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The anterior visual pathway in normal-tension glaucoma

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ABSTRACT

The aim of our study was to determine whether magnetic resonance imaging (MRI) could demonstrate changes to the anterior visual pathway in normal-tension glaucoma (NTG) with regard to optic nerve diameter (OND), optic nerve sheath diameter (OSD) and optic chiasm width when compared with a control group.
The study included 16 patients with NTG – ten women with a mean age of 63.6 (46-72) and six men with a mean age of 60 (47-68).
All patients underwent both a complete ophthalmologic examination and an examination of the anterior part of the visual pathway.
A complete MRI examination included the T2 coronal sequences, SSh (Single Shot technique) with fat sat (fat-supressed). We determined the OND and OSD at 4, 8, 16 and 20 mm posterior to the globe.
The study group was compared to a group of 12 healthy individuals – nine women with a mean age of 50 (46-61) and three men with a mean age of 58 (54-61).
Statistical analysis (Paired t-test) did not show any differences in measured values between both optic nerves in the NTG group and the control group.
When comparing the diameter values between patients with NTG and the control group (two-sample t-test), we found that the values differed for certain variables. However, this difference could have again been purely accidental. At any rate, in all cases where the values showed statistically significant differences, the values in patients with NTG were lower than in the control group and this applied to the vast majority of other variables as well.
Conclusion: The results showed differences in measured values, but these differences were not statistically significant, except for chiasm width which had statistical significance. We believe that chiasm width is more significant for NTG than OND or OSD.

KEYWORDS	normal tension glaucoma, optic nerve sheath diameter, optic nerve diameter, width chiasm, MRI

Introduction

Glaucoma is still defined as chronic, progressive neuropathy, characterized by excavation and atrophy of the optic disc and subsequent changes in the visual field. Current definitions do not discriminate between HTG and NTG. However, NTG is different from HTG in several aspects: Aside from intraocular pressure, there are differences in visual field impairment; more significantly, NTG affects the centre of the visual field and is associated with more pronounced defects of sensitivity [1,2,3,4]; nerve fibres of patients with NTG are more damaged in the central part of the retina, with damage of a focal character [5]; excavation is usually wider and deeper [6,7]; patients with NTG are also affected by vasospasms [8], nocturnal systemic hypotension, reduction of ocular pulse amplitude and fluctuations of ocular perfusion pressure [9,10,11], narrow retinal veins and later even by deteriorating rheological properties of the blood [12,13,14].

Currently there is much debate about abnormally low cerebrospinal fluid pressure (CSF-P), which in theory may have similar effects on the retrobulbar region of the orbit as increased IOP has on the trans-lamina cribrosa pressure differential [15,16,17].

The aim of our study was to determine whether changes to the anterior visual pathway with regard to optic nerve diameter (OND), optic nerve sheath diameter (OSD) and optic chiasm width could be demonstrated in subjects with NTG compared to a control group.

Materials and Methods

The study included 16 patients with NTG – ten women with a mean age of 63.6 (46-72) and six men with a mean age of 60 (47-68).

The study group was compared to a group of healthy individuals consisting of nine women with a mean age of 50 (46-61) and three men with a mean age of 58 (54-61).

The inclusion criteria were as follows: The diagnosis was based on a comprehensive ophthalmological examination consisting of pattern electroretinography and visual evoked potentials. For all patients, we conducted the visual field examination using the Medmont M700 (manufactured by Medmont International Pty Ltd, Australia) fast threshold glaucoma program. All patients had similar visual field impairment. None of them had any other ophthalmological or neurological disease nor did they use any topical antiglaucoma treatment.

Other inclusion criteria were: visual acuity of 1.0 or better, a refractive error not exceeding a 6.00 diopter sphere and/or a 2.00 diopter cylinder, clear ocular media with no clinically significant cataracts, open angle and no previous ocular surgery aside from uncomplicated cataract extraction.

MR examination:

The MR examination of the retrobulbar optic nerve was performed on the Philips Achieva 3T, TX series with 32-channel RF head coil SENSE. A complete MR examination included the coronal T2 sequences SSh with fat sat, slice width 3 mm, TR 1500 ms, TE 90-110 ms specifically for the retrobulbar space on the right and the left, sagittal T2 TSE, with a slice of 1, 5 mm, TR 3000 ms, TE 80 ms specifically for each retrobulbar space, transversal T2 TSE, a slice of 4 mm, TR 3000 ms, TE 80 ms, a coronal T1 TSE slice width of 2 mm, TR 450 ms, TE 10 ms and sagittal T1 TSE, with a slice of 2 mm, TR 450 and TE 10 mm. Results were processed on a Philips Extended MR WorkSpace workstation. Coronal T2 images were correlated with the sagittal plane for each bulbus. Measurement and evaluation was carried out in the coronal plane at a distance of 4, 8, 16 and 20 mm for the dorsal edge of the bulbus. Measured values of the external diameter of the sheath of the optic nerve in two perpendicular planes (OSD) and the external diameter of the optic nerve in two perpendicular planes (OND) were recorded. Optic chiasm width was detected on coronal T1 image, 2mm slide, at the level of horizontally aligned dumbbell-shaped object of chiasm, and this image was used for the measurement. **Figure No. 1 and 2**.

