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Amblyopia and Foveal Thickness

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1. Introduction

1.1 Definition

Amblyopia in Greek is dullness of vision. It is defined as poor unilateral or bilateral visual acuity due to poor perception in the presence of normal appearing globe.[1] It is caused by poor visual perception during the critical postnatal period required for maturation of the visual pathways and cortex. Clear and corresponding image is required for visual system development in animals including primates.

1.2 Epidemiology

The prevalence of amblyopia in the general population is probably between 2 and 2.5%. The wider range of 1-4% reflects differences in the degree of amblyopia, the studied population and the location. These figures represent the average of the prevalence in the different studies. The frequency of disorder has a socioeconomic impact. These patients have a greater risk for legal blindness if the fellow eye develops a blinding condition or sustain trauma. Indeed, patients with amblyopia as monocular patients are at a greater risk for trauma in the fellow eye although their visual field may be full.

1.3 Development of the visual system

The postnatal visual system development differs in different animals. In humans, the visual acuity improves usually until the age of 5 and this reflects the maturation of both the retina and the visual pathways.[2] The most critical period for amblyopia is the first 2 to 3 years of life.[1] The sensitivity of the visual system to abnormal perception is decreasing gradually afterwards. One should distinguish between the period when amblyopia may develop, which is until 9 years of age (although in most patients, it appears by the age of 5) and the period in which it is treatable, probably until the age of 17.[3]

1.4 Classification

Amblyopia is a result of three mechanisms: deprivation (obscuration of the image on its way to the retina (i.e., ptosis and media opacities), strabismus and refractive (anisometropic

or isoamteropic) all causing blurred or non-corresponding images on the fovea.[1] The pathophysiology common to all of these is abnormal binocular interaction and/ or vision deprivation. Strabismic amblyopia occurs in the non-fixating eye and is always unilateral. It occurs in tropia and is more common in esotropia than in exotropia and indeed esotropia is neonatal while exotropia may be neonatal or acquired later in life. It is caused by signaling inhibition of the deviating eye to avoid confusion because of different foveal images between the eyes. Strabismic amblyopia is applied only to cases where the amblyopia is a result of strabismus and not vice versa. In refractive amblyopia, signaling inhibition of the blurred image occurs and in deprivation, there is usually no image. Anisometropia of +2.00, -3.00 and astigmatism of 1.5D or more are associated with amblyopia. The presence of astigmatism causes amblyopia in the astigmatic meridian called meridional amblyopia. Isoametropia of +4.00, -8.00 and astigmatism of 2D or more are associated with bilateral amblyopia. Lesser amount of hypermetropia than myopia is associated with amblyopia because the inability to focus images on the fovea at any distance. While strabismic amblyopia and most of the anisometropic amblyopia are unilateral, isoametropic and some of the deprivative amblyopia are bilateral. Deprivative amblyopia is usually the most profound and most resistant to treatment of all three forms of amblyopia. If it is present in the first 3 months, irreversible nystagmus develops. The unilateral cases are usually the worst.

2. Clinical manifestations

The visual acuity is poorer in the amblyopic eye than in the fellow eye or than in normal eyes and cannot be corrected to full with spectacles or contact lenses. A poorer visual acuity is considered if the visual acuity is less in two Snellen lines or more. Differences in one line may just be fluctuation and within the normal deviation and this is true not only for amblyopia but for all other instances as well. The subject uses the fellow better eye for fixation. The patient sees single signs on the Snellen chart better than several signs in a row (crowding phenomenon or abnormal contour interaction). This is caused by larger receptive fields (larger group of photoreceptors working as a single unit) and lateral inhibition by adjacent fields on the fixating field. Under dim light, the visual acuity decreases in both eyes but the visual acuity of amblyopic eye becomes similar to the normal eye. Thus the decrease in visual acuity is slower in the amblyopic eye than in a normal eye. The use of neutral density filters decreases the visual acuity in the amblyopic eye in much lesser extent compared with eyes with other diseases. In addition, amblyopic eyes have decreased contrast sensitivity, perception of brightness and have longer reaction time.

