Magnetic resonance imaging of the brain in patients with normotensive and hypertensive glaucoma.

Martin Kyncl[1], Jan Lestak[1,2,3]* Nada Jiraskova[3] and Leos Navratil[2]

1. JL Clinic, V Hurkach 1296/10, Prague, Czech Republic
2. Czech Technical University in Prague (Faculty of Biomedical Engineering), Czech Republic
3. Charles University (Faculty of Medicine in Hradec Kralove), Czech Republic

Abstract

Objective: The aim of the study was to determine whether there is a correlation between changes in visual fields and degenerative changes in the brain of patients with hypertensive (HTG) and normotensive glaucoma (NTG) and whether these findings differ in both diagnostic groups.

Patients and methods of examination: The patient cohort comprised a total of three groups. The HTG group consisted of 5 women and 6 men (40-73 years) with the average age of 60.7 years. The second – NTG – group consisted of 11 women and 6 men (45-79 years) with the average age of 63.1 years. The Control group consisted of 9 women and 2 men (56-71) with the average age of 61.7 years. We conducted the visual field examination for all patients, using the Medmont M700 (manufactured by Medmont International Pty Ltd, Australia) fast threshold glaucoma program. We evaluated the pattern defect (PD). MRI examination included T2 TSE axial sequences. We quantified the amount of cerebral white matter T2 hyperintense lesions using the Fazekas scale and determined total cerebral atrophy by measurements of the bicaudate ratio.

Results

Conclusion: MR brain imaging revealed progression of the degenerative process as assessed by the bicaudate ratio, associated with disease advancement. Scoring

according to the Fazekas scale exposed lesions in the superficial as well as deep layers of white matter in both NTG and HTG.

Keywords: MRI, bicaudate ratio, Fazekas scale, visual field, hypertensive glaucoma, normotensive glaucoma

***Corresponding author:** Jan Lestak, MD, PhD, FEBO, MBA, LLA, DBA, FAOG JL Clinic, V Hurkach 1296/10, 158 00 Prague 5, Czech Republic, E-mail: lestak@seznam.cz

Introduction

It is generally acknowledged that there are differences between normotensive glaucoma (NTG) and hypertensive glaucoma (HTG), not only in terms of intraocular pressure but also in terms of the nature of changes to the field of vision; changes, for example, which extend more towards the centre and result in a more significant decrease in sensitivity [1,9,11,21].
Some of the typical differences include: a greater interference of nerve fibres with the centre of the retina in addition to focal characteristics [17]; a larger and deeper excavation in contrast to the lamina cribrosa, which is thinner [3,14]; vasospasms [4]; night systemic hypotension, reduced ocular pulse amplitude and fluctuation of ocular perfusion pressure [7, 12,15,16,19]; narrowed retinal veins; worsening haemorrheological blood quality [5, 6, 8]; etc.

Based on this information, we hypothesised that more severe ischaemic changes may occur in the brains of patients with NTG than in those with HTG. Therefore, the aim of our study was to determine whether there is a correlation between visual field changes and degenerative lesions in the brains of patients with hypertensive and normotensive glaucoma and whether these findings differ in both diagnostic groups.

Material and methods

The patient cohort consisted of three groups. The HTG group consisted of 5 women and 6 men (40-73 years) with the average age of 60.7 years. The second – NTG – group consisted of 11 women and 6 men (45-79 years) with the average age of 63.1 years. The Control group consisted of 9 women and 2 men (56-71) with the average age of 61.7 years. We conducted a visual field examination for all patients, using the Medmont M700 (manufactured by Medmont International Pty Ltd, Australia) fast threshold glaucoma program. We evaluated the pattern defect (PD).
No patient from the HTG group had pseudoexfoliation glaucoma [22].

