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RESEARCH

Pupillary response changes in Graves' disease

Graves hastalığında pupiller yanıt değişiklikleri

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Abstract

Purpose: The aim of this study was to investigate pupillary contraction and dilatation response changes in Graves' disease.

Materials and Methods: The patient group consisted of 55 euthyroid Graves patients and the control group consisted of 55 healthy individuals. Data from the right eyes of all participants were used. Static (scotopic, mesopic, photopic) and dynamic pupillometry measurements were performed with automatic pupillometry. The mean pupil dilatation speed was calculated according to dynamic measurements. Static measurements, dynamic measurements and the mean pupil dilatation speed data were compared between the patient and control groups.

Results: There was no statistically significant difference between two groups in all static and dynamic values and the mean pupil dilatation speed. The mean scotopic pupil diameter was 5.41±0.776 mm in Graves' group and 5.55±0.747 mm in the control group. The mean mesopic pupil diameter was 4.39±0.721 in Graves' group and 4.17±0.640 mm in the control group. The mean photopic pupil diameter was 3.45 ±0,549 mm in Graves' group and 3.29±0.679 mm in the control group. The mean dynamic pupil diameter 0th second was 3, 54±0.541 mm in Graves' group and 3.48±0.708 mm in the control group. The mean speed of pupil dilatation at 18th second was 0.116±0.031 mm/sec in Graves' group and 0.128±0.040 mm/sec in the control group. Age was found to be an independent factor on pupillary parameters.

Conclusion: The pupillary parameters of patients with euthyroid hormone levels were not affected. While pupillary responses appeared not to be affected in the case of euthyroidism, more studies including patients with hypothyroidism and hyperthyroidism are needed.

Keywords:. Autonomic nervous system, Graves' disease, pupil dilatation speed, pupillometry, thyroid function tests

Öz

Amaç: Bu çalışmanın amacı, Graves hastalığında pupiller kontraksiyon ve dilatasyon yanıt değişikliklerini araştırmaktı.

Gereç ve Yöntem: Hasta grubu 55 ötroid Graves hastasından ve kontrol grubu 55 sağlıklı bireyden oluşuyordu. Tüm katılımcıların sağ gözlerinden elde edilen veriler kullanıldı. Otomatik pupillometri ile statik (skotopik, mezopik, fotopik) ve dinamik pupillometri ölçümleri yapıldı. Dinamik ölçümlere göre ortalama pupil dilatasyon hızı hesaplandı. Hasta ve kontrol grupları arasında statik ölçümler, dinamik ölçümler ve ortalama pupil dilatasyon hızı verileri karşılaştırıldı.

Bulgular: Tüm statik ve dinamik değerler ve ortalama pupil dilatasyon hızı açısından iki grup arasında fark yoktu. Ortalama skotopik pupil çapı Graves grubunda 5,41±0,776 mm, kontrol grubunda 5,55±0,747 mm; ortalama mezopik pupil çapı Graves grubunda 4,39±0,721 mm, kontrol grubunda 4,17±0,640 mm; ortalama fotopik pupil çapı Graves grubunda 3,45 ±0,549 mm, kontrol grubunda 3,29±0,679 mm; ortalama dinamik pupil çapı 0. saniye Graves grubunda 3,54±0,541 mm, kontrol grubunda 3,48±0,708 mm; 18. saniyede ortalama pupil dilatasyon hızı Graves grubunda 0,116±0,031 mm/sn, kontrol grubunda 0,128±0,040 mm/sn olarak saptandı. Yaş pupiller parametreleri etkileyen bağımsız bir faktör olarak bulundu.

Sonuç: Graves hastalığında muhtemel bir otonomik bozukluk bildirilse de ötroidi durumundaki hastaların pupiller parametrelerinin etkilenmediği sonucuna vardık. Ötroidi durumunda pupiller yanıtlar etkilenmiyor gibi görünse de hipotroidi ve hipertroidi hastalarının da dahil edildiği çalışmalara ihtiyaç vardır.

