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Original Article / *Özgün Araştırma*

Investigation of the Pupil Diameter Differences in Anisometropic Amblyopia

Anizometropik Ambliyopide Pupil Çapı Farklarının Araştırılması

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Summary

Purpose: To study pupil diameter differences between amblyopic and fellow eyes in anisometropic amblyopia.

Material and Method: This study was carried out from medical records of 412 candidates for refractive surgery with excimer laser. 69 patients (21 males and 48 females) with anisometropic amblyopia were enrolled in this study. Mean age of subjects was 33.07±9.07 years. Pupil size measurements were performed with an ocular wavefront analyzer. Amblyopic eyes and fellow eyes were compared with regard to pupil diameter, spherical refractive error, magnitude of astigmatism, spherical equivalent, and best-corrected visual acuity on Snellen chart. Also, correlation analyses were performed to determine correlation coefficients and their significance between selected variables.

Results: Mean pupil diameter was 5.95±0.90 mm in amblyopic eyes and 6.15±0.90 mm in fellow eyes. Difference in mean pupil diameter between amblyopic and fellow eyes was statistically significant (p=0.01). Mean spherical refractive error (-2.96±6.21 D), mean astigmatic refractive error (-2.87±1.80 D), mean BCVA (0.44±0.19), and mean spherical equivalent (-4.40 ±2.92 D) in amblyopic eyes were statistically different from the values in fellow eyes (p=0.01). In addition, the analyses showed that the correlations between the magnitude of anisocoria and anisometropia, and between the magnitude of anisocoria and the depth of amblyopia were statistically insignificant.

Discussion: This study shows a relationship between anisocoria and amblyopia. The existence of such relationship helps both to diagnose amblyopia earlier and to unveil some hidden process in the pathophysiology of amblyopia. *(Turk J Ophthalmol 2013; 43: 45-50)*

Key Words: Amblyopia, anisocoria, anisometropia

Özet

Amaç: Anisometropik ambliyopide ambliyop ve sağlam gözler arasındaki pupil çap farkını çalışmak.

Gereç ve Yöntem: Bu çalışma 412 ekzimer lazer ile refraktif cerrahi adayının medikal kayıtlarıyla gerçekleştirildi. Anizometropik ambliyopili 69 (21 erkek ve 48 kadın) hasta çalışma kapsamına alındı. Vakaların ortalama yaşı 33,07±9,07 idi. Pupil çapı ölçümleri oküler wavefront analizörüyle yapıldı. Ambliyopik ve sağlam gözler; pupil çapı, sferik refraksiyon kusuru, astigmatizma miktarı, sferik ekuvalan ve Snellen eşelindeki en iyi düzeltilmiş görme keskinlikleri yönünden karşılaştırıldı. Ayrıca seçilen değişkenler arasında korelasyon katsayıları ve bunların önemliliğini bulmak için korelasyon analizleri yapıldı.

Sonuçlar: Ortalama pupil çapı ambliyop gözlerde 5,95±0,90 mm; sağlam gözlerde ise 6,15±0,90 mm idi. Ambliyopik ve sağlam gözler arasındaki ortalama pupil çap farkı istatistiki olarak anlamlıydı (p=0,01). Ambliyopik gözlerde ortalama sferik kırma kusuru (-2,96±6,21 D), ortalama astigmatik kırma kusuru (-2,87±1,80 D), ortalama en iyi görme keskinliği (0,44±0,19) ve ortalama sferik ekuvalan değerleri (-4,40±2,92 D) sağlam gözlere gore istatistiki olarak farklıydı (p=0,01). Ek olarak analizler; anizokorinin büyüklüğü ile anizometropinin büyüklüğü arasındaki ve anizokorinin büyüklüğü ve ambliyopinin derinliği arasındaki ilişkinin istatistiki olarak anlamsız olduğunu gösterdi.

