Investigating the Relationship Between Foveal Morphology and Refractive Error in a Population With Infantile Nystagmus Syndrome

Natasha Healey,[1–3] Eibhlin McLoone,[2] Gerald Mahon,[2] A. Jonathan Jackson,[2,4] Kathryn J. Saunders,[1] and Julie F. McClelland[1]

[1]The University of Ulster, Vision Science Research Group, Coleraine, Northern Ireland
[2]The Royal Group of Hospitals, Ophthalmology Department, Belfast, Northern Ireland
[3]Altnagelvin Area Hospital, Ophthalmology Department, Altnagelvin, Northern Ireland
[4]Australian College of Optometrists, Carlton, Victoria, Australia

PURPOSE. We explored associations between refractive error and foveal hypoplasia in infantile nystagmus syndrome (INS).

METHODS. We recruited 50 participants with INS (albinism $n = 33$, nonalbinism infantile nystagmus [NAIN] $n = 17$) aged 4 to 48 years. Cycloplegic refractive error and logMAR acuity were obtained. Spherical equivalent (SER), most ametropic meridian (MAM) refractive error, and better eye acuity (VA) were used for analyses. High resolution spectral-domain optical coherence tomography (SD-OCT) was used to obtain foveal scans, which were graded using the Foveal Hypoplasia Grading Scale. Associations between grades of severity of foveal hypoplasia, and refractive error and VA were explored.

RESULTS. Participants with more severe foveal hypoplasia had significantly higher MAMs and SERs (Kruskal-Wallis H test $P = 0.005$ and $P = 0.008$, respectively). There were no statistically significant associations between foveal hypoplasia and cylindrical refractive error (Kruskal-Wallis H test $P = 0.144$). Analyses demonstrated significant differences between participants with albinism or NAIN in terms of SER and MAM (Mann-Whitney U test $P = 0.001$). There were no statistically significant differences between astigmatic errors between participants with albinism and NAIN. Controlling for the effects of albinism, results demonstrated no significant associations between SER, and MAM and foveal hypoplasia (partial correlation $P > 0.05$). Poorer visual acuity was associated statistically significantly with more severe foveal hypoplasia (Kruskal-Wallis H test $P = 0.001$) and with a diagnosis of albinism (Mann-Whitney U test $P = 0.001$).

CONCLUSIONS. Increasing severity of foveal hypoplasia is associated with poorer VA, reflecting reduced cone density in INS. Individuals with INS also demonstrate a significant association between more severe foveal hypoplasia and increasing hyperopia. However, in the absence of albinism, there is no significant relation between refractive outcome and degree of foveal hypoplasia, suggesting that foveal maldevelopment in isolation does not impair significantly the emmetropization process. It likely is that impaired emmetropization evidenced in the albinism group may be attributed to the whole eye effect of albinism.

Keywords: refractive error, albinism, optical coherence tomography, foveal hypoplasia, congenital nystagmus

Infantile nystagmus syndrome (INS) is an ocular motor condition, defined by an involuntary, rhythmic oscillation of the eyes.[1] Nystagmus may occur in isolation, known as idiopathic infantile nystagmus (IIN), or in association with other disorders affecting the visual system, such as albinism.[2–5] A large proportion of people with nystagmus have conditions that affect the fovea, including those with albinism, aniridia, microphthalmos, achromatopsia, PAX 6 mutations, and isolated foveal hypoplasia (IFH).[6,7] Advances in ocular coherence tomography (OCT) have allowed observation of retinal anomalies, such as foveal hypoplasia in vivo.[8,9] Assessing foveal structure, using standardized grading scales to classify severity of foveal maldevelopment, has been promoted as a method of investigating visual acuity potential in individuals with nystagmus of various etiologies.[7] In addition to foveal malformation, individuals with nystagmus typically have high refractive errors.[10–13] It has been suggested that the high astigmatic refractive errors associated with nystagmus are associated with the corneal molding effects of the ocular oscillations; however, the origin of high spherical refractive errors in nystagmus is not clear.[5,14] The use of grading scales to categorize foveal anomalies imaged using OCT is a novel way to explore associations between foveal structure and refractive error.

