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ARTICLE

Evaluation of pupil responses and anterior chamber parameters in overactive bladder syndrome before and after antimuscarinic treatment

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Abstract

Purpose To evaluate the static and dynamic pupillometric responses and anterior chamber parameters in overactive bladder (OAB) patients before and after solifenacin succinate treatment and to compare these results with those of healthy control subjects.

Materials and methods Forty OAB patients who were planned to be treated with solifenacin succinate and 40 control subjects without any systemic or ocular diseases were included in the study. Following detailed ophthalmological examination, Pentacam imaging in order to detect anterior chamber angle, depth and volume; and static and dynamic pupillometry measurement in order to detect high-photopic (100 cd/m^2), low-photopic (10 cd/m^2), mesopic (1 cd/m^2) and scotopic (0.1 cd/m^2) pupil diameters, 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 performed at baseline and at the first month of treatment. Data from the right eyes of the participants were used for statistical analysis.

Results Baseline low- and high-photopic pupil diameters, duration of pupil contraction, latency of pupil dilatation and velocity of pupil dilatation values were significantly higher; and velocity of pupil contraction and duration of pupil dilation values were lower in the OAB group compared to the control group ($P < 0.05$ for all). One-month treatment with oral solifenacin succinate revealed higher scotopic and mesopic pupil diameters ($P = 0.042$, $P = 0.031$, respectively). Also, latency of pupil contraction was found to be increased and velocity of pupil dilatation was found to be decreased compared to pretreatment ($P = 0.003$, $P < 0.001$, respectively). We did not find any significant change in anterior chamber angle, depth and volume measured with Pentacam HR compared to pretreatment.

Conclusions Patients with OAB also have pupil abnormalities which probably reflect an underlying autonomic disorder that affects the bladder and pupils. One-month treatment of solifenacin succinate may lead to enlargement of pupil diameters under low illumination conditions and may lead to changes in dynamic pupillometric responses compatible with antimuscarinic treatment. Systemic antimuscarinic therapy has no effect on anterior chamber depth and intraocular pressure.

Introduction

Overactive bladder (OAB) is a common condition that is defined as "urinary urgency, usually accompanied by frequency and nocturia, with or without urge urinary incontinence" by the International Continence Society [1]. Antimuscarinic drugs have long been the mainstay of OAB pharmacotherapy. Acetylcholine released from parasympathetic post ganglionic neurons in the pelvic nerves in the bladder stimulates muscarinic M3 receptors in the bladder smooth muscle, causing bladder contraction. Antimuscarinic agents inhibit bladder contraction at different stages and significantly reduce the frequency of urination and the feeling of urgency by providing relaxation of the

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bladder smooth muscle. Adverse effects of these drugs such as dry mouth, constipation, headache, blurred vision, nausea, dyspepsia, dry eye symptoms have been reported due to their antimuscarinic action [2–4]. It has been reported that these drugs trigger acute angle-closure glaucoma, especially in high-risk patient groups (shallow anterior chamber and narrow angle) [5–7]. In addition, they have been reported to cause blurred vision by inhibiting accommodation and dilating pupils via M3 receptor blockage [2].

Recent developments in automated pupillometry devices have enabled quantitative, objective, noninvasive and repeatable measurements of pupil diameter in addition to the pupillary kinetics. Examination of pupillary light reflex is one way to evaluate the integrity of afferent visual pathways, and it is an indicator of the balance between the sympathetic dilator and parasympathetic constrictor systems [8, 9]. Parasympathetic dysfunction might cause relative mydriasis of the pupil in light conditions and diminished constrictor reflexes. Sympathetic dysfunction might cause relative miosis of the pupil in the dark, increased redilatation lag, and attenuation of the startle reflex, as observed in Horner's syndrome [10].

Solifenacin succinate (Kinzy, Abdi İbrahim Pharmaceuticals, Turkey) is a widely used treatment option for OAB. There are few studies in the literature investigating the effect of antimuscarinic agents both on pupil diameters and anterior segment parameters [11, 12]. These are conducted by using Pentacam, which has a low reliability and repeatability of static pupillometric measurements [13] and do not have any dynamic pupillometric measurements. Those aforementioned studies also did not investigate the baseline status of the pupillometric responses of the OAB patients when compared to control subjects. In the present study, we investigated the effects of solifenacin succinate on anterior segment parameters along with static and dynamic pupillary responses in patients with OAB who are frequently consulted to ophthalmologists before the initiation of the treatment [14]. In addition, by using an automated pupillometry system we aimed to evaluate pupillary responses of OAB patients when compared to healthy controls.

