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Long-Term Follow-Up of Scanning Laser Polarimetry and Confocal Scanning Laser Ophthalmoscopy in Normal Tension Glaucoma

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Abstract

Background: To investigate the potential of optic nerve head measurements using confocal scanning laser ophthalmoscopy (CSLO) and nerve fiber layer images by means of scanning laser polarimetry (SLP) in the long-term follow-up of normal tension glaucoma (NTG).

Methods: Retrospective study of 49 NTG patients with an average age of 65.5 years that have been followed for about 5 years. The long-term change of various parameters of perimetry, CSLO and SLP was examined for all patients. In addition patients were classified according to their Aulhorn glaucoma classification score as beginning (AGS<3) or advanced (AGS ≥ 3) and progressive and non-progressive NTG trying to reveal differences of the parameters in stage and time.

Results: Intraocular pressure (IOP), mean defect (perimetry), neuroretinal rim and CDR (CSLO) did not show significant changes over the time. In CSLO, average depth and cupping shape were significantly different over the time and between progressive and non-progressive NTG. SLP revealed significant decrease especially in the superior retinal nerve fiber layer (66.1 vs 57.3 µm), but only relative parameters such as NFI, superior ratio and ellipse modulation were different between beginning and advanced NTG.

Discussion: Our study points out that especially relative parameters in SLP such as ellipse modulation or NFI and CSLO-values of optic disc steepness and depth might be helpful in the follow-up of glaucoma patients. They show a better correlation to progression of the disease than classical parameters such as MD, IOP, neuroretinal rim or CDR.

Keywords: Normal tension glaucoma; Confocal scanning laser ophthalmoscopy; Scanning laser polarimetry; Perimetry; Follow-up; Glaucoma progression

Introduction

Glaucoma is one of the leading causes of blindness in people over 50 years of age [1]. The most frequent form of glaucoma is primary open-angle glaucoma (POAG). Elevated intraocular pressure (IOP) is found in approximately 50% of patients with glaucoma [2]. However, individuals can develop glaucomatous optic neuropathy in the absence of raised IOP. This is known as normal tension glaucoma (NTG) and accounts for 25-50% [3] to 50-66 % [4] of cases of open angle glaucoma.

Visual field defects, detected with standard achromatic perimetry (SAP), are the mainstay of demonstrating functional glaucomatous damage. However, it has been suggested that up to 35% of nerve fiber axons may already be damaged before SAP detects any functional visual field loss [5]. Furthermore, a longitudinal study over more than 7 years pointed out that perimetry results can deviate over the course of time, questioning the validity of the assessment of glaucoma progression [6]. A long-term study over 5 years showed similar clinical variability of laser scanning tomographic HRT measurements as compared to visual field parameters [7].

Although perimetry is still the reference standard for assessing visual function in patients with glaucoma, new technologies such as scanning laser polarimetry (SLP) or OCT have become an important tool for the analysis of the retinal nerve fiber layer in glaucoma diagnosis. However, there are only few studies on longitudinal nerve fiber layer thickness changes [8-12]. They all have pointed out that SLP may be a useful tool for longitudinal follow-up assessment of glaucoma e.g. because of its high reproducibility.

Long-term evaluations of all three diagnostic techniques (perimetry, SLP and CSLO) have not been performed so far, but early diagnosis and detection of changes of glaucomatous damage are very important for the treatment and prognosis of progressive neuropathies especially of normal tension glaucoma with its absence of elevated intraocular pressure and slow progression. Therefore, we compared long-term results of ophthalmologic standard examination techniques, CSLO, and SLP measurements of NTG patients to find out which of the parameters are potentially useful in the follow-up of these patients and might help to assess the progression of the disease besides perimetry with its known limitations.

Patients and Methods

Consecutive glaucoma patients from the glaucoma service of the University Eye Hospital, Essen. 49 NTG patients with an average age 65.5 years who had been followed for about 5 years were selected for this retrospective study. Patients were at least examined twice. The average time period between the first and the last examination was 59.9 ± 1.9 months.

Informed consent was obtained from each patient. Besides ophthalmologic standard examination with automated white on white 30 degrees perimetry (Twinfield Automatic Perimetry, Oculus, Wetzlar, Germany), CSLO (TopSS, software version 3.0.19, LDT, USA, currently Carl Zeiss Meditec, Jena, Germany), and SLP (GDx, software version 2.010 E, LDT, USA, currently Carl Zeiss Meditec, Jena, Germany) were performed. The diagnosis of glaucoma was established by typical visual field defects and optic disc damage. To ensure the diagnosis of NTG, in all patients, repeated intraocular pressure (IOP) measurements were recorded including daytime and nighttime on three consecutive days in the hospital. In NTG patients, untreated IOP was less than 22 mmHg. Twenty NTG patients did not have glaucoma medication at the first visit and 15 at the second visit. 8 patients underwent laser trabeculoplasty and 5 filtration surgery. Patients with other eye diseases or operations other than cataract surgery were excluded. Refraction was within ± 3.0 D.

