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Autonomic Pupillary Light Response in Central Serous Chorioretinopathy

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ABSTRACT
Objective: The aim of the study is to evaluate the autonomic nervous system (ANS) activity by assessing static and dynamic pupillary light responses in central serous chorioretinopathy (CSCR). **Materials and Methods:** A case-control study. Thirty eyes of 30 patients with CSCR who were previously diagnosed in our clinic were included in the study group, and 31 right eyes of 31 healthy participants were included in the control group. All participants underwent a complete ophthalmologic examination. Static and dynamic pupillometry values were measured with the Scheimpflug/Placido photo-based topography system, Sirius topographer (CSO, Firenze, Italy) and pupillary dilation velocities were calculated and compared between the groups. **Results:** The mean scotopic, mesopic, photopic pupil diameters as well as scotopic/photopic ratios were not statistically different in the study and control groups, with values of 4.98±0.87 mm vs. 5.05±0.98 mm, 3.86±0.82 mm vs. 3.86±0.83 mm, 2.94±0.60 mm vs. 2.87±0.57 mm and 1.72±0.20 vs. 1.77±0.22, respectively (p1=0.759, p2=0.997, p3=0.676, p4=0.304). Dynamic pupillometric values were also similar between the groups (p>0.05). Pupillary dilatation velocity was slower in the study group during the 2-4 second interval (p=0.013). **Conclusion:** Pupillary responses mediated by the ANS in CSCR patients are similar to those of healthy participants. This suggests that systemic hormonal factors and local choroidal responses, rather than sympathetic activation, should be prioritized in understanding the pathophysiology of CSCR.
Keywords: Autonomic Nervous System, Central Serous Chorioretinopathy, Pupillary Reflex.

Santral Seröz Koryoretinopati'de Otonom Pupil Işık Yanıtı

ÖZ
Amaç: Çalışmanın amacı santral seröz korioretinopatide (SSKR) statik ve dinamik pupil ışık yanıtlarını değerlendirerek otonom sinir sistemi (OSS) aktivitesini değerlendirmektir**. Gereç ve Yöntem:** Bir vaka-kontrol çalışması. Kliniğimizde daha önce tanı almış 30 SSKR hastasının 30 gözü çalışma grubuna, 31 sağlıklı katılımcının 31 sağ gözü ise kontrol grubuna dahil edildi. Tüm katılımcılara tam bir oftalmolojik muayene yapıldı. Statik ve dinamik pupillometre değerleri Scheimpflug/Placido foto-tabanlı topografi sistemi, Sirius topografı (CSO, Floransa, İtalya) ile ölçüldü ve pupil dilatasyon hızları hesaplandı ve gruplar arasında karşılaştırıldı. **Bulgular:** Çalışma ve kontrol gruplarında ortalama skotopik, mezopik, fotopik pupil çapları ve skotopik/fotopik oranlar istatistiksel olarak farklı değildi; sırasıyla 4,98±0,87 mm ile 5,05±0,98 mm, 3,86±0,82 mm ile 3,86±0,83 mm, 2,94±0,60 mm ile 2,87±0,57 mm ve 1,72±0,20 ile 1,77±0,22 idi (p1=0,759, p2=0,997, p3=0,676, p4=0,304). Dinamik pupillometrik değerler de gruplar arasında benzerdi (p>0,05). Çalışma grubunda pupil dilatasyon hızı 2-4 saniyelik aralıkta daha yavaştı (p=0,013). **Sonuç:** SSKR hastalarında OSS tarafından yönetilen pupilla yanıtları sağlıklı katılımcıların yanıtlarına benzerdir. Bu, SSKR'nin patofizyolojisini anlamada sempatik aktivasyondan ziyade sistemik hormonal faktörler ve lokal koroidal yanıtların önceliklendirilmesi gerektiğini düşündürmektedir.
Anahtar Kelimeler: Otonom Sinir Sistemi, Santral Seröz Koryoretinopati, Pupiller Reflex.