MRI examination of the brain was performed on the Philips Achieva 3T, TX series with a SENSE 32-channel RF head coil. For quantification of white matter T2 hyperintense lesions and for establishing the grade of cerebral atrophy by measuring the bicaudate ratio (BCR), we used transversal T2 TSE, a slice of 4 mm, TR 3000 ms, TE 80ms. The white matter lesions were attained from axial T2 sequences using the Fazekas scale.

Measurement:

Results were processed on a Philips Extended MR WorkSpace workstation. For use of the Fazekas scale, we divided the white matter of both cerebral hemispheres into periventricular (PVWM) and deep white matter (DWM); a grade was given for each, dependent on the size and confluence of the lesions. We used the scale from 0 to 3, where 0 indicated that the symptom was absent and grade 3 was defined as irregular periventricular T2 hypersignal extending into the deep white matter in PVWM, and 3 was defined as large confluent areas in DWM.

To derive the BCR, the distance between the 2 caudate nucleus apices was measured in millimetres and the value was divided by the maximum width of the skull at the same level. The bicaudate ratio (BCR) was measured on the axial T2 TSE slice on which the caudate nuclei produced the greatest amount of indentation on the lateral ventricles [2] .

For Fazekas scale definition: there are rating scales to grade the severity of white matter disease, the Fazekas scale being the most simple and commonly used. The Fazekas scale provides an overall impression of the presence of white matter

hyperintensities in the entire brain. It can be scored on transverse T2 (and/or FLAIR) images.

For the bicaudate ratio (BCR) (index): premise – enlarged ventricles increase the distance between the 2 caudate nuclei, resulting in a higher bicaudate ratio. A large value indicates a greater degree of cerebral atrophy. The bicaudate index is the ratio of the width of two lateral ventricles at the level of the head of the caudate nucleus to the distance between the outer tables of the skull at the same level. It can be a useful marker of ventricular volume and in the diagnosis of hydrocephalus, cerebral atrophy, etc.

Results

Results obtained from all patient groups are shown in Tables 1-3.

Sex/Age	BCR	Fazekas scale		Visual Field	
		PVWM	DWM	PD-RE	PD-LE
F/63	1.3/11.5	0	0	3.08	2.9
F/61	1.4/11.3	0	0	1.8	1.9
F/62	1.8/12.2	0	0	2.2	3.4
F/59	1.3/12.8	0	0	2.1	2.21
F/60	1.7/13.1	0	1	1.94	2.12
F/65	1.6/11.9	0	0	2.05	1.91
F/64	2.1/11.9	0	0	2.34	1.45
F/59	1.8/12.8	0	1	2.1	2.12
F/56	1.3/12.2	0	0	1.95	1.96
M/71	2.4/12.9	0	1	1.92	1.64
M/59	1.3/11.4	0	0	2.22	1.94

Table 1. Control group data summary.

Sex/Age	BCR	Fazekas scale		Visual Field	
		PVWM	DWM	PD-RE	PD-LE
F/79	2.1/12.2	0	1	11.7	17.41
F/69	2.0/11.6	1	1	3.1	10.25
F/51	1.8/11.8	0	0	1.79	1.85
F/45	1.5/11.4	0	0	10.11	2.65
F/71	1.9/12.0	0	0	3.72	1.95
F/62	1.5/12.4	1	1	1.98	2.31

F/60	1.1/11.7	0	0	2.42	2.08
F/65	1.8/12.3	1	1	2.51	8.19
F/66	1.5/12.4	0	0	1.53	2.07
F/70	1.8/11.9	0	1	1.66	2.02
F/67	2.0/12.4	0	0	5.58	4.6
M/60	1.3/12.2	0	0	1.78	1.87
M/67	1.8/12.1	1	1	1.33	1.69
M/63	1.7/11.7	2	2	2.01	2.59
M/58	2.0/12.5	0	1	4.87	7.04
M/53	1.7/12.1	0	0	1.97	1.53
M/67	2.8/12.3	1	1	5.18	5.88

Table 2. Summarised data from patients with NTG.

