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The Assessment of Pupil Cycle Time in Patients with Glaucoma

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Abstract

Purpose: To evaluate the value of pupil cycle time (PCT) measurements in patients with glaucoma.

Material and Methods: 40 eyes of 40 patients having primary open angle glaucoma and 35 eyes of 35 healthy subjects were enrolled in this study. In unilateral cases the glaucomatous was studied and in bilateral cases the studied eye was determined randomly in both groups when both eyes were eligible. All patients underwent ophthalmologic examinations, including best corrected visual acuity (BCVA), slit-lamp biomicroscopy, Goldmann applanation tonometry, gonioscopy, visual field testing, PCT measurement and optical coherence tomography (OCT). Two groups were compared using the chi-squared test for categorical variables and with the independent t test for non-categorical parameters. Correlations of PCT results with age of patients, duration of glaucoma (years), best corrected visual acuity (BCVA), mean deviation (MD) and pattern standard deviation (PSD) of visual field and OCT parameters were analyzed with Pearson correlation analysis test.

Results: Mean age was 63.5 ± 9.5 in glaucoma patients, and 62.2 ± 7.2 in healthy subjects (p=0.453). Rate of females was 62.5% in glaucoma patients, and 54.2% in healthy subjects (p=0.323). Mean PCT was 947.5 ± 65.5 ms in the glaucoma group, whereas it was 888 ± 33.8 ms in healthy subjects (p=0.030). There was a significant correlation between PCT and other variables including age of the patients (R: 0.331, p=0.001), duration of glaucoma (R: 0.457, p<0.001), BCVA (R:-0.396, p<0.001), ganglion cell-inner plexiform layer (GC-IPL) *thickness (R:-0.457, p<0.001)* and retinal nerve fiber layer thickness (RNFLT) (R:-0.676, p<0.001). There was a prominent lengthening of PCT while reducing BCVA, RNFLT and GC-IPL thickness.

Conclusion: PCT measurements showed a significant correlation with OCT parameters in our study. Further prospective studies are needed to evaluate the value of PCT in glaucoma patients.

Keywords: Glaucoma; Optical coherence tomography; Pupil cycle time

Introduction

A small beam or slit of light focused at the pupillary margin will induce regular persistent oscillations of the pupil. The average period of these cycles named pupil cycle time (PCT) may be easily measured and expressed in milliseconds (ms). The PCT is characteristic for any given individual, and shows little difference between a pair of normal eyes [1-3]. It has been used as an objective assessment of optic nerve function in various ophthalmic diseases [3-5]. Prolongation of the PCT may result in the impairment of the afferent or efferent pathways of the pupillary light reflex by some diseases including optic neuritis [4,5], optic nerve compression [6], space-occupying lesions [7], multiple sclerosis [8-10], central depressant drugs [11], progressive autonomic failure [12], familial dysautonomia [13] and diabetic autonomic neuropathy [14-16]. Miller and Thompson [1] reported that when the iris muscles were normally innervated and responsive, the PCT was dependent on the speed of conduction and the number and strength of optic nerve impulses. They also reported that the PCT was similar to visual evoked potential (VEP) latency time in that it can detect and quantitative subclinical defects in optic nerve conduction time. Glaucoma is one of the leading causes of optic neuropathy, in which apoptosis of retinal ganglion cells and progressive loss of retinal nerve fibers and optic nerve axons result in structural and functional deficits [17-22]. It is very well known that the afferent pathway of the pupillary reflex arc is disturbed due to optic neuropathy in glaucoma patients. Pupil cycle time might be prolonged because of this afferent pathway disturbance. To our knowledge, there has been no study evaluated by the PCT in patients with glaucoma. The objective of this study was to evaluate the PCT measurements of patients with glaucoma and to compare these measurements with age- and sex-matched healthy subjects. We also evaluated the correlation of PCT measurements with age of the patients, duration of glaucoma, best corrected visual acuity (BCVA), visual field (VF) parameters and optical coherence tomography (OCT) parameters.