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INTRODUCTION

Central serous chorioretinopathy (CSCR) is defined as serous detachment of the macula and commonly affects males of working age who present to retina clinics with complaints of metamorphopsia and visual impairment (Koizumi et al., 2024). Initially, disruption of the retinal pigment epithelium (RPE) was believed to be the primary cause of the disease (Maumenee, 1965). However, current research with advanced techniques for retinal imaging, like optical coherence tomography (OCT), have supported the hypothesis that choroidal imbalances—such as increased choroidal thickness, vascular dilation in the Haller layer, choriocapillaris dysfunction, and elevated hydrostatic pressure on the RPE—contribute to subretinal fluid leakage (Zhang et al., 2023). Despite these insights, the etiopathogenesis of the disease doesn't remain completely understood. While spontaneous recovery typically occurs within 4–6 months of symptom onset, the condition can sometimes become chronic, leading to RPE and/or photoreceptor atrophy or macular neovascularization, which may result in permanent vision loss (Feenstra et al., 2024).

Unlike retinal vascularity, choroidal vessels are directly influenced by the autonomic nervous system (ANS) (McDougal & Gamlin, 2015). It has been previously suggested that both sympathetic and parasympathetic pathways may be impaired in patients with CSCR (Tewari et al., 2006). Stress is also considered as a significant risk factor for CSCR, it upregulates the sympathetic pathway which leads to choroidal vasodilation and increases hydrostatic pressure (Scarinci et al., 2019; O'Connor et al., 2021). Pupillary light response serves as a reflection of ANS function and is a noninvasive, reproducible, and easily measurable alternative to more challenging tests like heart rate variability (HRV) (Venkata et al., 2020). In this study, we aimed to evaluate ANS activity in CSCR patients by analyzing pupillary response, one of the indicators of its function.

MATERIALS AND METHODS

Study type

This case-control study was conducted at the Ophthalmology Department of Balikesir University in accordance with the ethical standards of the Declaration of Helsinki. The study protocol was approved by ethical committee of the Balikesir University. Informed consent was taken from all participants prior to examinations.

Study group

Patients who have previously been diagnosed with CSCR in our clinic within the last 6 months and healthy controls of similar age and gender were included in the study. CSCR was diagnosed by OCT and fundus fluorescein angiography (FFA) images of the patients. The presence of subretinal fluid in the macula on OCT and typical CSCR leakage pattern on FFA were considered diagnostic. Patients with ocular diseases and conditions such as glaucoma, age-related macular degeneration, uveitis, optic neuropathy, pupillary anomalies, previously cataract surgery, grade 3-4 cataracts, history of any ocular trauma, as well as those with systemic diseases including diabetes, hypertension, heart diseases, thyroidal disorders, or any medication usage that could affect the ANS (e.g. antidepressants, hormones or vitamine supplements), or treatment with steroids in the last 6 months were excluded from the study.

Procedures

All participants went through a comprehensive ophthalmological examination, as well as, the static and dynamic pupillographic values were measured. Best corrected visual acuity (BCVA) was evaluated with the Snellen chart, followed by pupillography assessment by the Scheimpflug/Placido photo-based topography system, Sirius topographer (CSO, Firenze, Italy), using Phonix v2.6 software. After a 5-minute of dark adaptation, pupillary measurements were taken under 0.4 lux illumination for scotopic response, 4 lux for mesopic response, and 40 lux for photopic response (Cankurtaran et al., 2019; Prakash et al., 2016). To minimize accommodative effects, participants were instructed to look straight ahead without focusing on the light source. For dynamic measurements, 500 lux illumination was applied, followed by a gradual dimming of the light to measure the pupillary redilation speed per second (Cankurtaran et al., 2019). Participants were asked to refrain from consuming tea, coffee, cigarettes, or stimulant medications for at least 4 hours before the evaluation. All measurements were performed by the same clinician (YG), between 8:30 and 10:30 am to minimize circadian variabilities. In the study group, measurements were taken from the CSCR-affected eye, or in biateral cases, the more severely affected eye (based on subretinal fluid or chronicity). In the control group, the right eyes of all participants were evaluated. Additionally, a biomicroscopic anterior segment examination, intraocular pressure (IOP) measurement using non-contact tonometry, and fundus examination with non-contact lenses were performed.

