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Original Article

Is the Pupil Involved in Duane Syndrome? Static and Dynamic Pupillometry Characteristics

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Abstract

Objectives: Duane syndrome (DS) is typically characterized by abduction and/or adduction deficiency accompanied by eyelid and ocular motility disturbances. Maldevelopment or absence of the sixth nerve has been shown to be the causative factor. The aim of the present study was to investigate static and dynamic pupillary characteristics in patients with DS and compare the results with those of healthy eyes.

Materials and Methods: Patients with unilateral isolated DS and no history of ocular surgery were enrolled in the study. Healthy subjects with a best corrected visual acuity (BCVA) of 1.0 or higher were assigned to the control group. All subjects underwent complete ophthalmological examination and pupillometry measurements (MonPack One, Vision Monitor System, Metrovision, Perenchies, France) including static and dynamic pupil evaluation.

Results: A total of 74 patients (22 with DS and 52 healthy subjects) were included in the study. The mean age of the DS patients and healthy subjects was 11.05±5.19 and 12.54±4.05 years, respectively (p=0.188). There was no difference in sex distribution (p=0.502). Mean BCVA differed significantly between eyes with DS and healthy eyes, and between healthy eyes and the fellow eyes of DS patients (p<0.05). No significant difference was found in any static or dynamic pupillometry parameters (p>0.05 for all).

Conclusion: In the light of the results of the present study, the pupil seems to be not involved in DS. Larger studies including more patients with different types of DS in different age groups or comprising patients with non-isolated DS may reveal different findings.

Keywords: Duane syndrome, dynamic pupillometry, pupil, sixth nerve, static pupillometry

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Introduction

Duane syndrome (DS) is a special type of strabismus that has been recently classified among the congenital cranial dysinnervation disorders (CCDDs) and is encountered in 1-5% of patients with strabismus.[1,2] This syndrome is characterized by deficient abduction and/or adduction from birth, accompanied by globe retraction on attempted adduction, narrowing of the palpebral fissure, and exaggerated elevation/depression on adduction. The underlying pathology is the absence of the sixth cranial nerve at the nuclear or supranuclear level and/or maldevelopment of the nerve itself or the motor neurons of the abducens nucleus and aberrant innervation of the lateral rectus muscle, which is mainly responsible for the abnormal eye movements.[1] There is a simultaneous innervation of the medial and lateral rectus muscles and the latter is partially innervated by the branches of the oculomotor nerve.[1] Electromyographic studies showed co-contraction and synergistic innervation of the medial and lateral rectus muscles and even of the vertical rectus muscles in different positions of gaze. Abnormal innervation has also been found to cause subsequent fibrotic changes in the extraocular muscles.[3] Different classifications of DS have been proposed based on motility, electromyographical findings, and the extraocular muscles involved in abnormal co-contraction.[4]

Pupillary dynamics indicate sympathetic and parasympathetic modulation, so in fact the third cranial nerve is substantially involved. Pupillary involvement has been demonstrated in CCDDs.[5] As DS has also been categorized as a CCDD, possible involvement of the pupil has been hypothesized and evaluated objectively by pupillometry. Considering the miswiring of the oculomotor innervation present in DS, this altered innervation may affect static and dynamic pupillary features. Pupillary assessment is generally based solely on subjective evaluation. However, automated pupillometry in static and dynamic conditions allows quantitative measurement and may offer more objective information regarding the presence and extent of pupillary involvement in various diseases.

The aim of the present study was to determine the dynamic and static characteristics of the pupil in patients with DS and compare the results with those of normal subjects to assess whether dynamic and static pupillometric features are affected in DS.

Materials and Methods

The study was carried out in accordance with the Declaration of Helsinki upon approval by the Ethics Committee of Ankara Training and Research Hospital (E-19-82). Informed consent was obtained from all participants.