Sex/Age	B Ratio	Fazekas scale		Visual Field	
		PVWM	DWM	PD-RE	PD-LE
F/65	1.4/10.9	0	1	12.19	3.05
F/67	2.0/11.9	1	1	3.33	3.46
F/73	2.1/11.9	1	1	14.4	13.44
F/60	2.1/11.8	1	1	2.09	2.88
F/65	1.9/12.3	1	1	2.78	3.68
M/60	2.8/13.5	1	1	21.31	21.37
M/58	1.7/12.6	0	1	13.03	20.07
M/40	2.0/13.3	1	1	6.7	4.31
M/52	2.4/12.0	0	0	16.05	3.8
M/70	2.4/12.3	1	1	2.2	21.33
M/58	1.7/12.5	1	1	1.74	1.83

Table 3. Summarised data from patients with HTG.

The ANOVA test was used for comparisons of BCR between NTG, HTG, and Control groups. NTG (0.147682). HTG (0.166295) and Control (0.162191). As shown in Chart 1 and according to the ANOVA results (p=0.188), there was no significant difference in BCR between the tested groups. Lowest values were observed in the NTG group (Chart 1).

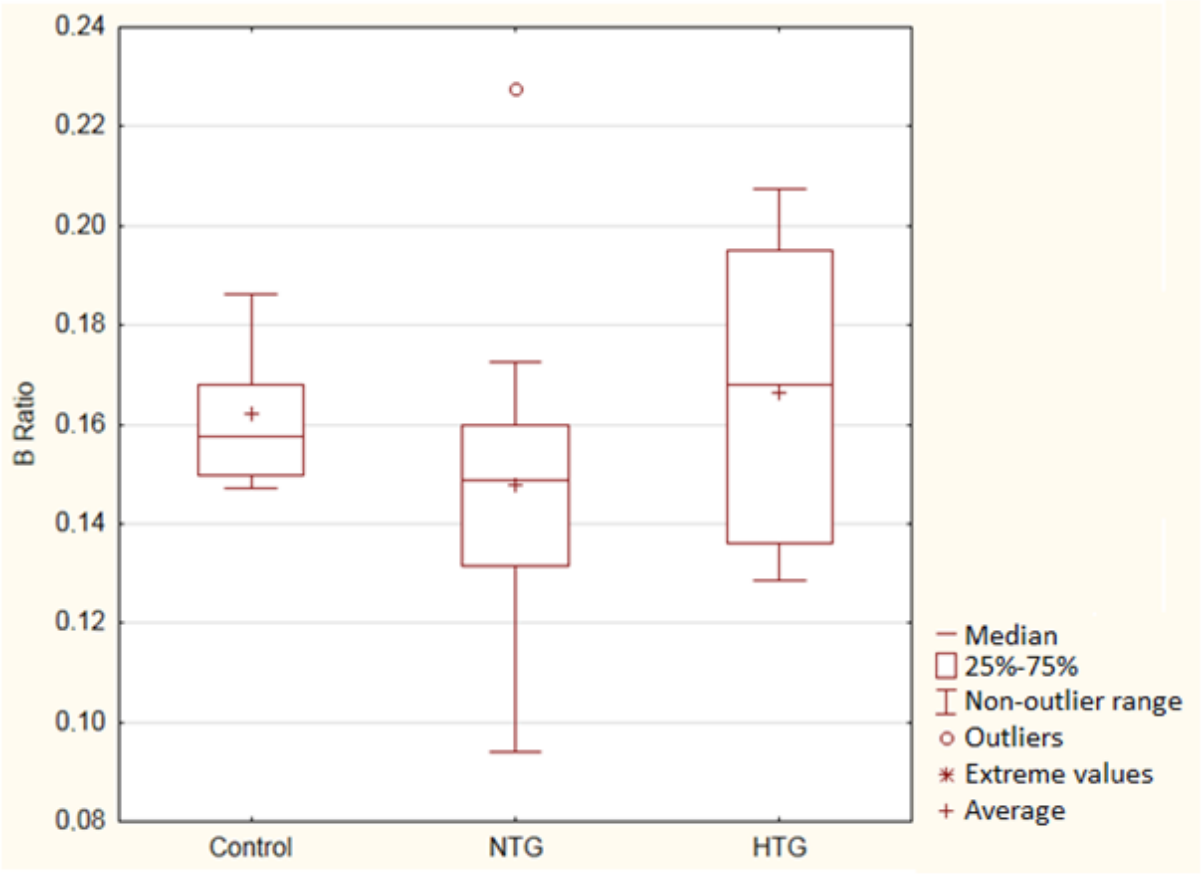