Anahtar kelimeler: Otonom sinir sistemi, Graves hastalığı, pupil dilatasyon hızı, pupillometri, tiroid fonksiyon testleri

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INTRODUCTION

Graves' disease (GD) is an autoimmune disease characterized by induction of the thyroid hormone production and enlargement of the thyroid gland, by antibodies against the TSH receptor (TRAb) [1]. While the prevalence in the population is between 1%-1.5%, the incidence has been reported as 20-40 cases/100,000/year[1,2]. Environmental and genetic factors are involved together in the pathogenesis of GD, which is more common in ages between the 30-50 years and in females compared to males[3]. In addition to thyroid dysfunction, extrathyroidal findings such as ophthalmopathy, dermopathy and acropathy can be observed in GD[2].

Graves' ophthalmopathy (GO) arises as a result of inflammation, congestion and volume increase which occurs due to the fact that orbital fibroblasts and adipocytes contain common antigens with thyroid tissue. Eyelid retraction, proptosis, ocular muscle involvement and optic neuropathy are the main signs of ophthalmopathy[4]. The most common clinical indication of GO is upper eyelid retraction[5]. Causes of upper eyelid retraction include sympathetic stimulation of the Müller's muscle[6]. It has been reported that high thyroid hormone levels stimulate the sympathetic nervous system in GD[7].

Pupillary reflexes are symmetrically ruled by the autonomic nervous system (ANS) in response to stimuli such as light and convergence. Miosis appears when the parasympathetic system stimulates the sphincter muscle, and mydriasis occurs when the sympathetic system stimulates the dilator muscle[8]. Accurate evaluation of pupillary reflexes is of great importance for clinicians in terms of diagnosis and treatment. Abnormalities of the ANS and variable thyroid hormone levels in Graves' disease may affect pupillary functions of patients and may cause changes and misevaluation of pupillary reflexes, which are used in the diagnosis of many diseases. There are very limited studies in the literature examining the relationship between thyroid diseases and pupillary functions[6,9]. There is only one study examining this relationship using automatic pupillometry[9]. Accordingly, it has been reported that differences occur in pupillary parameters of Graves' patients compared to healthy controls. In addition, patients with hyperthyroidism and euthyroidism were found to have similar pupillary functions[9]. Recently developed automatic pupillometries give fast and objective results about pupillary parameters. Abnormalities in pupillary functions that cannot be noticed by the observer can be revealed with automatic pupillometries. Therefore, we thought that pupillary parameters in GD might be affected due to autonomic nervous system changes and autoimmunity-induced inflammation, and in this study, we examined pupillary parameters of euthyroid Graves patients. We think that it can provide more information about pupillary function abnormalities that may occur subclinically in Graves' patients, even if there is no obvious clinical dysfunction.

MATERIALS AND METHODS

This cross-sectional study was conducted with the ophthalmology and endocrinology and metabolic diseases departments of Niğde Education and Research Hospital. Ethics Review Board of Niğde Ömer Halisdemir University was approved the study (Date: 14.04.2022, No: 2022/51) and written and verbal consent was taken from each patient before the examination. The study was organized according to principles of the Declaration of Helsinki. The follow-up of Graves' patients and the evaluation of the serum thyroid levels were performed by the endocrinology department and ophthalmological examination and pupillometry measurements of the patient and control groups were performed by the researchers of the ophthalmology department.

Sample

The study group was determined by selecting Graves patients who were consulted from the endocrinology department for the ophthalmological examination. Fifty-five of 62 patients consulted by the endocrinology outpatient clinic were included in the study. Seven Graves' patients were not included in the study due to the presence of additional systemic disease, use of beta-blockers, and sight-threatening GO. Fifty-five Graves patients and 55 healthy individuals were included in the study. Measurements of the participants' right eyes were used. The patient and control groups consisted of volunteers who did not have any eye disease other than refractive error and did not have any systemic disease other than GD. Best corrected visual acuity (BCVA) levels of all patients were 10/10 with or without correction according to the Snellen chart. Patients under the age of 18, patients with pregnancy and breastfeeding status, patients with myopia, hyperopia and

astigmatism greater than 3D, and patients who had undergone ocular surgery were excluded from the study. Patients with a history of radioactive iodine and thyroid surgery were not included in the study. Participants with cigarette or alcohol use and patients with chronic drug use other than thyroid hormone-regulating drugs were excluded from the study. Patients were asked not to consume foods and beverages containing caffeine for 24 hours before the examination.

