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Static and Dynamic Pupillary Characteristics in Clinically Unilateral Pseudoexfoliation Syndrome

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Disclosure

The authors report no conflicts of interest and have no proprietary interest in any of the materials mentioned in this article.

ABSTRACT

PURPOSE: To perform a comparison of static and dynamic pupillometry measurements in patients with clinically unilateral pseudoexfoliation syndrome (PES) and age-matched controls.

METHODS: This prospective cross-sectional study consisted of 38 patients with unilateral PES and 40 control participants. A quantitative pupillometry system was used to evaluate the pupil characteristics of eyes with PES (Group 1), clinically unaffected fellow eyes (Group 2), and healthy eyes (Group 3). Static pupillometry measurements including scotopic pupil diameter (PD), mesopic PD, low photopic PD and high photopic PD were undertaken. Subsequently, dynamic pupillometry measurements including resting diameter, amplitude of pupil contraction, latency of pupil contraction, duration of pupil contraction, velocity of pupil contraction, latency of pupil dilation, duration of pupil dilation, and velocity of pupil dilation were undertaken.

RESULTS: There were statistically significant differences between the groups with regard to scotopic PD, mesopic PD, and low photopic PD ($P<0.001$). The pairwise comparisons exhibited that Group 1 shows significantly lower PD values compared with Groups 2 and 3. Group 2 also had significantly lower PD values compared with Group 3. Additionally, Group 1 and 2 had statistically significantly lower values of amplitude of pupil contraction, velocity of pupil contraction, duration of pupil dilatation, and velocity of pupil dilatation values compared with Group 3. Moreover, Group 1 and 2 demonstrated statistically significantly prolonged latency of pupil dilatation compared with Group 3.

CONCLUSIONS: Static and dynamic pupil characteristics of affected eyes and their fellow eyes of cases with unilateral PES are different from the healthy subjects.

KEY WORDS: Dynamic pupillometry; Pupil diameter; Pseudoexfoliation syndrome; Static pupillometry.

INTRODUCTION

Pseudoexfoliation syndrome (PES) is an age-related systemic disorder of the extracellular matrix which is characterized by the progressive accumulation of an abnormal whitish, fibrillar pseudoexfoliative material (PXM) in many ocular tissues such as ciliary body, iris, iridocorneal angle, lens capsule, zonules, and corneal endothelium.[1] PES might affect up to 25% of the population over the age of 60 years, and its frequency increases with aging.[2] The abnormal deposition of PXM causes a broad spectrum of ocular manifestations in anterior segment such as increased intraocular pressure (IOP), phacodonesis, and blood-aqueous barrier dysfunction.[3,4] Additionally, cataract surgery in eyes with PES has higher incidence of intraoperative and postoperative complications, related mostly to poor mydriasis, lens subluxation, posterior synechiae, and vitreous loss.[4-6]

Up to 76% of patients with PES are initially diagnosed as having unilateral PES.[7] While the presence of PXM is frequently encountered as asymmetric, and clinically PES may be seen in only one eye of a patient, Parekh and colleagues[8] reported that 81% of the patients with clinically unilateral PES had PXM on either the lens capsule or conjunctival samples of the clinically unaffected eyes by using transmission electron microscopy. Moreover, several studies on the follow-up of the patients with unilateral PES documented that 74% to 81.6% of the unilateral cases became bilateral.[9,10] It can be proposed that unilateral PES is in fact a bilateral but asymmetric condition, and the percentage of unilateral disease decreases with aging. However, differences in the severity of PES might be responsible for different ocular morphological and biomechanical characteristics in both eyes of the same patient.[11-13]

Recent developments in automated pupillometry devices have enabled quantitative, objective, noninvasive, and repeatable measurements of pupil diameter (PD) as well as the pupillary kinetics. These measurements can be taken statically with the conditions of scotopic, mesopic, or photopic vision and dynamically.[14,15] It is well known that poor pupillary dilation,

owing to iris infiltration and fibrosis, has been reported in patients with PES. However, alterations in pupillary characteristics in patients with clinically unilateral PES have not been objectively investigated yet.