Evaluation of results performed by a single radiologist.

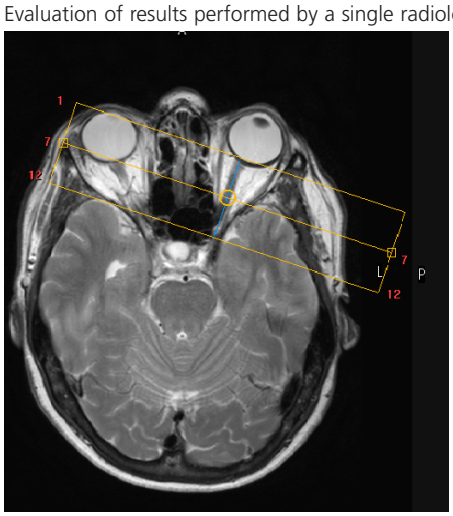
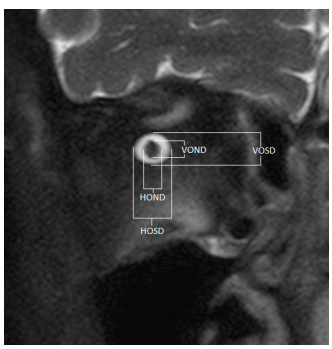
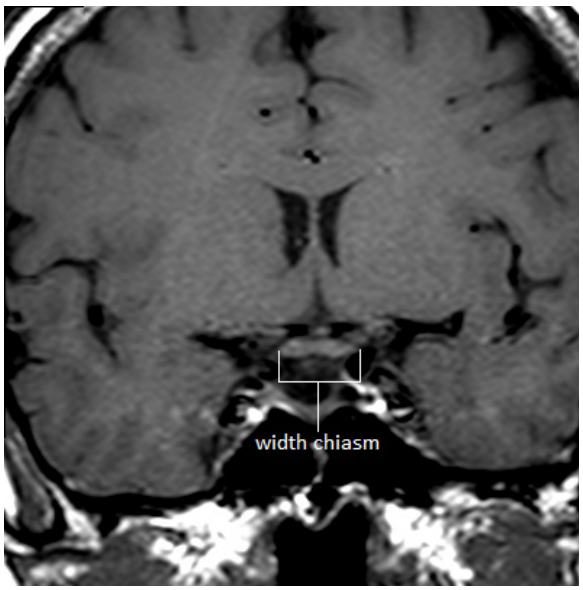


Figure 1. Planning of the plane perpendicular to the course of the left optic nerve, T2 axial TSE sequence, sections at a distance of 4, 8, 16 and 20 mm from the dorsal wall of bulbus.



a



b

Figure 2. The coronal plane of the optical nerve and the sheath of the optic nerve for the measurement of the OND and the OSD, T2 FatSat SSh, (a), the coronal plane for measuring the width of optic chiasm, 2 mm slice, T1 TSE (b)

Results

Table 1 summarizes values for the NTG group, measured by a single radiologist.

Distance	AM	SD	p
OND RV4	2.8	0.39	
OND LV4	3	0.39	0.098
OND RH4	2.48	0.4	
OND LH4	2.54	0.4	0.55
OSD RV4	5.66	0.71	
OSD LV4	5.3	0.63	0.03
OSD RH4	5.83	0.73	
OSD LH4	1.5	0.65	0.4
OND RV8	2.65	0.23	
OND LV8	2.67	0.25	0.74
OND RH8	2.28	0.36	
OND LH8	2.29	0.23	0.85
OSD RV8	4.78	0.64	
OSD LV8	4.59	0.54	0.19
OSD RH8	5.19	0.64	
OSD LH8	5.1	0.54	0.55
ONDRV16	2.58	0.36	
ONDLV16	2.44	0.44	0.13
ONDRH16	2.33	0.33	
ONDLH16	2.22	0.37	0.33
OSD RV16	4.26	0.38	
OSD LV16	4.6	0.48	0.09
OSDRH16	4.61	0.41	
OSD LH16	4.56	0.41	0.59
ONDRV20	2.47	0.45	
ONDLV20	2.28	0.33	0.09
ONDRH20	2.31	0.43	
ONDLH20	2.24	0.4	0.56
OSD RV20	4.1	0.47	
OSD LV20	3.96	0.69	0.16
OSDRH20	4.4	0.76	
OSD LH20	4.25	0.94	0.29