Our study aims to explore associations between refractive error and clinical grades of foveal hypoplasia in a population with nystagmus.

TABLE 1. Foveal Hypoplasia Classifications

Foveal Hypoplasia Grade	N Participants (%)		
	Total	Albinism	NAIN
0	8 (16)	0 (0)	8 (16)
1	6 (12)	0 (0)	6 (12)
2	0 (0)	0 (0)	0 (0)
3	18 (36)	15 (30)	3 (6)
4	18 (36)	18 (36)	0 (0)

METHODS

Participants

Our investigation formed part of a larger study exploring refractive error in a population with INS. We recruited 50 participants with nystagmus aged 4 to 48 years (median 15 years), including 24 females and 26 males (Table 1). Participants were identified and recruited via pediatric and adult low vision clinics at The Royal Group of Hospitals and Altnagelvin Area Hospital, Northern Ireland. Of the participants 33 (66%) were diagnosed with albinism and 17 (34%) were categorized with "nonalbinism infantile nystagmus" (NAIN). These 17 participants (NAIN) were a heterogeneous group of participants with idiopathic infantile nystagmus ($n = 8$) and isolated foveal hypoplasia or PAX 6 genetic mutations ($n = 9$); however, genetic testing was not available to confirm diagnoses. All diagnoses were made by the participant's Consultant Ophthalmologist and were recorded in hospital medical records. A diagnosis of albinism was confirmed by the presence of iris transillumination, foveal hypoplasia, nystagmus, and asymmetric visual evoked potentials. The NAIN group included eight patients with IIN (normal ocular examination and normal fovea on OCT) and nine patients with either isolated foveal hypoplasia or PAX 6 gene mutation (normal electrodiagnostic tests, no iris transillumination, OCT confirmed foveal hypoplasia). Unfortunately, genetic testing was not available to allow distinction between the latter two entities. Horizontal nystagmus was observed in 46 participants and rotatory nystagmus in four (NAIN) participants. Individuals with coexisting ocular or neurologic conditions were excluded. Informed consent was obtained from each participant (and parent where necessary). The research followed the tenets of the Declaration of Helsinki.

Procedure

Refractive error was determined with cycloplegic streak retinoscopy using one drop of 1% cyclopentolate hydrochloride (HCl). All cycloplegic refractions were performed by the
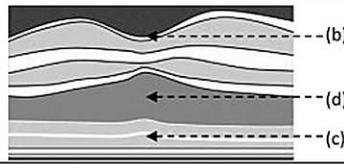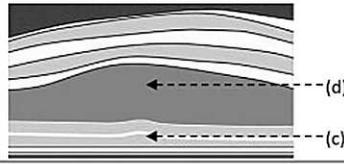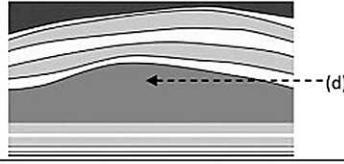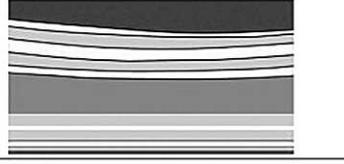