Chart legend translation:
Median
Non-outlier range
Outliers
Extreme values
Average

Chart 1. Box plot showing BCR values in the tested groups.

The ANOVA test was also used for comparisons of the Visual Field-PD parameter between NTG, HTG, and Control groups. As shown in Chart 2 and according to the ANOVA results (p=0.016), there was a significant difference in Visual Field-PD between the tested groups. The Control group reached markedly lowest values (2.36), followed by NTG (4.28), while the highest values were observed in the HTG group (7.16). According to Scheffe post hoc analysis, only the Control and HTG groups differed significantly (p=0.033) (Chart 2).

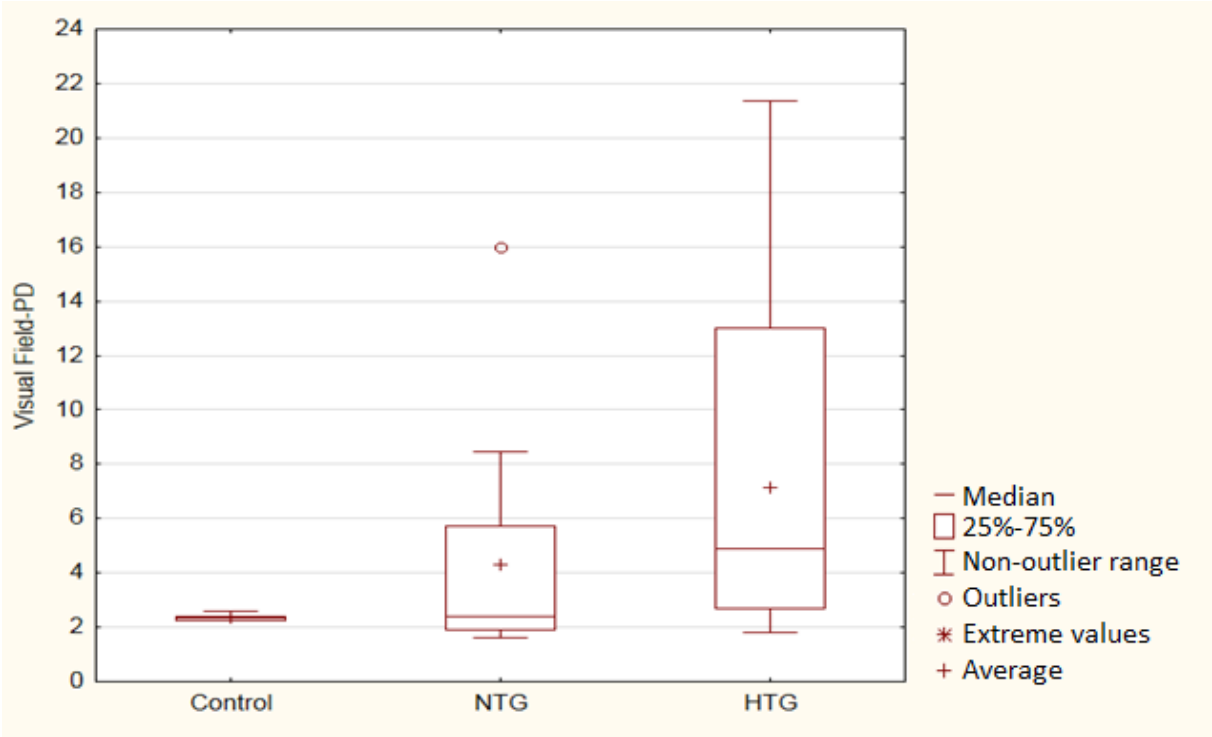

Chart 2. Box plot showing visual field pattern defects in each group.