Other parameters are normal and similar to normal eyes including light perception (visual threshold) and visual field. An afferent pupillary defect is not supposed to occur but is a variable finding.

3. Treatment

Bilateral amblyopia is treated by eliminating the cause of blurred image (removal of the deprivation cause, strabismus surgery or refractive error correction). Unilateral amblyopia is treated similarly along with periodical patching or other penalization of the fellow sound eye. Penalization of the sound eye is usually performed by instilling once drop of atropine sulfate 1% one a day at bedtime. This causes cycloplegia and blurred image in the sound eye and forces the visual system of the amblyopic eye to act. Treatment should be initiated immediately when the condition is diagnosed. The elimination of the deprivative obstacle should be performed as early as possible (usually 2-3 weeks after birth). In strabismic

amblyopia, anti-amblyopic treatment is initiated when the condition is diagnosed long before the surgery for strabismus. The reasons for this are improving the possibility to gain binocular vision if visual acuity is improved, easiness to determine the fixation patters, and the strabismus serves as a reminder to the parents on the importance of treatment. Surgery is performed only after achieving alternating fixation and equal visual acuity.

The length of patching or other penalization depends on the severity of the amblyopia. It is increased in direct proportion with the degree of the amblyopia. The follow-up frequency is also increased as the length of patching increases. Amblyopia is more easily reversible if it occurs later (ages 6-9) than earlier in life. Improvement of visual acuity should be both in single and multiple signs on Snellen chart and should be permanent. However, regression may occur and requires re-treatment.

Occlusion may be for full-time (all the day) for several days with one day off, or part time (several hours per day). Full-time occlusion is preserved for severe amblyopia with no binocular vision such as deprivative amblyopia. Full-time occlusion should not exceed one week per one year of age. Part-time treatment is preferred according to the Pediatric Eye Disease Investigator Group (PEDIG) studies because it has a similar outcome as full-time occlusion with less risk for development of amblyopia in the normal fellow eye, especially in the presence of binocular vision and mild amblyopia. Six hours per day of occlusion are sufficient for severe amblyopia of less than 20/100 and 2-3 hours per day for moderate one (better than 20/100). Contact lenses may be employed in anisometropia of more than 3.00D to prevent aniseikonia. However, this is more demanding treatment. Bilateral amblyopia in isoammteropia is usually not treated with occlusion and improves slowly spontaneously once refractive correction has been applied. In all cases, it is essential to rule out the development of amblyopia in the sound eye during treatment.

Obtaining compliance is difficult especially at the beginning of the treatment. The compliance becomes better as visual acuity of the amblyopic eye improves. Children try to remove or pick through the occluder. Therefore, it is better to use eye drops as penalization or a skin sticker rather than a sticker to the eyeglass. A full cooperation is required from the parents. They should be insisting on meticulous treatment for the full period. It is best to occlude when the child is at home under supervision of the parents and to occlude when the child is performing near tasks such as reading or doing homework. A close follow-up is required to ascertain improvement in visual acuity of the amblyopic eye and prevention of developing amblyopia in the fellow eye. In general, the follow-up intervals are one week per each year of life (e.g., a 2-year-old child is followed every 2 weeks). The follow-up includes visual acuity in each eye with full cycloplegic correction after refraction. If the visual acuity decreases, the reason for it should be disclosed. If the correction is not sufficient, it should be adjusted accordingly. If it is sufficient, an adjustment of the anti-amblyopic treatment should be performed. The length of occlusion is gradually decreased if the visual acuity improves to the desired level and no regression is observed in follow-up visits. Occlusion is gradually tapered according to the patient's response. Gradual decrease in occlusion time has been demonstrated to be associated with less recurrence rate than abrupt determination. If regression is noted, the treatment is re-initiated and continued over the vulnerable period (up to the age of 17). Follow-up until the age of 17 is necessary even if the optimal results have been achieved. Recurrence occurs in up to 75% of the patients usually within the first 13 months.[4] If treatment has not been successful after several (usually 6) months, it may be abandoned and visual function will not improve thereafter.

