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Bilateral Abnormalities of Optic Nerve Size and Eye Shape in Unilateral Amblyopia

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Abstract

Purpose—To evaluate the optic nerve (ON) size and globe shape in amblyopic eyes using high resolution magnetic resonance imaging (MRI), and to compare these values to the sound fellow eye and normal control eyes.

Design—Prospective case control study

Methods—Thirty-four amblyopic patients and 60 normal control patients were evaluated using surface coil MRI. Retrobulbar ON cross section, maximum globe cross section, globe non-circularity (globe major axis/minor axis), axial length (AL), and the ratio of AL to ON (AL/ON) were measured.

Results—Corrected logmar acuity of all 34 amblyopic eyes averaged 0.43 ± 0.30 . Mean retrobulbar optic nerve cross section was $9.7 \pm 2.4 \text{ mm}^2$, $9.5 \pm 2.3 \text{ mm}^2$, and $10.7 \pm 2.6 \text{ mm}^2$ for amblyopic, fellow, and normal ONs, respectively. While amblyopic and fellow ONs had similar cross sections, both were significantly ($p=0.02$) subnormal. AL/ON was $2.7 \pm 1.2 \text{ mm}^{-1}$, $2.7 \pm 1.0 \text{ mm}^{-1}$, and $2.3 \pm 0.5 \text{ mm}^{-1}$, respectively. While AL/ON significantly exceeded normal in amblyopic eyes ($p=0.01$), there was no significant difference between amblyopic and fellow eyes. Globe non-circularity of amblyopic (1.17 ± 0.07 , $p=0.002$) and fellow eyes (1.15 ± 0.04 , $p<0.001$) was significantly greater than control (1.11 ± 0.04), but amblyopic and fellow eyes did not differ significantly.

Conclusions—Unilateral amblyopia is associated with bilaterally but subclinically hypoplastic ONs, greater than normal AL/ON, and abnormally non-circular globe cross section. These factors evidently do not determine which of the two eyes will become amblyopic. Reduced circularity of amblyopic and fellow eyes may reflect optical causes of amblyopia, or bilateral dysregulation of globe shape secondary to amblyopia.

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Contribution to authors: design of study (SP, JD), conduct of study (SP, JD), data collection (SP, JD), data management (SP, JD), data analysis (SP, JD), data interpretation (SP, JD), preparation and review of manuscript (SP, JD)

This study was approved by the University of California, Los Angeles Institutional Review Board, and was in compliance with HIPAA and adhered to the Declaration of Helsinki and all federal and California state laws.

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Introduction

Amblyopia is a disorder causing reduction in best-corrected visual acuity in one or both eyes that cannot be attributed to the direct effect of a structural abnormality of the visual pathway. Amblyopia is believed to be caused by abnormal visual experience early in life due to strabismus, anisometropia, bilateral high refractive errors, or visual deprivation. Although the presence of amblyopia is usually associated with a structurally normal globe, several studies have challenged this concept with the proposal that in amblyopia there may exist sub-clinical abnormalities anterior to the striate cortex.¹⁻⁸ Although most authors accept Weisel and Hubel's⁹ classic animal evidence that the visual cortex is the main site of the defects associated with deprivation amblyopia, other authors have shown evidence supporting a different mechanism of visual loss in anisometropic and strabismic amblyopia.¹⁻⁸ In addition, autopsy studies have failed to demonstrate shrinkage of ocular dominance columns in humans with anisometropic and strabismic amblyopia.^{10, 11}

In a series of photographic studies,²⁻⁷ Lempert has asserted that eyes presumed amblyopic actually have abnormal appearing disks ("dysversion"), as well as abnormally small optic disks, axial length (AL), and an abnormally large ratio of AL to optic disk area (DA) compared to both the sound fellow eye and to normal controls. Lempert's claim of smaller optic disks in amblyopia is contradicted by several studies utilizing optical coherence tomography (OCT) or scanning laser polarimetry that failed to show a significant difference in optic nerve size or retinal nerve fiber layer (rNFL) thickness between amblyopic and control eyes.^{1, 12-17}

The mainstays of amblyopia therapy, occlusion and optical penalization of the dominant eye, are predicated on the assumption that the amblyopic eye's visual function is not limited by structural abnormalities in the visual pathway. If Lempert's postulate is correct that many presumed amblyopic eyes instead have unrecognized structural abnormalities that reduce visual function, then the rationale for the standard prescription of occlusion or penalization for all cases of amblyopia would require fundamental reassessment. We therefore believed it important to test Lempert's postulate using other methods.

