NORMAL TENSION VS HIGH TENSION GLAUCOMA: AN OVERVIEW

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SUMMARY

The study provides an up-to-date overview of pathogenesis, functional and structural changes in normal tension glaucoma (NTG) and its differences from high tension glaucomas (HTG).

The authors point to less known facts which make both diagnostic groups different. First of all, there are electrophysiological findings that verify pathology in the complete visual pathway in HTG in contrast to NTG where the retinal ganglion cell response is relatively normal but the abnormalities are in the visual pathway. This corresponds to the findings of functional magnetic resonance imaging of the brain with a significant decrease in activity in HTG compared to NTG. We found a higher decrease in activity in HTG following application of the colour paradigm compared to NTG where we did not see a similar difference. We also investigated the central corneal thickness (CCT) in both diagnostic groups. We did not find a statistically significant difference. However, we found the effect of CCT on progression of the changes in visual fields in HTG. In relation to suspicion of abnormally low cerebrospinal pressure and a possible cerebrovascular fluid flow disturbance in NTG, we examined the optic nerve thickness (OND) and optic nerve sheath diameter (OSD) at a distance of 4, 8, 16 and 20mm from the posterior pole of the eye. In the comparison with the healthy population, we did not find any abnormalities except for the width of the optic chiasma that was markedly lower in NTG. In relation to a possible impairment of cerebral perfusion we determined the degrees of cerebral atrophy using magnetic resonance imaging by measuring the bicaudate ratio (BCR) and white matter lesions using the Fazekas scale. We did not find a difference between HTG and NTG in BCR. We found statistically significant changes in BCR which correlated with the changes in visual fields. The higher values of the pattern defect were associated with increased brain atrophy (BCR). We did not detect similar relations in the Fazekas scale. We found a significant difference in this parameter among NTG, HTG and a control group. We found the most advanced changes in the patients with HTG.

Conclusion: In HTG, impairment of retinal ganglion cells and subsequently also their axons, including visual cortex occurs because of a high intraocular pressure. In NTG, the retinal ganglion cells are relatively normal like the visual cortex, but alteration occurs in their axons. The cause is not a high intraocular pressure but most probably ischemia.

Key words: normal tension glaucoma, structural and functional changes, differences from high tension glaucomas

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DEFINITION OF GLAUCOMAS

Glaucomas are still defined as a chronic progressive neuropathy with excavation and atrophy of the disc of the optic nerve, and subsequent changes in the visual field. This formulation does not accurately reflect the current state of knowledge and requires correction. In the more modern conception, it is possible to define glaucoma as a pathology in which progressive loss of retinal ganglion cells and their axons is manifested in changes in the visual field, with atrophy and excavation of the disc of the optic nerve. However, even this definition, emphasising damage to the retinal ganglion cells before damage to their axons is not complete, because it does not at the same time point to damage to the ganglion cells of the subcortical and cortical centres in the brain. The current definitions do not differentiate between high tension glaucoma (HTG) and normal tension glaucoma (NTG).

All the patients stated in this study underwent a complete ophthalmological examination, including intraocular pressure curve, central corneal thickness, gonioscopy, electrophys-

iological examination, perimetry and display methods of the retina. In the patients with NTG, introacular pressure was lower than 15 mm Hg.

INCIDENCE

The incidence of NTG differs according to different races. Cho and Kee demonstrated an incidence of NTG in 52-92% of primary open-angle glaucomas (POAG) in the Asian population [12]. A South African study by Rotchord et al. [28] demonstrated an incidence of NTG in 57.1% of POAG. In the white population the incidence of NTG was lower in comparison with the Asian and African population. Klein et al. in the Beaver Dam Eye Study, which included 4926 people, determined POAG in 104 individuals (2.1%). Of this number, 33 patients had NTG (31.7%) [15]. A study from northern Italy (Egna-Neumarkt Study) by the authors Bonomi et al. determined an incidence of POAG in 2% of the population. Of these 33% were cases of NTG [2].

PATHOGENESIS OF EXCAVATION

Many ophthalmologists are still of the opinion that acquired excavation of the papilla of the optic nerve is the consequence of intraocular pressure higher than ocular perfusion pressure, in which damage to the nerve fibres of the retinal ganglion cells leads to the onset and deepening of excavation. The pathogenesis of excavation of the optic nerve disc was summarised by Hayreh in 1974 into three factors, which are most probably responsible for this abnormality [8]:

1. destruction of nerve tissue in the prelaminar region,
2. distorsion of the lamina cribriformis in a backward direction, which originates through retrolaminar fibrosis and lack of normal support of the posterior section of the lamina due to its loss,
3. weakening of the lamina cribriformis.