In animal models, L-dopa and bicuculline have been demonstrated to reverse amblyopia.

However, they have not been used in humans because the first one showed only a temporary effect and the second can cause seizures.

4. Prevention

Prevention of amblyopia is of outmost importance. Screening of red reflex at birth should be done to all neonates. Screening programs at preschool and school children are also important.

5. Background

To date, no changes in gross anatomy of the eye were found in the human amblyopic eye. When optical coherence tomography (OCT) was employed to evaluate the overall macular thickness, volume and the retinal nerve fiber layer (RNFL) thickness, it was found that all were similar in one study between strabismic amblyopic and the fellow eyes in 14 patients.[5] Another study did report thicker RNFL in amblyopic eyes than in normal fellow eyes.[6] When the differences in RNFL thickness were compared between amblyopic eyes and normal eyes of other subjects, they were found to be statistically insignificant.[7] In this study, the foveal thickness in the amblyopic eyes was similar to normal control eyes ($p=0.551$), but the authors did not compare it with the normal fellow eye. It would be expected that any differences in the anatomy in vivo between amblyopic and normal eyes would be microscopic. One should also consider the reproducibility of the OCT and the normal variations between normal eyes at different ages. Therefore, to show differences, a comparison should be made first with the fellow normal eye in unilateral amblyopia.

We compared the foveal thickness of amblyopic eyes with the fellow normal eye by OCT. Furthermore, we compared the foveal thickness of amblyopic eyes that underwent successful occlusion therapy with amblyopic eyes refractory to treatment. Such a study has not been previously reported according to Medline® search. The rationale for the current study was that even if the gross anatomy is normal, subtle structural variations such as foveal hypoplasia might exist.

6. Methods

In a prospective study, we compared the foveal thickness of amblyopic eyes with the fellow normal eyes in unilateral strabismic and anisometropic amblyopia by OCT (spectral OCT/SLO, OTI, Ophthalmic Technologies, Toronto, Canada). The inclusion criteria included best-corrected visual acuity (BCVA) of 20/80 or less in the involved eye, BCVA of 20/25 or better of the fellow eye, normal eye exam of each eye and no explanation for the low visual acuity except for amblyopia, presence of one of the causes for amblyopia (anisometropia of more than –3.00D or more than +1.00D, or strabismus), no other ocular, neurologic or systemic disorders, and children between 4 and 10 years of age who can undergo OCT and be treated for amblyopia and that followed the treatment orders. All other patients were excluded from the study. Ocular and general medical history were obtained and the patients underwent a complete ophthalmic examination of each eye including visual acuity by Snellen charts, pupil reactions, slit lamp examination, dilated funduscopic examination with a slit lamp biomicroscopy and indirect ophthalmoscopy.

All eyes were analyzed by OCT. Measurement was performed at the thinnest point of the macular center, representing the fovea. Several topographic 3D, linear and radial scans were

obtained. The acceptance criteria of OCT included a central reflex, signal strength of at least 4 and standard deviation of the foveal thickness of less than 10% of the mean for each individual.

Amblyopic patients with refractive errors were treated by refractive full cycloplegic correction. Amblyopic patients with strabismus underwent strabismus surgery. All patients underwent occlusion (patching) therapy of the sound eye at least 6 for months and were followed according to previous recommendations.[3,8-10] Successful treatment was defined as an improvement in visual acuity in the amblyopic eye in at least 2 Snellen lines. The follow-up time ranged between 12 and 54 months.

Statistical analysis was performed with SPSS version 11.5 program (SPSS Inc., Chicago, IL, USA). Paired sample T-test was used for samples larger than 15 and Wilcoxon signed rank test was employed for smaller samples. Two-tailed $p<0.05$ was considered as statistically significant. Approval by the IRB/Ethics Committee was obtained and the patients' parents received a full explanation about the exam.

7. Patients

Nineteen children aged 4-10 with unilateral amblyopia were included. Ten patients had anisometropic (refractive) and 9 had strabismic amblyopia. Eight patients had successful occlusion therapy, while the other 11 had unsuccessful treatment.