Recently, our laboratory demonstrated that quantitative high resolution magnetic resonance imaging (MRI) is a valid and sensitive method for measuring retrobulbar optic nerve size.¹⁸ Given the lack of conclusive evidence for abnormal optic nerve or rNFL thickness in amblyopia, we chose to use MRI to study characteristics of the retrobulbar optic nerve and the globe in a typical clinical population with unilateral amblyopia. Since prior studies have shown a correlation between AL and optic nerve size^{19, 20}, an attempt was made to decrease this confounding variable by calculating and comparing the AL to ON ratio (AL/ON) in addition to simply comparing ON cross-sectional area. Furthermore, given the well-known correlation between hyperopia and astigmatism with refractive amblyopia, we used the MRI images to evaluate axial length and globe shape.

Methods

Amblyopia was diagnosed by history and clinical examination, and was defined as a decrease in best corrected visual acuity not attributable to any clinically detected structural abnormality of the eye. Furthermore, an underlying amblyogenic factor, including strabismus, anisometropia (defined as $\geq 1.5D$ difference in spherical equivalent or cylinder), or both, was required to be present. Visual acuity was measured monocularly using appropriate refractive correction using computer-presented single lines of high-contrast, black on white Snellen optotypes containing five letters per line, and incremented by a uniform 20% difference in size corresponding to a 0.1 logMAR increment. Refractive error was determined based on cycloplegic retinoscopy using a streak retinoscope with 67 cm working distance.

Control subjects consisted of healthy normal volunteers, as well as strabismic patients who had binocularly normal and equal corrected visual acuity, and who had no history of anisometropia. Subjects were excluded if they had any history of ocular surgery, known neurologic defects, or bilateral amblyopia. Amblyopic and control subjects had similar ages (Table). Nearly all amblyopic subjects had undergone treatment with spectacles and occlusion therapy during childhood. Although there were no specific inclusion or exclusion criteria related to age, subjects had to be deemed capable by the investigators of undergoing magnetic resonance imaging (MRI) without sedation.

Sixty normal and 34 amblyopic subjects were enrolled prospectively, and imaged by MRI, using an array of surface coils embedded in a face mask (Medical Advances. Sets of 17 to 18 contiguous quasicoronal images, 2 mm in thickness were obtained using a T1 pulse sequence (repetition time of 400 - 425 ms, echo time of 20-25 ms) encompassing a 256×256 matrix over a field of view (FOV) of 8 cm^2 ($312 \mu\text{m}$ resolution), except in 8 subjects in which a 6 cm^2 FOV ($234 \mu\text{m}$ resolution) was employed.

Images were analyzed using *Image J* (National Institutes of Health, Bethesda, MD). Quantitative analysis was performed only on images free of motion artifact. For each subject, the quasi-coronal image plane immediately posterior to globe-optic nerve junction (Fig. 1A) and the axial image plane passing closest to globe center (Fig. 1B) were analyzed. Using the quasi-coronal image, the optic nerve (ON) was outlined within the dural sheath using the digital cursor in *Image J*. This outline was used to compute ON cross-sectional area. Using the axial image, the globe was outlined using the digital cursor in *Image J*. This outline was used to fit an ellipse and compute the major and minor axes. In addition, the digital cursor was used to approximate a line from the posterior surface of the cornea to the retina, which represented axial length (AL).