Table 1. Summary of values measured in the NTG group (mm). Distance-distance from the bulb, OND-optic nerve diameter, OSD-optic nerve sheath diameter, R-right, L-left, V-vertical, H-horizontal, AM-arithmetic mean, SD-standard deviation

Because both the right and left side were measured at the same time in each patient, we used a Paired t-test for the comparison. The comparison shows that the diameter values measured on the right and left sides show no statistical differences in patients with normal-tension glaucoma, except for the OSD V4 variable – with a vertical optic nerve sheath diameter at a distance of 4 mm from the eye. However, this difference is most probably purely accidental. In the case of so many values being compared (i.e. Statistical fishing), the Bonferroni correction is used for the p-value, where the difference is considered significant only if the p value is less than 0.05/n and where n is the number of values being compared (in our case 16). The P-value for the OSD V4 variable would therefore have to be less than 0.05/16 = 0.003, which is not true in this case. Other variables show no differences between the right and left sides.

	AM	SD	p
OND RV4	2.96	0.45	
OND LV4	3.12	0.26	0.17
OND RH4	2.57	0.23	
OND LH4	2.72	0.34	0.19
OSD RV4	5.46	0.89	
OSD LV4	5.43	0.97	0.86
OSD RH4	5.91	0.72	
OSD LH4	6.6	0.97	0.55
OND RV8	2.93	0.41	
OND LV8	2.8	0.33	0.01
OND RH8	2.64	0.4	
OND LH8	2.64	0.39	1.0
OSD RV8	4.8	0.63	
OSD LV8	4.61	0.69	0.08
OSD RH8	5.4	0.7	
OSD LH8	5.3	0.47	0.39
ONDRV16	2.7	0.21	
ONDLV16	2.67	0.26	0.61
ONDRH16	2.62	0.3	
OND H16	2.62	0.25	1.0
OSD RV16	4.4	0.49	
OSD LV16	3.66	0.44	0.84
OSDRH16	4.94	0.5	
OSD LH16	4.87	0.34	0.53
ONDRV20	2.74	0.42	
ONDLV20	2.56	0.41	0.21
ONDRH20	2.55	0.29	
ONDLH20	2.53	0.37	0.83
OSD RV20	4.27	0.55	
OSD LV20	4.29	0.59	0.9
OSDRH20	4.83	0.49	
OSD LH20	4.65	0.74	0.34

Table 2. Summary of values measured in the control group (mm). Distance-distance from the bulb, OND-optic nerve diameter, OSD-optic nerve sheath diameter, R-right, L-left, V-vertical, H-horizontal, AM-arithmetic mean, SD-standard deviation

The control group summary shows that the average values on the right and left sides present no statistically significant differences, with the exception of the OND V8 variable – with a vertical optic nerve diameter at a distance of 8 mm from the eye. However, this difference is again most probably just purely accidental. The P-value for the OND V8 variable would have to be less than 0.05/12 = 0.004, which is again not true in this case. Other variables show no differences between the right and left sides.

A two-sample t-test was used to compare average values obtained from NTG patients and from the control group. The comparison shows that the average diameter values are different between the NTG patients and the control group for some variables.

However, this difference may be again purely accidental for some variables. At any rate, in all cases where the average values showed statistically significant differences, the values in patients with NTG were lower than in the control group (and this applied to the vast majority of other variables as well).

The drawback of this study is the non-homogeneity of both groups. The NTG group had an average age of 62.1 years, whereas the average age of the control group was 52.2 years. To ensure the best possible homogeneity of both groups, the seven oldest patients were excluded from the NTG group. The following data show that only 3 variables now remain statistically significant:

P=0.027 for the OND LH8 diameter

P=0.00003 for the OND LH16 diameter

P=0.044 for the OND LH20 diameter

Even here, the Bonferroni correction applies, where the difference is considered significant only if the p value is less than 0.05/n and where n is the number of values being compared (in our case 19). The P-value for potentially significant variables would therefore have to be less than 0.05/19 = 0.0026, which is only true for OND LH16. Other variables show no statistically significant differences between the right and left sides.

The most significant changes were recorded for chiasm width (Table 3).