8. Results

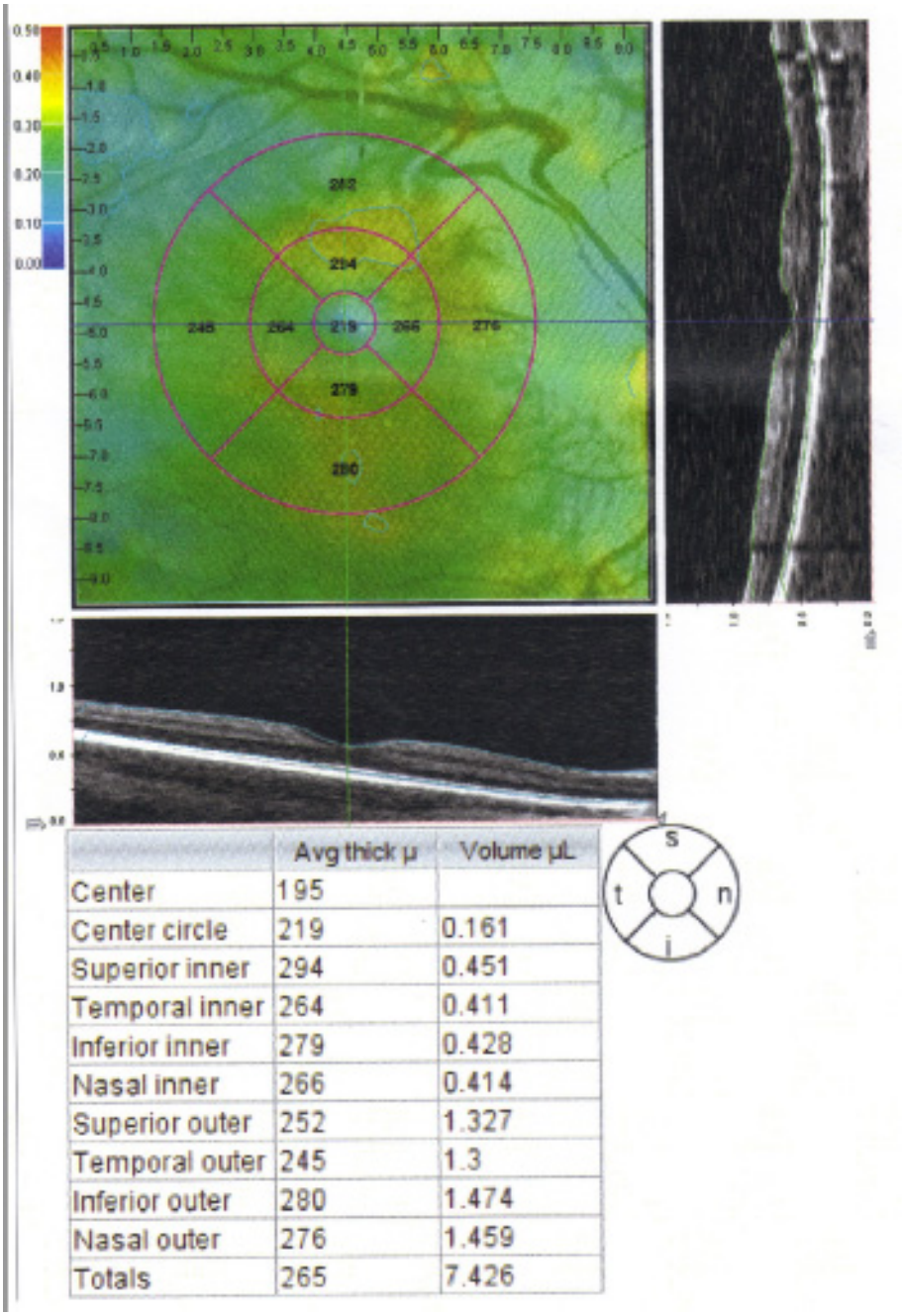
The foveal thickness in amblyopic eyes was 201±42 μm (average±SD) and in the normal fellow eyes 174±27 μm. The fovea was statistically thicker in the amblyopic eyes of whatever cause than in the normal fellow eye (p=0.011, paired sample T-test). The foveal thickness in eyes with anisometropic amblyopia (n=10) was 194±45 μm and in the fellow eyes of the same patients 167±23 μm (p=0.059, Wilcoxon signed rank test). The foveal thickness in eyes with strabismic amblyopia (n=9) was 210±39 μm and in the fellow eyes of the same patients 181± 30 μm (p=0.070, Wilcoxon signed rank test).