The mean ON cross-sectional area, AL/ON, globe non-circularity (ratio of major axis/minor axis), AL, and spherical equivalent were compared between amblyopic eyes and fellow eyes (primary study outcome), as well as with control eyes using a paired Student's t-test ($\alpha = 5\%$). An anisometropic index was calculated for the amblyopic and control patients, using the previously described formula:²¹

$$I_a = \sqrt{(S_1 - S_2)^2 + (S_1 - S_2)(C_1 - C_2) + 3/8(C_1 - C_2)^2 + (C_1 - C_2)/2\sin^2(AL_1 - AL_2)},$$

Where S_1 is the spherical power of the first eye, S_2 is the spherical power of the second eye, C_1 is the cylindrical power of the first eye, and C_2 is the cylindrical power of the second eye. An I_a value of 1.5 or greater was considered to represent significant anisometropia.

After the results were analyzed, retrospective power calculations were performed in any subgroups of patients in which no significant differences were found, in order to determine the sufficiency of our sample size. Prospective power calculations were not used, as there was no data on the standard deviation or variance of the parameters which we measured. Power calculations were done using a two-tailed test, with $\alpha=0.05$ and $\beta=0.20$.

Results

Thirty-four amblyopic patients and 60 control patients were identified. The amblyogenic factor was strabismus in 9 (26%), anisometropia in 6 (15%), and a combination of anisometropia and strabismus in 19 (59%) amblyopic subjects. Within the anisometropia group, 5 patients were anisometropic hyperopes, whereas 1 patient was an anisometropic myope. Within the mixed mechanism group, 16 patients were anisometropic hyperopes, and 3 patients were

anisometropic myopes. The Table presents amblyopic subject characteristics including age, visual acuity, spherical equivalent, and anisometropia index. There was no significant difference in mean age (32 ± 17 years vs. 36 ± 19 years) between amblyopic and control subjects, respectively.

Mean corrected logMAR visual acuity in amblyopic eyes (0.43 ± 0.30) was significantly worse than acuity in both fellow (0.01 ± 0.09) and control eyes (0.03 ± 0.1). Spherical equivalent refractive error did not differ significantly between amblyopic, fellow, and control eyes. However, since the standard deviation of the spherical equivalent for each group was relatively large, population skewness was calculated. All 3 distributions were negatively skewed, with skewness values of -1.9, -0.5, and -0.75 in amblyopic, fellow, and control eyes, respectively. This negative skewness indicates that more than half of each population had spherical equivalents larger than the mean.

The ON cross-sectional area, plotted in Fig. 2, was not significantly different between amblyopic ($9.7 \pm 2.4 \text{ mm}^2$) and fellow ($9.5 \pm 2.3 \text{ mm}^2$) eyes ($p=0.25$). However, there was a significant difference between both the amblyopic and the fellow eyes, when compared to control eyes ($10.7 \pm 2.6 \text{ mm}^2$; $p=0.02$ and $p=0.1$, respectively). The AL/ON ratio followed a similar trend (Fig. 3), with the amblyopic ($2.7 \pm 1.2 \text{ mm}^{-1}$, $p = 0.01$) and fellow (2.7 ± 1.0 , mm^{-1} , $p < 0.01$) eyes significantly different from control eyes ($2.3 \pm 0.5 \text{ mm}^{-1}$), but not from each other ($p = 0.5$). Globe non-circularity (Fig. 4) was also not significantly different between amblyopic (1.17 ± 0.07) and fellow (1.15 ± 0.06) eyes, but both groups differed significantly from control eyes (1.11 ± 0.04 , $p < 0.01$ for both groups). The AL was $23.8 \pm 1.6 \text{ mm}$, 24.1 ± 1.5 , and 23.8 ± 1.3 for the amblyopic, fellow, and control eyes, respectively; there was no significant difference of AL among the groups.