Statistical analysis

For statistical analyses, SPSS version 22.0 was used. The Shapiro-Wilk test was applied to assess the normality of the data distribution. Differences in descriptive data between the groups were analyzed using the Chi-square test. The Independent t-test and Mann-Whitney U test were used to compare group results. A p-value of <0.05 was considered statistically significant for all tests.

RESULTS

This study included 30 patients in the study group and 31 healthy participants in the control one. 70.0% (21) in the study group and 54.8% (17) in the control group were male ($p=0.222$). There were no statistically significant differences between the two groups in

terms of age, smoking status, spherical equivalent of refraction, or IOP values (p_1=0.400, p_2=0.906, p_3=0.075, p_4=0.074). Table 1 presents the demographic and clinical characteristics of both groups. In the study group, 14 patients had right, 10 had left, and 6 had bilateral eye involvement and in 25 patients (83.3%), the disease had persisted for more than 6 months.

The mean scotopic, mesopic, and photopic pupil diameters, scotopic/photopic pupil diameter ratios, and the average dynamic pupillometry values measured over 10 seconds are presented in Table 2. No significant differences were found between the groups in terms of static pupil diameters or the scotopic/photopic diameter ratios. Additionally, the velocity of increase in pupil diameter was calculated at 2-second intervals throughout the 10-second period (Table 2). The study group had significantly slower pupil dilation velocity (median 0.13 mm/sec) compared to the control group (median 0.22 mm/sec) specifically during the 2–4 second interval (p = 0.013) (Figure1).

Table 1: Demographic and clinical characteristics of participants and eyes in study and control groups.

	Study group (n=30)	**Control group (n=31)**	**P value**
Age (mean±)	49.80±11.19	47.32±11.61	0.400
Gender (M/F)	21/9	17/14	0.222
Smoking (n, %)	14 (46.7%)	14 (45.2%)	0.906
Spheric equivalant (SE, mean±)	0.40±1.04	-0.08±0.65	0.075
Intraocular pressure (IOP, mmHg, mean±)	15.43±3.49	14.03±2.39	0.074
Best corrected visual acuity (BCVA, mean±)	0.76±0.27	0.99±0.02	0.000
Central macular thickness (CMT, µm mean±)	284.03±90.36	234.77±29.82	0.009

Table 2: Static and dynamic pupillometric values and mean pupillary dilatation velocities measured between study and control groups

	Study group (n=30)	**Control group (n=31)**	**P value**
Static pupillometry (mm±SD)			
Scotopic	4.98±0.87	5.05±0.98	0.759
Mesopic	3.86±0.82	3.86±0.83	0.997
Photopic	2.94±0.60	2.87±0.57	0.676
Scotopik/photopic ratio	1.72±0.20	1.77±0.22	0.304
Dynamic pupillometry (mm±SD)			
0th second	2.99±0.58	2.95±0.49	0.757
2nd second	4.17±0.75	4.05±0.77	0.547
4th second	4.46±0.86	4.47±0.79	0.937
6th second	4.67±0.87	4.67±0.89	0.985
8th second	4.83±0.90	4.77±0.93	0.804
10th second	4.89±0.90	4.89±0.88	0.984
Pupillary dilatation velocity (mm/sec, median, minimum-maximum)			
0-2 second	0.60 (0.40-0.88)	0.52 (0.26-0.94)	0.147
2-4 second	0.13 (-0.06-0.50)	0.22 (-0.07-0.35)	0.013
4-6 second	0.11 (-0.07-0.23)	0.07 (-0.06-0.29)	0.591
6-8 second	0.07 (-0.08- 0.33)	0.06 (-0.09-0.31)	0.430
8-10 second	0.4 (-0.08-0.11)	0.03 (-0.09-0.51)	0.954

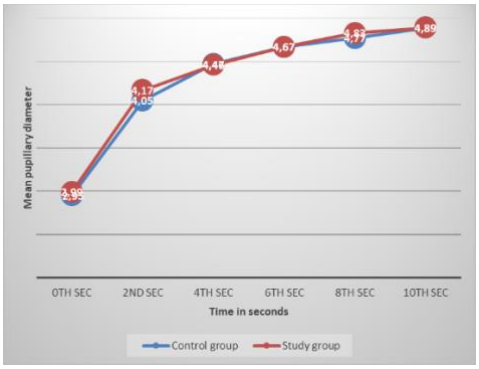

Figure 1: Mean pupil diameters measured in dynamic pupillometry in study and control groups.