FIGURE 1. Foveal Hypoplasia Grading Scale.[7] Illustrations detail features of foveal hypoplasia detectable from an OCT retinal image. Progressive loss of typical foveal characteristics is represented by increasing grades. Grade 1 (*shallow pit*) indicates the least amount of foveal hypoplasia, with grade 4 representing the most affected/severest foveal hypoplasia (absent fovea). Image replicated with permission from Thomas MG, Kumar A, Mohammad S, et al. Structural grading of foveal hypoplasia using spectral-domain optical coherence tomography a predictor of visual acuity? *Ophthalmology*. 2011;118:1653–1660. Copyright 2011, American Academy of Ophthalmology.
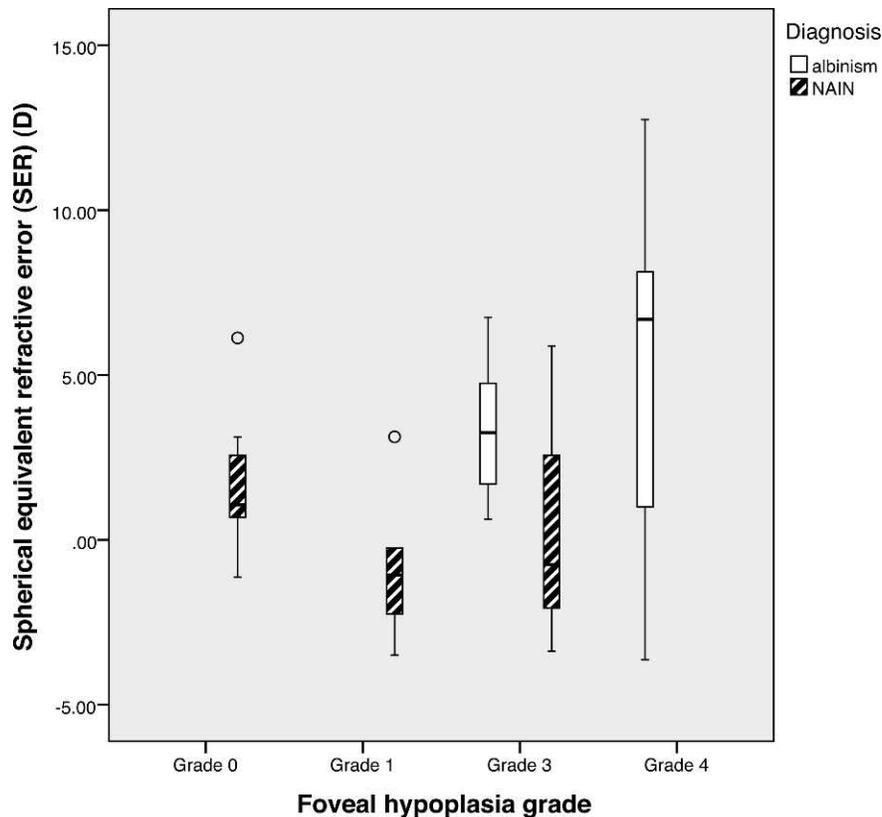
FIGURE 2. Foveal hypoplasia grade and SER. The *top* of the box represents the 75th percentile, the *bottom* of the box represents the 25th percentile, and the *middle line* represents the 50th percentile. The *whiskers* represent the highest and lowest values (excluding outliers). The *circles* represent outliers. Grade 1 foveal hypoplasia is significantly different from the other grades following post hoc analysis (Tamhane).

author (NH). Refractive error was recorded in conventional form, sphere, negative cylinder, and axis, and then converted into spherical equivalent (SER: sphere + 1/2 cylinder) for analysis. Most ametropic meridian (MAM) data also are presented. Best corrected monocular visual acuity (VA) was assessed using a Bailey-Lovie logMAR chart. Better eye data were used for analysis. In addition to refractions performed by NH, a subgroup of participants were refracted by AJJ, who confirmed the spherical and astigmatic corrections. Subjective refractions also were performed with older children and adults to confirm the astigmatic axes. NH and AJJ are optometrists with extensive experience in clinical optometric assessments of young children with low vision and, in particular, nystagmus.