Material and Methods

This study conducted at the Bozyaka Training and Research Hospital between April 2015 and September 2015. Patients with diagnosis of primary open angle glaucoma admitted to the Ophthalmology clinic were revised for the study; a total of 40 eyes of 40 patients were recruited as the study group. We have also admitted the control group consisted of 35 eyes of 35 age-matched and sex-matched healthy subjects who attended to our clinic for routine eye examination. The study was conducted in accordance with the tenets of

the Declaration of Helsinki, with local ethical approval from Ethics Committee of this hospital. An informed consent was obtained from all patients to perform the original measurements and to review their medical records. A comprehensive present and past history obtained from each subject, followed by all patients underwent screening examinations including auto kerato-refractometry, best corrected visual acuity (BCVA), slit-lamp examination, and intraocular pressure measurement by Goldmann applanation tonometry, gonioscopy and dilated fundus examination. Primary open-angle glaucoma (POAG) was defined by raised intraocular pressure (IOP) consistently above 21 mm Hg in at least one eye with a typical glaucomatous visual field and/or optic nerve head damage and an open, normal appearing anterior chamber angle (Schaffer III-IV angle in gonioscopy) with no other underlying disease.

Inclusion criteria for glaucoma patients

We included glaucoma patients who fulfilled the following criteria: age older than 40 years; best-corrected visual acuity over 0.5 (on the Snellen visual acuity scale); patients diagnosed as primary open angle glaucoma (POAG); reliable visual fields performed at ± 1 month from OCT imaging; refractive error within a ± 5 spherical diopter range, with less than ± 3 cylinder diopters. In unilateral cases the glaucomatous was studied and in bilateral cases one eye was randomly selected for inclusion to the study when both eyes were eligible.

Inclusion criteria for healthy subjects were age older than 40 years, best-corrected visual acuity over 0.8 or better (on the Snellen visual acuity scale), intraocular pressure equal or less than 21 mmHg, normal optic disc appearance and visual field results, reliable visual fields, refractive error within a ±5 spherical diopter range, with less than ±3 cylinder diopters. One eye was randomly selected for inclusion in the study when both eyes were eligible.

Exclusion criteria for glaucoma patients and healthy subjects

1) Patients with corneal opacity or dystrophy, uveitis, rubeosis iridis, vitreous hemorrhage, retinal vascular diseases, previous ocular trauma or ocular surgery,

2) Patients with a history of systemic disease that might affect autonomic function [12,13,23]. Acute/subacute dysautonomias, chronic autonomic failure syndrome, hereditary autonomic diseases, metabolic diseases (chronic renal failure, chronic liver disease), inflammatory diseases (Guillain-Barré syndrome, transverse myelitis), infectious diseases (bacterial: tetanus, parasitic: Chagas' disease, viral: HIV), neoplasia (brain tumors, paraneoplastic, to include adenocarcinomas of lung and pancreas), surgery (vagotomy and drainage procedures: "dumping syndrome") and trauma (cervical and high thoracic spinal cord transection)

3) Patients with neurologic or neuro-ophthalmologic disorders (multiple sclerosis, optic neuritis or neuropathies) [4-10].

4) Patients with drugs use causing autonomic dysfunction [11,23] (i.e., methyldopa, barbiturates, anaesthetics, antidepressant),

5) Patients with diabetes mellitus [14-16,23] were excluded due to the possible influence on pupillary reaction.

6) Patients not sufficiently cooperative for OCT and PCT measurements, and all eyes with a refractive spherical equivalent (myopic or hyperopic) >5 D or with high astigmatism (>3 D) were also excluded from this study (In order to reduce the effect of refractive error on OCT testing).

7) Three glaucoma patients and 2 control subjects were also excluded because of high variability of PCT measurements between the 2 examiners.

Visual field

The visual field (VF) was tested by the Humphrey Field Analyzer Model 750I (Humphrey Instruments Inc., San Leandro, CA, USA), using the program central 30-2, SITA-standard strategy. The global indexes a mean deviation (MD) and pattern standard deviation (PSD) were used for comparison of VF defect between the glaucoma patients and healthy subjects. A reliable VF test was defined as one with less than 20 % fixation loss and less than 15 % positive and negative catch trials. When the fixation losses were >20 %, the false-positive and false-negative rates >15 %, the visual field was considered to be unreliable and excluded from the analysis.