However, these changes are characteristic not only of glaucoma atrophy of the optic nerve disc, but also of other (mainly vascular) causes.

FUNCTIONAL AND STRUCTURAL CHANGES

One of the first impulses that led us to study glaucomas was the concurrent measurement of pattern electroretinogram (PERG) and pattern visual evoked potentials (PVEP) in a healthy 20 year old individual in 1987, first of all at an intraocular pressure (IOP) of 15 mmHg, and then after an increase to 40 mmHg. To our surprise, there was a blockade of neurotransmission on the level of the retinal ganglion cells, while PVEP changed only fractionally. It took a relatively long time before we found an explanation. We were aided in this by a study conducted by Shou et al., who demonstrated shrinkage of retinal ganglion cells following an increase of IOP on an animal model [31]. Before apoptosis is triggered, the ganglion cells succumb to shrinkage and cease to react.

In experimental glaucoma, changes of ERG (decrease of amplitudes by up to 50%) preceded changes in the retinal nerve fibre layer [6].

These facts, similarly to the conclusions of other authors [9, 24, 26], led us to the decision to use electrophysiological methods (PERG and PVEP) in order to determine the level and depth of damage in various types of high tension glaucomas and NTG.

Our cohort included 80 eyes of 40 patients. 10 patients had primary open-angle glaucoma (POAG), 10 pigmentary glaucoma (PG), 10 pseudoexfoliation glaucoma (PEXG) and 10 NTG. We compared the results of examination of the visual field, GDx, macular volume, PERG and PVEP in these patients with the results of 20 healthy individuals of comparable age and refraction.

On the basis of the above-stated examinations, we concluded the study as follows: high tension glaucomas damage the entire visual pathway, in contrast with NTG, in which we determined a relatively normal response of the retinal ganglion cells but significant changes in the visual pathway [18].

These conclusions inspired us to conduct a further examination of the visual cortex with the aid of functional magnetic resonance imaging. If they were correct, then it would be possible to assume that the activity of the visual cortex, examined with the aid of functional magnetic resonance imaging (fMRI), would be lower in HTG than in NTG.

First of all we compared the sum of sensitivities in the homolateral halves of the visual fields (fast threshold program on instrument Medmont M700 within the range of 0-22 degrees) in eight patients with various stages of HTG against the results of contralateral activity of the visual cortex with the aid of fMRI.

We evaluated the obtained data for HTG with the aid of a non-parametric Spearman correlation coefficient, which showed a medium-strong correlation between changes in the visual fields and brain activity. We demonstrated that in HTG, progression of the pathology corresponds with functional changes in the visual cortex [21].

In eight patients with various stages of NTG, the correlation coefficient did not show any correlation between changes in the visual fields and changes of the visual cortex. We concluded that HTG is manifested differently than NTG [21].

Because damage to all types of retinal ganglion cells primarily takes place in HTG, it is evident that there must also be a disorder of colour sense in these patients. In a further study we therefore attempted to determine whether the activity of fMRI changes upon the use of various stimulation. As a paradigm we used both black-white and yellow-blue stimulation, which had previously not been used in any cited study. We examined eight patients with HTG (in various stages of progression) and compared their results with those of eight healthy individuals. The results were surprising. We determined that the difference in the number of activated voxels in the patients with HTG was 59% upon

the use of black-white versus yellow-blue stimulation. In the control group only 2%. We thereby demonstrated that in HTG there is a greater decrease of fMRI activity upon the use of colour paradigms than black and white. If HTG was pathogenically the same group as NTG, then the fMRI finding would also be similar after colour stimulation [21].

For confirmation of this hypothesis, we examined eight patients with NTG and compared the results with those of eight healthy individuals. The average value of the difference in the number of activated voxels between black-white and yellow-blue stimulation in the patients with NTG was 6%. In the healthy individuals this difference was equal to 2%. In this experiment also we demonstrated that HTG pathogenically manifests itself differently from NTG [21].