Eight (42%) of the 19 patients experienced improvement in BCVA after occlusion therapy. Six of the 8 had anisometropic and 2 had strabismic amblyopia. From the group of 11 (58%) patients that did not show improvement in BCVA, 4 had anisometropic and 7 had strabismic amblyopia (p=1.000). The foveal thickness in the patients who showed no improvement in BCVA after treatment was 216±41 μm and in their fellow eyes 176±31 μm (p=0.016, Wilcoxon signed rank test) (Table 1). In those who showed improvement, the foveal thickness in the amblyopic eyes was 181±36 μm and in their fellow eyes 171±21 μm (p=0.297, Wilcoxon signed rank test). Examples of the topographic 3-dimensional OCT maps of an amblyopic and normal fellow eye are seen in figures 1 and 2.

Parameter	Amblyopic eye	Fellow eye	P-value
Total (n=19)	**201±42**	**174±27**	**0.011**
Refractive (n=10)	**194±45**	**167±23**	**0.059**
Strabismic (n=9)	**210±39**	**181±30**	**0.070**
VA improvement (n=8)	**216±41**	**176±31**	**0.016**
No VA improvement (n=11)	**181±36**	**171±21**	**0.297**

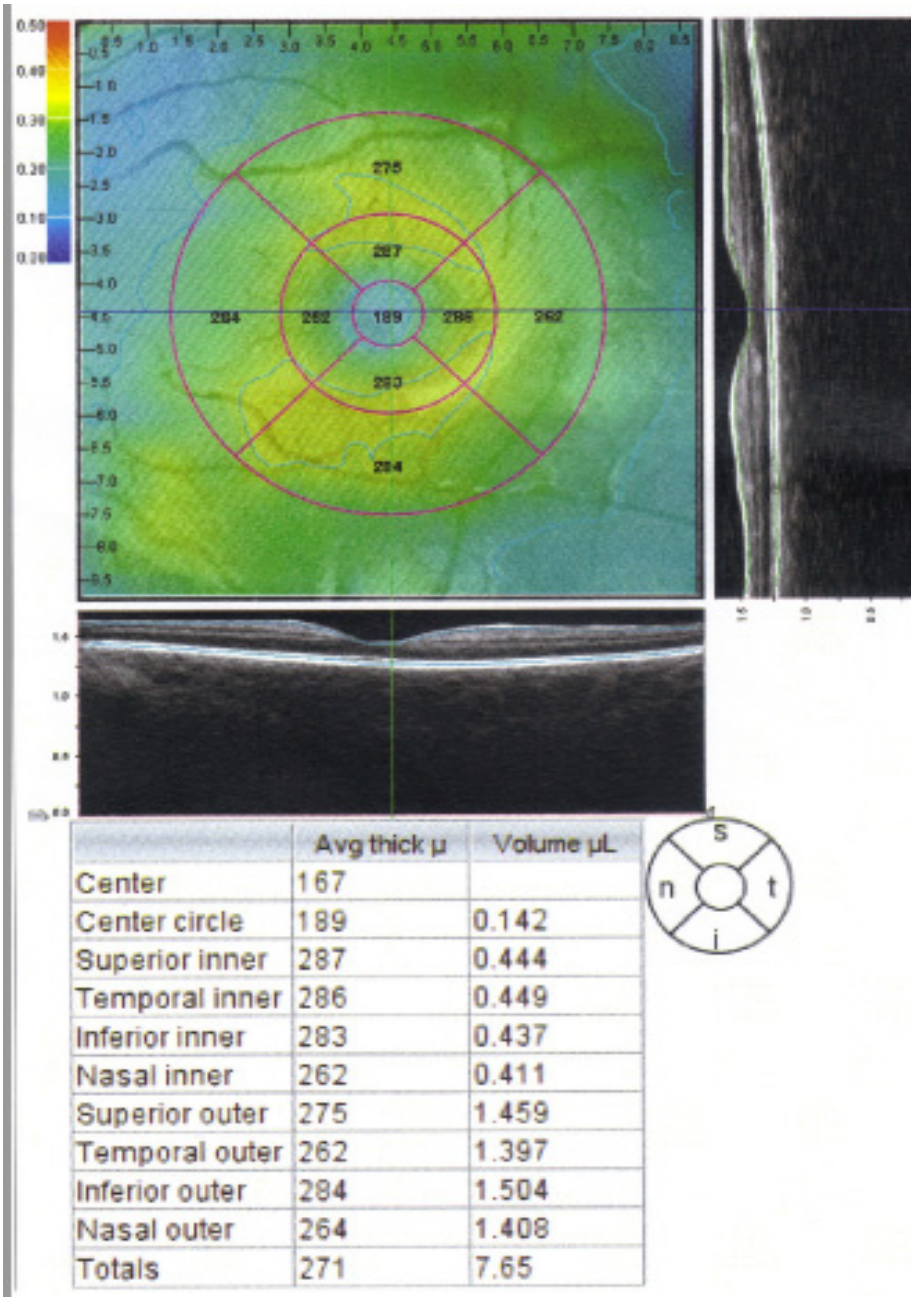
Mean±SD in μm

Table 1. The foveal thickness in μm as measured by optical coherence tomography in amblyopic versus the normal fellow eye.



	Avg thick µ	Volume µL
Center	195	
Center circle	219	0.161
Superior inner	294	0.451
Temporal inner	264	0.411
Inferior inner	279	0.428
Nasal inner	266	0.414
Superior outer	252	1.327
Temporal outer	245	1.3
Inferior outer	280	1.474
Nasal outer	276	1.459
Totals	265	7.426

Fig. 1. A topographic 3-dimensional OCT image of the right amblyopic eye of a 10-year-old boy that was refractory to treatment measured a foveal thickness of 195 µm.



	Avg thick µ	Volume µL
Center	167	
Center circle	189	0.142
Superior inner	287	0.444
Temporal inner	286	0.449
Inferior inner	283	0.437
Nasal inner	262	0.411
Superior outer	275	1.459
Temporal outer	262	1.397
Inferior outer	284	1.504
Nasal outer	264	1.408