Amblyopic subjects were evaluated in subgroups based on amblyogenic factor, including strabismus ($n = 9$), anisometropia ($n = 6$), and combined anisometropia with strabismus ($n = 19$). The numbers of patients with purely strabismic and purely anisometropic amblyopia were small. However, the group with combined anisometropic and strabismic amblyopia was relatively large, and reflected statistically significantly greater than normal AL/ON (amblyopic: $2.9 \pm 1.5 \text{ mm}^{-1}$, fellow: $3.1 \pm 1.2 \text{ mm}^{-1}$, control: $2.3 \pm 0.5 \text{ mm}^{-1}$) and non-circularity (amblyopic: 1.17 ± 0.06 , fellow: 1.16 ± 0.07 , control: 1.11 ± 0.04) in both the amblyopic and dominant eyes ($p < 0.03$ for all comparisons). In the anisometropic group, five of the subjects had a smaller ON and larger AL/ON than the control eyes means. The sole patient whose ON was larger than the control mean was hyperopic anisometropia.

Retrospective power calculations were done for subgroups in which no significant differences were found (pure anisometropic and pure strabismic amblyopia). In order to have sufficient power ($\alpha=0.05$, $\beta=0.20$) to conclude absence of significant ($>10\%$) difference between amblyopic and fellow eyes, required sample size for the two respective groups would be 35 and 36 subjects for ON, 48 and 14 subjects for globe circularity, and 97 and 190 subjects for AL/ON. Therefore, the present study lacked power to reach conclusions concerning possible significant differences exceeding 10% in pure anisometropic or pure strabismic amblyopia. Statistical power was adequate for the overall amblyopic population and “mixed” amblyopic groups to rule out significant differences between amblyopic and fellow eyes for ON, circularity, and AL/ON.

Discussion

The contemporary concept of amblyopia is a disorder arising not in the eye or anterior visual pathway, but as a result of aberrant neural plasticity in the cerebral cortex.²² Thus, modern therapies for amblyopia emphasize chronic manipulation of visual experience to reduce

competitive interocular interactions and promote central processing of visual afferent information from the amblyopic eye. Fundamental to the current clinical understanding of amblyopia is the presumption that vision in the amblyopic eye is not limited by structural abnormality of the eye or anterior visual pathway, such as the ON.

Previous studies have conflicted regarding ON size in amblyopic and fellow eyes. In several photographic studies, Lempert has characterized the ON to be smaller in amblyopic than in sound fellow eyes, motivating his postulate that amblyopic eyes have decreased visual acuity due to ON hypoplasia and reduced innervation of retinal areas, resulting in enlarged retinal receptor fields.²⁻⁷ Lempert theorizes that decreased vision in presumed amblyopic eyes is due to an asymmetric defect in neuro-retinal development due to a gestational insult. Lempert proposed that this putative insult initiates developmental cascades that not only cause asymmetric ON hypoplasia, but also impair development of binocular interactions and the normal feedback mechanisms influencing ocular growth, leading to strabismus and anisometropia.⁷ While Lempert's proposal is provocative, several OCT studies of amblyopic ON size have detected very few statistically significant differences in ON size or retinal nerve fiber layer (rNFL) thickness.^{1, 8, 12-17} Furthermore, in studies which did show differences, Yen *et al.*⁸ found that amblyopic eyes had significantly thicker rNFL than fellow eyes, while Repka *et al.*¹⁷ and Colen *et al.*¹ found the amblyopic ON to be non-significantly smaller, with a non-significantly thinner rNFL.

Lempert's challenge to conventional thinking about amblyopia is quite fundamental, as the rationale for occlusion therapy would be undermined if asymmetric structural ON abnormalities were determined to be the etiology of presumed amblyopic visual loss in even a significant minority of cases. Our study addressed this controversy by employing high-resolution surface coil MRI to characterize the ON, globe shape, and AL in amblyopic and fellow eyes. Although MRI is different than optic disk photography, both techniques evaluate optic nerve size directly, and measure a portion of the disk that is constituted predominantly of axons and a small amount of connective tissue. The validity of MRI measurement of ON size, and the relative predominance of axons over connective tissue in the retrobulbar ON, have been verified by quantitative histology and MRI in cadaveric specimens.¹⁸