Visual field defects were assessed according to the glaucoma classification of Aulhorn (GCA) [13]. (stage 0: no visual field defects; stage 1+2: mild defects, i.e. relative scotomas (1) and/or absolute (2) scotomas, but without connection to the blind spot; stage 3: moderate defects, i.e. arcuate scotomas with connection to the blind spot; stage 4: advanced defects, i.e. absolute scotomas of more than one quadrant; stage 5: subtotal visual field defect, only temporal rest)

Patients were classified according to their Aulhorn glaucoma stages (AGS) in automated perimetry at the beginning of the study, with AGS<3 being defined as beginning disease and AGS ≥ 3 being defined as advanced disease. Follow-up results were compared and progression of glaucoma was defined as a decrease in perimetry of at least one stage in GCA.

CSLO: The optic disc was analyzed with a TopSS laser topographic scanning system (TopSS, software version 3.0.19, LDT, San Diego, California currently Carl Zeiss Meditec, Jena, Germany), a device that uses a galliumaluminium- arsenide laser (wavelength 780 nm, maximal retinal illumination 0.025 Watt/cm^2). The TopSS presents 14 variables as the result of its analysis of the optic disc. One of the variables, the average diameter (AD), is arbitrarily set by the operator who draws an ellipse at the rim of the optic disc and therefore represents operator input rather than a measurement of TopSS. The remaining TopSS variables are defined as follows: effective area (EA) is the cup area located 100 µm below the total area; neuroretinal rim area (NRA) is the difference between the total area and the effective area; volume below (VB) is the volume of the cup below the effective area; volume above (VA) is the volume of all tissue or structures within the neuroretinal rim area above the effective area; average cup depth (ACD) is the average of all height values within the cup; and cup to disc ratio (CDR) is the ratio between the effective area and the total area; cupping shape is the third moment of height modulation of the contour line, giving a measure of the steepness of the optic disc excavation.

SLP: The thickness of the peripapillary nerve fibre layer was determined using a GDx (Carl Zeiss Meditec, Jena, Germany) which is based on an aluminium-arsenic laser (wavelength 780 nm, maximal retinal illumination 0.025 Watt/cm^2) as reported elsewhere [14].

The long-term change of the various parameters was examined for all patients. In addition patients were classified according to their GCA score as beginning (AGS<3) or advanced (AGS ≥ 3) and progressive (at least one AGS worse in second examination) and non-progressive NTG trying to reveal differences of the parameters in stage and time. Differences of the various parameters (cf. Table 2) between a) first and second examination (time), b) beginning and advanced disease, c) progressive and non-progressive disease were evaluated. For statistical analysis t-test was used. P<0.05 was considered as the level of significance. Results are given as mean ± standard deviation.

Results

At the beginning of the examination period, 36 patients (73.5 %) showed an AGS <3 (beginning disease) and 13 (26.5 %) an AGS ≥ 3 (advanced disease). In 32 (65.3 %) patients the AGS remained unchanged (no progression) and in 17 (34.7 %) patients AGS increased (progression) (Table 1).

	AGS<3 beginning	AGS ≥ 3 advanced	%
total	36	13	100
no progression	24	8	65.3
progression	12	5	34.7
%	73.5	26.5	

Table 1: Distribution of NTG patients according to qualitative perimetric results (Aulhorn glaucoma stages AGS); beginning (AGS<3) and advanced stages (AGS ≥ 3); progressive and non-progressive disease (n).

Table 2 summarizes the statistical results of the various parameters as to time, stage and progression.

Perimetry

Over all 49 patients, mean defect (MD) changed non-significantly during the examination period (from 2.2. to 3.7 dB). Those with advanced disease showed significantly higher MD than those with beginning disease (Figure 1). Only in those patients with progressive disease, MD changed significantly over time.

Intraocular pressure

Intraocular pressure (IOP) did not change significantly between the first and second examination. In those patients with advanced disease, IOP was significantly lower than in those with beginning disease (Figure 2).