Twenty-two patients with unilateral isolated DS and 52 healthy subjects were recruited. Healthy subjects in the control group had a decimal best corrected visual acuity (BCVA) of 1.0 or higher and no accompanying ocular or systemic diseases. Only data from the right eyes of the healthy subjects were included in the statistical analysis for this group. In the DS group, the affected eyes and the fellow unaffected eyes were analyzed separately. Participants with ocular or systemic comorbidity, ocular structural abnormalities, history of ocular surgery, recent or current history of drug or alcohol use, or poor cooperation with the tests were excluded. None of the patients with DS had concurrent systemic abnormalities. Subjects who had ≥1.00 diopters (D) spherical equivalent refractive error were excluded. Considering the proven effect of age on pupillometry measurements, we ensured the groups were matched in terms of mean age. In addition, only nonsmokers were enrolled in both groups due to the effects of smoking on pupil size.[6]

All patients underwent complete ophthalmological work-up including BCVA, slit-lamp biomicroscopy, and dilated fundus examination. Subjects with known or suspected glaucoma or other ocular diseases, hyperopia or myopia ≥1.00 D, and astigmatism ≥1.00 D were excluded. DS was categorized according to the Huber classification.[7] In brief, type 1 was defined as associated with marked limitation or complete absence of abduction, normal or slightly defective adduction, and globe retraction in adduction; type 2 was defined as associated with limitation of adduction and normal or slightly affected abduction; and type 3 as limitation in both abduction and adduction.[7] The same experienced ophthalmologist (M.A.S.) performed static and dynamic pupillometry measurements with the same pupillometry device (MonPack One, Vision Monitor System, Metrovision, Perenchies, France), during the same time of day and in the same environmental conditions under controlled ambient lightening without prior ophthalmological examination requiring contact or pupillary dilation. All patients were asked to fixate on the target located at the center. Only high-quality and artefact-free images were used in the study. Recordings including extreme eye movements and artefacts were excluded. The pupillometry system contains a high-resolution camera that enables assessment of both pupils at the same time under different, predetermined and precise states of illumination. It allows quantitative and accurate static and dynamic evaluation.[8] The average values from three consecutive measurements were included in the analysis.

The pupil contours were automatically delineated by the software. Static pupillometric analysis included pupil diameter in four different ambient light conditions: photopic high (100 cd/mm^2) and low (10 cd/mm^2), mesopic (1 cd/mm^2), and scotopic (0.1 cd/mm^2). Dynamic pupillometry measurements were carried out under white light flashes after five minutes of dark adaptation. Both pupil traces were measured simultaneously. Dynamic analysis included resting diameter of the pupil (mm); the amplitude (mm), latency (ms), duration (ms), and velocity (mm/s) of constriction; and the latency (ms), duration (ms), and velocity (mm/s) of dilation.

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics version 23.0 software (IBM Corp., Armonk, NY, USA). Descriptive statistics were expressed as mean ± standard deviation or median (min-max) according to the data distribution.

Numerical variables were evaluated for normality of data distribution by using Kolmogorov-Smirnov test. Independent samples t tests were used to compare the means of two groups. When the data were not normally distributed, Mann-Whitney U test was used to compare two groups. In comparisons between dependent groups, paired samples t-tests were used for normally distributed data and Wilcoxon test for non-normally distributed data. Yates' chi-square test was used to compare categorical variables between groups. P<0.05 was accepted as statistically significant.

Results

The study included a total of 74 subjects. The study group consisted of 22 patients with isolated DS (14 female, 8 male) and the control group consisted of 52 healthy subjects (27 female, 25 male; p=0.502 for gender). The mean age of the groups was 11.05±5.19 and 12.54±4.05 years, respectively (p=0.188). Most patients had type 1 DS (19 patients, 86.4%), followed by type 2 (2 patients, 9.1%) and type 3 (1 patient, 4.5%). The left eye was involved in 16 (72.7%) of the DS patients.

The mean BCVA was 0.94±0.17 (0.3-1.0) in eyes with DS, 0.97±0.61 in the fellow eyes, and 1.0±0.0 in the control group. BCVA differed significantly between eyes with DS and the control group (p=0.007), as well as between the fellow eyes and the control group (p=0.007).