Tartışma: Bu çalışma anizokori ve ambliyopi arasında bir ilişki olduğunu gösterir. Böyle bir ilişkinin varlığı hem ambliyopiyi erken teşhis etmeye hem de ambliyopinin patofizyolojisindeki gizli süreçleri açığa çıkarmaya yardımcı olur. *(Turk J Ophthalmol 2013; 43: 45-50)*

Anahtar Kelimeler: Ambliyopi, anizokori, anizometropi

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Introduction

Amblyopia is defined as a decrease in best-corrected visual acuity due to abnormal visual experience in early childhood resulting in functional changes in the central visual system and its prevalence was reported as nearly 2%- 4% in previous studies.[1-3] Amblyopia, being one of the leading causes of preventable visual loss, is a serious public health problem.[4] Since early diagnosis and effective treatment are crucial in prevention of this disease,[5] developing diagnostic tests, capable of detecting amblyopia in the early childhood, are mandatory. However, there is not a single diagnostic test, accepted by the whole scientific community with a wide consensus. Instead, there are multiple studies reporting some clinical conditions supposed to be associated with amblyopia. For instance, pupil disorders such as relative afferent pupillary defect and impairment in pupillary light reflexes were reported to be found in amblyopia.[6-8]

Relationship between the pupil and amblyopia was proposed to be a logical possibility, and various studies were performed to elucidate this relationship. Kase et al.[9] reported that the latencies of the direct pupillary reflexes were longer when the amblyopic eyes were stimulated. There are many studies that reported relative afferent pupillary defects (RAPDs) in amblyopic eyes.[8,10,11] Donahue et al.[12] found that amblyopia produced a global depression of focal pupillary responses across the entire 30 degrees field. All these studies indicate that there is an impaired mechanism affecting the pupil physiology in amblyopia.

Although many pupil disorders have been defined to be in relation with amblyopia, relations between anisocoria and amblyopia have not been studied extensively. In only one study, this question was addressed.[13] Although this study hinted that anisocoria might be a suspected sign of anisometropia and/or amblyopia, the lack of clear evidence is still present. The current study was performed to give a satisfactory scientific response to this challenge, and the aim of the study was to investigate whether there was a relationship between anisocoria and anisometropic amblyopia.

Material and Methods

All cases of this retrospective study were candidates for refractive surgery. Medical records of the 412 refractive surgery candidates were examined in detail. Anisometropic amblyopia was defined as a difference in the best-corrected visual acuity between the eyes of at least 2 lines on the Snellen visual acuity charts.[14] Anisometropia was defined as an interocular spherical equivalent refractive error difference of 3.0 D or more or a cylindrical difference of 1.5 D or more. Using this anisometropic amblyopia definition, seventy-eight cases of 412 cases were considered as having anisometropic amblyopia. After that, cases were reevaluated whether they had some conditions, accepted as exclusion criteria. In determination of exclusion criteria, all conditions that have potential effects on pupil size were considered. For instance; cases with history of past eye surgery or trauma, cataract, glaucoma and uveitis were not included into the study; also the patients who had systemic problems like oculomotor nerve palsy, Horner's syndrome, diabetes mellitus, syphilis, temporal arteritis, paraneoplastic syndromes were excluded. Of these 78 patients, 2 cases were excluded due to juvenile cataract, 3 cases - due to strabismus, 3 cases - because of high intraocular pressure, and one case was excluded due to degenerative myopia. In the ophthalmologic examinations of the remaining 69 cases, there was not any pathology that explained visual acuity decrease other than anisometropic amblyopia. So, these 69 patients (21 males, 48 females) were enrolled in the study.

A detailed ophthalmologic examination was performed for all the cases including uncorrected visual acuity, best-corrected visual acuity on the Snellen visual acuity charts, manifest spherical refraction, cycloplegic refraction, wavefront analysis (COAS Ocular wavefront analyzer,

AMO WaveFront Sciences, Albuquerque, NM, USA), autorefractometry (Potec PRK-5000, Potec Co., Ltd., Daejeon, Korea), slit-lamp examination of the anterior segment, and fundoscopy. All refractive data was converted to minus cylinder form to prevent confusion during statistical analysis.