Methods

This prospective clinical study included 40 patients who had been diagnosed with OAB and who were planned to be treated with 5 mg/day oral solifenacin succinate and 40 healthy control subjects without any systemic or ocular disorders. The study was designed in accordance with the tenets of Declaration of Helsinki and approved by the Ankara Numune Training and Research Hospital Ethics Committee. Written informed consent was obtained from all participants prior to the participation of the study.

All participants underwent a detailed ophthalmological examination including best corrected visual acuity (BCVA) testing with Snellen chart, intraocular pressure (IOP) measurement with noncontact tonometry, anterior segment examination with slit-lamp biomicroscope and dilated fundus examination. Subjects with a BCVA equal to or greater than 20/20 according to the Snellen chart and without the history of any ocular problem were included in the study. Anterior chamber depth was evaluated by van Herick method and cases with Grade I and II were excluded due to the risk of angle-closure following systemic antimuscarinic use. The patients with a history or finding of contact lens use or any corneal disorder such as dry eye disease, keratitis, corneal scar, ectatic corneal disorders and cornea guttata; ocular trauma or surgery; glaucoma and pseudoexfoliation syndrome; uveitis; pupillary abnormalities and anisocoria; use of any eye drops and systemic medication besides solifenacin succinate (alpha blocker, tropicamide, pilocarpine, cyclopentolate and narcotic-derived medications, sympathomimetic etc.) that may affect pupil or iris mechanics; smoking as it could affect pupillary diameter [15] and who have any systemic diseases such as diabetes mellitus, neurological or other diseases of the visual pathways and those who cannot tolerate the examinations were also excluded from the study.

Following the detailed ophthalmic assessment, all subjects in the OAB and control groups underwent static and dynamic pupillometry measurement (MonPack One, Vision Monitor System, Metrovision, Pérenchies, France) and imaging with Scheimpflug corneal topography (Pentacam® HR, Oculus Optikgeräte GmbH, Wetzlar, Germany) in order to detect anterior chamber angle, depth and volume. All measurements repeated in the first month both in the OAB group and the control group.

All pupillometry measurements were performed by the same clinician (EY) and the same automated pupillometry system was used. No contact ocular examination or pupillary dilatation was performed before the procedure. Only high-quality images were included to minimize clinician induced errors. To minimize the effect of circadian rhythm on the pupillary responses, all pupillary measurements were performed at the same time interval of the day (between 10 am and 12 am) and under the same environmental conditions [16]. Proprietary analysis software was used for automatic static and dynamic pupillometry measurement. This software allows participants to draw the pupil contour automatically on images to ensure that measurements are taken under accurate and controlled lighting conditions. Static pupillometry measurements were measured in four different intensity of illumination medium. These were scotopic (0.1 cd/m^2), mesopic (1 cd/m^2), low-photopic (10 cd/m^2), and high-photopic (100 cd/m^2) conditions and measurements were recorded as scotopic pupil diameter,