Procedure

Age, gender, disease duration, medications used, and serum thyroid function test values (free triiodothyronine (fT3), free thyroxine (fT4) and thyroid stimulating hormone (TSH)) of all Graves patients were recorded. Only euthyroid Graves patients were included in the patient group. All participants underwent a detailed examination including BCVA, measurement of intraocular pressure with a pneumatic tonometer, color vision, light reflexes, eye movements, anterior segment examination with the slit lamp, and the fundus examination after iris dilatation. All participants' eye pressure corrected according to the pachymetry were within normal limits. The optic nerve was evaluated by Humphrey visual field examination and retinal nerve fiber layer analysis.

The European Graves' Orbitopathy Group (EUGOGO) staging and Clinical Activity score (CAS) were used to evaluate GO stage and activity in all patients[5]. According to EUGOGO Classification; eyelid retraction less than 2 mm, mild soft tissue involvement, exophthalmos smaller than 3 mm, absence of diplopia, or temporary diplopia, corneal exposure sensitive to lubricants are mild stage; lid retraction greater than 2 mm, moderate or severe soft tissue involvement, exophthalmos of 3 mm or more, and fixed diplopia are moderate to severe stage and the patients with optic neuropathy or corneal destruction are classified as the sight-threatening stage. The CAS was determined by assigning a score of 1 for each presenting finding (spontaneous orbital pain, gaze evoked orbital pain, eyelid swelling, eyelid erythema, conjunctival redness, chemosis, and caruncle/plica inflammation). If the total value is 3 and above, it was considered as activation. Inactive disease was defined as CAS less than 3. In our study, there was no patient in the clinical activation. The amount of proptosis was measured by a single investigator (GYB) with a Hertel exophthalmometer. Orbital magnetic resonance imaging (MRI) was used for the muscle and the soft tissue involvement. The patients were divided into 3 groups according to their drug use: those who did not use any drugs, those who used antithyroid drugs (Propycil and Thyromazol), and those who received thyroid replacement therapy (levothyroxine). Patients using beta-blockers were not included in the study due to the drug's autonomic nervous system effects.

Pupillometry measurement

Measurements were taken by one researcher (GYB) at the same time (11:00-12:00) to minimize the effects of diurnal rhythm on the iris. Pupillary functions were examined with the Sirius Topographer (Costruzione Strumenti Oftalmici, Florence, Italy). The results were evaluated by two researchers (GYB-KRZ). While taking the measurements, the participants were told to look at a target 3 meters away with fellow eyes to keep accommodative reflex from happening. After 5 minutes of dark adaptation, scotopic (0,4 lux illumination), mesopic (4lux illumination), photopic (40lux illumination) measurements were taken. After the photopic measurement, dynamic measurements were taken at 500lux illumination. After 500lux lighting is turned off, the pupil dilatation can be observed and instantly analyze pupil size from photopic conditions to the absence of light (scotopic conditions). Thus, the pupil dilatation speeds (PDS) are calculated according to the desired time interval during the dilatation phase (mm/sec). We obtained the PDS by using the measurements at the 18th second, which is the longest second that our patients could adapt. We also compared the first dynamic measurement value at the 0th second between groups. Static measurements, first dynamic pupillometry values and the mean PDS at the 18th second were recorded.

All static measurements, dynamic values at the 0th second and the mean PDS at the 18th second of the patient and control groups were compared with each other. The correlation between serum fT3-fT4 and TSH levels and pupillary parameters in the patient group was evaluated. In addition, independent factors affecting pupillary parameters were examined.

Statistical analysis

Statistical analyzes were performed on STATA 14 packages. The study population was determined as 84 (42 patient-42 healhty volunteer) with G-power program by taking α=0.05, effect size=0.80, power

(1-β) =0.95 at a confidence level of 95%. Histogram and analytical methods (Kolmogorov Smirnov/Shapiro-Wilk Test) were used to evaluate the variables in terms of normal distribution.