Totals	271	7.65

Fig. 2. A topographic 3-dimensional OCT image of the left normal eye of the same patient as in figure 1 measured a foveal thickness of 167 µm. The fovea was thinner in this normal eye than the amblyopic eye.

9. Discussion

Amblyopic eyes are classically considered as having a normal structure.[1] The only changes that have been found were smaller parvocellular cells in layers II, III and V in the ipsilateral lateral geniculate body, layers I, IV and VI of the contralateral lateral geniculate body and reduction in the number of cells in the primary (striate) visual cortex V1 receiving input from the affected eye.[11,12] Reduction was noted in the number of cells receiving binocular input. An increase in the number of cortical cells responding to a contour orientation also occurs. Positron emission tomography demonstrated a reduced cortical activity under visual stimulation of the amblyopic eye.[13]

We found that in the amblyopic eyes the fovea was thicker than in the normal fellow eyes. This was common both for anisometropic and strabismic eyes. Our finding is supported by a recent study in 3,529 children aged 6-12 years that found thicker fovea in amblyopic eyes than in the normal fellow eyes by 5μm.[14] These and our results differ from a recent evaluation of the foveal thickness that did not show statistically significant differences ($p=0.551$) of the foveae in patients with unilateral anisometropic and strabismic amblyopia compared with normal subjects.[7] Nonetheless, the authors did not compare the amblyopic eye with the normal fellow eyes and therefore, did not have an internal control. The differences between our study and the previous one probably relate to variability of foveal thickness in different individuals and indeed such differences were found between different individuals in our study and therefore the standard deviation between different individual was quite high.

