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ORIGINAL ARTICLE

Is overactive bladder a nervous or bladder disorder? Autonomic imaging in patients with overactive bladder via dynamic pupillometry

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Abstract
Purpose To evaluate the changes in dynamic pupillometry in patients with idiopathic overactive bladder (OAB).
Methods The study included 40 female patients with idiopathic OAB and 40 healthy female volunteers as a control group. Demographic and clinical data were recorded. Dynamic pupillometric parameters were measured with a commercially available unit (MonPack One, Metrovision, France) at baseline and on the 30th day of treatment with an antimuscarinic treatment (drug-agent) (solifenacin 5 mg daily). Initial, minimum, maximum and mean pupil diameters, the latency and duration of contraction and dilatation of the pupil, the amplitude of contraction and dilatation velocity were automatically measured and compared between the groups.
Results There were no significant differences between two groups with respect to age and body mass index ($p = 0.288$, 0.755, respectively). The measurements of initial, minimum and mean pupil diameters were significantly lower in patients with OAB compared to healthy controls ($p = 0.007$, 0.002, 0.001, respectively). OAB patients had significantly longer latency of pupil dilatation, latency of pupil contraction and shorter duration of pupil contraction than control group ($p = 0.028$, 0.029, 0.021, respectively). After the antimuscarinic treatment, latency of pupil contraction, latency of pupil dilatation and duration of pupil contraction shortened significantly (all $p < 0.001$). Pupil dilatation velocity increased significantly during the treatment ($p < 0.001$).
Conclusions The dynamic pupillometric findings in this study imply impaired autonomic dysfunction, mostly the increased parasympathetic action, in OAB patients and the modulatory effects of antimuscarinic treatment.

Keywords Overactive bladder · Autonomic nervous system · Pupillometry · Parasympathetic nervous system · Sympathetic nervous system

Introduction

Overactive bladder (OAB) is a clinical definition characterized by urgency, usually with urinary frequency and nocturia with or without incontinence, without any infectious or other causes such as neurological, urological, systemic and metabolic diseases and drug usage which may explain the symptoms [1, 2]. In the USA, Japan and Europe, the prevalence of OAB has been reported to be approximately 12–17 % in the adult population, and it seems to increase [3–5].

The pathophysiology of OAB is complex, multifactorial and still largely unknown. Factors might include changes in the bladder itself, or central nervous system changes innervating the bladder [6–8]. Some studies which have focused on the anatomical and pathophysiological background of bladder activity have indicated that the bladder

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is controlled by the autonomic nervous system (ANS) [9]. Therefore, ANS dysfunction possibly has a significant role in the pathogenesis of OAB.

The pupil is innervated only by the ANS and innervated by both the parasympathetic nervous system (PNS) and the sympathetic nervous system (SNS). Therefore, pupillary functional changes are important in the monitoring of ANS activity [10]. Assessment of the pupil via pupillometry is a simple, sensitive and noninvasive imaging method, which gives valuable information about the balance between both branches of the ANS. The value of pupillometry in the evaluation of ANS function was shown in some studies [11, 12]. There are numerous clinical applications of pupillometry including sleep medicine, ophthalmological research, testing the effects of drugs on the ANS, assessment of autonomic neuropathies, assessment of brain injuries and psychophysiological disorders [10, 13].

In this study, it was aimed to explore the dynamic pupillometric changes in OAB patients and the effects of antimuscarinic treatment on the ANS via dynamic pupillometric measurements.

Materials and methods

The study was performed in the urology and ophthalmology outpatient clinics of Etimesgut Military Hospital between March 2015 and December 2015. The study included 40 female patients diagnosed with idiopathic OAB-dry and 40 healthy female subjects as a control group. Approval of all participants was obtained. The study was conducted in accordance with the tenets of the Declaration of Helsinki and approved by the Institutional Ethics Committee.

Inclusion criteria of the patients

Female patients, aged over 18 years, were firstly diagnosed idiopathic OAB-dry consisted with the diagnostic criteria of the International Continence Society (ICS) [3], no previous treatment with anticholinergics, normal findings in physical and genitourinary examination.