For PVWM comparison between NTG, HTG and Control groups, Fazekas scale rates were analysed by the Chi-square test of independence and the data were arranged in a contingency table. As shown in Chart 3, in the percentage frequency table and by the Chi-square test (p=0.0018), the groups differed significantly as for the Fazekas scale – PVWM. The contingency coefficient C=0.495 indicates a moderate association. In all cases of the Control group, the Fazekas scale – PVWM grade equalled 0. Higher scores of the Fazekas scale – PVWM of 1 or 2 occurred most frequently in the HTG group (Chart 3).

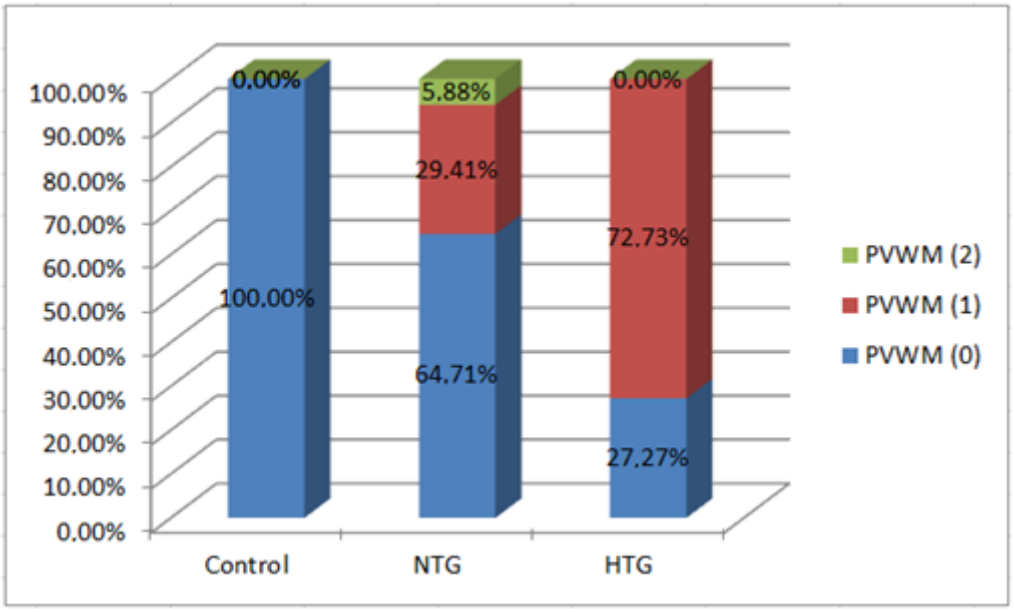

Chart 3. Fazekas scale – PVWM grades in each group.

Fazekas scale – DWM score in NTG, HTG, and Control groups was analysed by Chi-square test of independence for the contingency table. Chart 4, percentage frequency table, and the Chi-square test (p=0.01) revealed significant differences between the groups in the Fazekas scale – DWM parameter. The contingency coefficient C=0.437 indicates a moderate association. Higher scores of the Fazekas scale – DWM of 1 or 2 occurred most frequently in the HTG group (Chart 4).