If HTG results in damage to the ganglion cells diffusely throughout the entire retina, then the changes in the visual fields must be different also in NTG. It is known from the literature that NTG has perimetric changes mainly paracentrally, and these defects have a deeper decrease in sensitivity. In order to confirm these conclusions, we examined the visual field using the fast threshold program with the instrument Medmont M700 on 25 patients with HTG and 25 patients with NTG. Both groups had approximately the same changes in the visual fields. None of the patients had any other ophthalmological or neurological pathology. In all the patients we observed the pattern defect (PD) and overall defect (OD) of the visual field. We subsequently compared PD and OD in both groups. The statistical analysis demonstrated that PD is statistically greater than OD ($p = 0.0001$) in patients with NTG. By contrast, patients with HTG had statistically higher values of OD in comparison with PD ($p = 0.0001$). This conclusion also confirmed the above findings of differences in changes in the visual fields in both groups [17].

The conclusions of our studies on the visual field are in accordance with studies by other authors, who have demonstrated changes in the visual field in NTG more in the paracentral section, in which these changes had deeper defects of sensitivity [1, 16, 29]. Also corresponding to these conclusions is OCT angiography, which demonstrated that in the case of NTG the map of vascular density of the surface and deep layers was significantly reduced in no. 7 and 11 around the disc of the optic nerve [30].

Because the pathology of the occurrence of excavation on the optic nerve disc in NTG is different than in HTG, we expressed our disagreement with the results of certain authors relating to the thickness of the outer layers of the eye. The aim of this study was to determine whether any difference exists in central corneal thickness (CCT) in patients with HTG and NTG, and subsequently to compare corrected CCT (CCT correction) in both types of glaucomas by means of application of prostaglandins. We included in our cohort 50 patients with HTG (100 eyes) and 50 patients with NTG (100 eyes). Anti-glaucomatous agents, if indicated, had been used by the patients for at least the last five years. The exclusion criteria were corneal pathologies, conditions after laser procedures on the cornea and high ametropia. In all patients CCT was measured with the aid of an ultrasonic Tomey Handy Pachymeter SP100 by the same doctor. A statistical evaluation demonstrated that in the case of CCT and CCT correction, the values were lower in the group of patients with NTG than in the patients with HTG. 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 statistically insignificant (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 by means of this study [19].

We determined the issue of the progression of changes in the visual field in dependency on CCT in 132 eyes of 67 patients with HTG (40 women and 27 men). In the case of two women we included only one eye due to vision below 0.1. In all eyes intraocular pressure was below 18 mmHg after prior compensation of CCT. We compared changes (PD) in the fast threshold glaucoma program from two examinations with a time interval of five years. The statistical analysis demonstrated a weak, indirect dependency of CCT on PD. The thinner the cornea, the greater the progression of changes in the visual field ($r = -0.2675$, $p = 0.0043$). We demonstrated a similar dependency also of the influence of initial changes on their progression. The greater the changes in PD, the greater the progression. Although this study did not relate to NTG, it is possible to assume that a loss of nerve fibres in the retrolaminar region may lead to the progression of changes in the visual fields even at normal intraocular pressure [20].

We were interested in structural changes in the peripheral part of the visual pathway. For assessment of the size of the corpus geniculatum laterale (CGL) in HTG and NTG, we used MRI to examine a group of 9 patients with HTG and 9 patients with NTG. We compared the sum of sensitivities in the homolateral halves of the visual field (within the range of 0 to 22 degrees) with the size of the contralateral CGL. We compared the results of the measurement with a group of 9 healthy individuals, and then subjected the results to a statistical analysis.

We determined a reduction of CGL in both HTG and NTG ($p=0.0001$). However, the reduction of the CGL was not statistically dependent on the stage of progression of changes in the visual fields either in HTG or in NTG [17].

At present there is a great deal of discussion in relation to NTG concerning abnormally low cerebrospinal fluid pressure (CSF-P), which may have a similar effect in the pathogenesis of the disease on the retrobulbar region of the orbit as increased intraocular pressure has on the lamina cribriformis. Vasospasm, nocturnal systemic hypotension, reduction of ocular pulse amplitude and fluctuation of ocular perfusion pressure, constricted retinal veins and deterioration of rheological properties of blood are regularly described in patients with NTG, and may be linked with lower intracranial pressure. The lite-

rature also documents a relationship between fluctuation of blood flow and intracranial pressure.

