Comparison of Interpupillary Distance, Pupillary Diameter and Corneal Reflex Measured with Plusoptix A09 in Normally Developing Children and Autism*

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Abstract

Aim: Autism Spectrum Disorder (ASD) is a developmental disorder that can present with an abnormality of the autonomic nervous system (ANS symptoms).

Method: In this study, 38 eyes of 19 ASD were included with 19 healthy children (control group). Participants were analyzed according to their characteristics. Here, used the Plusoptix A09 devices to measure the difference in pupil size, corneal reflex, and interpupillary distance (IPD) between ASD and healthy children.

Results: The mean age±standard deviation (SD) for the autism group was 4,6±2,5 years (range 2-11 years). In the group of normally developing children, the mean age was±SD 5,02±2,6 years (range 2-11 years). The size of the right pupil (p=0,006) and left pupil (p=0,007) was found to be significantly different in the control and experimental groups. IPD (p=0,000) was statistically significant between groups unlike the corneal reflex was not (p=0,173). The p-value is less than 0,05 in all statistical results.

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ETHICAL STATEMENT: The protocol was approved by the Ethics Committee of the Üsküdar University, Turkey (number: 61351342/2020-526, date: 26.11.2020). Parents or caregivers provided written informed consent. The study was conducted following the 1964 Declaration of Helsinki. Child participants also gave oral consent before participation.

Conclusion: As a result, pupil diameter and IPD of children with autism were found to be larger than the control group, but there was no significant difference in corneal reflex. Pupillary measurements reveal differences between people with ASD.

Keywords: Autism spectrum disorders, cornea, reflex, pupillary.

Normal Gelişim Gösteren Çocuklar ve Otizmli Çocuklarda Plusoptix A09 ile Ölçülen Pupil Çapı, Korneal Refleks ve İnterpupiller Mesafenin Karşılaştırılması

Öz

Amaç: Otizm Spektrum Bozukluğu (OSB) belirtileri, otonom sinir sisteminin (ANS) anormal işleyişinden kaynaklanabilir.

Yöntem: Çalışmada 19 sağlıklı çocuk (kontrol grubu) ile 19 otizm hastasının 38 gözü dahil edildi. Her iki grubun pupil çapı, interpupiller mesafe ve korneal refleks ölçümleri analiz edildi. Ölçümlerde Plusoptix A09 marka cihaz kullanıldı.

Bulgular: Otizm grubu için ortalama yaş±standart sapma (SD) 4,6±2,5 yıl (aralık 2-11 yıl) idi. Kontrol grubu için ortalama yaş±SD 5,02±2,6 yıl (aralık 2-11 yıl) idi. Sağ gözbebeği (p=0,006) ve sol gözbebeği (p=0,007) pupil çapları kontrol ve deney gruplarında anlamlı olarak farklı bulundu. İnterpupiller mesafe (p=0,000) otistik ve kontrol gruplarında anlamlı olarak farklıydı ancak kornea refleksi, kontrol ve otistik gruplarda anlamlı farklılık göstermedi (p=0,173). Tüm istatistiksel sonuçlarda p değeri 0,5'ten küçüktür.

Sonuç: Sonuç olarak, otizmli çocukların pupil çapı ve interpupiller mesafesi kontrol grubuna göre daha büyük bulundu. Pupil ölçümleri, OSB olan ve olmayan kişiler arasındaki farklılıkları ortaya koymaktadır.

Anahtar Sözcükler: Otizm spektrum bozukluğu, kornea, refleks, pupiller.