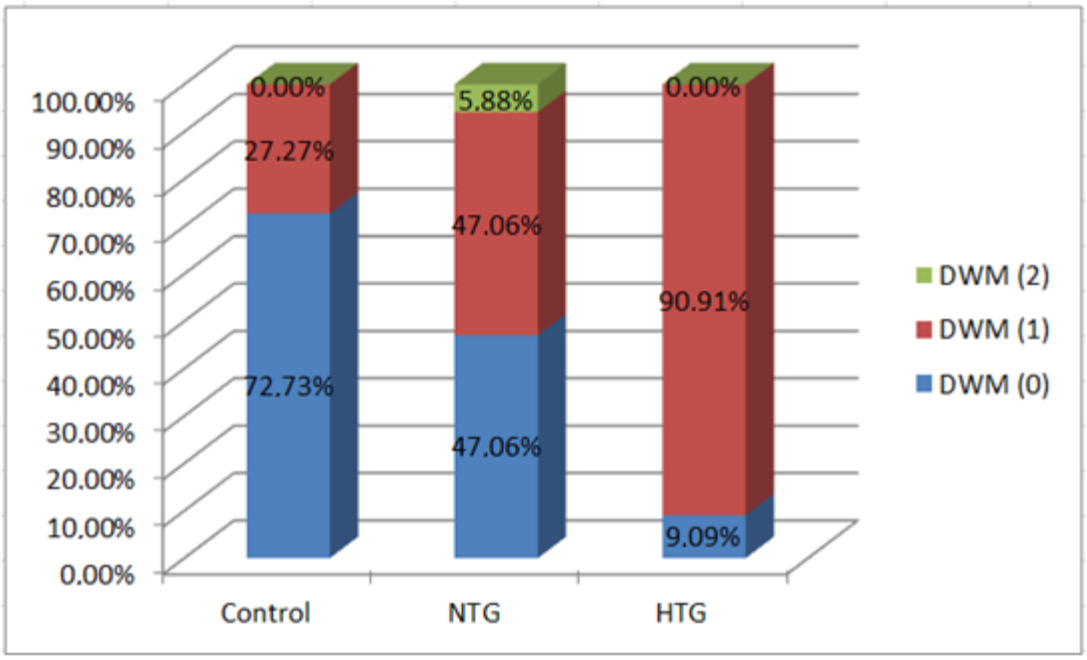

Chart 4. Fazekas scale – DWM grades in each group.

For association evaluation of the Visual Field PD with BCR, we used correlation analysis (two continuous variables). A correlation coefficient (r) of + 0.363 suggests a moderately strong and direct correlation, meaning that higher levels of Visual Field PD are associated with a mild increase of BCR. The resulting p value of 0.0231 indicates a statistically significant association between the Visual Field PD and BCR.

For association evaluation of the Visual Field PD and Fazekas scale – PVWM, the Kruskal-Wallis test was employed (one variable was continuous — Visual Field PD — while the other was categorical — Fazekas scale – PVWM; moreover, the data did not fulfil the normality assumption).

The resulting p value of the Kruskal-Wallis of 0.444 confirms a non-significant correlation between the Visual Field PD and the Fazekas scale – PVWM. These results suggest that the Visual Field PD values do not differ significantly in grades 0, 1, and 2 of the Fazekas scale – PVWM.

For association evaluation of the Visual Field PD and Fazekas scale – DWM, we used the Kruskal-Wallis test (one variable was continuous — Visual Field PD — while the other was categorical — Fazekas scale – DWM; moreover, the data did not fulfil the normality assumption). The resulting p value of the Kruskal-Wallis of 0.0722 shows a non-significant correlation between the Visual Field PD and the Fazekas scale – DWM (in this case, however, the p value is near the significance threshold of 0.05). These results suggest that the Visual Field PD values do not differ significantly in grades 0, 1, and 2 of the Fazekas scale – DWM.

Discussion

In a comparative study, Ong *et al*. (1995) reported on larger cerebral infarcts and more severe corpus callosum atrophy in patients with NTG as compared to control individuals, suggesting a greater degree of neuronal degeneration, possibly on an ischaemic basis in NTG [13].