Chiasm width		SD		p
NTG	control	NTG	control	
12.4	13.33	1.9	1.7	0.004

Table 3. Average chiasm width (mm). SD-standard deviation

Discussion

In the last few years, studies have been published which try to contribute to the clarification of optic disc excavations in patients with NTG. Recent experimental, clinical and anatomic investigations suggest that some patients with NTG may have abnormally low cerebrospinal fluid pressure (CSF-P) in the retrobulbar space.

This topic has been extensively covered by Fleischman et al. [18] and Wostyn et al. [19]. Therefore, this discussion will focus only on the confirmation or disproval of some conclusions.

Many ophthalmologists still believe that acquired excavation (cupping) of the optic nerve disc is a result of intraocular pressure being higher than ocular perfusion pressure. Expert

reports provide some important information on the issues of disc excavation. In a study of 319 persons (457 discs), Jonas et al. [20] described the size of the optic nerve disc and its excavation in healthy individuals. The authors specified its horizontal diameter to be 1.76 +/- 0.31 mm and vertical diameter to be 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 c/d ratio) was 0.39 +/- 0.28 horizontally and 0.34 +/- 0.25 vertically. In 93.2 % of the discs, the horizontal diameter exceeded the vertical diameter. In the Czech literature, Malis et al. [21] investigated the size of the neuroretinal rim in relation to age in an examination of 116 healthy eyes (116 persons). They found that in the third decade its size dropped, whereas the c/d ratio increased by 9.74 %. In the fourth decade it increased 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 [22] into three factors most likely responsible for this abnormality. The first involves the destruction of neural tissue in the prelaminar region. The second considers the backward bowing of the lamina cribrosa, due to retrolaminar fibrosis and the absence of the normal support given posteriorly to the lamina cribrosa as a result of its disappearance. The weakened lamina cribrosa is the third factor. Interestingly, these changes are not only characteristic of the glaucoma changes to the disc but also of other, mainly vascular, changes.

Logically, it can be deduced that the loss of axons of retinal ganglion cells must lead to the narrowing of the optic nerve. Similar findings can therefore be expected in both hypertensive and normotensive glaucoma. Regarding the OSD values, it can also be deduced that these values should also be lower. The results of our study confirmed these conclusions, although they were not statistically significant. The most significant changes were recorded for chiasm width; its value was significantly lower ($p = 0.004$) in patients with NTG.

Our results are in line with the works of Kashiwagi et al. [23], Berdahl et al. [15], Zhang et al. [24] and Wang et al. [17]. In our work we performed measurements similar to those of Wang et al. [17] (3, 9 and 15 mm). The only difference was that we tried to capture the whole intraorbital section of the optic nerve (4, 8, 16 and 20 mm) in addition to chiasm width.

This difference in relation to the work of Jaggi et al. 2012, which measured the OSD using CT technology, has been explained in detail in the work of Wang et al. [17]. We are in agreement with this explanation.

The question of lower intracerebral pressure, which should be pathognomic for the development of excavation in patients with NTG, remains.

In the initial sections of our work, we referred to vasospasms, nocturnal systemic hypotension, reduction of ocular pulse amplitude and fluctuation of ocular perfusion pressure, narrow retinal veins and deteriorating rheological properties of the blood. The literature also reports a similar relationship between blood flow velocity fluctuations and intracranial pressure [25, 26].

The anatomical landmark of interest is the lamina cribrosa, a thin area of scleral tissue that separates two differentially pressurized compartments – the intraocular space and the orbital

subarachnoid space. The difference in pressure between these two fluid spaces is termed translaminar pressure. When described as a function of pressure across the tissues of the optic nerve and the lamina cribrosa, the term is more accurately stated as the translaminar pressure gradient. It is hypothesized that an elevated, posteriorly-directed pressure differential may contribute to optic nerve damage, which produces posterior bowing of the lamina cribrosa, often seen in patients with glaucoma [18].

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

The size of the optic chiasm examined also by Wagner et all. In the group age range of 40-60 years for men, the width of chiasma was 14.1 mm, 14.2 mm for women. For the group of patients older 60 years have seen a decline of its width to 13.8 mm in males, and 13.7 mm in females [27]. Similar values we have seen even in our control group with smaller number of patients, however.

Regarding the size of the chiasm, this parameter proved to be the most important in our study. We have not seen similar findings regarding this change in the literature.

Conclusion

All measured OND and OSD values were lower in the NTG group, but these differences were not statistically significant. Only optic chiasm width showed statistical significance ($p = 0.004$). We believe that chiasm width is more significant for NTG than OND or OSD.

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