Introduction

Autism spectrum disorders (ASDs) are neurodevelopmental conditions relevant to impaired communication, behavior, and socialization. The Centres for Disease Control and Prevention (CDC) reported that approximately 1 in 44 children in the United States (U.S.) is diagnosed with ASD in 2021[1]. ASD symptoms may be characterized by clinical manifestations resulting from the defective function of the autonomic nervous system (ANS). ASD symptomology may result from a basic cognitive impairment caused by ANS dysregulation, and these physiological effects may differ from those of normal children[2]. Although atypical findings are not a diagnostic criterion for ASD, studies show that autistic individuals have ANS symptoms different from neurotypical ones. These ANS responses include higher skin conductivity, the strength and rate of the heartbeat (HR), and the diameter and elasticity of artery walls, and respiratory rate. For instance, Goodwin et al. reported that people with ASD had a normal heart rate in response to potentially stressful stimuli[3]. This study has proposed pupillary and corneal differences. The corneal reflex and

diameter of the pupil are mainly affected by light and sympathetic system activity and reflect subtle findings that serve to analyze attentional and perceptual events in a neurobehavioral context[4]. In addition, the pupil is associated with many physiological and psychological factors, comprising cognitive effort, stimulation, attention, memory, learning and perception. This study also has proposed differences in interpupillary distance (IPD). ASDs result from changes in the brain due to neurodevelopmental impairment from the embryonic period, resulting in the morphological development of faces of autistic children differing from those of children with typical development. Detailed IPD measurements may also reveal differences in facial morphological changes in ASD.

In general, autorefractory devices are included in studies to obtain information about eye refraction defects. The main advantages of the Plusoptix A09 Photoscreener (Gmbh, Nuremberg, Germany) is easy to carry and quickly measures pupil diameter, corneal reflex and IPD with a working distance of approximately 1 m[5,6].

To best knowledge, this is the first study to compare Plusoptix A09 to detect IPD, pupillary size, and cornea reflex measurement differences between normally developing children and ASD.

Material and Methods

Subjects and Procedures

This double-blinded pilot study was conducted with 19 autistic children and 19 healthy children, ages 2-11 years. Children (n=19) were recruited from the project's websites, advertisements, and via outpatient clinical units. The sample group was selected in conformity with the ASD DSM-IV criteria and psychiatric interviews. Autistic children were prospectively enrolled.

Children participated who fulfilled the following criteria:

1. Autism to diagnose was by DSM-IV criteria and the Autism Diagnostic Interview-Revised criteria.

2. Aged 2-11 years,

3. Written informed consent signed by caregivers.

Plusoptix® A09

Plusoptix is a small portable infrared computer mountable camera device. In this study, the measurements of both groups were taken from a distance of 1 meter with a binocular photorefractometer under the same conditions, without cycloplegia (Plusoptix® A09, GmbH, Nuremberg, Germany)[7]. Plusoptix A09 can measure a pupil size of 4.0-8.0 mm from a distance of 0.1 mm[8]. Eccentric photorefraction is used as a measurement basis. The device provides

convenience in terms of pediatric evaluation with its remarkable features. The pupillary measurements were performed by an ophthalmologist (author İŞ) in the outpatient clinical unit. The brightness level in the room was controlled via the lux meter application. Corneal reflex, Pupil size (mm), and IPD (mm) were measured at least three times after each participant was left in a room with a light level of 8 cd/m^2 for 2 minutes, and the average value of 3 consecutive consistent measurements was recorded.

Statistical Analysis

The Statistical Package for Social Science (SPSS) version 22.00 was used for statistical analysis. Qualitative data were presented as numbers and percentages, and quantitative data as mean and standard deviation (SD). The normality of variables was tested by the Kolmogorov–Smirnov test. Analyses of the data distributions confirmed the normality and homogeneity of variance. Independent samples t-test for normal distribution fits of statistical difference between quantitative data of two independent groups (autism and normally developing children) and non-parametric comparison was determined using the Mann-Whitney U test. A two-tailed test for comparing equality of proportions was applied at a 5% alpha level and a P value less than 0,05 was considered statistically significant.

Study Ethics

The protocol was approved by the Ethics Committee of the Üsküdar University, Turkey (number: 61351342/2020-526, date: 26.11.2020). Parents or caregivers provided written informed consent. The study was conducted following the 1964 Declaration of Helsinki. Child participants also gave oral consent before participation.