Wavefront analyses were performed in mesopic pupil conditions. All patients were told to wait thirty minutes in a dim room, having an illumination of 3.8 lux, prior to the examination, because standardizing the level of dark adaptation is very difficult between the cases. Illumination was measured by a light meter (CEM DT- 1301, Shenzhen Everbest Machinery Industry Co., Ltd., Shenzhen, China). In addition, illumination of the examination room was measured as 0.6 lux. Each patient's pupil size was measured using the same device under the same illumination levels.

Mesopic pupil sizes were measured with a COAS Ocular wavefront analyzer (AMO WaveFront Sciences, Albuquerque, NM, USA) with software version 1.43.2. The COAS Ocular wavefront analyzer has a Hartmann-Shack sensor (CLAS-2D, AMO WaveFront Sciences, Albuquerque, NM, USA) for measuring the eye's aberrations. Wavefront measurements were performed in a standard way. The patient positions his head on a chin rest and then fixates the center of a circular grid. This circular grid is optically fogged by about 1.5 D. The patient fixates on a red-light-emitting diode target. Target light is "fogged" to infinity to relax accommodation. A reference box on a video monitor is aligned with the pupil and then a single measurement with one click of a button is taken. Wavefront analyzer can acquire simultaneous image of the pupil that is used to measure pupil size to the nearest 0.1mm objectively. After the measurement, the attached computer displays that pupil size value. Three readings of each eye were taken. The clearest image was used for the study of pupil diameter data.

Amblyopic and fellow eyes of the cases were compared with regard to pupil diameter, spherical refractive error (D), magnitude of astigmatism (D), spherical equivalent (D), and best-corrected visual acuity on the Snellen visual acuity charts. Because measurements of each eye were accepted as independent variables, the mean values were compared with independent student's t-test. Pearson correlation analyses were performed to determine

correlation coefficients and their significance between selected variables. A p-value below 0.05 was considered statistically significant. All statistical analyses were performed with SPSS version 16.0 software (SPSS Inc., Chicago, USA)

Results

Sixty-nine patients who had anisometropic amblyopia were included in this study. Twenty-one of them were male and forty-eight were female. Since all study subjects were refractive surgery candidates, and mostly young persons are more inclined for these surgeries, study cohort consisted of young subjects. Therefore, the mean age of the subjects was highly low, 33.07±9.07 years.

The mean pupil diameter in amblyopic eyes (5.95±0.90) was smaller than in fellow eyes (6.15±0.90), and the difference in pupil diameter between the two groups was statistically significant (p=0.013). The distributions of mesopic pupil diameters in each group are shown as a box-plot graphic in Figure 1.

As it was expected, the mean spherical refractive error in amblyopic eyes (-2.96±6.26 D) was different than fellow eyes (-0.29±2.64 D), and this difference was statistically significant (p=0.001). In addition, the difference between the two groups regarding the astigmatic refractive error was significant (p=0.001). The mean astigmatic refractive error was -2.87±1.80 D in amblyopic eyes and -1.22±1.41 D in fellow eyes. In addition, the mean spherical equivalent of amblyopia group (-4.40±2.92 D) was statistically different than the mean spherical equivalent of fellow eyes (-0.89±5.93 D) (p=0.001). Accordingly, the mean best-corrected visual acuity was 0.44±0.19 in amblyopic eyes and 0.96±0.09 in fellow eyes on the Snellen visual acuity charts. The difference between them was also statistically significant (p=0.001). In Table 1, all these data are summarized concisely, showing mean, standard deviation, and standard error of mean.

The correlation between magnitude of anisocoria and anisometropia was analyzed by Pearson correlation analysis. This analysis showed that the correlation was statistically insignificant and the correlation coefficient was r=-0.180 and p=0.138. In order to test the possible correlation between magnitude of anisocoria and the best-corrected visual acuity difference between amblyopic and fellow eyes, correlation analysis and drawing of a scatter plot were performed. The correlation coefficient between these two variables was r=0.069 and p=0.572. In addition, the scatter plot, shown in Figure 2, demonstrates that the correlation is insignificant.