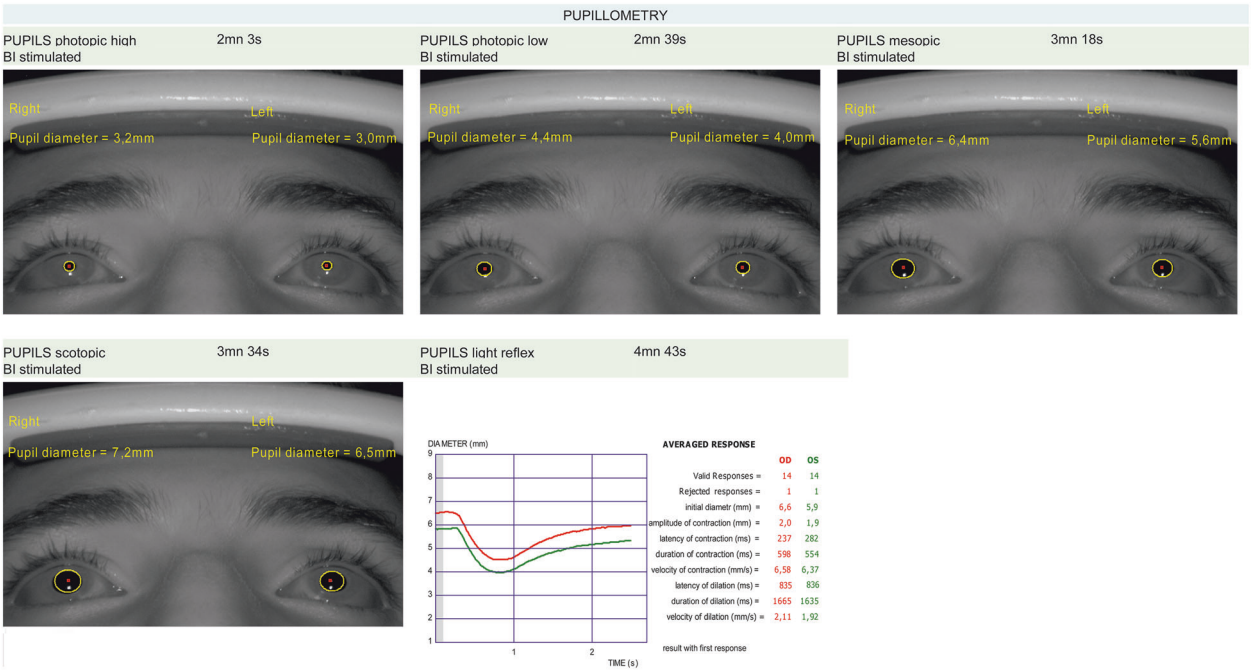

Fig. 1 A pupillometry output. Static pupil diameters in four different intensity of illumination condition (scotopic, mesopic, low-photopic, and high-photopic) and dynamic pupillometry responses are seen.

mesopic pupil diameter, low-photopic pupil diameter, and high-photopic pupil diameter (Fig. 1). In darkness, after 5 min of dark adaptation, dynamic pupillometry measurements were obtained. Each measurement was derived from averaging the responses to 25 stimulus presentations over 90 seconds using white light flashes (stimulation ON time 200 ms, stimulation OFF time 3300 ms; total brightness 100 cd/m^2; total intensity 20 lux), and then this process was repeated a further two times resulting in a total of 75 repetitions of the light stimulus responses for each participant. Images of both eyes were obtained and processed in real-time (30 images/sec). An interpolation algorithm software resamples the data at 1 KHz, which provide more accurate measurement of the response time. The luminance output was measured using a Minolta (Konica Minolta Sensing Americas, Inc.) 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 (Figs. 1 and 2).

Data collection with Scheimpflug imaging was performed with a Scheimpflug corneal imaging device. The measurements were performed by the same clinician trained to use the device (EY). Dark conditions were provided to prevent reflections during the procedure. After the clinician fixed the pupil to the centre of the eye with the real-time image on the device's monitor, the system automatically recorded 50 images with the help of a rotating Scheimpflug camera within 2 seconds. Automatic motion mode was used to reduce the clinician-dependent error rate. Measurements with an image quality of 95% or more were considered appropriate for analysis. At the end of the measurement, anterior chamber angle, depth and volume values were recorded for each case (Fig. 3).

Statistical analysis

The research data were analysed via SPSS (Statistical Package for Social Sciences, SPSS Inc., Chicago, IL). The data only from the right eyes of patients used for statistical analysis. Descriptive statistics were presented as mean ± standard deviation (minimum–maximum), frequency distribution and percentage. Pearson Chi-square test was used to evaluate categorical variables. The normal distribution of the variables was examined using visual (histogram and probability graphs) and analytical methods (Kolmogorov–Smirnov Test/ Shapiro–Wilk Test). For variables that were not normally distributed; Mann–Whitney U-test between two independent groups and Wilcoxon signed ranks test between two dependent groups were used as statistical methods. For the variables with normal distribution, Student's *t*-test was used for statistical significance between two independent groups and Paired Samples *t*-test was used between two dependent groups. Statistical significance level was accepted as $p < 0.05$.

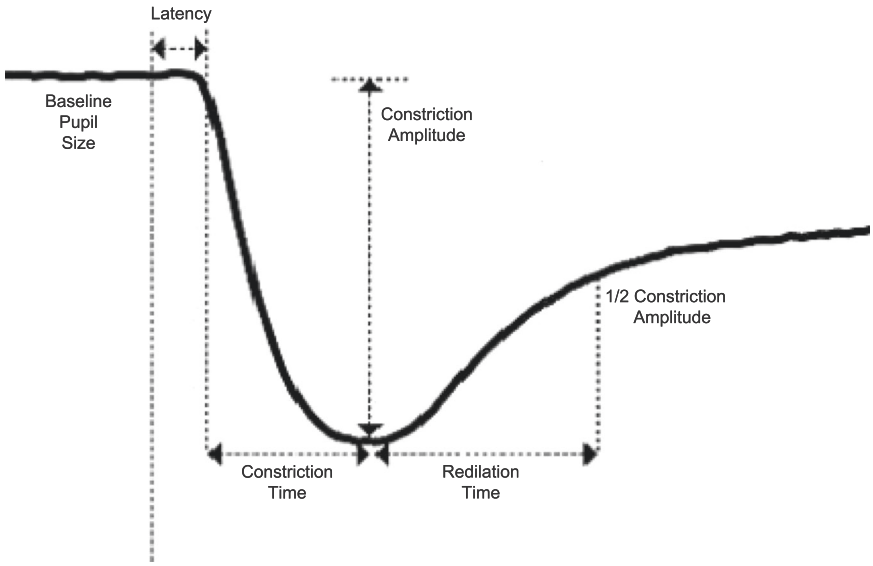

Fig. 2 A detailed diagram of the stimulus protocol and pupil response profile is seen. On the *y*-axis, the pupil size is expressed as normalised pupil diameter, and on the *x*-axis, the time is given in seconds.

