The role of retinal diagnostic imaging methods in early diagnosis and management of glaucoma

PhD Thesis

Csilla Ajtony, MD

Doctoral School Head:
Prof. Sámuel Komoly, MD, PhD, DSc

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Prof. Tamás Dóczi, MD, PhD, DSc, member of the Hungarian Academy of Sciences
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Prof. Zsolt Biró, MD, PhD, Med. Habil.
Opponents: Prof. Gábor Holló, MD, PhD, DSc, Budapest
Ervin Berényi, MD, PhD, Med. Habil., Debrecen
Examination Committee: Prof. László Lénárd, MD, PhD, DSc, member of the Hungarian Academy of Sciences
Zoltán Rékási, MD, PhD, Med. Habil.
Ferenc Kövér, MD, PhD

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1. INTRODUCTION

Glaucoma is a group of diseases, one of the optic neuropathies with a common pathway of irreversible retinal ganglion cell decay and axonal loss. There are two main forms of the disease: primary and secondary, the latter connected to some other ophthalmological or general disease. Both forms can be further divided based on the angle width to open-angle and closed-angle glaucoma.

Glaucoma, the second leading cause of blindness worldwide affects an estimated 60.5 million people, 13% percent of those found in Europe. This number can even be prognosticated to increase up to 80 million by 2020 due to the general aging of the population. There are 8.5 million people in the world gone blind of the disease on their both eyes, and this number can reach 11.2 millions within 10 years.

In the Caucasian population the primary open-angle form can be found in about 80% of all glaucoma cases, 25% of them to be found in Europe. Prevalence of the disease in the 40-years-old population within the same region is 1.5-3%, and the incidence among 40-50 years old people is 30/100.000, but this number raises to 80/100.000 by the age of 60, and even further up to 180/100.000 by the age of 70.

Primary open-angle glaucoma is a symptomless disease, also called „the sneaky robber of vision”. This is the reason why the number of undiagnosed cases is thought to be 50-67%, even in the developed part of the world.

Glaucoma cannot be cured, but early diagnosis and adequate treatment can slow the progression of nerve fiber loss and preserve the functional vision for the individual. This is the reason why early diagnosis or even screening for glaucoma is so important.

There are three well-established ‘gold standard’ tests used by ophthalmologists to diagnose glaucoma: IOP measurements, visual field tests and (stereoscopic) assessment of the optic nerve. Together, these methods provide information on both structural and functional defects.

The measurement of IOP is not always a precise indication of glaucoma. Individually, IOP is highly variable, and even at low IOP the risk of glaucoma
cannot be ruled out. Additionally, IOP does not indicate the extent of damage, thus, in the diagnosis of glaucoma this parameter can only be used alongside other evidence, such as optic disc or visual field damage for a positive outcome. Visual field testing is the marker of the actual visual function characteristic for the disease. However, it may take several examinations before an accurate baseline is obtained. Also, long-term fluctuations in the field tests can often occur, hence, in combination with the subjective matter of the test, the accuracy of this method of diagnosis still in question.

Retinal nerve fiber loss is an early sign of glaucoma. Detection of structural remodeling and progression is fundamental in glaucoma diagnosis and follow-up. This is mostly impossible by conventional methods because of their insensitivity, subjectivity and non-qualitative nature.

**Current retinal diagnostic imaging**

Correspondingly, it is hardly surprising, that new imaging techniques may significantly assist clinicians in diagnosing glaucoma. Three useful tools have been introduced to the clinical practice: scanning laser polarimetry (SLP), confocal scanning laser ophthalmoscopy (CSLO) and optical coherence tomography (OCT). These modalities help clinicians in everyday glaucoma management, in general documentation of the condition of optic nerve head and the retinal nerve fiber layer – in quantitative, objective and reproducible way.

My thesis is based on the very questions and challenges that prevail during glaucoma diagnosis and follow-up, according to the three gold standard diagnostic methods revealed previously.

My focus has been on glaucoma as the process of a neurodegenerative disease, and one of its main characteristics, the damage of the retinal nerve fiber layer. The extent of nerve fiber layer loss and the development of consecutive visual field damage have been analyzed, alongside of the role of automated standard perimetry in early diagnosis of glaucoma, the evaluation of the relationship between intraocular pressure and nerve fiber layer thickness, complete
with exploration of structural changes detectable during early, perimetrically yet uneffected glaucoma follow-up. For answering these questions we employed standard automated perimetry for visual field testing, optical coherence tomography as an imaging tool, and Goldmann applanation tonometry for intraocular pressure (IOP) measurement.