All static and dynamic pupillometry results are given in detail in Tables 1 and 2. No significant difference was found in any of the static or dynamic pupillometry parameters (p>0.05 for all).

Discussion

DS has been categorized as one of the CCDDs.[9] Skeletal defects, neural defects involving the third, fourth, and sixth cranial nerves, and ocular associations including cataract and optic nerve and pupillary abnormalities have been described in DS.[9,10] CCDDs encompass various clinical entities such as Moebius syndrome, DS, monocular elevation deficiency, Brown syndrome, congenital fibrosis of the extraocular muscles, and horizontal gaze palsy.[9] The main underlying pathology in this group is the developmental abnormality of one or more cranial nerves.[9]

DS can be associated with anterior and posterior segment abnormalities as well as systemic abnormalities such as renal, vertebral, and cardiac abnormalities, and can also be associated with specific syndromes (i.e., Goldenhar syndrome).[10,11] The molecular etiology of many CCDDs has been recently identified.

Table 1. Static pupillometry findings in all groups

	Eyes with DS (mean ± SD) N=22	Fellow eyes in DS (mean ± SD) N=22	Control group (mean ± SD) N=52	p*	p**	p***
High photopic PD (mm)	3.23±0.36	3.39±0.86	3.17±0.92	0.320	0.338	0.792
Low photopic PD (mm)	4.06±0.75	4.12±0.84	4.06±0.69	0.293	0.762	0.972
Mesopic PD (mm)	5.44±1.05	5.51±1.09	5.62±0.89	0.284	0.648	0.444
Scotopic PD (mm)	6.66±1.01	6.64±1.20	7.06±0.78	0.881	0.075	0.072

PD: Pupil diameter, SD: Standard deviation, p*: Comparison of eyes with DS and fellow eyes (paired t-test), p**: Comparison of fellow eyes in DS patients and the control group (independent samples t-test); p***: Comparison of eyes with DS and the control group (independent samples t-test)

Table 2. Dynamic pupillometry parameters in all groups

	Eyes with DS (mean ± SD) N=22	Fellow eyes in DS (mean ± SD) N=22	Control group (mean ± SD) N=52	p*	p**	p***
Resting diameter (mm)	6.12±0.92	6.24±0.82	6.37±0.66	0.064	0.484	0.193
Pupil constriction						
Amplitude (mm)	1.97±0.32	1.96±0.34	2.35±2.65	0.862	0.502	0.512
Latency (ms)	242.18±53.75	247.04±49.58	242.90±61.44	0.687	0.781	0.962
Duration (ms)	604.59±75.02	601.86±80.23	618.29±83.78	0.879	0.438	0.510
Velocity (mm/s)	6.24±1.03	6.07±0.84	6.12±1.03	0.400	0.853	0.645
Pupil dilation						
Latency (ms)	846.77±48.50	858.00±70.30	861.19±69.59	0.479	0.858	0.380
Duration (ms)	1603.73±129.28	1592.77±102.86	1619.15±65.64	0.568	0.190	0.498
Velocity (mm/s)	2.37±0.50	2.41±0.34	2.36±0.81	0.630	0.756	0.954

SD: Standard deviation, p*: Comparison of eyes with DS and fellow eyes (paired t test), p**: Comparison of fellow eyes in DS patients and the control group (independent samples t-test), p***: Comparison of eyes with DS and the control group (independent samples t-test)

The clinical picture is mainly caused by cranial nerve miswiring, migration failure, anomaly of axonal guidance, and subsequent muscular changes such as fibrosis.[9]

As the third cranial nerve is involved in DS mainly in terms of lateral rectus muscle innervation, possible alteration of pupillary function was hypothesized. To document pupillary function in an objective manner, we preferred automated static and dynamic pupillometry in the present study.