Mesopic pupil size might be dependent on refractive status. For this reason, smaller mesopic pupil sizes in amblyopic eyes might be caused by refractive error. In order to test this possibility, comparison of amblyopic and fellow eyes in regard to refractive status, taking spherical equivalents as a more reliable parameter, was performed. The mean spherical equivalents were -4.40±5.93D in amblyopic eyes and -0.89±2.92 D in fellow eyes. The difference between the two groups was statistically significant (p=0.001).

The subjects were grouped as less than 0.25 mm, 0.25-0.49 mm, 0.50-0.74 mm, 0.75-0.99 mm, and more than 1 mm according to the magnitude of anisocoria. The magnitude of anisocoria was more than 0.5 mm in 31% of subjects. Distribution of frequencies is displayed in Figure 3, as percentage of subjects.

Discussion

In this study, we tried to figure out whether there was a relationship between mesopic pupil size and anisometropic amblyopia. The results showed that patients with anisometropic amblyopia had a smaller pupil size in their amblyopic eyes. Also the correlations between the magnitude of anisocoria and anisometropia

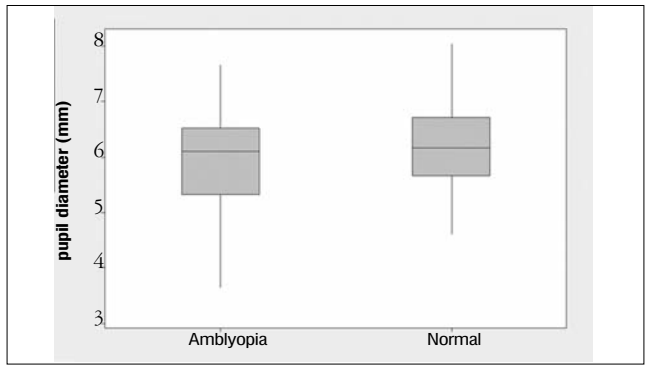

Figure 1. Distribution of mesopic pupil diameters in amblyopic eyes and fellow eyes

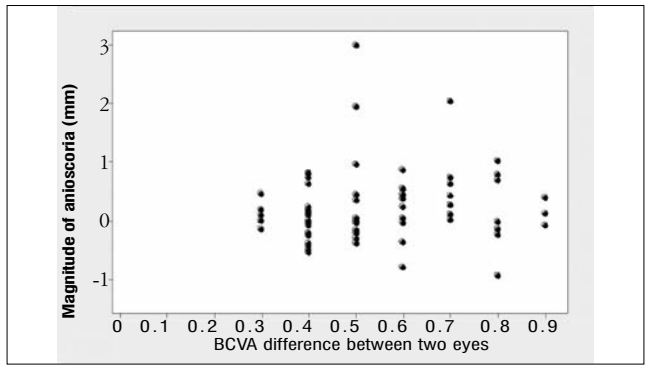

Figure 2. The scatter plot diagram, displaying the relationship between the magnitude of anisocoria and difference in BCVA

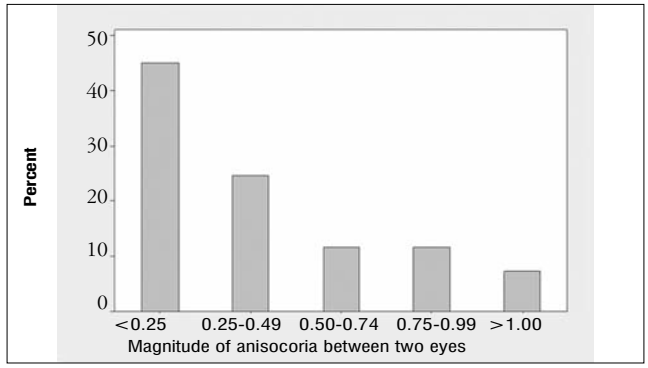

Figure 3. Frequency distribution of subgroups, formed according to the magnitude of anisocoria

and between the magnitude of anisocoria and amblyopia were insignificant.