In the descriptive statistics part of the data, categorical variables are given as numbers and percentages; continuous variables are presented with mean ± standard deviation. We used chi-square test for categorical (demographic and clinical) variables to evaluate differences between groups.

In the comparison of pupillary parameters between the patient and control groups, independent t test was used. The correlation between serum fT3-fT4 and TSH levels and pupillary parameters was evaluated by Pearson correlation analysis. Multiple linear regression analysis was used for independent factors on pupillary parameters. p value <0.05 was considered statistically significant.

RESULTS

The mean age of the Graves group, which included 48 female (f) and 7 male (m) eyes, was 38.87±12.251 years, and the mean age of the control group, which included 43 female and 12 male eyes, was 40.95±14.998 years. The groups were not different in terms of age (p=0.429) and gender (p=0.207). The mean duration of GD in the patient group was 23.2±36.95 (range: 0.5-180) months. According to the EUGOGO staging system, there were 30 eyes without eye involvement (26 f/4 m), 13 eyes (11 f/2 m) in mild stage, 12 eyes (11 f/1 m) in moderate to severe stage, and there were no patients in sight-threatening stage (Table1).

The mean serum fT3 level of the patient group was 3.38±0.64 pg/ml, the mean serum fT4 level was 1.14±0.25 ng/dl, and the mean serum TSH level was 1.29±1.52 μIU/ml.

According to the drug therapy used by the patients, there were 14 patients (12 f/2 m) who did not receive any treatment, 33 patients (30 f/3 m) who received only antithyroid therapy, and 8 patients (6 f/2 m) who received thyroid replacement therapy (Table 1).

The comparison of static measurements, first dynamic pupillometry values and the mean PDS between the patient and control groups are showed in Table 2. There is no difference terms of scotopic, mesopic, photopic, dynamic and PDS values between the two groups (p= 0.351, p=0.095, p=0.163, p=0.569 and p=0.072 respectively).

In Table 3, the correlation between duration of disease, serum fT3, fT4 and TSH and pupillary parameters was evaluated. Although pupillary parameters seemed to have the positive correlation with serum fT3-fT4 levels and the negative correlation with serum TSH levels, these relationships were not statistically significant. There was a significant negative correlation between disease duration and scotopic (p= 0.039) and mesopic (p= 0.047) values. In Table 4, independent factors affecting pupillary parameters are examined. Disease duration lost its effect on scotopic and mesopic values and age appeared to be the only significant factor. On the other hand, PDS appeared to be unaffected by disease duration, age, disease stage and thyroid hormone-regulating drug use (p>0.05 for all).

Table1. Clinical characteristics of the Graves' Patients

Variable	Number of Patient (female/male)
No GO	30 (26/4)
Mild stage GO	13 (11/2)
Moderate to severe GO	12 (11/1)
Sight-threatening GO	-
No drug use	14 (12/2)
Antithyroid drugs	33 (30/3)
Thyroid replacement drugs	8 (6/2)

GO: Graves Orbitopathy

Table 2. Comparison of the pupillometry analysis and the mean speed of pupil dilatation at 18th second results between the Graves' patients and control group

	Graves group (Mean ± SD) (n = 55)	Control group (Mean ± SD) (n = 55)	P
Mean scotopic pupil diameter (mm)	5.41±0.776	5.55±0.747	0.351
Mean mesopic pupil diameter (mm)	4.39±0.721	4.17±0.640	0.095
Mean photopic pupil diameter (mm)	3.45 ±0.549	3.29±0.679	0.163
Mean dynamic pupil diameter 0th second (mm)	3.54±0.541	3.48±0.708	0.569
Mean speed of pupil dilatation at 18th second (mm/sec)	0.116±0.031	0.128±0.040	0.072

SD: standard deviation, mm/sec: millimeter/second.