Measurement of pupil cycle time

Pupil cycle time was measured using the method described by Miller et al. [1]. The patient was seated at a slit lamp in a dimly illuminated room and asked to look into the far distance. A thin, horizontally aligned beam of light with moderate intensity, measuring 9 mm in length and 0.5 mm in width, was focused from below the lower inferior pupillary margin, for initiation of pupil cycle constriction and dilation. An electronic stopwatch measuring $1/100^{th}$ of a second measured PCT. The time taken to reach 90 cycles (three runs of 30 cycles each) in seconds was multiplied by 1000/90 to obtain PCT in milliseconds/cycle. All PCT measurements were performed at the same time of the day, in the morning (between 09:00 and 10:00 am). For each eye, PCT was measured independently by two blinded clinicians (O.K. and E.K.), and the mean values were recorded. Eyes with more than a 10 % difference in measurements between the interpreters were excluded from the study. The PCT measurement was completed approximately within 5 minutes for each individual.

Optical coherence tomography

Optical coherence tomography was performed using Cirrus-HD OCT 4000 version 6.5 (Carl Zeiss Meditec Inc, Dublin, CA) by one of the authors (O.K). Peripapillary retinal nerve fiber layer thickness (RNFLT) was acquired with the optic disc cube 200 × 200 protocol that images the optic disc in a 6 mm × 6 mm region. The mean RNFLT and those forming individual quadrants were obtained. Macular ganglion cell-inner plexiform layer (GC-IPL) thickness was obtained using the macular cube 512 × 128 protocol that images a 6 mm x 6mm area centered at the fovea. The GC-IPL thickness was derived automatically by the machine software over an elliptical annulus (2 mm × 2.4 mm radius), excluding the central foveal region (0.5 mm × 0.6 mm radius).

Statistical analysis

All statistical analyses were performed with SPSS for Windows version 11.5 (SPSS Inc., Chicago, IL). Two groups were compared using chi-squared test for categorical variables and an independent t-test for non-categorical parameters. Correlations of PCT results with age of the patients and control subjects, duration of glaucoma (years), BCVA, MD and PSD of visual field, and OCT findings were analyzed using Pearson correlation analysis.

Results

Mean age was 63.5 ± 9.5 in glaucoma patients, and 62.2 ± 7.2 in healthy subjects. The rate for females was 62.5 % in glaucoma patients, and 54.2 % in healthy subjects. There were no statistically significant differences between the groups for ages and gender (p=0.453, p=0.323 respectively). Mean duration of disease was 6.3 ± 2.3 years in patients with glaucoma (range: 2 to 13 years).

The demographic and clinical information for each group are summarized in Table 1. Statistically significant differences were found between the groups in regard to BCVA and MD (respectively p<0.001, p=0.031).

POAG (40 eyes of 40 subjects)		**Healthy subjects (35 eyes of 35 subjects)**	**P value**
Age (yrs) (mean ± SD)	63.5 ± 9.5 (range, 44 to 80)	62.2 ± 7.2 (range, 42 to 76)	0.453
Gender (Male/Female)	15/25	16/19	0.323
BCVA (mean ± SD)	0.77 ± 0.25 (range, 0.5 to 0.9)	1.0 ± 0.0 (range, 1.0)	<0.001*
Cup/Disc Ratio	0.54 ± 0.18 (range, 0.3 to 0.9)	0.29 ± 0.08 (range, 0.16 to 0.42)	<0.001*
PSD (mean ± SD)	3.9 ± 2.7 (range, 1.4 to 14.3)	1.6 ± 0.2 (range, 1.5 to 6.6)	<0.001*
*Statistically significant. POAG: Primary Open-Angle Glaucoma; BCVA: Best Corrected Visual Acuity; MD: Mean Deviation; PSD: Pattern Standard Deviation			

Table 1: Characteristics of patients with glaucoma and healthy subjects.

RNFLT and GC-IPL thickness in all sectors were significantly lower in the glaucoma group compared with the healthy subjects (p<0.001, p<0.001, respectively). The results of the RNFLT and GC-IPL thickness analyses are presented in Table 2.