Pupil size differences in amblyopia were not studied extensively up to now, despite, many of pupil defects were discussed in amblyopia. There is only one paper in the literature that mentioned about this issue. In this paper, it was found that four out of five children who had anisocoria were later diagnosed as anisometropic and/or amblyopic, and on the reciprocal terms, four of eight children who had anisometropia and/or amblyopia had previously presented with anisocoria.[13] We know that anisometropic amblyopia is diagnosed later than the other types of amblyopias.[15] So, every suspicious sign of anisometropic amblyopia is crucial. Thus, we think that the relationship between the pupil size and anisometropic amblyopia, if it would be proved to exist, is very considerable.

In this current study, it was found that the mean mesopic pupil size was smaller in amblyopic eyes. Investigation of relationship between the magnitude of anisocoria and anisometropia would yield some possible associations. However, the correlation between anisocoria and anisometropia was insignificant. In addition, difference with regard to BCVA between amblyopic and fellow eyes did not show an association with the magnitude of anisocoria. This lack of correlations might be the result of some possible factors. Firstly, distribution range of anisocoria was very small in contrast to very large range of distribution of both anisometropia and depth of amblyopia. It is very difficult to find such possible association when the distribution of variables shows so much incongruity. Secondly, some unknown factors other than depth of amblyopia and anisometropia may contribute to the emergence of anisocoria, making this process a highly complex one, difficult to analyze and to draw simple conclusions.

Although the magnitude of anisocoria found in this study is minute, its possible role in the early diagnosis of amblyopia is crucial. The visual differences between the two eyes are not easy for the patient to notice due to the condition of sound fellow eye. Especially, in cases with a 20/20 vision in one eye, most of the time amblyopia diagnosis is only made in later years of life causing loss of valuable opportunity for a successful treatment. On the other hand, a difference between pupil sizes, anisocoria, is observed and noticed very early by parents. An alarming sign like a disproportion in pupil sizes is one of the main motives for parents to seek a medical consultation. This opportunity, taking anisocoria as a possible sign of amblyopia, both in screening examinations and in patients seeking a medical advice, is useful to diagnose such cases early and timely.

It is known that the pupil size differences may be observed in subjects without any abnormal or pathologic condition and these cases are diagnosed as "physiologic anisocoria".[16] This clinical entity was estimated to be encountered in general population at nearly 20%.[17-19] Although there is no widely accepted scientific criteria for the amount of physiological anisocoria, an anisocoria more than 0.4 mm was reported as clinically significant anisocoria.[17,18] In the current study, proportion of cases with magnitude of anisocoria more than 0.5 mm was 0.31. This high proportion of clinically significant anisocoria supports the hypothesis that there would be an association between anisometropic amblyopia and anisocoria.

Although the exact pathophysiology of amblyopia still remains to be elucidated, there is abundant evidence suggesting that major pathology of amblyopia is related to the primary visual cortex.[20,21] However, there are reported pathologies including the lateral geniculate nucleus and neuroretinal dysfunctions in amblyopia that were not related with the primary visual cortex.[22-24] These reports hint that the physiopathology of amblyopia is very complicated and it appears that various pathologies in visual system might occur in this disorder. Beside these pathologies, visual functions other than visual acuity might be impaired, like pupillary functions.

Loewenfeld[18] supposed that an imbalance and asymmetry with the supranuclear control of the Edinger-Westphal nucleus causes physiologic anisocoria. In spite of that, a sympathetic imbalance was suggested to be in charged with this condition by Rosenberg.[25] So, we understand that a deficiency in autonomic nervous system may present in physiologic anisocoria. Therefore, it must be considered that a similar pathophysiology may exist in amblyopia.