All our investigations were performed according to the tenets of the Helsinki Declaration and approved by the Ethical Committee of the University of Pécs.

My work is divided into four independent chapters based on the following series of studies detailed below:

1. Structure-function relationship
2. Structural and functional parameters in preperimetric glaucoma
3. Relationship between IOP and nerve fiber layer thickness
4. Morphological changes during preperimetric glaucoma follow-up

2. OBJECTIVES
2.1 Structure-function relationship
- to investigate the correlation between retinal nerve fiber layer (RNFL) loss detected by optical coherence tomography (OCT) and the extent of visual field (VF) defect in primary open-angle glaucoma
- to evaluate the strength and pattern of relationship between VF sensitivity and RNFL thickness in healthy subjects, patients with perimetrically uneffected glaucoma and those with perimetric glaucoma
- to define the approximate average peripapillary RNFL thickness where visual field abnormalities characteristic of glaucoma start to appear

2.2 Structural and functional parameters in preperimetric glaucoma
- is there any morphological attenuation in peripapillary nerve fiber layer thickness detectable by objective imaging when comparing preperimetric glaucoma patients with healthy individuals
- is there any structural or functional parameter that is able to separate early glaucoma patients from normals
- to study the ability of standard automated perimetry to detect retinal sensitivity loss in early glaucoma

2.3 Relationship between IOP and nerve fiber layer thickness

- to define the relationship between IOP and RNFL thickness determined under clinical conditions
- to determine the effect of IOP on glaucomatous structural damage in healthy persons, ocular hypertensive patients (subjects with IOP >21 mmHg, but no structural or functional damage), patients with low-tension and high-tension glaucoma

2.4 Morphological changes during preperimetric glaucoma follow-up

During an average of 3.7 years follow-up period:

- to evaluate the percentage of progression in morphologically impaired but functionally uneffected preperimetric glaucoma
- to define the rate, pattern and localization of structural changes
- to determine the reliability of structural follow-up in the management of the disease

3. METHODS

3.1 Structure-function relationship

We reviewed data of 266 patients who were referred to the Department of Ophthalmology, University of Pécs, Clinical Center between November 2004 and September 2005. We defined the extent of nerve fiber layer loss related to the visual field defect regardless of the low-tension or high-tension nature of the disease.

Patients had SITA Standard 30-2 perimetry (Humphrey Systems Model 750, Dublin, California, USA). For comparison, we used Humphrey global indeces mean deviation (MD), pattern standard deviation (PSD), and we also calculated mean sensitivity (MS) by recording each point on the dB scale except two points for the blind spot.

Optical Coherence Tomography was performed with Stratus OCT (Carl Zeiss Meditec Inc., Dublin, CA) with software version 3.0 without a built-in normative database. The RNFL Thickness Average Analysis Report, using Fast
RNFL Thickness scan with 3 sequential circular scans of 3.4 mm diameter over the optic disc, was performed. For statistical analysis, data of the left eye were converted into right eye format. For calculations we compared peripapillary average (AVG) thickness data.

Statistical analysis was performed on a personal computer using Microsoft Excel 11.0 and SPSS 11.0 software. In all statistical analyses, results exhibiting a p<0.05 value was considered statistically significant.

3.2 Structural and functional parameters in preperimetric glaucoma

This study included 114 eyes of 114 preperimetric glaucoma (PPG) patients with normal visual fields and glaucomatous appearance of the optic disc and 92 randomly selected eyes of 92 age-matched normal subjects. A complete clinical ophthalmological evaluation (visual acuity testing, intraocular pressure measurement (IOP), slit-lamp stereo biomicroscopy and indirect ophthalmoscopy) were performed in patients older that 35 years of age and having good-quality scans obtained in peripapillary RNFL thickness evaluation by OCT (Signal Strength >7), and a reliable standard automated perimetry (SAP). Data for analyses were mean deviation (MD), calculated mean sensitivity (MS) and pattern standard deviation (PSD).

Statistical analysis was carried out by Microsoft Excel 11.0 and SPSS 11.0 software, and Independent samples t-test, receiver operating characteristics curve (ROC) were employed. In all statistical analyses, results with a p<0.05 value were considered statistically significant.