From this perspective, the aims of this present study were to evaluate the static and dynamic pupil characteristics of affected eyes and their fellow unaffected eyes of subjects with clinically unilateral PES and to compare these values with otherwise healthy subjects using an automatic quantitative pupillometry system.

METHODS

This prospective cross-sectional study was carried out from March 2016 to December 2017 at a tertiary ophthalmology clinic. The study protocol was approved by the ethics committee and the study was carried out in accordance with the Declaration of Helsinki. Written informed consent was obtained from the each individual participant.

Patients with clinical evidence of unilateral PXM were included in this study. The study population consisted of 38 unilateral PES patients and 40 age- and sex-matched control participants. Participants were selected from patients who consulted at the outpatient clinic for routine refractive evaluation.

Phakic patients presenting with clinically unilaterally detectable PXM on the lens surface and/or pupillary border, pupillary ruff defects, and transillumination defects were considered for this present study. The fellow eyes of subjects with no apparent clinical signs of PXM accumulation were accepted as subclinical PES. Presence or absence of PXM was confirmed after pupillary dilation. Eyes were separated into PXM positive, clinically normal contralateral, and normal control groups. The PXM positive eyes of patients with clinically unilateral PES were classified as the Group 1, the fellow eyes of patients with clinically unilateral PES (subclinical PES) were classified as the Group 2, and right eyes of the controls were accepted as the Group 3.

The subjects that had a a history of previous ocular surgery or laser treatment, head or orbital trauma, uveitis, ocular or orbital inflammation, and ocular disease other than PES were not included in the study. Patients with known or suspected ocular hypertension or glaucoma, dry eye syndrome, hyperopia or myopia more than 3.00 diopters (D), and astigmatism more than 1.00 D were excluded. All eyes included in the study had IOP less than 21 mm Hg and open angles (grade 2, using the van Herick method). Since smoking may be associated with changes in pupil size[16], only non-smokers were included. Moreover, we only included participants who had not used drugs or consumed alcohol during the previous year; had no diagnosis of diabetes mellitus; had taken no systemic medications during the last three months; and had not used any anti-prostate drugs such as prazosin, terazosin, or tamsulosin. Participants with any of the following conditions, which may affect pupillary motility, were also excluded: iris and/or pupil anomalies such as coloboma, anisocoria, synechia, and sphincter tear; topical medications that may affect iris mechanics such as tropicamide, cyclopentolate, pilocarpin, and narcotic-derived medications; neurological disease or other diseases of the visual pathways; and those who were not cooperative enough to undergo pupillometry examinations. To grade lens opacities of the participants, we used the Lens Opacities Classification System III (LOCS III). We excluded participants who had cataracts graded greater than two on the LOCS III.

Participants underwent a full ophthalmic assessment including best-corrected visual acuity using the Snellen chart, gonioscopy with a Goldman three-mirror lens, IOP measurement using a Goldmann applanation tonometer, slit-lamp biomicroscopy, and dilated fundus examination. The refraction measurements were performed using the same automatic refractor-keratometer device (Canon RF-K2 Full Auto Ref-Keratometer, Japan) for each participant. The spherical equivalent (spherical component + 1/2 cylinder component) was used to calculate the refractive error. Additionally, eye movements were evaluated in all

aspects of view and the clinical swinging flashlight test was performed to determine the afferent pupillary defects.

The same clinician performed pupillometry measurements using the same automatic quantitative pupillometry system (MonPack One, Vision Monitor System, Metrovision, France). Before the pupillometry examination, any contact ocular examination and pupil dilatation were not performed. The quantitative pupillometry system was equipped with near infrared illumination and high-resolution camera (880 nm) that allowed the clinician to take measurements from binocular pupils under complete darkness and to provide precise control of stimulation parameters. The stimulus was white, obtained from a full-field backlight combining red (632 nm), green (523 nm), and blue (465 nm) light-emitting diode sources. This system allowed the clinician to take both static and dynamic pupillometry measurements and to perform accurate measurements of pupil size (accuracy = 0.1 mm).[14] Three consecutive measurements were taken for each participant and average values were selected for data analysis. Additionally, the automatic-release mode of the device was used to minimize examiner-induced errors, and only the images with high quality were included in the study. To minimize the effect of circadian variation on pupillary response[17], all pupillary measurements were performed at the same time of day (between 10 a.m. and 12 p.m.) and in the same environmental conditions. To control fixation stability during pupil recording, we required participants to fixate on a target in the center of the test field while stimuli were presented. Furthermore, we only used pupil recordings in the study analysis if eye movements were within five degrees of the central fixation axis of the optical system and infrared camera plane. During measurement, pupil contours of the participants were outlined on the image to allow us to control measurement accuracy and proprietary analysis. We used the proprietary analysis software of the device to conduct automatic static and dynamic pupillometry. This software automatically outlined the pupillary contours of the participants on the images,