Careful review of the OCT images indicated that the foveal thickening was due to either thicker outer retinal layers or immature retinal tissue. The structural feature of the foveae in amblyopic eyes is hypoplasia similar to albinotic and nanophthalmic eyes.[15-18] The fovea is thicker and flatter in these eyes. Since there are no histologic preparations of the retina in amblyopic eyes, it is impossible to determine the exact composition of the foveal area. However, in oculocutaneous albinism the retinal tissue was intact and the Bruch's layer was thickened in one specimen.[19]

We found that amblyopic eyes refractory to occlusion therapy had thicker fovea than those of the normal fellow eyes, while the differences in thickness between amblyopic eyes that responded to treatment and the fellow eyes were insignificant. This finding could have been different if patients and their parents would not be cooperative. No previous study addressed this issue and therefore we cannot compare our data with previous ones.

In our study, patients with anisometropic amblyopia had not statistical significant success of the occlusion therapy compared with patients with strabismic amblyopia. The differences in foveal thickness in the amblyopic and the sound fellow eyes in each group were not statistically significant although they were marginal in the amblyopic eyes of the anisometropic group. The higher number of anisometropic patients that underwent successful occlusion therapy might explain this tendency. A larger population will be required to confirm if the foveal thickness differs in these two groups and if the type of the amblyopia is the cause for different foveal thickness rather than treatment success. The higher success of occlusion therapy in anisometropic amblyopia than in strabismic amblyopia might be related to the thinner foveae in anisometropic patients. Thicker foveae were found in strabismic than in anisometropic amblyopia in another study as well ($p=0.046$).[7]

In our sample, the foveae of the amblyopic eyes were thicker than in the fellow normal eyes except for one in which the thickness was the same and another 3 with thicker normal fovea. Two of these patients experienced an improvement in BCVA after occlusion therapy. If in all future patients, the fovea of the amblyopic eye will be thicker than in the fellow normal eye, the foveal thickness may serve as a prognostic factor for improvement after proper therapy. To validate this, more patients should be recruited and a scale should be established for the measures that may predict improvement or non-improvement. It is possible that there will be patients in whom the fovea in the amblyopic eye would be thinner than in the normal fellow eye and would not experience an improvement in BCVA after treatment. In such event, it may not be possible to predict the success of a treatment based on the foveal thickness at least in those patients.

In patients with bilateral amblyopia, measurements of each fovea and a comparison with normal foveae will be needed. In such cases, the differences might be subtle as after comparing unilateral amblyopic eyes with normal controls and prediction of successful treatment may be difficult. According to our findings, it might be worthwhile to create a database for foveal thickness in the normal population according to age, since the foveal thickness may change with age.[20] In addition, a correlation between BCVA and foveal thickness might be established as well.

OCT measurements in children are demanding because of inattention, especially in children under age 4. In addition, amblyopic eyes tend to fixate less and if nystagmus is present, clear images may not be possible to obtain, unless the eye is mechanically fixated. We should also consider the accuracy and reproducibility of the OCT. When assessing thin layers as in the fovea, if the accuracy and reproducibility are not perfect, subtle differences may not be measured accurately, even if the image resolution is of 2μm. For macular thickness, OCT was found accurate and reproducible[21] and it is expected that with better technologies including high-resolution Fourier-domain OCT, this problem will be solved.

It will be interesting to verify our results in amblyopic adults and to find what is the foveal thickness in children that had regression after treatment. The last and the most intriguing issue is whether treatment influences the foveal thickness. Since the fovea, as well as other structures such as the lateral geniculate body and visual cortex, continue to develop after birth (the "critical" period), it is tempting to hypothesize that in successful treatment, the foveal thickness might also change.

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