Table 3. Correlation analysis results between serum fT3, fT4, TSH, disease duration and the pupillary parameters

	fT3 levels r/p	fT4 levels r/p	TSH levels r/p	Disease duration r/p
Mean scotopic pupil diameter	0.209/0.126	0.08/0.516	-0.204/0.136	-0.280/0.039
Mean mesopic pupil diameter	0.071/0.608	0.092/0.502	-0.141/0.306	-0.269/0.047
Mean photopic pupil diameter	0.163/0.236	0.148/0.280	-0.155/0.209	-0.196/0.152
Mean dynamic pupil diameter 0th second	0.159/0.247	0.108/0.434	-0.163/0.235	-0.192/0.160
Mean speed of pupil dilatation at 18th second	0.131/0.340	0.015/0.914	-0.109/0.428	-0.181/0.187

fT3: free triiodothyronine, fT4: free thyroxine, TSH: thyroid stimulating hormone

Table 4. Linear regression analysis for independent factors affecting the pupillary parameters

		B	SE	β	t	p	
Mean scotopic pupil diameter	Age	-0.022	0.009	-0.347	-2.582	0.013	R=0.532R²=0.283 F=4,922p=0.002
	Drug use	-0.161	0,173	-0.123	-0.934	0.355	
	Disease duration	-0.005	0.003	-0.226	-1.825	0.074	
	Disease stage	0.146	0.158	0.117	0.924	0.360	
Mean mesopic pupil diameter	Age	-0.119	0.008	-0.329	-2.415	0.019	R=0.513R²=0.263 F=4.468p=0.004
	Drug use	-0.189	0.163	-0.155	-1.160	0.252	
	Disease duration	-0.004	0.002	-0.213	-1.699	0.096	
	Disease stage	0.094	0.149	0.082	0.636	0.528	
Mean photopic pupil diameter	Age	-0.016	0.006	-0.347	-2.491	0.016	R=0.478R²=0.229 F=3.704p=0.010
	Drug use	-0.142	0.127	-0.153	-1.120	0.268	
	Disease duration	-0.002	0.002	-0.145	-1.130	0.264	
	Disease stage	0.034	0.116	0.038	0.293	0.771	
Mean dynamic pupil diameter 0th second	Age	-0.018	0.006	-0.409	-3.012	0.004	R=0.517R²=0.267 F=4.555p=0.003
	Drug use	-0.148	0.122	-0.162	-1.218	0.229	
	Disease duration	-0.002	0.002	-0.147	-1.172	0.247	

	Disease stage	-0.033	0.111	-0.038	-0.297	0.767	
Mean speed of pupil dilatation at 18th second	Age	0.000	0.000	-0.082	-0.541	0.591	$R=0.279 R^2=0.078$ $F=1.055 p=0.389$
	Drug use	0.000	0.008	-0.007	-0.048	0.962	
	Disease duration	0.000	0.000	-0.155	-1.106	0.274	
	Disease stage	0.009	0.007	0.172	1.201	0.235	

SE: standard error

DISCUSSION

Graves' ophthalmopathy (GO) is the most common extrathyroidal finding of GD[10]. One of the important complications that threatens vision in GO is the presence of optic neuropathy[11]. Light reflexes are great importance in the examination of optic nerve functions. In addition, it has been reported that sympathetic discharge in GD may affect pupillary functions[12]. Small changes in pupillary functions may not be recognized in ophthalmological examinations based on clinician observation. With the new generation automatic pupillometers, more objective and quantitative data can be obtained. Studies examining pupillary parameters in GD are almost nonexistent. In our study, it was observed that static and dynamic pupillary functions of euthyroid Graves patients were not different from healthy controls. In addition, serum fT3, fT4 and TSH showed no correlation with pupillary parameters. Although the duration of the disease seemed to affect scotopic and mesopic values in our study, age was found to be the only independent factor affecting pupillary parameters.