ensuring that measurements were accurate and taken under controlled lighting conditions (Figure 1). Subsequently, the software performed an analysis of temporal and average response to successive visual stimuli with automated quantification of the following parameters: latency and duration of contraction and dilatation (ms); initial, minimum, maximum, and mean pupil diameter (mm); amplitude of contraction (mm); and contraction and dilatation speed (velocity) of the pupil (mm/s) (Figure 1).

The static pupillometry measurements were taken under several illumination levels to measure pupil size in scotopic (0.1 cd/m2), mesopic (1 cd/m2), low photopic (10 cd/m2), and high photopic (100 cd/m2) vision conditions. Scotopic PD, mesopic PD, low photopic PD, and high photopic PD values were recorded (Figure 1). In darkness, after five minutes of darkness adaptation, dynamic pupillometry measurements were obtained for the duration of 90 seconds. Participants were examined using white light flashes (stimulation ON time 200 ms, stimulation OFF time 3300 ms; total luminance 100 cd/m2; total intensity 20 lux). The images of both eyes were acquired and processed in real time (30 images per second). The luminance output was measured using a Minolta LS100 luminance meter. The average response to successive visual stimuli (light flashes) was quantified using the following parameters: resting diameter, amplitude of pupil contraction, latency of pupil contraction, duration of pupil contraction, velocity of pupil contraction, latency of pupil dilation, duration of pupil dilation, and velocity of pupil dilation (Figure 1).

STATISTICAL ANALYSIS

An a priori power analysis using the PASS 11 calculation software (Power and Sample Size, version 11) told us that we should enroll at least 25 eyes from each group in the study. We enrolled 38 patients with clinically unilateral PEX and 40 control subjects. Accordingly, we found the power of our study to be 88.5%. The data obtained from the study were entered into the computer and analyzed using the Statistical Package for Social Sciences (SPSS)

version 22.0 for Windows (SPSS Inc., Chicago, IL). Descriptive statistics are presented as mean ± standard deviations, frequency distributions and percentages. Chi-square test was used in the analysis of categorical variables. Normal distribution of the variables was tested using visual (histogram and probability graphs) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk Test). Equality of variances was checked by the Levene test. The one-way analysis of variance, Welch analysis of variance, and Kruskal–Wallis tests were used to determine if there were any significant differences between the three groups. Paired t, Games–Howell, Wilcoxon, and Siegel–Castellan tests were performed as the post hoc tests for pairwise comparisons. A probability level of $p<0.05$ was considered statistically significant.

RESULTS

Thirty-eight patients (16 men and 22 women) with a mean age of 68.0 ± 6.2 years with unilateral PES and 40 normal subjects (22 men and 18 women) with a mean age of 65.6 ± 5.7 years were analyzed. There were no significant differences between the groups with regard to age and gender ($P > 0.05$, for each one; Table1). The mean values of the BCVA and refractive error were also similar between 3 groups ($P > 0.05$, for each one Table 1). The mean IOP of the Groups 1, 2, and 3 were 17.12 ± 3.75 mmHg, 14.74 ± 3.08 mmHg, and 13.88 ± 4.29 mmHg, respectively. The IOP values showed a statistically significant elevation in Group 1 compared with Groups 2 and 3 ($P < 0.001$). The demographics and clinical characteristics of the groups are illustrated in Table 1.