Characteristics	**POAG (40 eyes of 40 subjects)**	**Healthy subjects (35 eyes of 35 subjects)**	**P value**
RNFLT (μm) ± SD			
Average	85.1 ± 28.1	95.2 ± 25.3	<0.001*
Superior	101 ± 27.4	118.8 ± 9.4	<0.001*
Nasal	69.6 ± 13.3	73.1 ± 6.9	0.045*
Inferior	106.3 ± 26.9	119.8 ± 17.8	0.001*
Temporal	62 ± 12.8	69.3 ± 2.07	0.012*
GC-IPL thickness (μm) ± SD			
Average	77.1 ± 16.8	82.4 ± 4.7	<0.001*
Superior	77.7 ± 12.4	84 ± 5.5	0.030*
Superiortemporal	76.6 ± 11.3	79.7 ± 4.5	0.024*
Superiornasal	77.9 ± 11.7	84 ± 4.1	0.002*
Inferior	75.9 ± 11.7	82.8 ± 4.5	<0.001*
Inferiortemporal	77.0 ± 11.3	81.7 ± 4.01	<0.001*
Inferiornasal	76.7 ± 11.1	81.7 ± 4.01	<0.001*
*Statistically significant POAG: Primary Open-Angle Glaucoma; RNFLT: Retinal Nerve Fiber Layer Thickness; GC-IPL: Ganglion Cell-Inner Plexiform Layer			

Table 2: Results of RNFLT and GC-IPL thickness of patients with POAG and healthy subjects.

The mean PCT measurements of 40 glaucoma patients was 947.5 ± 65.5 ms (range: 830 to 1140 ms), whereas the mean PCT of 35 healthy subjects was 888 ± 33.8 ms (range: 760 to 990 ms) (p<0.001).

There was no correlation between PCT measurements and cup-disc ratio of the patients with glaucoma (R=0.028, p=0.779). There was also no significant correlation between PCT measurements and MD of the glaucoma patients (R=0.117, p=0.246).

The age of the patients and duration of the glaucoma were found to be positively correlated with PCT measurements (R=0.331, p=0.001, R=0.457, p<0.001 respectively). Correlation of PCT and age was also positively correlated in control group (R=0.314, p=0.008). On the other hand, there was a prominent lengthening of PCT with reducing BCVA, RNFLT, GC-IPL thickness (p<0.001, p<0.001, p<0.001 respectively). The results of correlations analysis are summarized in Table 3.

Dependent variable	R value	P value
Age	0.331	0.001*
Duration of glaucoma	0.457	<0.001*
BCVA	-0.396	<0.001*
Cup-disc ratio	0.028	0.770
Visual Field parameters		
MD	0.117	0.240
PSD	0.495	<0.001*
RNFLT		
Superior	-0.595	<0.001*
Nasal	-0.521	<0.001*
Inferior	-0.637	<0.001*
Temporal	-0.457	<0.001*
GC-IPL thickness		
Superior	-0.677	<0.001*
Superiortemporal	-0.676	<0.001*
Superiornasal	-0.684	<0.001*
Inferior	-0.717	<0.001*
Inferiortemporal	-0.770	<0.001*
Inferiornasal	-0.676	<0.001*

*Statistically significant
BCVA: Best Corrected Visual Acuity; MD: Mean Deviation, PSD: pattern standard Deviation; RNFLT: Retinal Nerve Fiber Layer Thickness; GC-IPL: Ganglion Cellinner Plexiform Layer

Table 3: Correlation of PCT measurements with age, duration of glaucoma, BCVA, Cup-disc ratio, Visual field parameters (MD, PSD), RNFLT and GC-IPL thickness.

Discussion

Pupil cycle time is a fast, simple, and reliable clinic test of optic nerve function. It has a great advantage of being objective and quantitative for each eye individually. The PCT measurements might be used in the clinical evaluation of an optic nerve. There are several studies in the literature about PCT measurements [1-21]. Kaur et al. [15] reported that the PCT of diabetic patients was prolonged when compared to nondiabetics, and there was also prolongation of PCT with increasing age and diabetes duration. Similar finding were reported by Martyn et al. [14], Kim et al [16].

In the present study, the mean PCT of patients with glaucoma was 947.5 ± 65.5 ms, whereas mean PCT of healthy subjects was 888 ± 33.8 ms. The PCT of patients with glaucoma was prolonged when compared to controls. The cause of prolongation in patients with glaucoma might be due to glaucomatous optic neuropathy that leads to deterioration at the afferent pathways of the pupillary reflex arc. We evaluated the correlation of PCT results with BCVA, VF and OCT parameters. Our results clearly indicate a prominent lengthening of PCT measurements with reducing BCVA, RNFLT and GC-IPL thickness. There was a moderate to strong negative correlation of PCT measurements with RNFLT and GC-IPL thickness. We also found a relationship between an evident lengthening of PCT with increasing duration of glaucoma.