SLP

As to the absolute thickness values of the RNFL there was a highly significant reduction over the time esp. of the average thickness (60.7 vs 55.2 µm), ellipse average (61.6 vs 56.5 µm) and especially the superior average (66.1 vs 57.3 µm) and superior integral. These values, however, did not differ significantly between beginning and advanced or progressive and non-progressive patients (cf Table 2). The inferior average thickness did not change significantly (73.2 vs 70.0 µm) over

time, but was significantly different between beginning and advanced stages.

	exam 1 vs 2	beg vs adv	Progr vs non progr
MD	ns	p<0.001	ns
IOP	ns	p<0.001	ns
Number	p<0.001	p<0.05	ns
Symmetry	ns	ns	ns
Superior ratio	p<0.005	p<0.02	ns
Inferior ratio	ns	p<0.001	ns
Superior/nasal	ns	ns	ns
Maximal modulation	ns	p<0.005	ns
Ellipse modulation	ns	p<0.001	p<0.05
Average thickness	p<0.005	ns	ns
Ellipse average	p<0.001	ns	ns
Superior average	p<0.001	ns	ns
Inferior average	ns	ns	ns
Superior integral	p<0.001	ns	ns
Average diameter	ns	p<0.001	ns
Effective area	ns	p<0.05	ns
Cupping shape	p<0.001	ns	p<0.05
Volume below	ns	ns	ns
Average depth	p<0.05	ns	p<0.02
Mean contour depth	p<0.05	ns	p<0.02
Volume above	ns	ns	ns
NRR area	ns	ns	ns
CDR	ns	ns	ns
Horiz. CDR	ns	ns	p<0.05
Vert. CDR	ns	ns	ns

Table 2: Differences (level of significance) of the various parameters between a) first and second examination (time), b) beginning and advanced disease, c) progressive and non-progressive disease.

Regarding the relative and calculated values of the GDx, there was a significant change over the time of the parameters „The Number"(NFI) and „Superior ratio". Both these and also inferior ratio, maximal modulation and ellipse modulation showed a significant difference between beginning and advanced stages (Figure 3 a,b). Ellipse modulation was significantly different between progressive and non-progressive NTG (Figure 3c), "The Number" only tended to differ between these groups (ns).

CSLO

CSLO assessment revealed that neuroretinal rim area did not change statistically over time, stage or progression. CDR values in CSLO also did not change significantly over time.

Measurement values of the excavation depth such as cupping shape, average depth and mean contour depth, however, changed significantly over the time. In these values as well as the horizontal CDR significant differences could also be found between progressive and non-progressive NTG eyes (Table 2 and Figure 4).

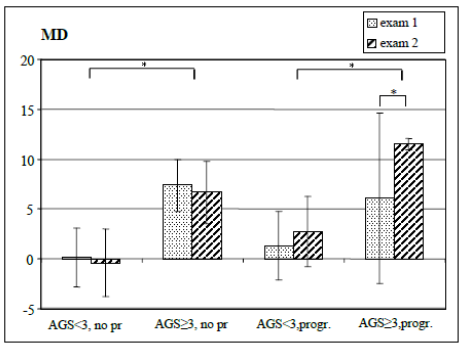

Figure 1: Mean defect in standard achromatic perimetry in NTG patients; as to time (examination 1 and 2), stage (beginning AGS<3 and advanced disease AGS>3) and progression (progressive and non-progressive); mean ± std; *p< 0.05.

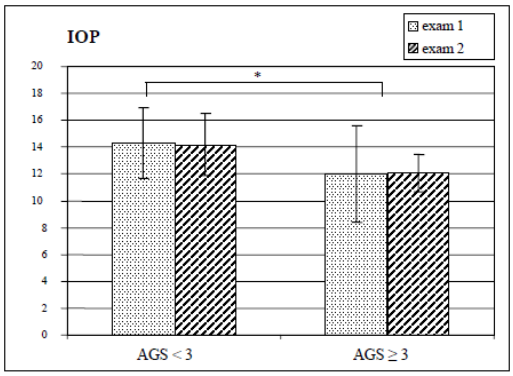

Figure 2: Intraocular pressure in NTG patients; as to time (examination 1 and 2) and stage (beginning AGS<3 and advanced disease AGS>3); mean ± std; * p<0.05.

Discussion

In this retrospective longitudinal study over 5 years, we examined NTG patients who were assessed with standard glaucoma diagnostic techniques (IOP and perimetry) and two additional diagnostic methods, SLP and CSLO.

Of course, due to the retrospective character there are several limitations of our study such as the lack of an age-matched control group, the mix of patients with and without surgical intervention etc. However, our results at least give some hints which parameters of SLP or CSLO might be helpful in addition to repeated visual field testing to assess the progression of the glaucoma disease. This also might be helpful in those patients who are not able to perform perimetry with sufficient quality or reproducibility.