As shown in Table 2, all static pupillometry measurements were lowest in Group 1 and highest in Group 3. There were statistically significant differences between the groups with regard to scotopic PD, mesopic PD, and low photopic PD ($P <0.001$, for each one). When these parameters (scotopic PD, mesopic PD, and low photopic PD) were compared between the groups, the pairwise comparisons exhibited that Group 1 reveals significantly lower PD values compared with Groups 2 and 3. Additionally, Group 2 also had significantly

lower PD values compared with Group 3. Conversely, the mean values of high photopic PD were similar between all groups (P = 0.120).

Dynamic pupillary characteristics of the groups are displayed in Table 3. There were no significant differences between the study and control groups with regard to latency of pupil contraction and duration of pupil contraction values (P = 0.151 and P = 0.285). On the other hand, the resting diameter measurements were statistically significantly lowest in Group 1 and largest in Group 3. Moreover, Groups 1 and 2 had statistically significantly lower values of amplitude of pupil contraction, velocity of pupil contraction, duration of pupil dilatation, and velocity of pupil dilatation values compared with Group 3. Additionally, Groups 1 and 2 demonstrated statistically significantly prolonged latency of pupil dilatation values compared with Group 3. However, the results were similar between the Groups 1 and 2.

DISCUSSION

In this study, static and dynamic pupillometry were conducted on the cases with clinically unilateral PES and healthy subjects to determine the differences in static and dynamic pupil characteristics of affected eyes and their fellow eyes of cases with clinically unilateral PES and healthy control eyes. To the best of our knowledge, this is the first study to evaluate the static and dynamic pupil characteristics obtained using an automatic quantitative pupillometry system (Vision Monitor System, Metrovision, France) in subjects with clinically unilateral PES.

Clinicians examine the pupil by observing and measuring pupil size, shape, symmetry, response to light and response to near reflex. Pupillary examinations can help clinicians to diagnose many ocular and neurological disorders, and may relate to history of medication, surgery or trauma.[18-20] On the other hand, subjective analysis of pupillary parameters can be affected by significant inter-observer changeability due to the factors such as differences in

ambient illumination, the intensity of the light stimulus, and the examiner's experience. Pupillometry can be used to obtain automatic, multiple, quantitative measurements of pupillary response to light under controlled, ambient lightening conditions. This improves the repeatability of the measurements, solves the problem of examiner-dependent errors and reduces false negative responses.[14,15,21]

The hallmark clinical finding of PES is the deposition of PXM on the anterior lens capsule and pupillary border. Iris changes are often seen early in the course of PES and caused by progressive accumulation of PXM in the iris stroma. The eyes with PES usually show inadequate pupillary dilation mainly owing to the rigidity and fibrosis caused by iris sphincter muscle involvement. There are limited studies investigating the PDs and pupil kinetics in PES subjects. Yulek and colleagues[22] investigated the dynamic function of iris muscle in 15 subjects with asymmetric PES by using videonystagmography. They measured the percent of change in pupil diameter in one second during the change in PD during fixation to an accommodative target, during the light reaction, during the convergence-induced miosis, and finally during the divergence-induced mydriasis, both at fixed speed. They reported that the differences between control group and affected eyes of asymmetric PES subjects as well as between the affected and unaffected eyes of the patients with asymmetric PES were statistically significant. Ulviye and colleagues[23] evaluated the mean pupil size under scotopic, mesopic, photopic and dynamic conditions in 46 patients with PES by using an infrared pupillometer, that integrated within CSO Sirius corneal topographer, and compared the results those in healthy subjects. They revealed all measurements including scotopic, mesopic, photopic as well as dynamic pupil sizes are statistically significantly lower in the PES group than the control group. We also confirmed these findings that scotopic, mesopic and low photopic PDs, and the resting diameter are statistically significantly lowest in affected eyes of cases with clinically unilateral PES and largest in healthy eyes in this present study. We also

showed that the fellow eyes of the cases with clinically unilateral PES had significantly smaller pupil size than healthy eyes. On the other hand, Yasar and colleagues[24] evaluated the diagnostic value of a handheld pupillometer device to discriminate the eyes with PES from healthy eyes and proposed that the precision of PD in discriminating PES is low (AUC 0.56, sensitivity 14%, specificity 94% in ROC analysis). However, their study used a simple handheld monocular pupillometry device, which could have increased the variability of binocular measurements in the same subject, and they were unable to obtain the measurements in different illumination conditions. Moreover, their study is also limited by not having taken into account the diurnal variability of pupillary characteristics.