OCT Image Acquisition

High-resolution spectral-domain OCT (SD-OCT) equipment was used to acquire tomographs from the participants. Two data collection centers were used and images were acquired using two different pieces of SD-OCT equipment: The Optovue SD-OCT (Optovue Inc., Fremont, CA) and Topcon 3D OCT-2000 System (Topcon Medical Systems, Inc., Oakland, NJ). Strict protocols ensured interequipment variability was kept to a minimum. Using a customizable raster scan, a 6×6 mm scan was imaged of the fovea area (5 µm axial resolution). The raster scan was composed of 17 parallel line scans (17×512 A scans, with 26,000 A scans occurring per second). Each raster scan took 0.34 seconds. Total foveal thickness (TFT) was calculated from one piece of equipment (Optovue SD-OCT; Optovue Inc.). Total foveal thickness was measured from the outer retina at the level of the RPE to the internal limiting membrane

ILM/retinal nerve fiber layer (RNFL). These are standardized reference points on all instruments due to their high reflectivity and are used commonly to calculate retinal thickness.[15] On occasions, where it was not possible to identify a foveal reflex, the optic nerve head was used as a reference point and the scan was positioned over the foveal area. To increase accuracy, where necessary, a 7 mm horizontal line placed at the equator of the optic disc and offset by 5° inferiorly was superimposed post scan to assess foveal location. Once the correct location was determined, all measurements were taken at this point. A minimum of two to five scans were required to obtain a clear foveal image. The participant's head was held in the primary position using the chin rest and forehead bar. The participant fixated a target spotlight inside each instrument. Participants were allowed a short break from image capture between measurements. The secondary dilation effects following instillation of cycloplegia were used advantageously during OCT scanning. Images were obtained from both eyes.

Foveal Hypoplasia Grading Scale

OCT images were graded using the Foveal Hypoplasia Grading Scale[7] (Fig. 1). Images were graded separately by two authors (NH and GM), and both graders were unaware of the other's results. The resultant grades agreed in all cases.

RESULTS

There was no significant difference between the ages of participants in each group (one way ANOVA $P = 0.583$). The
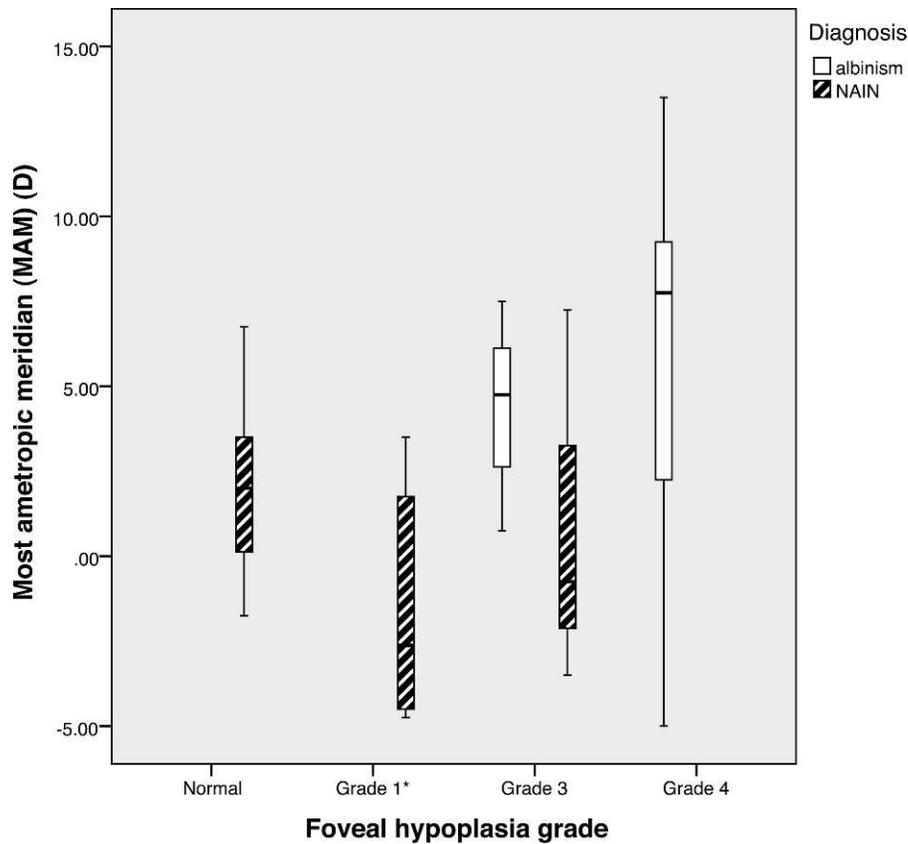
FIGURE 3. Foveal hypoplasia grade and most ametropic meridian. The *top* of the box represents the 75th percentile, the *bottom* of the box represents the 25th percentile, and the *middle line* represents the 50th percentile. The *whiskers* represent the highest and lowest values (excluding outliers). *Grade 1 foveal hypoplasia is significantly different from the other grades following post hoc analysis (Tamhane).