Table 1. Descriptive statistics and results of two group comparisons with regard to pupil size (mm), spherical error (D), cylindrical error (D), spherical equivalent (D) and best corrected visual acuity on the Snellen visual acuity charts

		Mean	Std. Deviation	P value
Pupil size (mm)	Control	6.15	0.90	0.013
	Amblyopia	5.95	0.90	
Spherical error (D)	Control	-0.29	2.64	0.001
	Amblyopia	-2.96	6.21	
Cylindrical error (D)	Control	-1.22	1.41	
	Amblyopia	-2.87	1.80	0.001
Spherical equivalent (D)	Control	-0.89	5.93	0.001
	Amblyopia	-4.40	2.92	
Best corrected visual acuity	Control	0.96	0.09	0.001
	Amblyopia	0.44	0.19	

The neurotransmitters including catecholamines, glutamate, acetylcholine, c-AMP, GABA and serotonin were reported to be in relationship with the development of amblyopia.[2,27] There are many studies about the levodopa, a precursor of dopamine and noradrenaline, administration in amblyopia treatment. It has been shown to improve the visual acuity and some other visual functions like contrast sensitivity and fixation point scotomas in amblyopia.[28-30] The effect of levodopa on the visual system has been demonstrated at the retinal and cortical level.[31,32] Nevertheless, the exact mechanism of levodopa action and the specific regions that act on the visual system are cryptic.[33] The neurotransmitters mentioned above play an essential role in the sympathetic and parasympathetic innervations in the central nervous system. Thus, we hypothesize that the anisocoria finding in our study may represent the impairment and asymmetry in autonomic nervous system caused by the altering mechanisms in amblyopia. Anisocoria found in amblyopia can be the aggravated form of physiologic anisocoria.

It is reported that refractive error difference may affect the mesopic pupil size. Cakmak et al.[34] found that mesopic pupil size had a significant correlation with the magnitude of refractive error. They reported that myopes had a larger mesopic pupil diameter and also astigmatism had a significant effect on mesopic pupil size. Taking into account these findings some degree of pupil size difference between amblyopic and fellow eyes might be related to the effect of refractive difference. In this current study, the mean spherical equivalent of amblyopia group (-4.40±2.92 D) was statistically different than of the mean spherical equivalent (-0.89 ±5.93 D) ($p=0.001$). Taking into account this result, it would be expected that pupil size would be greater in amblyopia group due to more myopic refractive error in this group. This result might be interpolated as magnitude of anisocoria would be greater in amblyopia cases with pronounced hyperopia.

Photopic pupil size measurements do not yield reproducible results. Because pupil size differs depending on the amount of light exposure and efforts to standardize a given amount of light exposure is more difficult to achieve. In addition, pupil is not static and many other factors may cause change in its size. On the other hand, mesopic pupil size measurements are easier to standardize. That's why we took the mesopic measurements as more acceptable and less prone to default.

Measuring the pupil size with wavefront analyzer is one of the employed methods. There are studies reporting the success of the pupil size measurements with wavefront aberrometer when compared with other devices that are used to measure pupil size.[35,36] Results of these studies support both reliability and validity of these measurements.

It may be proposed that the accommodation could affect the pupil size as the patients focused on a near target while taking the measurements in this study. However, during pupil size measurements, the target lights were fogged to infinity for relaxing accommodation. That's why it is expected that accommodation effect on pupil size to be minimal. Similarly, Salmon et al.[37] found that instrumental myopia because of the accommodation was 0.1 D, while viewing the fixation targets projected to infinity with COAS wavefront analyzer. So, the accommodation effect on the pupil size was considerably negligible.

This study has some limitations. First of all, though, a very strict standardization of mesopic pupil size measurements, performed at the same time but not simultaneously with both pupils, minimized measurement variations which could arise because of medications, illumination levels and accommodation, simultaneous measurements of both eyes would yield more accurate results. Future studies employing binocular simultaneous measurements might help to show possible minute variations caused by lack of binocular simultaneous measurements.

The other limitation of this study is the high mean age of the subjects, as we have to investigate the course of the amblyopia after the pathology has established a long time ago. The current study is not a longitudinal study and very planned further longitudinal studies may reveal effects of amblyopia on mesopic pupil size in very early beginning periods and its change over a long-time course.

In conclusion, this study shows a relationship between anisocoria and amblyopia. The existence of such relationship helps both to diagnose amblyopia earlier and to unveil some hidden process in the pathophysiology of amblyopia.

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