This current study also investigated the pupil dynamics including latency, duration, and velocity of pupil constriction and re-dilation in cases with clinically unilateral PES. Our results indicated that both the affected and fellow eyes of unilateral PES patients show statistically significantly differences with regard to amplitude of pupil contraction, velocity of pupil contraction, latency of pupil dilatation, duration of pupil dilatation, and velocity of pupil dilatation values when compared to healthy eyes. However, these values were statistically insignificant between the affected and fellow eyes of cases with unilateral PES. These results may suggest that subclinical deposition and accumulation of PXM in the iris muscles of fellow eyes of clinically unilateral PES cases could be responsible for these altered pupillary kinetics. There are also a variety of studies confirming that ocular PES is a part of a systemic condition and PXM was found on the samples of the clinically unaffected eyes of cases with unilateral PES patients.[3,8,25,26]

The results of this current study also revealed that latency of pupil contraction and duration of pupil contraction values were not different between the study eyes and healthy eyes. Histopathological and ultrastructural studies investigating the iris changes in PES demonstrated that PXM are observed consistently in association with fibroblasts and

melanocytes in the iris stroma, endothelial cells and pericytes of vessels, both anterior and posterior pigment epithelial cells, and muscle cells of sphincter and dilator muscles.[27,28] However, according to our findings, it might be proposed that PXM could affect the dilator muscles more profoundly than the sphincter muscles of iris.

This study had a number of limitations. For instance, it consisted of a relatively small number of patients, which can affect the validity of our results and their significance. Another limitation is that, it was performed cross-sectionally, so the generalizability of the present findings might be limited.

To conclude, this study revealed that static and dynamic pupil characteristics of affected eyes and their fellow eyes of cases with clinically unilateral PES are different from the healthy subjects. However, dynamic pupil measurements are similar between affected and fellow eyes. This may confirm that unilateral PES is in fact a bilateral but asymmetric condition. Additionally, our results may have shed light in understanding the effect of PXM accumulation on dilator and sphincter muscles of iris in eyes with PES. Clinical implications of altered static and dynamic pupillary characteristics in PES warrant further comprehensive clinical studies.

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FIGURE LEGENDS

Figure 1: An output of static and dynamic pupillary characteristics via the automatic quantitative pupillary measurement system (Vision Monitor System, Metrovision, France) is seen.

Table 1. Demographics and clinical characteristics of the groups.

	Group 1 (n=38)	**Group 2 (n=38)**	**Group 3 (n=40)**	**P**
Age, years (Mean±SD) (Range)	68.0 ± 6.2 (58 to 78)	68.0 ± 6.2 (58 to78)	65.6 ± 5.7 (53 to 74)	0.162¶
Male/Female (n/n)	16/22	16/22	22/18	0.417*
BCVA, Snellen (Mean±SD) (Range)	0.83±0.18 (0.5 to 1.0)	0.87±0.14 (0.6 to 1.0)	0.91±0.10 (0.6 to 1.0)	0.307¶
Refraction, SE, (Mean±SD) (Range)	0.77±1.20 (-2.00 to +2.25)	1.01±1.40 (-2.50 to +2.50)	0.65±1.34 (-2.25 to +1.75)	0.105¶

BCVA: Best corrected visual acuity; SE: Spherical equivalent.
SD, Standard deviation
* Chi-square test

¶Significance in analysis of variance

Table 2. Static pupillometry measurements of the groups.

	Group 1 (n=38)	**Group 2 (n=38)**	**Group 3 (n=40)**	**P**
Scotopic PD, Mean±SD (mm)	4.35 ± 0.85	4.80 ± 0.96	5.30 ± 0.92	**<0.001[a] <0.001[b], <0.001[c], <0.001[d]**
Mesopic PD, Mean±SD (mm)	4.11 ± 0.64	4.21 ± 0.66	4.40 ± 0.80	**<0.001[a] 0.006[b], <0.001[c], 0.001[d]**
Low photopic PD, Mean±SD (mm)	3.13 ± 0.59	3.22 ± 0.61	3.34 ± 0.67	**0.001[a] 0.004[b], <0.001[c], <0.001[d]**
High photopic PD, Mean±SD (mm)	2.00 ± 0.50	2.03 ± 0.61	2.05 ± 0.57	0.120[a]

PD: Pupil diameter
SD, Standard deviation
[a]Significance in Welch analysis of variance (comparison among three groups)

[b]Significance between Group 1 and Group 2 (Paired t test) (pairwise comparison).