mean age of participants was 218 ± 109 months in the albinism group and 199 ± 121 months in the NAIN group.

OCT images were obtained successfully from both eyes of 50 participants and graded according to the criteria described by Thomas et al.[7] (Fig. 1). Better eye images were used for analysis.

A Kolmogorov-Smirnov test for normality demonstrated a normal distribution for all data used in analyses ($P > 0.05$), however nonparametric analyses were applied due to the discrepancy in participant numbers in each group. There was no significant effect of age on foveal hypoplasia grade (regression analysis $P = 0.249$) and, as the study group was 100% white, any effects of ethnicity could not be explored.

Refractive Error

Cycloplegic refractive error data were obtained from all participants. SER in the better eye ranged from −3.63 to +12.75 diopters (D, mean +3.03 ± 3.98 D). The MAM refractive error ranged from −5.00 to +13.50 D (mean +3.68 ± 4.78 D). Cylindrical refractive errors ranged from 0 to −4.50 cylinder diopters (DC, mean −2.23 ± 1.35 DC).

Statistically significant associations were observed between grade of foveal hypoplasia and SER (Kruskal-Wallis $P = 0.008$) and MAM (Kruskal-Wallis $P = 0.005$; Figs. 2, 3). Those participants with more severe foveal hypoplasia tended to have higher refractive errors.

There were no statistically significant associations between foveal hypoplasia grade and cylindrical refractive error (Kruskal-Wallis $P = 0.144$).

Table 2 demonstrates significant differences between participants diagnosed with albinism and those with NAIN in terms of SER (Mann-Whitney U test $P = 0.001$) and MAM (Mann-Whitney U test $P = 0.001$). There were no statically significant differences in magnitude of astigmatic errors between participant groups (Mann-Whitney U test $P = 0.423$). Three participants with NAIN and grade 3 foveal hypoplasia had a range of refractive errors (SERs −0.75, +1.25, and +5.88 D; MAMs −0.75, +2.50, and 7.25 D).

Controlling for the effects of albinism demonstrated no significant associations between refractive error (SER or MAM) and foveal hypoplasia severity (partial correlation $P > 0.05$).

Visual Acuity

VA (best corrected) data were available from all participants. Better eye mean visual acuity ranged from −0.08 to 1.26 logMAR (mean 0.50 ± 0.30 logMAR).

TABLE 2. Mean Refractive Error Components Participants With Albinism and IIN

Diagnosis	Mean MAM, D	Mean SER, D	Mean Cylindrical Refractive Error, DC
Albinism, $n = 33$	+5.27 ± 4.49	+4.27 ± 3.96	−2.34 ± 1.38
NAIN, $n = 17$	0.59 ± 3.69	0.61 ± 2.80	−2.00 ± 1.33

Poorer visual acuity, using better eye data, was associated statistically significantly with more severe foveal hypoplasia (Kruskal Wallis *H* test *P* = 0.0001, Fig. 4). A statistically significant difference in VA between the two groups also was noted, with participants with albinism demonstrating poorer acuity (0.60 ± 0.32 logMAR) than those without (0.33 ± 0.18 logMAR, Mann-Whitney *U* test *P* = 0.01).