The results of the present study demonstrate a symmetric bilateral reduction in ON size, AL, and AL/ON ratio in amblyopic subjects. Although all of these parameters were significantly different from normal control eyes, there were no statistically significant differences between amblyopic and fellow eyes in amblyopia subjects. Furthermore, the small differences in ON size detected in this study are probably not clinically significant, since in several congenital cranial dysinnervation disorders studied by similar MRI technique, even statistically significant ON hypoplasia was associated with little or no reduction in visual acuity. In 8 eyes with Duane's radial ray syndrome having normal mean acuity (-0.02 logMAR), mean ON cross section was 8.90 ± 0.44 , not significantly smaller than the control group in that study, but slightly smaller than both amblyopic and fellow ONs in the current study.²³ In 16 eyes with dominant Duane syndrome linked to chromosome 2 (DURS2) having normal mean acuity (0.04 logMAR), mean ON cross section was 6.85 mm^2 , significantly smaller by about 25% than normal control in that study.²⁴ In congenital fibrosis of the extraocular muscles type 1 (CFEOM1), a 30 - 40% mean reduction in retrobulbar ON cross section (6.7 mm^2 immediately retrobulbar) was associated with 0.3 mean logMAR acuity, even in severely ophthalmoplegic eyes frequently affected by exposure keratopathy.²⁵ Taken together, these studies suggest that ON size does not limit visual acuity if ON cross section is at least 75% of normal. It deserves mention that the smallest ON cross sections in the present study were in normal fellow eyes of amblyopic subjects, and that a normally sighted control subject had a smaller ON cross section than that of the most severely amblyopic eye (Figure 1).

Our finding of abnormally small ON size, AL, and AL/ON supports a claim of Lempert. These findings crucially demonstrate the sensitivity of our MRI method to the foregoing abnormalities, making the additional negative findings persuasive. Importantly contradicting Lempert, however, is the present failure to demonstrate significant differences between amblyopic and fellow eyes in our general amblyopic population, or in any amblyopic subgroup. Therefore, we cannot attribute the asymmetrically decreased visual acuity in our amblyopic subjects to sub-clinical ON hypoplasia.

Lempert has recently expanded his thesis by demonstrating an increased ratio of retinal to ON area in amblyopic versus sound fellow eyes; he theorized that a higher retinal surface area to ON area ratio in amblyopes results in an “expanded retinal receptor area” that might explain abnormalities in visual field, contrast sensitivity, and motion detection.⁶ Lempert's reasoning assumes equal photoreceptor density in hyperopic and myopic eyes. This concept has been indirectly verified by several histopathologic studies that have demonstrated increased retinal photoreceptor and nerve fiber counts in eyes with larger optic discs.²⁶⁻²⁸ In addition, large optic discs have been correlated with larger AL.^{19, 20} However, these relationships are not clearly linear; and furthermore, to extrapolate these findings to amblyopia, it must be assumed that decreased photoreceptor and nerve fiber counts correlate linearly with decreased visual acuity. Lempert estimated retinal area assuming the retina forms a perfect sphere with diameter related to AL.⁶ Statistically, such an approach amounts only to a square law weighting of AL that fails to account for photoreceptor spacing, peripheral retinal stretching, or globe non-circularity. Despite collecting similar primary data, we did not consider Lempert's retinal area estimation method to be adequately justified to employ in the present analysis.

Amblyopic and fellow eyes in our study both demonstrated reduced globe circularity. Since anisometric astigmatism is a known cause of amblyopia, this finding might at first glance appear to reflect an optical cause of amblyopia, except that the non-circularity was similarly present in the dominant fellow eye. Alternative etiologies are therefore implicated. One possible explanation is a secondary bilateral dysregulation of globe shape resulting from, but not causing, the amblyopia. Also possible might be a developmental insult that not only predisposes to anisometropia or strabismus, but also affects both ONs, and the development of both globes, as postulated by Lempert.⁷

Functional abnormalities in the “sound” fellow eye of amblyopic patients are well recognized. For example, contrast sensitivity was found by Leguire *et al.* to be abnormal in both the amblyopic and fellow eyes of untreated amblyopic patients.²⁹ Giaschi, *et al.*³⁰ demonstrated degraded motion detection in clinically unaffected eyes of amblyopic children. This subtle functional defect might reflect mild but bilateral ON hypoplasia in amblyopia.