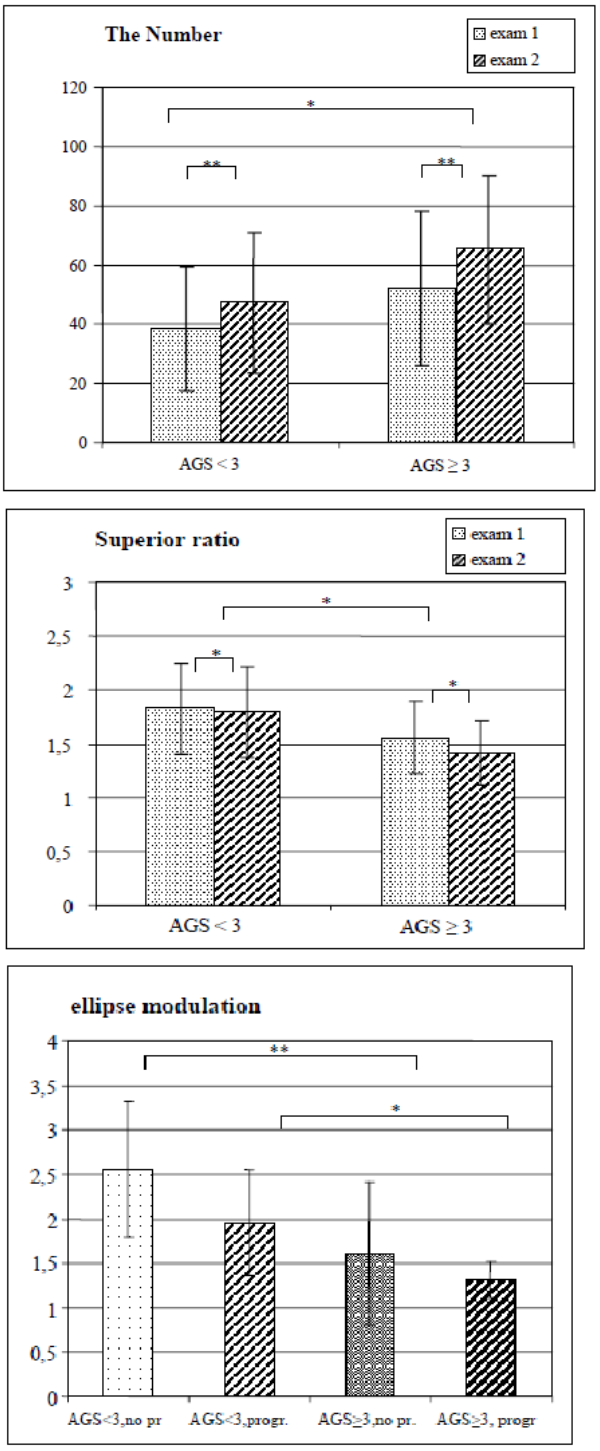

Figure 3: Scanning polarimetric results in NTG patients; as to time (examination 1 and 2), stage (beginning AGS<3 and advanced disease AGS>3) and progression (progressive and non-progressive); mean ± std; *p<0.05; **p<0.01.