Exclusion criteria of the patients

Patients with abnormal urological findings (residual urine >40 ml, urinary infection, urinary stone disease, history of neurogenic bladder, previous or present bladder tumor), endocrine, neurological, metabolic and systemic disorders, history of pelvic surgery or radiotherapy, ophthalmological disorders, use of systemic or topical medication, presence of pregnancy, having a body mass index (BMI) ≥30, alcoholism and malignancy.

The control group participants were selected among healthy female hospital staff. Control group subjects did not have any known systemic, urologic or ophthalmologic disease.

Each participant underwent a complete ophthalmological examination including best-corrected visual acuity (BCVA), slit-lamp biomicroscopy, fundoscopy and intraocular pressure measurement by applanation tonometry. Participants with a Snellen best-corrected visual acuity <1.0 or any factor that could affect pupillary response, and sympathetic or parasympathetic function were excluded.

Clinical evaluation

Participants were selected among patients presented with OAB-defined as urgency, with or without urge incontinence, and usually associated with frequency and nocturia, as defined by the International Continence Society [2]. Only OAB-dry patients were enrolled. A 3-day voiding chart, uroflowmetry with residual urine control and urine analyses was recorded to diagnose the OAB. The International Consultation on Incontinence Questionnaire-Short Form Turkish (ICIQ-SF-T) was completed by all patients. The control subjects filled ICIQ-SF-T to exclude OAB symptoms definitely [3, 14].

Dynamic pupillometric measurements

Dynamic pupillometric measurements were performed with a commercially available instrument (MonPack One, Metrovision, France). The stimulator was equipped with a near-infrared illumination (880 nm) and a high-resolution infrared image sensor that provided a measurement of pupil parameters even in full darkness.

Initially, binocular pupillometric measurements were performed in darkness after a 5-min dark adaptation. Then, dynamic pupillometric data were obtained using white light flashes (stimulation on time 200 ms, stimulation off time 3300 ms, total luminance 100 cd/m^2, total intensity 20 $cd.s/m^2$). The images of both eyes were obtained and processed in real time with 30 images per second. The proprietary analysis software automatically defined pupil contour of the images, providing the precision of the measurements (precision = 0.1 mm) under controlled lighting conditions. Then, the analysis of the average and temporal response to successive visual stimuli was automatically performed for the following parameters: initial, minimum, maximum and mean pupil diameters in millimeters, the duration and latency of contraction and dilatation in milliseconds, the amplitude of contraction in millimeters, and dilatation and contraction velocity in millimeters per second.

Dynamic pupillometric measurements were performed between 10:00 a.m. and 12:00 p.m. in order to overcome the influence of daytime variations on the results [15]. At least 8 h of sleep was required the preceding night without the use of cigarettes, alcohol or caffeine.

Main outcome results

The dynamic pupillometric measurements were obtained for the control subjects and the patients with OAB on day 0. Then, the patients with OAB started to use an antimuscarinic agent (solifenacin 5 mg daily). Finally, the patients with OAB reevaluated with dynamic pupillometry on the 30th day of the treatment.

Statistical analysis

According to the previous data [16–18], this study should recruit 30 individuals for each group to have a power of 80 % and a type I error level of 5 % to detect a minimum clinically significant difference of pupil diameter of 0.5 mm. A 25 % of dropout has been predicted since follow-up, so 40 patients and control subjects were enrolled in each group.

IBM SPSS Statistics for MAC version 23.0 was used to analyze the data. Continuous variables were first assessed for normality using the Kolmogorov–Smirnov test. As variables followed the normal distribution of scores, parametric tests were selected; otherwise, nonparametric tests were used. The Chi-square test was used for categorical variables. The comparison between two dependent groups (baseline and on-treatment periods), the paired t test was used for data with normal distribution and the Wilcoxon test for data without normal distribution. The comparisons between two independent groups were evaluated by independent samples t test and Mann–Whitney U tests for data with or without normal distribution, respectively. Statistical significance was accepted at $p < 0.05$.