3.3 Relationship between IOP and nerve fiber layer thickness

Our third series of studies included 205 glaucoma patients, 26 subjects with ocular hypertension and 141 healthy subjects. All patients had diurnal IOP curve registrations in sitting position. Group classification was made according to patients’ untreated diurnal peak IOP. Structural and functional tests were performed as detailed above. The effect of IOP was further enhanced by subdivision of the healthy and the low-pressure glaucoma group, all with IOP below 21 mmHg, into two subgroups, one in the low-teens (N1, G1), and the other in the high-teens (N2, G2).
Means comparison by one-way ANOVA, Pearson correlation, regression analysis between RNFL and IOP were performed in statistical calculations using Microsoft Excel 11.0 és SPSS 11.0, and results with a p<0.05 value were considered statistically significant.

3.4 Morphological changes during preperimetric glaucoma follow-up

Our observational cohort study included 112 eyes of 112 preperimetric glaucoma patients followed for a mean of 3.7 years.

Time-domain optical coherence tomography images were taken yearly along with visual field tests performed by Humphrey Field Analyzer SITA Standard 24-2 strategy every 4-6 months during follow-up. Average RNFL thickness, quarter (superior, nasal, inferior, temporal) and clock hour (1-12) thickness data were registered for analysis. Criteria for progression were defined by the appearance of visual field defect, based on Glaucoma Hemifield Test result outside normal limits and/or a pattern standard deviation (PSD) outside the 95% confidence limits (p<0.05), in two consecutive test findings.

Statistical analysis using SPSS 16.0 included Independent samples t-test, linear regression analysis to define the rate of change in RNFL thickness over time. In all statistical analyses, results with a p<0.05 value were considered statistically significant.

4. RESULTS

4.1 Structure-function relationship

Correlation between AVG and MS, MD or PSD were all significant at p=0.01 level in the POAG group, with Pearson coefficients of 0.733, 0.718 and -0.689, respectively. In contrast, for eyes in the normal and PPG group no significant association could be detected between AVG and either of the corresponding VF parameters.

Relationship between RNFL thickness and VF parameters within groups were characterized by regression analysis using linear and curvilinear (quadratic) models, the latter giving the better curve fit in the POAG group, with higher determination coefficient (R²). VF parameters were treated as dependent variables and RNFL thickness as independent variable in all regression analyses.
Scatterplots with regression curves of AVG vs MD revealed that structural changes have no effect on functional parameters in normals ($R^2=0.012$), or PPG eyes ($R^2=0.015$) while there was a marked effect in POAG eyes ($R^2=0.723$).

To assess a differentiation parameter other than dividing our glaucoma patients on the basis of their SAP results, ROC curves were generated and sensitivities at fixed specificity ($\geq 90\%$) were calculated for each test parameter (VF and OCT). The cutoff point for PSD value was 1.9 dB with 78% sensitivity and 90.2% specificity. Based on this finding, we subdivided both our clinically PPG and POAG groups by this particular PSD value. Eyes of the POAG group with PSD <1.9 dB reverted in their Pearson correlation coefficients similar to the values found for the PPG group, but those with PSD >1.9 dB have been shown to still exhibit a strong curvilinear relationship between RNFL AVG and VF parameters ($r=0.727$, $p<0.01$, $R^2=0.711$). It is notable that almost all of the eyes in the preperimetric group had a RNFL thickness value of 68.0 µm and above, and separation of our patients based on their PSD values showed an almost identical minimum RNFL AVG value (70.73 µm).

4.2 Structural and functional parameters in preperimetric glaucoma

VF global indices MD, PSD and mean sensitivity (MS), from RNFL measurements peripapillary average thickness (AVG) were used for comparative analysis. We calculated MS data in our groups because we assumed that in contrast to MD, this is an actual parameter individually characteristic to the patient and it is not attenuated by age-normalization based on the built-in normative database or by RNFL AVG, that is also a directly measurable, actual and individual parameter of the patient.

Sensitivity and specificity for each examined parameter was defined by employing a ROC analysis. Both visual field sensitivity (MS) and average peripapillary thickness (AVG) showed significant attenuation compared to normals, but their own discriminating power was not reliable enough to distinguish early glaucoma from healthy subjects (AVG sensitivity 74%, specificity 53%, MS sensitivity 88%, specificity 64%).
4.3 Relationship between IOP and nerve fiber layer thickness

For purposes of comparison between groups RNFL AVG thickness had to be adjusted for age. Significant correlation was found between IOP and RNFL AVG thickness in high-tension glaucoma group ($r=-0.432$).