[c]Significance between Group 1 and Group 3 (Games–Howell test) (pairwise comparison).

[d]Significance between group 2 and Group 3 (Games–Howell test) (pairwise comparison).

Table 3. Dynamic pupillometry measurements of the groups.

	Group 1 (n=38)	**Group 2 (n=38)**	**Group 3 (n=40)**	**P**
Resting diameter, Mean±SD (mm)	4.26 ± 0.64	4.43 ± 0.80	4.70 ± 0.90	**<0.001**[a] **<0.001**[b], **<0.001**[c], **<0.001**[d]
Amplitude of pupil contraction, Mean±SD (mm)	1.15 ± 0.37	1.25 ± 0.46	1.65 ± 0.30	**<0.001**[a] 0.163[b], **<0.001**[c], **0.004**[d]
Latency of pupil contraction, median, (min-max) (ms)	281 (41-339)	275 (38-443)	235 (97-434)	0.151[w]
Duration of pupil contraction, Mean±SD (ms)	673.2 ± 203.6	640.7 ± 166.7	592.3 ± 115.1	0.285[a] **0.014**[a]
Velocity of pupil contraction, Mean±SD (mm/s)	4.33 ± 1.38	4.59 ± 1.35	5.17 ± 0.77	0.442[b], **0.005**[c], **0.010**[d]
Latency of pupil dilation, median, (min-max) (ms)	914 (638-1471)	884 (596-1416)	840 (554-1034)	**<0.001**[w] 0.250[x], **<0.001**[y], **0.003**[z]
Duration of pupil dilation, Mean±SD (ms)	1609.6 ± 183.5	1501.7 ± 130.1	1406.4 ± 106.1	**0.007**[a] 0.201[b], **0.003**[c], **0.015**[d]
Velocity of pupil dilation, Mean±SD (mm/s)	1.81 ± 0.46	1.91 ± 1.08	2.23 ± 1.14	**0.010**[a] 0.758[b], **0.003**[c], **0.008**[d]

SD, Standard deviation
[a]Significance in Welch analysis of variance (comparison among three groups)

[b]Significance between Group 1 and Group 2 (Paired t test) (pairwise comparison).

[c]Significance between Group 1 and Group 3 (Games–Howell test) (pairwise comparison).

[d]Significance between group 2 and Group 3 (Games–Howell test) (pairwise comparison).

[w]Significance in Kruskal-Wallis (comparison among three groups)

[x]Significance between Group 1 and Group 2 (Wilcoxon test) (pairwise comparison).

[y]Significance between Group 1 and Group 3 (Siegel–Castellan test) (pairwise comparison).

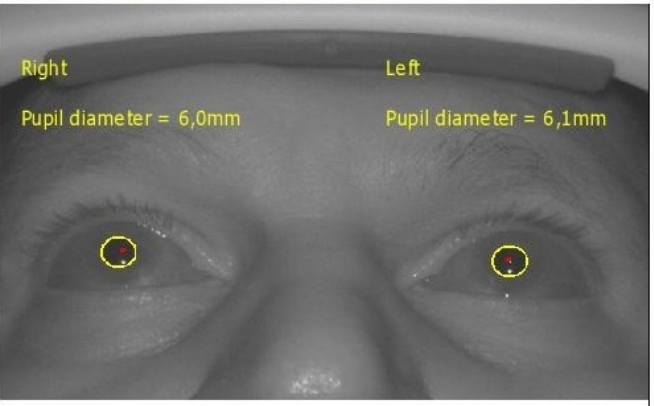
[z]Significance between group 2 and Group 3 (Siegel–Castellan test) (pairwise comparison).

patient's ID :
file number :
birth date :