Although the measurement of PCT would appear to be simple and reliable, a large range of PCT values in normal subjects is obvious from previous studies and sometimes these values may be equal or exceed to the measured values of patients known to be abnormal. This is a significant issue which questions the validity of the procedure as a clinical test for optic nerve functions. For instance, Hamilton et al. [3] reported that a mean PCT value of 814 ms with an upper limit of normal at 935 ms was established for normal subjects, whereas Wybar et al. [9] reported 980 ms as being the average PCT value for abnormal subjects. The size of the normal range is related to the measure's ability to discriminate abnormality from normality, and a wide range of PCT values from normal subjects is insufficient for a general test [24]. Variations of age and pupil size of subjects may explain a wide range confusing PCT values amongst subjects reported in our study. Manor et al. [25] suggested that the PCT showed an evident tendency to increase with age. They also reported that the mean PCT in the group aged from 10 to 49 years was 739 ± 74 ms whereas the mean PCT in the age group of 50 to 79 years was 872 ± 83 ms. Only 2% of eyes from the group aged from 10 to 49 years had a PCT above 954 ms, while 23.9 % had a PCT longer than 954 ms in the elder patients' group (60-79 years). Miller et al. [1] studied 50 normal subjects aged between 12 to 50 years. They found a mean PCT of 822 ± 69 ms in the group as a whole. There was a PCT longer than 954 ms in only 5% of this normal population. These authors also demonstrated that normal subjects over the age of 50 years showed a clear tendency to have a longer PCT. These studies could explain that why our study had a wide range of PCT values. In our study, the subject ages showed a broad distribution (range, 42 to 80) and the subjects were found to be positively correlated with PCT values. As elderly subjects having high values of PCT measurements. It causes to be a wide range of PCT values. On the other hand, Howarth et al. [26] suggested that PCT was seen to depend upon pupil size, increasing monotonically but nonlinearly as size increased. The waveform of pupil cycling is typically sawtooth, contraction being much faster than dilation. They also suggested that there was considerable variation amongst subjects in the range of pupil sizes where pupil cycling could be elicited. This finding can also explain the variations amongst subjects in the measured PCT values. Given that pupil size of subjects was not measured in our study, we could not show the effect pupil size on PCT measurement in our study. There was also a wide range of PCT in glaucoma patients. In this study, the glaucoma patients had a wide spectrum. There was patients with mild to severe glaucoma and this can be observed from the wide

range of cup/disc ratio, MD and PSD values which were demonstrated in Table 1. This wide range of glaucoma might be the reason of wide range of PCT.

Other limitations of the PCT test are that it cannot be performed in patients with severe afferent defect and it is invalid if the patient is receiving medications that might affect pupil reactions or if the efferent limb of the reflex arc is affected (i.e., damaged iris musculature by trauma or prior surgery), Furthermore, the presence of the senile miosis which brings small amplitude cycles so difficult to measure in an accurate manner.

There are several limitations of our study. First, we investigated only a small number of patients with glaucoma and controls. The small population size had limited statistical power to detect small differences in PCT measurements between patients with glaucoma and controls. Secondly, all of the patients were Caucasian. This is important, because recent studies showed that differences in PCT measurements might be associated with ethnic differences [1-21]. Thus, further studies including a larger number of subjects of different ethnicities and will be necessary to confirm our findings.

Visual field testing and OCT have traditionally been used for evaluation of progressive damage in glaucoma. However, detecting glaucoma progression can be challenging, and there is currently no consensus on how to define and evaluate progressive change in glaucoma. In light of our findings, we believe that in spite of encouraging results about PCT, it is too early to conclude that PCT test may use as a complementary or additional method for assessing the progression of glaucoma patients in clinical practice. However, it should be emphasized that the results of our study should be strengthened with further studies.

In conclusion, this clinical pilot study could demonstrate the likely success and feasibility of a much larger study investigating the association between PCT and patients with glaucoma. Though we tried to recruit as many samples as possible, we accept that the small samples of this study may cause weakening in statistical results. Prospective studies with larger sample sizes are needed for the assurance of our conclusion.

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