Regression analysis was used to explore the effect of the independent variable (IOP) on changes of the dependent variable (RNFL thickness). We might assume that the level of IOP can be attributed to 22% of the overall change in AVG peripapillary RNFL thickness ($R^2=0.22$).

In healthy individuals, ocular hypertensives and both low-tension glaucoma groups negligible correlation and regression was found. The role of IOP remains still unclear in low-tension glaucoma development.

4.4 Morphological changes during preperimetric glaucoma follow-up

Twenty-three eyes (20%) of the total 112 exhibited visual field defect during follow-up and were called progressors hereunder. The average (AVG) RNFL thickness measurements showed a frequency distribution skewed to the thinner average measurements, namely 70% of progressors had AVG thickness below 80 μm at baseline. An arbitrary thickness value of 80 μm divided them into two groups based on the baseline peripapillary average RNFL thickness, one below 80 μm (Group A) and the other above 80 μm (Group B). The change of RNFL thickness over time was evaluated by regression analysis. The rate of change in Group A (RNFL AVG below 80 μm at baseline) was -0.46 μm/year, $R^2=0.935$ and in Group B (RNFL AVG above 80 μm at baseline) -2.44 μm/year, $R^2=0.957$.

To investigate the pattern of peripapillary RNFL thinning among progressors, we evaluated the change in each clock hour segment, as well. We could detect significant RNFL thickness decrease in Group A at the temporal clock hour segments, while in Group B this pattern seemed to be more diffusely distributed around the disc.
5. DISCUSSION – SIGNIFICANCE OF NOVEL FINDINGS IN CLINICAL PRACTICE

5.1 Structure-function relationship

We were first to publish data estimating the threshold value of glaucomatous RNFL loss in the presence of VF defects, as non-invasively measured by Stratus OCT.

a) Strong relationship between structure and function ($r=0.718$, $R^2=0.723$) could be detected at a range around 70 µm of average peripapillary thickness with a cutoff value of the functional parameter PSD above 1.9.

b.) Using OCT, the average RNFL thickness in normal eyes has been reported to vary from 90 to 128 µm. Thus, a mean value of RFNL thickness around 70 µm – even considering its wide range of interindividual variability – might exhibit a profound threshold value representing a turning point in glaucomatous structural changes. This observation is also consistent with postmortem histologic measurements in patients with glaucoma, indicating that at least 25-40% of retinal ganglion cells were lost before abnormalities were statistically detected by automated visual field testing.

5.2 Structural and functional parameters in preperimetric glaucoma

a) Functional deterioration (retinal mean sensitivity) can be observed along with structural decline in the process of glaucoma, which can be detected by standard automated perimetry.

b) The peripapillary nerve fiber layer thickness loss is detectable at the early stage of glaucoma, although it cannot be used to discriminate healthy from glaucoma subjects due to its poor sensitivity/specificity.

5.3 The relationship between IOP and nerve fiber layer thickness

a) Previous findings by others report that visual field asymmetry could not be explained by the actual difference in IOP among low-tension glaucoma patients. Our findings evaluating the relationship between IOP and the retinal nerve fiber thickness could also support this observation on the structural level.
b) In high-tension glaucoma the effect of IOP can be estimated to contribute to about 22% of the total structural changes, and this presumes the existence of pathogen factors others than IOP as well.

5.4 Morphological changes during preperimetric glaucoma follow-up

a) There is no continuous structural decline during the functional progression of preperimetric glaucoma.

b) The rate and pattern of nerve fiber layer loss might differ among subjects having thinner or thicker RNFL thickness at baseline.

In summary, we can conclude that in evaluating the structure and function of the glaucoma pathology we achieved results that could serve as the basis for our future investigations and may influence our routine clinical glaucoma management.

We revealed the critical relationship of structure and function, the usefulness of standard automated perimetry in early glaucoma.

We evaluated the effect of IOP in the structural pathology from an everyday aspect, and our findings support data by others seeking the effect of IOP on functional deterioration.

One of the most important points in glaucoma management is the ability to detect progression. We hope our findings could also be useful in this respect, due to defining a non-linear and non-uniform pattern of structural progression among preperimetric glaucoma patients.

Our results were based on the use of retinal imaging, automated perimetry and conventional applanation tonometry in clinical routine practice.
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AWARDS RELATED TO THE WORK OF THE THESIS

International Glaucoma Symposium (IGS) 2005 – Poster 2nd Prize
MSD Hungary Ophthalmology Prize 2007 – 1st Prize