrees was compared with the chiasma width obtained by MRI examination. Using a paired t-test and Spearman's correlation coefficient, we found a reduction in chiasm width in both groups. HTG (P=0.0003), NTG (P=0.001). Chiasma narrowing showed a weak correlation with changes in visual fields in HTG (r=0.139) and a moderate correlation in NTG (r=0.375) [30].

This finding also speaks to the fact that these are two distinct diagnostic groups. By the fact that NTG is associated with blood flow disturbances, we hypothesised that NTG patients may have ischaemic changes in the brain that could be more profound than in HTG patients. Therefore, the aim of further investigation was to determine whether there is a correlation between changes in visual fields and degenerative forests in HTG and NTG patients, and whether these changes are the same in both groups. The HTG group consisted of 5 women and 6 men. The NTG group consisted of 11 women and 6 men. The control group consisted of 9 women and 2 men. All groups had the same mean age. All patients were subjected to perimeter examination with a rapid threshold program. No HTG patient had pseudoexfoliative glaucoma. To determine the degree of cerebral atrophy by measuring the Bicaudate Ratio (BCR), we used MRI. Brain white matter lesions were obtained using the Fazekas scale. For the Fazekas scale, we divided the white matter of both cerebral hemispheres into Periventricular (PVWM) and Deep White Matter (DWM); we determined the degree of lesions for each, depending on the size and confluence of the lesions. To do this, we used a scale of 0 to 3, where 0 meant no lesion and 3 was also defined as large confluent areas in the DWM. We found no difference in BCR in the two groups of HTG and NTG. We found statistically significant changes in BCR that correlated with changes in visual fields. Higher PD values were associated with greater brain atrophy BCR. We did not detect similar relationships in PVWM and DWM. We found a significant difference in PVWM and DWM between NTG, HTG and the control group. The most advanced changes were observed in HTG patients [17].

In addition to the above structural changes, systemic disorders are characteristic of NTG. The best known are vasospasms [31], nocturnal systemic hypotension, reduction in ocular pulse amplitude and fluctuations in ocular perfusion pressure [32-34], narrow retinal veins [35].

A higher prevalence of obstructive sleep apnoea/hypopnoea was noted in NTG [36] and a higher incidence of cerebrovascular disorders [37], myocardial infarcts [38] and diabetes mellitus with peripheral blood flow disorder [39].

NTG patients had abnormal blood parameters (high blood viscosity, erythrocyte aggregability, low erythrocyte resistance and low erythrocyte deformability) compared to the healthy population. All these parameters may have an impact on optic nerve hypoperfusion [40,41].

Flamer and Konieczka consider the issue of vascular dysfunction (lean physique, hypotension, cold feet, agility, athletic physique) comprehensively and call it Flammer syndrome, which is very close to NTG. On the other hand, obesity, hypertension, dyslipaemia, hypokinesia, diabetes mellitus, and smoking, point to arteriosclerosis and are close to HTG [42].

However, we did not prove the original idea of possible vascular brain damage in NTG patients. We can only speculate whether vascular damage to the anterior optic nerve in NTG is purely selective [17].

Treatment of HTG and NTG

Reduction of IOP is of cardinal importance in HTG [43]. Zarei et al., who analysed 1162 communications (from 2011 to 2017) on NTG, recommend antiglaucomatous treatment for this disease in the first place. If this treatment is not sufficient, then surgical reduction of IOP is necessary [44].

In their paper, Symes and Mikelberg report the results of an analysis of 419 ophthalmologists surveyed, who prescribe prostaglandins as the first choice treatment for NTG in 88 % and brimonidine in 10% of patients [45].

A similar procedure is carried out by Korean ophthalmologists [46]. Even in recent papers, surgical procedures to reduce IOP are recommended for NTG [47-50]. Since the treatment results of our studies do not correspond to the recommendations of the authors cited above, we take the liberty to present the interesting results of our recent investigations. We think that, in NTG, haemodynamic disturbance plays a very important role, especially in the region of the optic nerve target and its anterior part.

Effect of prostaglandins and beta blockers on the progression of HTG and NTG

If we address the issue of the effect of treatment on the progression of HTG and NTG, it is necessary to point out the difference in the changes in the fields of view in the two groups evaluated.

As discussed in the chapter on functional changes, the OD is more specific for the diagnosis and progression of visual field changes (as examined by the Medmont device) in HTG and for NTG PD [17].

Therefore, in further work, we evaluated the OD and PD

of the visual field when assessing the effect of treatment. The aim was to evaluate the progression of visual field changes in patients with HTG and NTG over 5 years after prostaglandin and beta-blocker treatment. Then, in NTG, also without antiglaucoma therapy.

In the HTG group, we followed 12 patients, with central corneal thickness (CCT-568 um) who were treated with prostaglandins, and 12 patients (CCT=544 um) who were treated with beta blockers. The IOP was in the range of 12-18 mm Hg throughout the follow-up period.

The NTG group consisted of three subgroups. The first subgroup consisted of 10 patients who were treated with beta blockers. The second subgroup consisted of 14 patients treated with Prostaglandins (PG). The third subgroup consisted of 18 patients who were untreated. The IOP was in the range of 8-12 mmHg throughout the follow-up period. No treatment was changed during this time.

We did not observe a statistically significant difference in HTG over time with treatment with prostaglandins in PD (P=0.35) and OD (P=0.09), nor with beta blockers (P=0.37 and 0.23, respectively). It is worth noting here that OD after PG treatment approached a statistically significant change.

For NTG, the largest changes in PD (P=0.0001) were in untreated patients. OD did not show statistically significant changes (P=0.25). Similarly, patients on prostaglandins had a statistically significant difference in PD (P=0.04), OD showed no statistically significant changes (P=0.4). We did not observe statistically significant differences in progression in NTG treated with beta blockers PD (P=0.7), OD (P=0.4).

Antiglaucomatous treatment with PGs and beta blockers is essential in HTG. However, beta blockers have a greater protective effect on the visual field. This cannot be said for NTG, where we only demonstrated this effect after beta blocker treatment [51].

Betaxolol, brimonidine and carteolol in the treatment of NTG

Following the above work "Effect of prostaglandins and beta blockers on the progression of hypertensive and normotensive glaucomas", we considered whether some ophthalmologics from the beta-blocker series have a different effect on NTG progression than brimonidine [51].

We evaluated a cohort of 30 patients with NTG. The first group consisted of 20 eyes of 10 patients treated with betaxolol; the second group also consisted of 20 eyes of 10 patients treated with brimonidine, and the third group consisted of the same number of eyes treated with carteolol. The visual field was examined with a rapid threshold glaucoma program on a Medmont M700 instrument. We compared visual field PD over a three-year period. We did not observe a statistically significant difference in PD in any group. We did not find a difference in the assessment of the other measured parameters either. Topical treatment with betaxolol, brimonidine or carteolol is important in NTG. All these drugs had a protective effect on the visual field. We did not observe any differences between them [52].

Conclusion

According to our long-term research, we can state that these are two different diseases. In HTG, a high IOP value plays a cardinal role. In NTG, it is probably ischaemia of the optic nerve. We can only hope that most ophthalmologists would agree with these conclusions.

Competing Interests

The authors declare that there are no competing interests associated with the manuscript.

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Author Contribution

All authors contributed equally to this article

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