Results

In this study, 40 eyes of 40 patients (35 females, five males) with a mean age of 52.7 ± 12.3 years (31–72 years) using oral solifenacin succinate for OAB and 40 eyes of 40 healthy control subjects (35 females, five males) with a mean age of 50.1 ± 7.8 years (30–69 years) were included in the study. No significant differences were determined between the groups with respect to age and gender distribution ($p = 0.124$ and $p = 1.0$, respectively). The mean IOP was 14.98 ± 3.63 mmHg in the OAB group and 14.40 ± 2.84 mmHg in the control group ($p = 0.414$). In the OAB group the mean IOP was 15.34 ± 5.37 mmHg in the first month and was not changed significantly compared to baseline ($p = 0.659$).

The distribution of static and dynamic pupillometry measurements and anterior chamber parameters of OAB and control group at the beginning of the study is presented in detail in Table 1. Before the treatment, the low-photopic and high-photopic pupil diameters were significantly higher in the OAB group ($p = 0.016$ and $p < 0.001$, respectively); and there were no statistically significant differences with respect to scotopic and mesopic pupil diameters ($p = 0.628$ and $P = 0.802$, respectively). Of the dynamic pupillometric parameters, duration of pupil contraction, latency of pupil dilation and velocity of pupil dilatation values were significantly higher in the OAB group ($p < 0.001$, $p = 0.001$, $p < 0.001$, respectively); however, velocity of pupil contraction and duration of pupil dilation values were significantly lower in the OAB group ($p = 0.024$ and $p < 0.001$, respectively). There were no statistically significant differences between two groups with respect to resting diameter, amplitude of pupil contraction, latency of pupil contraction values ($p = 0.633$, $p = 0.513$, $p = 0.969$, respectively). There were no significant differences between the OAB and the control eyes with respect to anterior chamber parameters (angle, volume and depth) at the beginning of the study ($p > 0.05$ for all).

Distribution of pretreatment and post-treatment static and dynamic pupillometry values and anterior chamber parameters in the OAB group are presented in Table 2 in detail. There was a statistically significant increase in scotopic and mesopic pupil diameters at the first month of treatment compared to pretreatment ($p = 0.042$, $p = 0.031$, respectively). Low-photopic and high-photopic pupil diameters were also increased but this difference was not significant ($p = 0.123$, $p = 0.156$, respectively). Of the dynamic pupillometric values, latency of pupil contraction was increased significantly, while velocity of pupil dilatation was decreased significantly ($p = 0.003$, $p < 0.001$, respectively). The other dynamic pupillometric values were not significantly changed ($p > 0.05$ for all). In the OAB group anterior chamber angle, volume and depth were not significantly changed at the first month compared to pretreatment ($p = 0.065$, $p = 0.666$, $p = 0.332$, respectively).

Distribution of baseline and first-month static and dynamic pupillometry values and anterior chamber parameters in the control group are presented in Table 3 in detail. We did not find any statistically significant changes with respect to pupillometry values and anterior chamber parameters between baseline and first month in control group ($p > 0.05$ for all).

Discussion

In this study, we found some baseline differences in the static and dynamic pupillary responses of the OAB group