In accordance, Stroman *et al.* (1995) showed that cerebral small-vessel ischaemia is more common in patients with NTG and potentially indirectly reflects a vascular cause of the optic nerve head damage, at least in subgroups of patients [18]. It is important to emphasise that this study only compared NTG patients with healthy control subjects.

An MRI study of ischaemic changes in the brains of patients with pseudoexfoliation syndrome and glaucoma was performed by Yüksel *et al*. It showed significantly larger hyperintense white matter lesions in these patients as compared to healthy age-matched individuals [22].

It is unclear whether altered blood flow in the progression of glaucoma results from localised retrobulbar vascular insufficiency or a more extensive central neurological process involving the entire cerebral circulation [5].

We found no significant differences in BCR in our patients. We observed statistically significant changes in BCR when correlated with the visual field changes. Higher Visual Field PD was accompanied by more extensive brain atrophy (BCR). We did not detect a similar association with PVWM and DWM.

We found a significant difference in PVWM and DWM between the NTG, HTG and the Control group. The most severe changes were present in patients with HTG.

Our results are in agreement with a study published by Suzuki *et al*., where a relatively deeper depression in the inferior pericentral visual field in NTG patients with signs indicative of ischaemic changes in brain MRI was confirmed [20].

Using the PERG and PVEP examination technique, 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 centres of vision in the brain). In normotensive glaucoma, however, the ganglion cell layer was relatively normal, but significant pathological changes were found in the optic pathway [10]. Based on this information, we assumed that the white matter changes could be more severe in patients with NTG than in those with HTG. However, we were not able to confirm this hypothesis by MR brain imaging.

Conclusion

MR brain imaging detected progressive degenerative changes associated with disease progression, as evaluated by the bicaudate ratio. Grading according to the Fazekas scale revealed lesions in the superficial as well as deep layers of white matter in both NTG and HTG.

The study protocol was approved by the local Ethics Committee and the study was performed in accordance with Good Clinical Practice and the Declaration of Helsinki.

Acknowledgements

Grant support, research funding and proprietary interest is none, and presentation at meeting is also none.

Conflict of interest statement

The authors state that there are no conflicts of interest regarding the publication of this article.

References

1.Araie M, Yamagami J, Suziki Y. Visual field defects in normal-tension | and high-tension glaucoma. Ophthalmology 1993; 100: 1808-1814

2.Brickman AM, Honig LS, Scarmeas N, Tatarina O, Sanders L, Albert MS, Brandt J, Blacker D and Stern Y. Measuring cerebral atrophy and white matter hyperintensity burden to predict the rate of cognitive decline in Alzheimer disease. Arch Neurol. 2008 Sep; 65(9): 1202–1208. doi: 10.1001/archneur.65.9.1202)

3. Eid TE, Spaeth GL, Moster MR, Augburger JJ. Quantitative differences | between the optic nerve head and peripapillary retina in low-tension glaucoma and high-tension primary open-angle glaucoma. Am J Ophthalmol 1997;124: 805-813

4. Flammer J, Prünte C. Ocular vasospasm. 1: Functional circulatory disorders in the visual system, a working hypothesis. KlinMblAugenheilk 1991;198:411-412

5. Harris A, Siesky B, Zarfati D, Haine CL, Catoira Y, Sines DT, McCranor L, Garzozi HJ. Relationship of cerebral blood flow and central visual function in primary open-angle glaucoma. J Glaucoma. 2007 Jan;16(1):159-163

6. Chang M, Yoo C, Kim SW, Kim YY. Retinal vessel diameter, retinal nerve fiber layer thickness, and intraocular pressure in Korean patients with normal-tension glaucoma. Am J Ophthalmol 2011;151:100-105

7. Charlson ME, de Moraes CG, Link A, Wells MT, Harmon G, Peterson JC, Ritch R, Liebmann JM. Nocturnal systemic hypotension increases the risk of glaucoma progression

Ophthalmology. 2015 Apr;122(4):e25-6. doi: 10.1016/j.ophtha.2014.08.042

8.Cheng HC, Chan CM, Yeh SI, Yu JH, Liu DZ. The hemorrheological mechanisms in normal tension glaucoma. Curr Eye Res 2011;36:647-653
Iester M, De Feo F, Douglas GR. Visual field loss morphology in high- and | normal-tension glaucoma. J Ophthalmol 2012; 327326.Epub 2012:Feb 8.