Foveal Thickness

Foveal thickness measures were obtained from 31 participants (62%). There were no statistically significant associations between foveal thickness and refractive error (SER or MAM) or visual acuity (regression analyses *P* > 0.05).

Mean foveal thickness measures were greater in subjects with albinism (*n* = 24, 261.2 ± 28.5 μm) than those without albinism (*n* = 7, mean 227.4 ± 35.2 μm, Mann-Whitney *U* test *P* = 0.016).

DISCUSSION

Our study successfully obtained OCT images of foveal morphology from 50 children and adults with nystagmus in a clinical setting. A spectrum of foveal hypoplasia was demonstrated within our study group, similar to that reported by others.[16,17]

To our knowledge, our study is the first to explore foveal hypoplasia severity in relation to refractive error in individuals with nystagmus. The cylindrical component of refractive error was unrelated to foveal hypoplasia. All participants in our study displayed high cylindrical refractive errors (particularly WTR), which are likely to be associated with the constant rhythmic oscillations of the eye in nystagmus, which may mold the cornea.[5,14] When either SER or MAM was considered, a significant association was found between foveal hypoplasia severity and increasingly hyperopic spherical refractive error. However, this association disappeared when participants with albinism were excluded from the analysis. The results suggested that, in individuals with INS without albinism, the maldevelopment of the fovea has a limited impact on refractive outcome, supporting the conclusions drawn from primate studies that suggest that the fovea does not have a central role in the emmetropization process.[18,19] By contrast, the whole eye effects of albinism appear to have impaired emmetropization in the albinism group. The additional structural anomalies in albinism include central and peripheral retinal anomalies, such as reduced cone density at the macula, impaired foveal cone specialization, and reduced numbers of rod photoreceptors,[16,20] all of which may contribute to disruption in normal visual experience required for typical emmetropization. Some caution must be applied when comparing the data from the present group of human participants with INS to primates undergoing foveal ablation. In the latter group, the monkeys being studied were subject to a period of normal visual development before ablation, whereas infants with INS are likely to have had abnormal visual experience from birth.

It is not possible within the limits of current data to separate fully the contributions to refractive outcome of the various structural and functional anomalies in albinism. Further work prospectively investigating refractive error development in different albinism subtypes with varying levels of retinal and foveal maldevelopment may inform this issue.
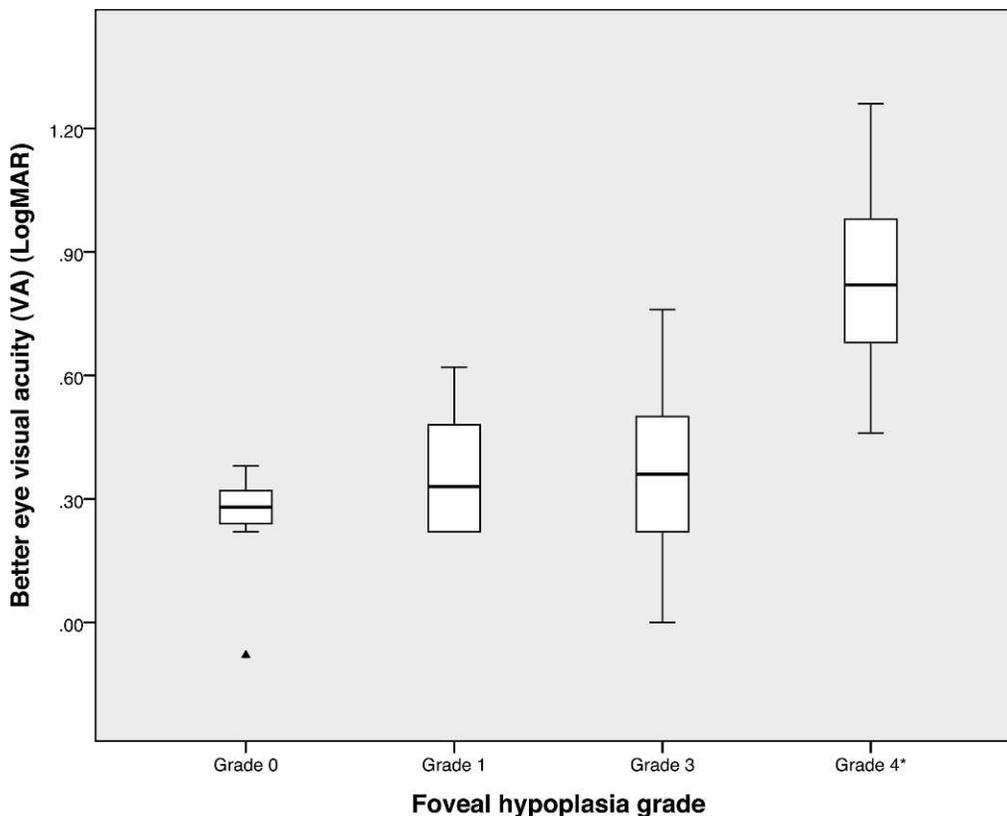