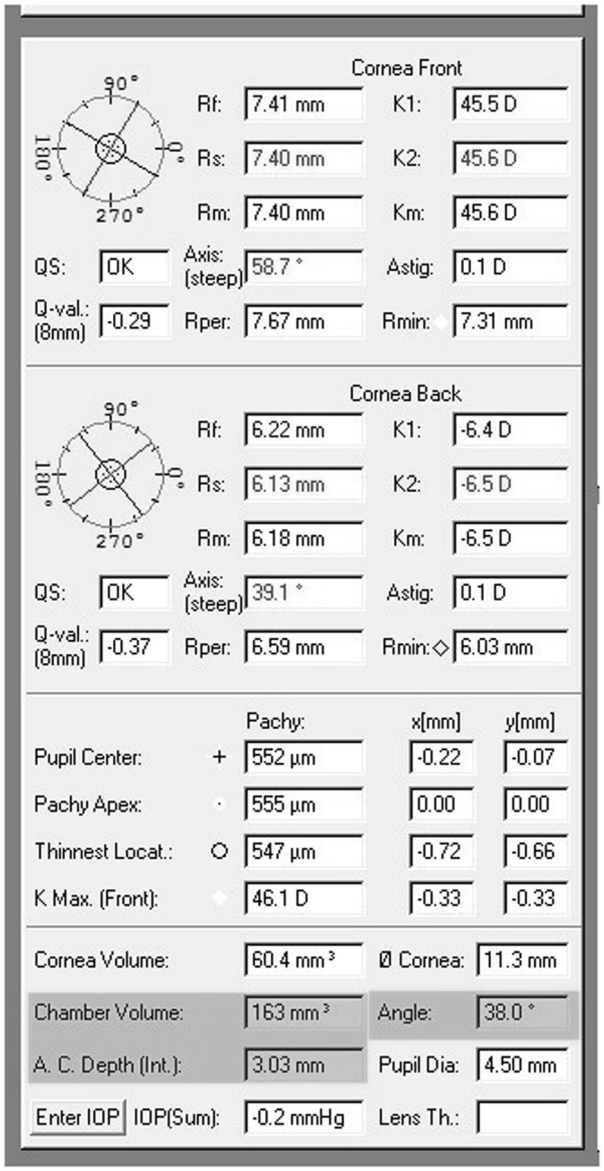

Fig. 3 Output of the anterior chamber parameters with Scheimpflug imaging system (Pentacam® HR). Anterior chamber volume, angle, and depth parameters are seen as highlighted.

when compared to the control group and it seems likely that these changes are reflections of a widespread underlying autonomic disorder in OAB. According to Muppidi et al. the velocity of pupil contraction and the amplitude of pupil contraction are pupillary parasympathetic markers while velocity of pupil dilation is a sympathetic marker [17]. At baseline, low-photopic and high-photopic pupil diameters were found to be higher in the OAB group. Muppidi suggested that increased pupil diameter at a higher intensity of illumination indicates a parasympathetic impairment whereas Bremner [18] enounced that measurement of resting pupil diameter on its own is only of very limited value in diagnosing parasympathetic lesions. Increase of the duration of pupil contraction and decrease of the velocity of pupil contraction in the OAB group seems to be compatible with parasympathetic impairment. However, in another study, Bremner [19] stated that observation of the speed of pupillary constriction in response to a light stimulus cannot be used in isolation to make inferences about pathology—instead, it must be interpreted in the context of the response amplitude. In the current study, despite the lower value of contraction velocity, the absence of a significant change in the contraction amplitude makes it difficult to interpret these findings as a decrease in parasympathetic activation. The velocity of pupil dilation was found to be higher, which indicates an increased sympathetic tone.

Although this data reveal that autonomic nervous system imbalance is involved in the pathophysiology of OAB, there is no consensus regarding which part of this imbalance (parasympathetic or sympathetic) prevails. The idea that the autonomic nervous system is affected in OAB has been reached by evaluating heart rate variability in several studies. First, Blanc et al. [20] hypothesized that subclinical autonomic nervous system dysfunction may be a causative factor of OAB. Next, Choi et al. [21] also reported the hypothesis of an autonomic imbalance associated with OAB. Hubeaux et al. [22] accentuated this autonomic balance dysfunction most extensively by assessing heart rate variability during filling cystometry. They noted the predominance of parasympathetic activity when the bladder was empty and a preponderance of sympathetic activity at the end of bladder filling in women with OAB, which could suggest that bladder filling induces a global sympathetic response in women with OAB. The same authors designed another study [23], which demonstrated that sympathetic dysfunction might be predominant over parasympathetic dysfunction in OAB patients. Further, Ates et al. [24] reported sympathetic dysfunction in OAB patients by assessing sympathetic skin response. Based on all aforementioned data, it seems that in the OAB there is an extensive autonomic imbalance that affects the bladder, pupils, and probably many other organs under autonomic control.

We also investigated the effect of systemic antimuscarinic treatment on pupillary dynamics of OAB patients and found an increase in scotopic and mesopic pupil diameters in the first month of oral solifenacin succinate treatment. Although this finding is compatible with the antimuscarinic effect of solifenacin succinate treatment, it would be more plausible if the antimuscarinic effect was seen in photopic conditions in which parasympathetic tone is maximal. In order to explain this finding, we can just only speculate on some possible explanations. First of all, although parasympathetic dive is greater in bright condition, perhaps the number of M3 receptors or sensitivity of receptors to the solifenacin may not be as much as expected

Table 1 Distribution of static and dynamic pupillometry values and anterior chamber parameters of the groups at the beginning of the study.