Coefficient of variability (CV) is a normalized index that gives important knowledge about the distribution of a set of values. CV is the ratio of standard deviation (SD) to mean. CV was also used in the evaluation of the findings.

Results

As four patients in the OAB group did not attend the second visit after treatment, the study was completed with 36 patients in the OAB group. Flow diagram of this study is shown in Fig. 1.

The demographic and clinical characteristics of the OAB and the control groups are shown in Table 1. There were no significant differences between the OAB and control groups in respect of age and body mass index. Mean ICIQ-SF-T score of the OAB group was significantly higher than that of the control group. Uroflowmetry measurements and 3-day bladder diaries of OAB group are also shown in Table 1.

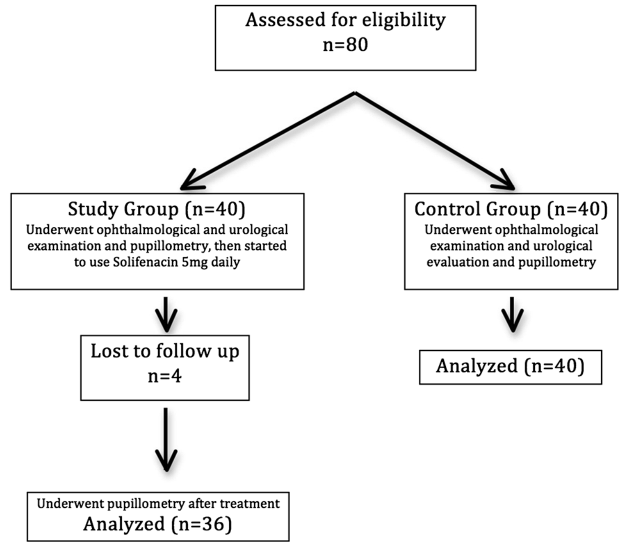

Fig. 1 Flow diagram of the study

Table 2 shows the differences in pupillometric data between the patients with OAB in the pretreatment period and healthy control subjects. Initial, minimum and mean pupil diameters were significantly lower in patients with OAB compared to healthy controls. OAB patients had significantly longer latency of pupil dilatation, latency of pupil contraction and shorter duration of pupil contraction than control group ($p = 0.028$, $p = 0.029$, $p = 0.021$, respectively). There were no significant differences between two groups in respect of the other parameters (Table 2).

It is also seen from Table 2 that although OAB patients had smaller pupil diameters, they had bigger standard deviations with respect to control subjects. This means that the coefficient of variabilities (SD/mean) of pupil diameters is higher in OAB patients.

The comparisons before and after the antimuscarinic treatment are shown in Table 3. The measurements of latency of pupil contraction, latency of pupil dilatation and duration of pupil contraction shortened significantly during the treatment ($p < 0.001$, $p < 0.001$, $p < 0.001$). The pupil dilatation velocity increased significantly ($p < 0.001$). There was no significant alteration in the amplitude of pupil contraction, pupil contraction velocity, duration of pupil dilatation, all (initial, maximum, minimum and mean) pupil diameters.

Table 1 Baseline characteristics of subjects

Parameters	Overactive bladder $n = 40$ [mean ± standard deviation (min–max)]	Control $n = 40$ [mean ± standard deviation (min–max)]	p
Age	32.6 ± 12.1 (20–56)	28.5 ± 12.1 (20–45)	0.288
BMI	22.6 ± 1.9 (20-27)	22.7 ± 2.6 (19–28)	0.755
ICIQ-SF-T score	18.3 ± 1.8 (15–21)	3.9 ± 0.3 (1–7)	<0.001
Uroflow			
Max.flow	27.6 ± 4.5 (20–37)		
Med.flow	15.7 ± 2.9 (11–22)		
Volume (voided)	299 ± 77.3 (160–450)		
Volume (residual)	14.7 ± 11.3 (0–38)		
Voiding frequency			
<0.5 h	5		
0.5–1 h	18		
1–2 h	17		
>2 h	–		

Table 2 Comparison of the pupillometric measurements between control subjects and overactive bladder (OAB) patients before the treatment