The aim of our study was to determine whether magnetic resonance imaging (MRI) can demonstrate changes in the anterior part of the visual pathway in NTG patients with regard to the optic nerve diameter (OND), optic nerve sheath diameter (OSD) and the size of the chiasma in comparison with a control group. The study incorporated 16 patients with NTG. All the patients had undergone a complete ocular examination and MRI examination of the anterior section of the visual pathway. We determined OND and OSD at a distance of 4, 8, 16 and 20 mm from the posterior pole of the eye. We compared the results with a group of 12 healthy individuals. A statistical analysis (pair t-test) did not demonstrate any differences in the measured values between both optic nerves in NTG and the control group. Upon a comparison of values of diameter between patients with NTG and the control group, we determined that the values are different for certain variables. However, this difference may be purely random. In all cases where the values showed statistically significant differences, the values in the patients with NTG were lower than in the control group.

Our results showed differences in the measured values, but these differences were not statistically significant, with the exception of the width of the chiasma. In our opinion, the width of the chiasma is far more important for NTG than OSD or OND [17].

Also in accordance with our conclusions is the study by Lindén et al., who did not determine increased intracranial pressure, translaminar pressure or a correlation between changes in the visual fields and these quantities in a group of 13 patients with NTG, even upon change of body position from horizontal to vertical [23].

In parallel with this issue, the flow of cerebrospinal fluid is also examined in relation to NTG [14]. If this dynamic in the subarachnoid spaces was impaired, this would lead to a constriction of the optic nerve sheaths. We did not record anything of this kind in our study.

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

Since NTG is linked with a disorder of blood perfusion, we expressed the following hypothesis. Ischaemic changes in a brain may appear in patients with NTG, which could be deeper than in patients with HTG. As a result, the aim of our next examination was to determine whether there exists a correlation between changes in the visual fields and degenerative lesions in patients with HTG and NTG, and whether these changes are the same in both groups. The HTG group was composed of five women and six men. The group of patients with NTG was composed of eleven women and six men. The control group comprised nine women and two men. All the groups had the same average age. In all patients we performed an examination of the perimeter using the fast threshold program, and we determined the value of PD. None of the patients with HTG had pseudoexfoliation glaucoma. In order to determine the degree of brain atrophy by measurement of the bicaudate ratio (BCR) we used MRI examination. We obtained lesions of white brain matter by using the Fazekas scale. For the Fazekas scale, we divided the white matter of both brain hemispheres into periventricular white matter (PVWM) and deep white matter (DWM); we determined the degree of lesions for each region separately, depending on the size and confluence of the lesions. For this purpose we used a scale of 0 to 3, in which 0 meant no finding and 3 was defined as large confluent areas in DWM.

We did not determine a difference in BCR in any of the groups (either HTG or NTG). We determined statistically significant changes in BCR which correlated with changes in the visual fields. Higher PD values were linked with larger brain atrophy (BCR). We did not detect similar relationships in the case of PVWM and DWM. We determined a significant difference in PVWM and DWM between NTG, HTG and the control group. We recorded the most advanced changes in patients with HTG [17].

SYSTEMIC DISORDERS

In addition to the above-stated structural changes, NTG is also characterised by systemic disorders. The best known are vasospasms [5], nocturnal systemic hypotension, reduction of ocular pulse amplitude and fluctuation of ocular perfusion pressure [25, 27, 32], and constricted retinal veins [10]. A higher prevalence of obstructive sleep apnoea/hypopnoea has been recorded in NTG [22], as well as a higher incidence of strokes [33] and heart attacks [3], and diabetes mellitus with disorder of peripheral blood perfusion [13]. Patients with NTG had abnormal blood parameters (high blood viscosity, erythrocyte aggregation, low resistance of erythrocytes and low deformability of erythrocytes) in comparison with the healthy population. All these parameters may have an influence on hypoperfusion of the optic nerve [7, 11]. Flammer and Konieczka address the issue of vascular dysfunction (slim figure, hypotension, cold feet, agility) comprehensively, and refer to it as Flammer syndrome, which is very closely linked to NTG. By contrast, obesity, hypertension, dyslipidemia, hypokinesis, diabetes mellitus and smoking lead toward atherosclerosis and are closely linked to HTG [4].

CONCLUSION

In HTG the influence of high intraocular pressure leads to damage to retinal ganglion cells and subsequently also their axons, including the visual cortex. In NTG the retinal ganglion cells are relatively normal, similarly to the visual cortex, but there is alteration in their axons. The cause is not high intraocular pressure, but most probably ischaemia. As a result, NTG should be classified under a different designation, and the therapeutic approach should not consist only in reducing intraocular pressure.

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