To our knowledge, apart from our study, the only study evaluating pupillary parameters in GD with automatic pupillometry was presented by Serbest et al[9]. They included 20 hyperthyroid eyes, 20 euthyroid eyes and 40 healthy eyes in their study using one eye of each patient. While Serbest et al.[9] found that all static values of Graves' patients (hyperthyroid + euthyroid) were significantly larger than the control group, they found lower PDS and higher pupillary contraction delay. They did not present any difference in pupillary contraction speed. In addition, they did not find a significant difference in all static and dynamic values between the measurements of hyperthyroid and euthyroid patients, and they reported that hyperthyroidism had no effect on the parameters. With these results, they reported that even if serum thyroid hormone levels are normal, autoimmune pathways in GD pathogenesis can affect pupillary parameters by increasing sympathetic activity at the level of adrenergic receptors. Apart from this study, the relationship between thyroid and pupillary functions was studied using infrared television pupillography, video pupillography, or devices such as a computer-assisted infrared optometer and pupillometer[12,13,14]. Noh et al.[12] found no difference in pupil widths in their study including 12 patients with GD and 12 healthy controls.

Higashi et al.[13] reported that amplitude of constriction, velocities of constriction and dilatation were significantly reduced in patients with hyperthyroidism. Hreidarsson et al.[14] examined the pupillary parameters of 5 thyrotoxicosis patients treated with methimazole and thyroxine before and after treatment. After adapting to the dark, they examined the parameters including resting pupil size, contraction delay time, amplitude of constriction, maximum velocity of contraction, maximum re-dilatation velocity, and re-dilatation time, and they found an increase only in the maximum contraction velocity after the treatment. Our study, in which patients with euthyroid Graves had similar pupillary functions as healthy controls, showed different results from the study of Serbest et al.[9] and supports the study of Noah et al.[11]

In our study, we included right eyes of each patient, like Serbest et al.[9] In addition, unlike to Serbest et al.[9], we included patients with moderate to severe stage according to EUGOGO but excluded patients with only sight-threatening stage from the study. In addition, there were not patients with hyperthyroidism or hypothyroidism in our Graves' patient group. Since Serbest et al.'s study evaluated newly diagnosed Graves' patients, it has a lower duration of disease compared to our study. The commercial pupillometers used were different from each other, but both studies evaluated static and dynamic pupillary functions. While Serbest et al. found a significant dilatation in all static values in Graves' patients, we found no difference in two

groups. Although disorders in pupillary functions may be observed in the early stages of the disease, autoregulation may occur during the disease.

The pupil has a wide range of motion, up to 7.5-8 mm in complete mydriasis and 1.5-2 mm in complete myosis[15]. Pupil contraction speed is related to the parasympathetic system, and PDS is related to the sympathetic system[15]. Contrary to Serbest et al.[9], we found that PDS of euthyroid Graves patients was not affected in our study. Only age was found to be effective as an independent factor on static and dynamic parameters in euthyroid Graves patients. Disease duration, disease stage, and drug use were ineffective on parameters. There were significant differences in terms of age, gender and number of patients in the subgroups formed according to disease stages and drug use. Controlled studies with similar groups in terms of age, gender and number formed according to Graves' stages and drug use may yield higher reliability results. When the correlation of serum fT3, fT4 and TSH with pupillary parameters were evaluated, we did not find a significant relationship. This result in our study is compatible with Serbest et al.'s finding no difference in the measurements between the hyperthyroid and euthyroid groups.

To our knowledge, our study is the first to examine pupillary parameters in Graves' patients with automatic pupillometry of Sirius Topographer (CSO, Firenze, Italy). The advantage of our study was that we attempted to reach a wider population by including Graves patients without eye involvement and all stages except the sight-threatening stage. However, our study has some limitations. Since the subgroups formed according to the drugs used by the patients and the stage of the disease were different from each other in terms of age, gender and number, we could not make an evaluation between the subgroups. In our study, only euthyroid patients were evaluated. We did not include hyperthyroid and hypothyroid patients in our study. Although we did not detect a significant correlation with pupillary parameters at normal thyroid levels, we could not provide information about pupillary parameters according to thyroid hormone levels. In addition, we did not exclude the use of antithyroid drugs, but the target site of antithyroid drugs is not the nervous system, and side effects such as central nervous system vasculitis and peripheral neuritis are very rare and reported only in the form of case reports[16,17]. Apart from these, we could not provide data on miosis dynamics because the pupillometry device we used did not have the relevant feature.

In conclusion, it was observed that the pupillary parameters of Graves patients with normal thyroid levels were not affected. It is clear that more prospective and controlled studies are needed to determine pupillary functions in Graves' disease.

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