FIGURE 4. Better eye visual acuity for each grade of fovea hypoplasia. The *top* of the box represents the 75th percentile, the *bottom* of the box represents the 25th percentile, and the *middle line* represents the 50th percentile. The *whiskers* represent the highest and lowest values (excluding outliers). The *triangle* represents an extreme value. *Grade 4 foveal hypoplasia is significantly different from the other grades following post hoc analysis (Tamhane).

Visual Acuity

A wide range of visual acuities were recorded in our study. Similar to our study, Thomas et al. also demonstrated an association between more severe foveal hypoplasia and poorer visual acuity, reflecting the impact of cone density at the fovea.[7] However, unlike their albinism group, no participant in our study demonstrated grade 2 foveal hypoplasia. Similar to the study of Thomas et al.,[7] participants in our study with more severe foveal hypoplasia and poorer acuity typically were individuals with albinism. The majority of albinism cases of Thomas et al. had grade 3 foveal hypoplasia.[7] Our study's albinism group demonstrated a greater visual impairment (median VA 0.83 logMAR) and a greater severity of foveal hypoplasia (higher prevalence of grade 4 foveal hypoplasia) than that reported by Thomas et al.[7]

Foveal Thickness

The mean total foveal thickness of the participants with albinism in our study was slightly thinner than that reported by Mohammad et al.[21] in a group of 47 subjects with albinism (309 ± 24.0 μm). This may reflect the different OCT instrumentation used in our study.

Grade 1 Foveal Hypoplasia

Participants in our study with grade 1 foveal hypoplasia and a diagnosis of IIN showed a greater tendency for myopia. Thomas et al. reported that the majority of their participants with grade 1 foveal hypoplasia had IFH or PAX 6 mutation.[7] It may be possible that further investigation of the etiology of those subjects in our study with grade 1 foveal hypoplasia may elicit a more nuanced diagnosis. This may suggest a role for OCT imaging in aiding diagnosis in cases of INS with an ambiguous diagnosis.

No participant in the study had grade 2 foveal hypoplasia. A larger sample population including the full spectrum of foveal hypoplasia gradings would be valuable in further exploration of these issues.

Conclusions

Individuals with infantile nystagmus syndrome commonly have foveal hypoplasia. Increasing severity of foveal hypoplasia is associated with increasing hyperopia among individuals with INS. However, in the absence of albinism there is no significant relation between refractive outcome and degree of foveal hypoplasia suggesting that foveal maldevelopment in isolation does not impair the emmetropization process significantly. It is likely that impaired emmetropization evidenced in the albinism group may be attributed to the whole eye effect of albinism.