Limitations of the present study deserve consideration. While the diagnosis of amblyopia was made clinically by an experienced pediatric ophthalmologist, as for any patient there always exists the possibility of undetected structural lesions not involving the ON. This limitation is generically applicable to all studies of human amblyopia. Although we have histologically validated MRI as a tool to measure retrobulbar ON size,²³ MRI resolution is less than that of OCT and some forms of digital photography. However, unlike photographic methods, MRI is free from inaccuracy induced by refractive error and other optical factors. Both photography and MRI include both ON axons and connective tissue, while OCT can directly measure the peripapillary retinal nerve fiber layer contribution to the ON.

The amblyopic population studied here included strabismic, anisometric, and combined etiologies. “Pure” etiologies of amblyopia (especially strabismic) are rarer than those with combined strabismus and anisometropia²⁸, and therefore are difficult to enroll in significant numbers for studies. The current group of amblyopic subjects was recruited over multiple years

from an academic practice specializing in pediatric ophthalmology and strabismus, and has the merit of reflecting a realistic clinical sample of amblyopic patients. To recruit an adequate sample of patients with purely strabismic and purely anisometropic amblyopia for MRI studies would require a resource-intensive, multi-center effort. However, the findings are statistically significant in the general and mixed amblyopic population, and strongly suggest that ON size is not the factor that determines which eye will become amblyopic in affected patients.

Although our study supports the finding of statistically subnormal retrobulbar ONs and abnormal globe shape in both eyes of patients with unilateral amblyopia, these parameters did not differ significantly between amblyopic and fellow eyes. Optic nerve size and globe shape therefore do not determine which of the two eyes becomes amblyopic, and do not directly cause the visual acuity deficit in amblyopia.

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Biographies

Stacy L. Pineles, MD, graduated from the University of Pennsylvania of Medicine. She then completed a residency at the Jules Stein eye Institute at UCLA in opnthalmology. After finishing a fellowship in Pediatric Ophthalmology and strabismus at UCLA in 2009, she will be a fellow in Neuro-Ophthalmology at the scheie Eye Institute, University of Pennsylvania.

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Figure 1. Representative MRI images utilized to measure optic nerve cross-section and globe circularity in patients with unilateral amblyopia and controls (* $p < 0.05$).
A. Representative quasi-coronal MRI used to measure optic nerve cross-section within the dural sheath, **B.** Representative axial MRI used to measure axial length and globe circularity.

Figure 2. Box plot of mean optic nerve cross sectional area in the amblyopic and fellow eyes of patients with unilateral amblyopia and control eyes (* $p < 0.05$). Optic nerves in amblyopic and fellow eyes were significantly smaller than control eyes ($p = 0.02$, 0.01 , respectively). There was no statistically significant difference between amblyopic and fellow eyes ($p = 0.25$).

Figure 3. Box plot of mean ratio of optic nerve cross-sectional area to axial length in the amblyopic and fellow eyes of patients with unilateral amblyopia and control eyes (* $p < 0.05$).

Amblyopic and fellow eyes had significantly larger ratios than control eyes ($p = 0.01$, < 0.01 , respectively). There was no statistically significant difference between amblyopic and fellow eyes ($p = 0.5$)

Figure 4. Box plot of mean globe non-circularity (major axis/minor axis of globe) in the amblyopic and fellow eyes of patients with unilateral amblyopia and control eyes. Amblyopic and fellow eyes were significantly less circular than control eyes ($p < 0.01$ for both groups). There was no statistically significant difference between amblyopic and fellow eyes ($p = 0.25$)

Table 1
Subject Characteristics in study of optic nerve size and globe shape in patients with unilateral amblyopia.

	Amblyopic Eyes (n=34)	P-value	Fellow Eyes (n=34)	P-value	Control Eyes (n=119)
Age (years)	32±17	----		0.4	36±19
Visual acuity (logmar)	0.43±0.3	< 0.001	0.01±0.09	0.3	0.03±0.1
Spherical Equivalent (diopters)	-1.3±6	0.8	-1.0±4	0.7	-1.0±2
Anisometropia Index	2.6	----	----	<0.01	0.4