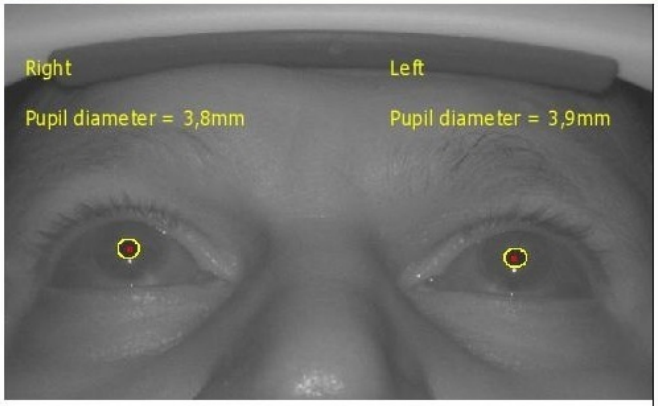
Rx :
exam. date : 23/05/2016 11:23
exam :

PUPILLOMETRY

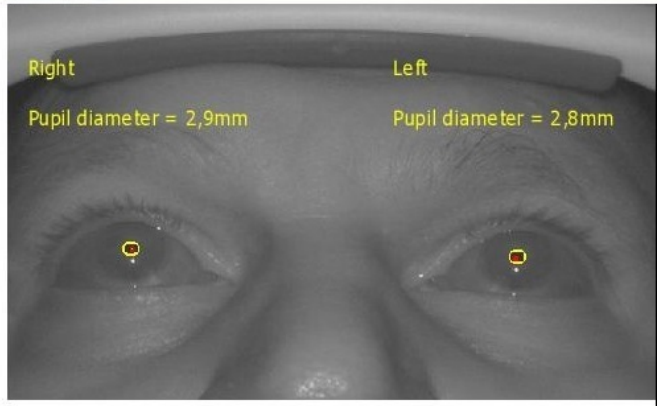
PUPILS scotopic 0mn 53s
BI stimulated



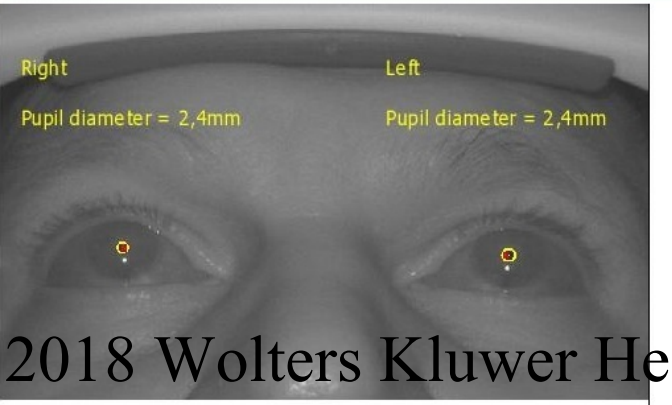
PUPILS mesopic 0mn 40s
BI stimulated



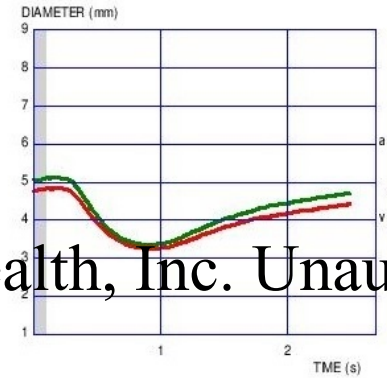
PUPILS photopic low 0mn 24s
BI stimulated



PUPILS photopic high 0mn 10s
BI stimulated



PUPILS light reflex 1mn 53s
BI stimulated



AVERAGED RESPONSE

	OD	OS
Valid Responses =	12	12
Rejected responses =	0	0
initial diameter(mm)=	4,8	5,1
amplitude of contraction(mm)=	1,6	1,8
latency of contraction(ms)=	280	274
duration of contraction(ms)=	688	634
velocity of contraction(mm/s)=	4,57	4,93
latency of dilation(ms)=	968	908
duration of dilation(ms)=	1	1
velocity of dilation(mm/s)=	1,40	1,64

result with first response