Results

A total of 19 children with autism between the ages of 2 and 11; 17 boys and 2 girls, participated in the study. None of the children with ASD use psychiatric medication. 19 normally developing children between the ages of 2 and 11; 14 boys and 5 girls were selected as the control group. Baseline characteristics of the participants are given in Table 1.

Table 1. Study group characteristics

	Autism (n=19)	Control (n=19)
Age, months (MD±SD)	4,6 ± 2,5	5,02 ± 2,6
Male	17	14
Female	2	5
Use of psychiatric drugs (%)	NA	NA

MD: Mean difference; NA: not applicable; SD: Standard deviation

Examined between-group differences in pupillary size, corneal reflex, and IPD using a repeated-measures. All results are given in Table 2.

Table 2. Changes in eye measurements

	Eye measurements		
Variables	**Autism**	**Control**	**p**
Pupil size (mm)			
Left eye	7,03±0,46	5,94 ± 0,89	,007
Right eye	7,03±0,44	5,94 ±0,97	,006
Interpupillary Distance (mm)	53,89±3,67	47,47±3,28	,000
Corneal Reflex	3,49±2,21	2,96±2,41	,173

**p<0,05; mm: millimeter*

The mean ± SD of right eye pupillary size was 7,03±0,44mm in the autistic group, while it was 5,94±0,89mm in the control group. The mean±SD of left eye pupillary size was 7,03±0,46mm in the autistic group, while it was 5,94±0,97mm in the control group. The size of right pupil (p<0,05) and left pupil (p<0,05) were found to be significant difference in the control and autistic groups (Mann–Whitney U-test). Therefore, these analyzes confirmed that study parameters, which also obtained from the control group, were appropriate and that stimulating conditions led to marked physiological differences in pupillary diameter.

The next assessed the IPD among ASD and healthy children variables. The mean±SD of IPD was 53,89±3,67 mm in the autistic group, while it was 47,47±3,28 mm in the control group. When the control and ASD groups were compared, the IPD value was found to be significantly different (p<0,05; Independent samples t-test).

The mean±SD of corneal reflex was 3,49±2,21 in the autistic group, while it was 2,96±2,41mm in the control group. Corneal reflex was not found to be significantly different in the control and autistic groups p>0,05 (Mann–Whitney U-test).

Discussion

To the best of knowledge, it was difficult to discuss study results as no similar study has been done before. Two hypotheses were tested in this study. First, it was tried to determine whether the corneal reflex and pupillary size were different in children with ASD. Second, when comparing autistic children with normally developing children, they were asked whether IPD differed from healthy controls in the evidence that they had a subtle but distinct facial phenotype. Studies with photorefractive devices are generally used in the investigation of eye disorders/diseases related to neurodevelopment disorders. Ugurbas et al. reported that in a cohort of 182 mentally retarded children, 32% were at risk for amblyopia using plusoptiX S04[9]. This is the first cohort study to test these hypotheses among healthy and ASD children by using the photorefractive device.

Clinical studies use morphological methods to detect malformations, including increased head size, external ear rotation, wide nostrils, foot and hand sizes[10-12]. In these changes, especially increased IPD has started to draw attention[13]. The distance between the centers of the pupillary is the IPD and is related to stereoscopic function. IPD varies commonly according to age, gender, and race. For example, Yıldıray et al. found that men have a significantly higher IPD than women in Turkish society[14]. Arıcı et al. divided 45 patients without ocular pathology other than refractive error into two groups and measured the IPD of the 1st group consisting of 21 people with Plusoptix S08 and Potec PRK-6000 devices, and significant results were found in the measurements[15]. In addition, it may be associated with many neurodevelopmental disorders that cause morphological changes. Performed by the same data analysis for ASD and control children with the plusoptiX A09 device.

The measurement of IPD on Magnetic resonance imaging (MRI) scans is another strategy, Hardan et al. measured the interlens and interorbital distances on MRI scans and found no differences between the two groups (40 ASD and 41 healthy controls) on any measurements[16]. On the contrary, the distance between IPD measured with the plusoptiX A09 device was higher than the control group in this study. Singman et al. measured IPD in 236 patients (142 orthophoric, 97 esotropic, and 17 were exotropic) with the same device but different samples and statistical results were not obtained due to the number of patient groups[17].