Before treatment	OAB group ($n = 40$) Mean ± SD (range)	Control group ($n = 40$) Mean ± SD (range)	p
Scotopic pupil diameter (mm)	6.04 ± 0.79 (3.8–8.0)	6.13 ± 0.72 (4.5–7.5)	0.628[a]
Mesopic pupil diameter (mm)	4.58 ± 0.67 (3.2–5.8)	4.62 ± 0.92 (3.0–6.8)	0.802[b]
Low-photopic pupil diameter (mm)	3.58 ± 0.41 (2.8–4.8)	3.39 ± 0.51 (2.4–4.8)	**0.016**[b]
High-photopic pupil diameter (mm)	3.14 ± 0.40 (2.2–4.3)	2.78 ± 0.35 (2.1–3.6)	**<0.001**[b]
Resting diameter (mm)	5.46 ± 0.67 (4.1–6.7)	5.39 ± 0.80 (3.9–7.2)	0.633[b]
Amplitude of pupil contraction (mm)	1.64 ± 0.38 (0.3–2.2)	1.74 ± 0.27 (1.3–2.4)	0.513[b]
Latency of pupil contraction (ms)	257.0 ± 48.6 (138–327)	261.8 ± 38.8 (111–301)	0.969[b]
Duration of pupil contraction (ms)	704.1 ± 166.0 (415–1284)	594.9 ± 61.6 (422–753)	**<0.001**[b]
Velocity of pupil contraction (mm/s)	5.01 ± 1.27 (2.57–8.85)	5.55 ± 0.78 (4.25–7.61)	**0.024**[a]
Latency of pupil dilation (ms)	930.6 ± 124.9 (701–1300)	854.2 ± 57.6 (696–967)	**0.001**[b]
Duration of pupil dilation (ms)	1490.1 ± 223.3 (432–1763)	1621.1 ± 68.9 (1463–1804)	**<0.001**[b]
Velocity of pupil dilation (mm/s)	2.63 ± 1.10 (1.41–7.95)	1.92 ± 0.36 (1.33–3.06)	**<0.001**[b]
Anterior chamber angle (°)	31.9 ± 5.2 (19.7–40.6)	32.3 ± 6.0 (22.3–49.2)	0.900[b]
Anterior chamber volume (mm^3)	135.3 ± 29.9 (71–201)	143.6 ± 31.2 (85–212)	0.329[b]
Anterior chamber depth (mm)	2.61 ± 0.37 (1.39–3.40)	2.71 ± 0.32 (2.22–3.60)	0.384[b]

Bold values indicate $p < 0.05$.

OAB overactive bladder, *SD* standard deviation.

[a]Student's *t*-test.

[b]Mann–Whitney U-Test.

Table 2 Distribution of static and dynamic pupillometry values and anterior chamber parameters of pretreatment and post-treatment in OAB group.

OAB group ($n = 40$)	Pretreatment Mean ± SD (range)	Post-treatment Mean ± SD (range)	p
Scotopic pupil diameter (mm)	6.04 ± 0.79 (3.8–8.0)	6.18 ± 0.86 (3.3–8.0)	**0.042**[a]
Mesopic pupil diameter (mm)	4.58 ± 0.67 (3.2–5.8)	4.77 ± 0.79 (3.5–6.4)	**0.031**[b]
Low-photopic pupil diameter (mm)	3.58 ± 0.41 (2.8–4.8)	3.69 ± 0.51 (2.9–5.0)	0.123[b]
High-photopic pupil diameter (mm)	3.14 ± 0.40 (2.2–4.3)	3.20 ± 0.44 (2.3–4.4)	0.156[b]
Resting diameter (mm)	5.46 ± 0.67 (4.1–6.7)	5.39 ± 0.68 (3.3–7.1)	0.306[a]
Amplitude of pupil contraction (mm)	1.64 ± 0.38 (0.3–2.2)	1.64 ± 0.40 (0.1–2.4)	0.510[b]
Latency of pupil contraction (ms)	257.0 ± 48.6 (138–327)	275.8 ± 59.2 (149–501)	**0.003**[b]
Duration of pupil contraction (ms)	704.1 ± 166.0 (415–1284)	681.7 ± 134.4 (434–1005)	0.989[b]
Velocity of pupil contraction (mm/s)	5.01 ± 1.27 (2.57–8.85)	5.10 ± 1.43 (0.37–8.76)	0.452[a]
Latency of pupil dilation (ms)	930.6 ± 124.9 (701–1300)	934.7 ± 89.9 (785–1106)	0.781[a]
Duration of pupil dilation (ms)	1490.1 ± 223.3 (432–1763)	1532.2 ± 126.2 (1235–1699)	0.225[b]
Velocity of pupil dilation (mm/s)	2.63 ± 1.10 (1.41–7.95)	2.37 ± 1.16 (0.57–7.96)	**<0.001**[b]
Anterior chamber angle (°)	31.9 ± 5.2 (19.7–40.6)	31.2 ± 4.9 (20.9–41.4)	0.065[a]
Anterior chamber volume (mm^3)	135.3 ± 29.9 (71–201)	134.8 ± 29.8 (72–200)	0.666[a]
Anterior chamber depth (mm)	2.61 ± 0.37 (1.39–3.40)	2.64 ± 0.32 (1.91–3.35)	0.332[a]

Bold values indicate $p < 0.05$.