Parameters	Control group ($n = 40$)	OAB group ($n = 40$)	p
Initial pupil diameter (mm)	5.58 ± 0.51	5.03 ± 0.79	***0.007***
Maximum pupil diameter (mm)	5.99 ± 0.54	5.79 ± 0.89	0.623
Minimum pupil diameter (mm)	3.67 ± 0.54	3.08 ± 0.66	***0.002***
Mean pupil diameter (mm)	5.02 ± 0.53	4.42 ± 0.66	***0.001***
Amplitude of pupil contraction (mm)	1.66 ± 0.31	1.54 ± 0.42	0.109
Latency of pupil dilatation (ms)	851.32 ± 97.09	967.60 ± 303.77	***0.028***
Latency of pupil contraction (ms)	263.37 ± 56.87	300.70 ± 92.23	***0.029***
Duration of pupil contraction (ms)	587.99 ± 96.35	733.15 ± 341.97	***0.021***
Pupil contraction velocity (mm/s)	4.94 ± 1.37	4.69 ± 1.11	0.372
Pupil dilatation velocity (mm/s)	2.01 ± 0.74	1.99 ± 0.44	0.287
Duration of pupil dilatation (ms)	1584.65 ± 149.24	1458.37 ± 310.49	0.059

Bold italic values represent the significance ($p < 0.05$)

Table 3 Comparison of pupil measurements before and after treatment in overactive bladder group

Parameters	OAB group, pretreatment ($n = 36$)	OAB group 30th day of treatment ($n = 36$)	p
Initial pupil diameter (mm)	4.99 ± 0.79	4.88 ± 0.39	0.453
Maximum pupil diameter (mm)	5.71 ± 0.78	5.62 ± 0.35	0.341
Minimum pupil diameter (mm)	2.94 ± 0.54	3.05 ± 0.31	0.251
Mean pupil diameter (mm)	4.51 ± 0.76	4.39 ± 0.31	0.392
Amplitude of pupil contraction (mm)	1.37 ± 0.43	1.47 ± 0.41	0.490
Latency of pupil dilatation (ms)	1019.88 ± 318.82	779.09 ± 137.85	***<0.001***
Latency of pupil contraction (ms)	308.19 ± 95.36	281.28 ± 27.99	***<0.001***
Duration of pupil contraction (ms)	712.50 ± 247.23	500.03 ± 135.99	***<0.001***
Pupil contraction velocity (mm/s)	4.49 ± 1.15	4.82 ± 1.23	0.290
Pupil dilatation velocity (mm/s)	1.78 ± 0.45	2.65 ± 1.07	***<0.001***
Duration of pupil dilatation (ms)	1396.88 ± 318.39	1448.01 ± 437.49	0.782

Bold italic values reprsent the significance ($p < 0.05$)

Discussion

Irrespective of the physiopathologic meaning of the findings, this study showed significant differences in pupillographic and pupillometric changes between patients with OAB and control subjects. The findings imply altered autonomic function in OAB patients. In addition, this study also showed that anticholinergic treatment affects pupillometric functions in OAB patients.

The parasympathetic fibers transmitted via oculomotor nerve synapse in the ciliary ganglion in the orbita. The postganglionic fibers enter the ocular globe in short ciliary nerves and innervate both ciliary muscle and sphincter pupilla muscle. The sympathetic fibers synapse in the superior cervical ganglion, enter the orbita around ophthalmic artery, enter the ocular globe in long ciliary nerves and short ciliary nerves and innervate dilatator pupilla muscle.

In this study, we found significantly smaller initial, minimum and mean pupil diameters in patients with OAB with respect to control subjects. Maximum pupil diameters were also smaller in OAB patients; however, the difference was statistically significant. These findings are important, because smaller pupil diameters imply increased parasympathetic tone in the 'sphincter pupilla' muscle. This finding is plausible and also compatible with the findings of increased parasympathetic action in patients with OAB [19, 20]. Increased CV values in OAB patients are also an important finding in the evaluation of the results. It is apparent that disease states are the deviation from health and disease states cause increased variability in biological measurements. So, from the statistical point of view, increased CV data in OAB patients support that the pathological state is in OAB patients, but not in the healthy control subjects.