DISCUSSION

Unlike retinal vessels, choroidal vessels are under the control of the ANS (McDougal & Gamlin, 2015). The ANS influences the sphincter pupillae muscle via parasympathetic innervation through the ciliary ganglion, resulting in miosis, and the dilator pupillae muscle via postsynaptic sympathetic innervation from the superior cervical ganglion, causing mydriasis. It is known that choroidal vascularity is impaired in CSCR patients (Min et al., 2018). Limited studies assessing HRV have suggested an imbalance in sympathetic and parasympathetic pathways in these patients, with increased sympathetic activity and decreased parasympathetic activity (Tewari et al., 2006; Hwang et al., 2024). Additionally, Zhou et al. examined pupillary light response, task-evoked pupillary responses, and HRV in CSCR patients, detecting sympathetic activation and reduced parasympathetic function in this population (Zhou et al., 2022). In the present study, pupillary light responses in eyes with CSCR were evaluated both statically-under scotopic, mesopic, and photopic conditions-, and dynamically, and were compared with the healthy eyes. No statistically significant differences were observed. However, the absence of sympathetic activation in pupillary light response is insufficient to conclude that the ANS is ineffective in CSCR. The ANS operates through extensive central and peripheral pathways (Gibbons, 2019). While cardiac autonomic functions assessed via HRV have been reported to correlate with pupillary light response (Venkata et al., 2020), the choroidal vascular effects may involve distinct pathways. Moreover, attributing CSCR etiopathogenesis solely to ANS dysfunction is inadequate. Leclercq et al. reported that all choroidal vessels are under neuronal control and that mineralocorticoid receptor overexpression may lead to changes in neuronal intracellular organelles and myelin, causing choroidal neuropathy and pachychoroid appearance (Leclercq et al., 2023). These findings suggest that systemic hormonal and local neuronal disruptions may play a more dominant role in CSCR pathophysiology.

Dynamic pupillometry allows the observation of pupillary responses during the transition from photopic to scotopic conditions, providing valuable insights, particularly into sympathetic pathways in terms of timing and velocity. In this study, pupillary diameters were measured at 2-second intervals over a total duration of 10 seconds. No significant differences were observed in pupillary diameters or dilation velocities between the groups, except for a slower dilation velocity in the 2–4 second interval in the study group. In our opinion, this difference in dilation velocity during the 2–4 second interval may be incidental when evaluated alongside other markers. Pupillary responses have previously been used to assess autonomic activity in diabetic patients and those with erectile dysfunction (Cankurtaran et al., 2019; Jain et al., 2018). However, the pupillary response represents only a single component of the ANS. In CSCR, the ANS may also exert its effects through vascular pathways, or local autoregulatory and non-neuronal mechanisms may play a role.

Study Limitations and Strengths

The primary limitation of our study is the small sample size. Additionally, commonly used tests for evaluating the ANS, such as HRV, were not performed. Most of the patients in the study group had chronic CSCR. Autonomic sympathetic activity may be a risk factor in the initial development of the disease, the condition might become chronic over time due to RPE and choroidal damage, even after sympathetic activity normalizes.

CONCLUSION

In conclusion, no significant differences were found in autonomic pupillary responses between CSCR patients and healthy participants. This suggests that systemic hormonal factors and local choroidal responses may play a more critical act in the pathophysiology of CSCR than sympathetic activation. Further studies with larger patient groups and evaluations of other components of the ANS are needed.

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Conflict of Interest

The author declare no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Author Contributions

Plan, design: DA, EK; **Material, methods and data collection:** YG, DA; **Data analysis and comments:** DA, YG; **Writing and corrections:** DA, EK.

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