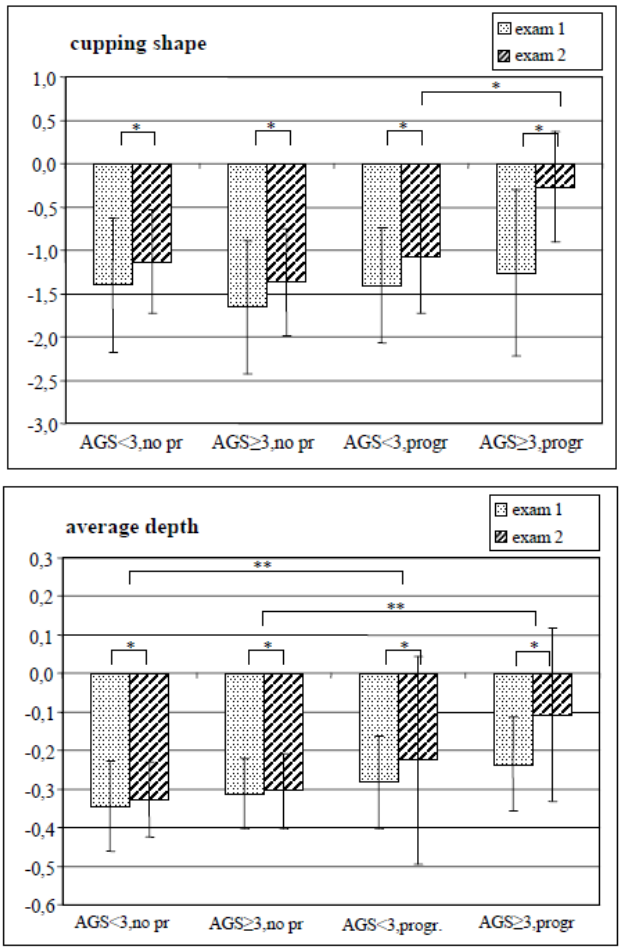

Figure 4: CSLO results in NTG patients; as to time (examination 1 and 2), stage (beginning AGS<3 and advanced disease AGS>3) and progression (progressive and non-progressive); mean ± std; *p<0.05; **p<0.01.

On average, mean IOP remained unchanged in NTG patients over the course of the study, and MD in standard achromatic perimetry showed no significant change. Presumably, due to the more aggressive therapy IOP was significantly lower in the advanced NTG group.

As expected, mean defect of the visual field analysis was higher in patients with advanced stages of glaucoma and it increased over time in those patients with progressive disease. Approximately two thirds of the patients showed no progression of AGS stages.

In SLP, a significant loss of the superior nerve fiber bundle thickness could be detected which is reflected in the reduction of parameters such as superior average, whereas inferior average remained unchanged. Similarly, a dissociation between superior and inferior nerve fiber layers can be found in patients with anterior ischemic optic neuropathy [15]. However, it is unclear which risk factors are involved in this finding other than increased intraocular pressure.

In general, this interpretation should consider reports that physiological change in the nerve fiber layer thickness does occur with age [16-18]. These changes, however, would be expected to occur over a longer term, most likely in the context of decades, and to a much lesser extent [19]. Hence, the variation in NTG patients in the present study demonstrates changes beyond those we would normally have expected. Therefore, they can be interpreted as a sign of disease.

The SLP results presented here are supported by two studies, which detected an increased loss in retinal nerve fiber layer thickness in NTG patients [8] and POAG patients [16] compared to age-matched controls. However, in these studies, no CSLO measurements were applied. Furthermore, patients were observed only over a maximum of 18 months.

In our study we found a decrease of the absolute thickness values of the polarimetric measurements over the time. However, these parameters did not change significantly with the severity of the NTG or with the progression. Here it seems to us, that the relative (calculated) values (e.g. ratio, modulation) are more interesting in the follow-up, as they are different between beginning and advanced glaucoma and in part also between progression and non-progression. Makabe et al. [12] also pointed out that especially the "Number" (NFI) is useful in longitudinal analysis of glaucoma. This is supported by our results, although the "Number" in our study marginally missed significance as to progression.

Mohammadi et al. [20] also found that SLP parameters inferior ratio and ellipse modulation are significant predictors of visual field conversion in glaucoma suspects. It is worth mentioning that especially ellipse modulation in our study, too, is the parameter with the highest significance. In another study [10], however, absolute RNFL thickness changes were greater in eyes with progressive glaucoma compared to eyes with stable disease.

Regarding the scanning laser tomographic (CSLO) results it is obvious that parameters such as neuroretinal rim area and CDR are not very helpful in the assessment of glaucomatous damage changes. Here, parameters that measure the steepness and depth of the optic disc (average depth, cupping shape) were better able to show differences between progression and non-progression.

Alencar et al. [11] also found that measurement of neuroretinal rim area was not able to discriminate progressing from stable glaucoma.

From histological studies, it is known that a degeneration of 20-50% of nerve fibers leads to impairment of the visual field [5,2,22]. Clinical studies confirm that in glaucoma, the loss of nerve fibers precedes changes at the optic disc, and visual field defects [23-25].

The main threat from glaucoma is blindness, caused by progressive loss of retinal ganglion cell axons, which results in a decrease of the retinal nerve fiber layer thickness. Consequently, the measurement of the decreasing nerve fiber layer thickness can provide important information for the early diagnosis and treatment of glaucoma. Hence, a diagnostic technique that could reveal nerve fiber loss would be able to permit therapy initiation at beginning glaucoma and optimize therapy control in already diagnosed glaucoma patients. Therefore, it is important to know that certain scanning laser polarimetric (esp. modulation, ratio) and scanning laser tomographic (steepness, depth) parameters may be helpful in the follow-up of glaucoma patients, especially in normal tension glaucoma, the therapy of which is particularly challenging.

Further (prospective) studies perhaps including the new OCT techniques are necessary to strengthen the evidence of these results.

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