In this study, we also found significantly increased 'duration of pupil contraction' and significantly increased 'latency of pupil dilatation'. Duration of pupil contraction is the time period between the beginning and end of sphincter muscle contraction. A longer contraction time is possibly related with the increased parasympathetic action. Latency of pupil dilatation is the time period between the end of light stimulus and the beginning of pupillary dilatation. The longer latency of pupillary dilatation is compatible with the increased parasympathetic tone in OAB patients. OAB patients had significantly higher 'latency of pupil contraction'. Latency of pupil contraction is the time period between the beginning of the light stimulus and the beginning of the pupillary muscle contraction. A lower latency of pupil contraction would be plausible in OAB patients, and this finding waits for evaluations in future studies.

In this study, we also found significant changes in the pupillometric data during the anticholinergic treatment. Those pupillometric changes were also compatible with decreased parasympathetic action after anticholinergic treatment. Latency of pupil dilatation and duration of pupil contraction significantly decreased during the treatment. These findings are compatible with decreased parasympathetic activity during anticholinergic treatment. In addition, latency of pupil contraction that was also increased in OAB patients with respect to control subjects also decreased after the treatment. After these findings, we may assume that 'latency of pupil contraction' should also be related to autonomic changes that occur in OAB patients. However, the authors of this study are unable to suggest a plausible explanation for this finding. A significant difference during the treatment increased pupil dilatation. This finding is also compatible with the decreased parasympathetic action during the treatment.

Sympathetic innervation originates in the thoracolumbar outflow of the spinal cord, while parasympathetic and somatic innervation has its origin in the sacral segments. At the level of the bladder, acetylcholine is released by parasympathetic postganglionic neurons in the pelvic nerve, and this stimulates M3 muscarinic receptors in the bladder smooth muscle, resulting in contraction [21]. Therefore, as a first-line treatment option, an antimuscarinic agent was used for the OAB patients. These agents are known to affect various steps of detrusor contraction by acting on the central nervous system control mechanisms, blocking acetylcholine, which is the main neurotransmitter in the bladder, via M3 muscarinic receptor activity, by exerting a direct effect to relax the smooth muscles and by regulating other substances thought to have a modulating effect on the bladder [22].

Demir et al. used heart rate interval variation, heart rate response to Valsalva maneuver and sympathetic skin response as autonomic testing tools. The authors found parasympathetic hyperactivity in children with OAB [20]. Liao and Jaw reported significant differences in the time and frequency domains of heart rate variability (HRV) between 33 patients with OAB and 176 controls. They concluded HRV could be used as a simple and noninvasive autonomic imaging tool to evaluate ANS dysfunction in OAB and other neuronal conditions [19]. Our results in this study are compatible with the results of those studies.

The absence of urodynamic evaluation (UE) is a limitation of this study; correlating pupillometric findings would have added new findings about the relation of autonomic and pupillometric functions in OAB patients. A second limitation may be the value of 0.5 mm pupil size difference that was used in the calculation of required sample size of the groups. In fact, 0.5 mm may be regarded as 'a high difference' by some ophthalmologists and a lower value would have increased the value of the findings.

Conclusion

In this study, parasympathetic hyperactivation was found in patients with OAB via pupillometry. The decrease in the autonomic dysfunction was also observed at the 1st month of antimuscarinic treatment. It can be considered that functional studies such as pupillometry would be helpful for the understanding of OAB or bladder dysfunction and serve as an aid to the development of therapeutic options for these pathological conditions.

Auhtors' contribution Y Aydogmus was involved in project development, data collection and manuscript writing. S Uzun collected the data and wrote the manuscript. FC Gundogan was involved in data analysis and manuscript editing. UH Ulas was involved in manuscript editing and final review. T Ebiloglu collected and analyzed the data. MT Goktas was involved in project development and manuscript editing.

Compliance with ethical standards

Conflict of interest The authors declare that they had no conflicts of interests.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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