9. Iester M, De Feo F, Douglas GR. Visual field loss morphology in high- and | normal-tension glaucoma. J Ophthalmol 2012; 327326.Epub 2012:Feb 8.

10.Lešták, J., Nutterová, E., Pitrová, Š., Krejčová, H., Bartošová, L., Forgáčová, V.: High tension versus normal tension glaucoma. A comparison of structural and functional examinations. J Clinic Exp Ophthalmol 2012, S:5, http://dx.doi.org/10.4172/2155-9570.S5-006. ISSN: 2155-9570

11.Murata H, Tomidokoro A, Matsuo H, Tomita G, Araie M. | Frequency doubling technology perimetry in open-angle glaucoma eyes with hemifield visual field damage: comparison of high-tension and normal-tension groups.J Glaucoma 2007;16: 9-13

12. Okuno T, Sugiyama T, Kojima S, Nakajima M, Ikeda T. Diurnal variation | in microcirculation of ocular fundus and visual field change in normal-tension glaucoma. Eye
(Lon) 2004;18:697-702

13. Ong K , Farinelli A, Billson F, Houang M, Stern M. Comparative study of brain magnetic resonance imaging findings in patients with lowtension glaucoma and control subjects. Ophthalmology. 1995 Nov;102(11):1632-1638.

14. Park HY, Jeon SH, Park CK. Enhanced depth imaging detects lamina | cribrosa thickness differences in normal tension glaucoma and primary | open-angle glaucoma. Ophthalmology
2012;119:10-20

15. Plange N, Remky A, Arend O. Colour Doppler imaging and fluorescein | filling defects of the optic disc in normal tension glaucoma. Br J Ophthalmol 2003;87:731-736

16. Schwenn O, Troost R, Vogel A, Grus F, Beck S, Pfeiffer N. Ocular pulse | amplitude in patients with open angle glaucoma, normal tension | glaucoma, and ocular
hypertension. Br J Ophthalmol 2002;86:981-984

17. Shin IH, Kang SY, Hong S, Kim SK, Seong GJ, Ma KT, Kim CY. | Comparison of OCT
and HRT findings among normal tension glaucoma, | and high tension glaucoma. Korean J Ophthalmol 2008; 22: 236-241

18. Stroman GA , Stewart WC, Golnik KC, Curé JK, Olinger RE. Magnetic resonance imaging in patients with low tension glaucoma. Arch Ophthalmol. 1995;113:168-172.

19. Sung KR, Lee S, Park SB, Choi J, Kim ST, Yun SC, Kang SY, Cho JW, | Kook MS. Twenty-four hour perfusion pressure fluctuation and risk | of normal-tension glaucoma progression. Invest Ophthalmol Vis Sci2009; 50:266-527

20. Suzuki J , Tomidokoro A, Araie M, Tomita G, Yamagami J, Okubo T, Masumoto T.
Visual field damage in normaltension glaucoma patients with or without ischemic changes in cerebral magnetic resonance imaging. Jpn J Ophthalmol. 2004;48:340-344.

21. Thonginnetra O, Greenstein VC, Chu D, Liebmann JM, Ritch R, Hood | DC. Normal versus high tension glaucoma: a comparison of functional | and structural defects. J Glaucoma 2010; 19:151-157.

22. Yüksel N, Anik Y, Altintaş O, Onur I, Cağlar Y, Demirci A. Magnetic resonance imaging of the brain in patients with pseudoexfoliation syndrome and glaucoma. Ophthalmologica. 2006;220(2):125-130