The plusoptiX A09 photo screeners infrared video autorefractors capable of measuring non-cycloplegic refraction binocularly capture multiple images within seconds and yield average pupil size and deviation of the eyes. Since infrared light is used in the device, the pupil size is kept constant and the hippus effect is minimal. This device can take simultaneous pupillary

measurements. Since it works from a distance of about 1 meter, the risk of threat is lower for children with autism compared to other devices[18]. According to the literature research by 2022 March, there are very few reports on normative data regarding pupil size but the measurement technique and the samples were generally different compared to this study. Martineau et al. reported a study comparing pupil size during presentation of black and visual stimulus slides on children (19 ASD, mean age 118 months; 19 mentally age-matched controls, mean age 87 months, and chronologically age-matched 19 controls, mean age 118 months) and smaller pupil sizes in children with ASD[19]. Silbert et al. published the correlation between anisocoria and pupil size measured with the plusoptiX A04 and A09 photo screeners in children without neurodevelopmental disorders. They defined positive values of anisocoria indicate that the right pupil size was larger than; the negative values, the left pupil[18]. Although they recorded the mean pupil size between the two eyes, they did not make a measurement comparing children with ASD. According to Sepeta et al., children with ASD had a smaller pupil size when they looked at happy faces compared to the control group These authors interpreted these divergent findings as an indication of decreased sensitivity to the reward value of social stimuli in children with ASD[20]. In contrast, the pupil diameter was found to be larger in the absence of stimulus compared to the control group in study results. In support of study results, Anderson and Colombo found larger tonic pupil size in the ASD group[21] but Rubin reported contradictory results, including the early finding of smaller pupil sizes during pupil dilation in children with ASD[22].

According to the available literature, this is the first study to examine the corneal reflex difference of a Plusoptix A09 photo-scanner, and in light of study results, the corneal reflex value of Plusoptix A09 may not be a reliable tool for screening risk factors for the child with ASD ($p>0.05$). However, further research with larger sample groups is needed. There have been few studies of ASD reporting generally pupillary light reflex. Fan et al. found that the ASD group showed significantly smaller contraction amplitude, lower contraction velocity and longer pupillary light reflex latency than typically developing children[23]. In conclusion, the Plusoptix devices can provide a rapid and easy method of ocular disorders screening in young children and detecting risk factors. However, it can also be used to evaluate different parameters of diseases related to neurodevelopmental disorders, such as ASD selected in this study.

Strengths and Limitations

COVID-19 pandemic caused some disruptions and deficiencies in the experimental setup. Importantly, 11 children were diagnosed with COVID-19, the study was continued with 19 children with ASD.

Conclusion

In this study, focused on 38 subjects 19 of which are suffering from ASD, and the remaining 19 healthy subjects. First, participants' characteristics were analyzed for difference in pupil size, corneal reflex, and IPD using plusoptix A09 devices. The results are promising to underline the differences in pupil size. Considering the effect size of the results of this study, small sample size may be appropriate; however, studies on a larger sample will also make it possible to additionally evaluate the effects of age when ASD is first diagnosed. Therefore, future studies examining the relationship between the pupil and optic nerve structure and brain functions will help to further understand the interpupillary biomarkers for the diagnosis of ASD. In addition, since study group of normally developing children is heterogeneous in that the findings are more indicative, it will be necessary to repeat this study with different clinical controls (eg, Cerebral palsy, down syndrome mental retardation, etc.) to determine whether this response is specific to ASD. Finally, some ANS responses such as unable to make eye contact, respiration rate and HR are correlated with ASD. However, no such relationship has been found with pupil size and interpupillary differences before. Study results may suggest that using a yet simple method may lead to significant pupil and interpupillary differences associated with individual differences in the diagnosis of ASD by the plusoptix A09 device. However, studies with larger sample groups are needed.

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