Pupil size is precisely adjusted by a balance between the parasympathetic (cholinergic) and sympathetic (adrenergic) autonomic nervous systems. However, there are many other potential contributing factors in daily life, including background illumination, respiration (as inspiratory mydriasis and expiratory miosis), emotional arousal, and age.[12,13,14,15] Pupillary size can be affected by age (i.e., senile miosis), accommodative status, and environmental light conditions, but may not be dependent on gender, refractive error, or iris color.[16] Furthermore, anticholinergic and sympathomimetic agents, antihistamines, and antiepileptics can cause pupillary dilation. Autonomic disorders such as generalized autonomic neuropathy, central nervous system infections such as syphilis, ocular/cranial trauma, cerebrovascular events, and ocular inflammation can also affect pupil size.

Automated pupillometry enables objective and noninvasive measurements of static and dynamic pupillary function. Tekin et al.[17] reported normative values for dynamic and static pupillometry in healthy individuals and investigated the effect of age and gender in a cohort of 155 patients. They demonstrated pupil diameter was greatest in the adolescent group and did not differ by sex.[17] They found that resting diameter and pupil constriction/dilation velocity were negatively correlated with age, whereas latency of pupil constriction was positively correlated with age.[17]

Pupillometry has been studied in a variety of systemic diseases and its role in the detection of autonomic dysfunction has been largely questioned in the literature. The investigation of pupillary profiles in neurodegenerative diseases show that pupil dynamics can be significantly altered and may also be used as indicators in the early diagnosis, assessment of progression, and follow-up of disease. Studies investigating light-induced pupillary responses in Alzheimer's disease showed that redilation velocity/rate was the most consistently altered characteristic.[18]

Park et al.[19] evaluated pupillary function with dynamic pupillometry in patients with multiple system atrophy, in which prominent autonomic dysfunction is the distinctive feature. They found that average constriction and dilation velocities were lower in these patients compared to healthy controls and showed that these parameters slowed as symptom scores increased.[19]

Study Limitations

The present study had certain limitations. All environmental conditions including background illumination and time of day were standardized as much as possible to minimize the effects of confounding factors. However, several factors such as the patient's emotional state or previous night's sleep cannot be feasibly standardized. Another drawback of the study is that the analysis of pupillary characteristics was cross-sectional. The effect of time and extraocular muscle surgery on dynamic and static pupillometry measurements are still unknown. Furthermore, there was no electromyographical evaluation of the extraocular muscles in order to ascertain the innervation pattern and aberrant innervation. This assessment may gain importance when more patients with different types of DS are studied. The difficulty of finding patients with unilateral isolated DS who had no history of ocular surgery and were cooperative with the measurements, as well as age-/gender-/and refractive error-matched healthy eyes, restricted recruitment of subjects. Larger studies with greater numbers in each group and different types of DS may yield different results. The relatively small number of patients with DS may affect the validity of the study results and their significance.

Conclusion

This study was conducted to examine static and dynamic pupillometry parameters in patients with unilateral DS and healthy controls. Pupillary examination is almost always subjective since it is generally performed by the clinician and is prone to interobserver variability. However, automated pupillometry provides quantitative measurements. In particular, dynamic assessment allows the evaluation of pupillary characteristics under conditions that are almost the same as real life.

To the best of our knowledge, this is the first study investigating static and dynamic pupillometric characteristics in a quantitative manner in patients with DS. Static and dynamic pupillometry parameters were similar between the eyes with DS, the fellow eyes of the DS patients, and the control group. This may confirm that there is no objective pupillometric parameter indicating pupillary involvement in DS. However, pupillary characteristics in DS and in other CCDDs warrant further comprehensive clinical studies.

Ethics

Ethics Committee Approval: The study was carried out in accordance with the Declaration of Helsinki upon approval by the Ethics Committee of Ankara Training and Research Hospital (E-19-82).

Informed Consent: Informed consent was obtained from all participants.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: M.A.Ş., Concept: H.T.Ş., M.A.Ş., Design: H.T.Ş., Data Collection or Processing: H.T.Ş., M.Ö.Y., Analysis or Interpretation: J.K., H.T.Ş., Literature Search: H.T.Ş., Writing: H.T.Ş.

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