OAB overactive bladder, *SD* standard deviation.

[a]Paired samples *t*-tests.

[b]Wilcoxon signed rank tests.

to produce an increase in pupil size. Altered iris mechanics may be another plausible explanation. Further, measurement of resting pupil diameter on its own may not be adequate enough to diagnose parasympathetic impairment as mentioned above [18].

Of the dynamic pupillometry parameters, we found a significant increase in latency of pupil contraction and a significant decrease in velocity of pupil dilation in the first month of treatment compared to pretreatment. These two changes show that there is a decrease in pupillary kinetics,

Table 3 Distribution of static and dynamic pupillometry values and anterior chamber parameters of baseline and 1st month in control group.

Control group ($n = 40$)	Baseline Mean ± SD (range)	1st month Mean ± SD (range)	p
Scotopic pupil diameter (mm)	6.13 ± 0.72 (4.5–7.5)	6.00 ± 0.79 (4.1–7.5)	0.056[a]
Mesopic pupil diameter (mm)	4.62 ± 0.92 (3.0–6.8)	4.66 ± 0.96 (3.0–6.7)	0.089[b]
Low-photopic pupil diameter (mm)	3.39 ± 0.51 (2.4–4.8)	3.33 ± 0.57 (2.4–4.9)	0.098[b]
High-photopic pupil diameter (mm)	2.78 ± 0.35 (2.1–3.6)	2.76 ± 0.37 (2.1–3.5)	0.589[b]
Resting diameter (mm)	5.39 ± 0.80 (3.9–7.2)	5.32 ± 0.90 (3.2–7.0)	0.063[b]
Amplitude of pupil contraction (mm)	1.74 ± 0.27 (1.3–2.4)	1.69 ± 0.30 (1.1–2.4)	0.413[b]
Latency of pupil contraction (ms)	261.8 ± 38.8 (111–301)	267.1 ± 26.3 (179–305)	0.993[b]
Duration of pupil contraction (ms)	594.9 ± 61.6 (422–753)	594.2 ± 62.6 (456–753)	0.985[b]
Velocity of pupil contraction (mm/s)	5.55 ± 0.78 (4.25–7.61)	5.49 ± 0.79 (3.72–7.62)	0.383[a]
Latency of pupil dilation (ms)	854.2 ± 57.6 (696–967)	858.8 ± 63.4 (728–968)	0.466[b]
Duration of pupil dilation (ms)	1621.1 ± 68.9 (1463–1804)	1601.0 ± 87.1 (1280–1737)	0.112[b]
Velocity of pupil dilation (mm/s)	1.92 ± 0.36 (1.33–3.06)	1.94 ± 0.40 (1.19–3.05)	0.566[a]
Anterior chamber angle (°)	32.3 ± 6.0 (22.3–49.2)	32.8 ± 5.8 (22.6–49.0)	0.164[b]
Anterior chamber volume (mm^3)	143.6 ± 31.2 (85–212)	143.0 ± 31.0 (88–210)	0.704[b]
Anterior chamber depth (mm)	2.71 ± 0.32 (2.22–3.60)	2.71 ± 0.33 (2.20–3.58)	0.659[b]

SD standard deviation.

[a]Paired samples *t*-tests.

[b]Wilcoxon signed rank tests.

which can be explained by inhibition of the muscarinic cholinergic receptors. The decrease in velocity of pupil dilation could also be interpreted as a decreased sympathetic activation during antimuscarinic treatment. This finding may indicate that the balance between the sympathetic and parasympathetic systems is beyond the known simple opposition relationship in OAB.

Surprisingly we found much more little effect of antimuscarinic treatment on pupil responses. This can be explained for two reasons. First, this could be due to adaptive changes such as the upregulation of M3 receptors. Second, M3 receptor selectivity of solifenacin on iris muscles may not be adequate to produce extensive effects. It has been suggested that [25, 26] solifenacin has greater selectivity for muscarinic receptors of the bladder than for those in the salivary gland.

In the OAB group, we did not find a statistically significant change in anterior chamber angle, depth, and volume at the first month of treatment as well as in the IOP compared to pretreatment. Based on these data, we think that there is no need to consult an ophthalmologist for pretreatment assessment of OAB patients who do not have a history of narrow-angle glaucoma.

In our study, no significant change for pupillary and anterior chamber measurements of the healthy control group was detected between the baseline and first month. Hence, we can say that the automated quantitative pupillometry and Scheimpflug corneal imaging used in our study are both repeatable and reliable systems. Bedei et al. investigated the reliability and reproducibility of two different Scheimpflug analyzers and reported that the Pentacam HR system gave stable and reproducible results in the measurement of anterior chamber angle, volume, and depth parameters [27].

Goktas [11] and Telek et al. [12] investigated the effects of tolterodine on anterior segment parameters and pupil diameter in patients with OAB. In both of these studies which pupil diameters were measured with the Pentacam system, the authors did not find any significant change in pupil diameter and anterior segment parameters. However, the repeatability of pupillary measurement with Pentacam is poor [13] and this system does not allow pupil measurement under different illumination conditions and dynamic pupillometric measurements as well. Our study differs from these two studies that we assessed pupillary responses through an objective and a standardized device which provides us repeatable and reliable results and also dynamic pupillary responses.

Altan-Yaycıoğlu et al. studied the effect of two different antimuscarinic drugs (tolterodine and oxybutynin) on pupil diameters in OAB patients [28]. In the tolterodine group, they found a significant increase in pupil diameter in the dim light in the first month, while no change was observed in the oxybutynin group. However, no significant change was detected with both medications in the bright light. Although the increase of the pupil diameter in the dim light supports our findings in this study, the pupil diameters were measured with the ruler of the slit-lamp biomicroscope, which is a subjective and error-prone method.

Aydoğmuş et al. investigated pupillary diameters with an automated pupillometry system in the OAB patients who

started solifenacin succinate treatment and in healthy individuals [29]. They found smaller static pupil diameters in the OAB group and interpreted this finding as to the consequence of increased parasympathetic tone. In their study, however, we do not have the knowledge of illumination conditions that static pupil measurements performed. On the contrary, we found larger pupil diameters in photopic conditions in the OAB group, which demonstrates a parasympathetic under activation. Of the dynamic pupillary responses, they found prolonged contraction time and latency of pupil dilatation, which were extrapolated as a result of increased parasympathetic action. Indeed, the most robust parameters for detecting parasympathetic activity are the amplitude and velocity of contraction [30, 31]. The different findings between these two similarly constructed studies reveal that the nature of autonomic imbalance of OAB require more consideration and further research including more patient, and more frequently performed pupillometric measurements. In the literature, there is no evidence that the severity of OAB is taken into account, which may cause different or contradictory results.

Aydoğmuş et al. did not found any significant differences in static pupil diameters in first month of solifenacin treatment whereas we found larger scotopic and mesopic pupil diameters. They also reported decreased contraction latency, duration of contraction, the latency of dilatation, and increased dilatation velocity whereas we found increased latency of contraction and decreased velocity of dilation oppositely. Although it seems clear that antimuscarinic therapy has an impact on pupillary responses, it will be premature to say anything about the pattern or standards of these changes. As we mentioned above, the fact that the OAB patients have different disease severity may be an explanation for these contradictory results between two studies. This may be a point to be considered for future studies.

The strength of our study is the data collection with a standardized imaging modality that allows objective assessment of static and dynamic pupillary responses along with anterior chamber parameters. Performing initial and first-month measurements of both the OAB and control groups is another strength of our study. The short follow-up period of our study and the relatively low number of participants are the main limitations. Further prospective and prolonged studies are needed to determine whether these effects are temporary or persistent during the long follow-up period or with treatment cessation.

In summary, we concluded that patients with OAB also have pupil abnormalities which probably reflect an underlying autonomic disorder that affects the bladder, pupils and probably many other organs under autonomic control. Also, solifenacin treatment leads to an increase in static pupil diameters and significant changes in pupillary dynamics while did not produce any effect on anterior chamber angle, depth, and volume. For OAB patients who do not have a history of narrow-angle glaucoma, there is no need for pretreatment ophthalmic assessment. Further comprehensive and prolonged clinical studies are needed to examine whether the effects we obtained in this study are temporary or persistent and have any clinical relevance.

Summary

What was known before

- Solifenacin succinate therapy has some effects on the eye such as dry eye symptoms, blurred vision and may trigger acute angle-closure glaucoma.

What this study adds

- Patients with OAB also have pupil abnormalities, which probably reflect an underlying autonomic disorder that affects the bladder, pupils and probably many other organs under autonomic control.
- Systemic antimuscarinic therapy has no effect on anterior chamber depth and intraocular pressure.
- There is no need to consult an ophthalmologist for pretreatment assessment of OAB patients who do not have a history of narrow-angle glaucoma.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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