Acknowledgments

Disclosure: **N. Healey**, None; **E. McLoone**, None; **G. Mahon**, None; **A.J. Jackson**, None; **K.J. Saunders**, None; **J.F. McClelland**, None

References

1. Fu VL, Bilonick RA, Felius J, et al. Visual acuity development of children with infantile nystagmus syndrome. *Invest Ophthalmol Vis Sci*. 2011;14:1404–1411.
2. Self J, Lotery A. A review of the molecular genetics of congenital idiopathic nystagmus (CIN). *Ophthalmic Genet*. 2007;28:187–191.
3. Edmunds RT. Vision in albinos. *Arch Ophthalmol*. 1949;2:755–767.
4. Summers CG. Vision in albinism. *Trans Am Ophthalmol Soc*. 1996;94:1095–1155.
5. Wildsoet CF, Oswald PJ, Clark S. Albinism: its implications for refractive development. *Invest Ophthalmol Vis Sci*. 2000;41:1–7.
6. Mota A, Fonseca S, Carneiro A, Magalhães A, Brandão E, Falcão-Reis F. Isolated foveal hypoplasia: tomographic, angiographic and autofluorescence patterns. *Case Rep Ophthalmol Med*. 2012;2012:864958.
7. Thomas MG, Kumar A, Mohammad S, et al. Structural grading of foveal hypoplasia using spectral-domain optical coherence tomography a predictor of visual acuity? *Ophthalmology*. 2011;118:1653–1660.
8. Recchia FM, Carvalho-Recchia CA, Trese MT. Optical coherence tomography in the diagnosis of foveal hypoplasia. *Arch Ophthalmol*. 2002;120:1587–1588.
9. Meyer CH, Lapolice DJ, Freedman SF. Foveal hypoplasia in oculocutaneous albinism demonstrated by optical coherence tomography. *Am J Ophthalmol*. 2002;133:409–410.
10. Weiss AH, Kelly JP. Acuity development in infantile nystagmus. *Invest Ophthalmol Vis Sci*. 2007;48:4093–4099.
11. Casteels I, Harris CM, Shawkat F, et al. Nystagmus in infancy. *Br J Ophthalmol*. 1992;76:434–437.
12. Khanna S, Dell'Osso LF. The diagnosis and treatment of infantile nystagmus syndrome (INS). *Sci World J*. 2006;6:1385–1397.
13. Wang J, Wyatt LM, Felius, J et al. Onset and progression of with-the-rule astigmatism in children with infantile nystagmus syndrome. *Invest Ophthalmol Vis Sci*. 2010;51:594–601.
14. Grosvenor T. Etiology of astigmatism. *Am J Optom Physiol Opt*. 1978;55:214–218.
15. Mahon G, McCrudden J. Optical coherence tomography (OCT) – is it simply pattern recognition? *Optom Pract*. 2011;12:63–75.
16. McAllister JT, Dubis AM, Tait DM, et al. Arrested development: high-resolution imaging of foveal morphology in albinism. *Vision Res*. 2010;50:810–817.
17. Harvey PS, King RA, Summers CG. Spectrum of foveal development in albinism detected with optical coherence tomography. *J AAPOS*. 2006;10:237–242.
18. Smith EL III, Ramamirtham R, Qiao-Grider Y, et al. Effects of foveal ablation on emmetropization and form-deprivation myopia. *Invest Ophthalmol Vis Sci*. 2007;48:3914–3922.
19. Huang J, Hung LF, Smith EL III. Effects of foveal ablation on the pattern of peripheral refractive errors in normal and form-deprived infant rhesus monkeys (Macaca mulatta). *Invest Ophthalmol Vis Sci*. 2011;16:6428–6434.
20. Donatien P, Jeffrey G. Correlation between rod photoreceptor numbers and levels of ocular pigmentation. *Inves Ophthalmol Vis Sci*. 2006;43:1198–1203.
21. Mohammad S, Gottlob I, Kumar A, et al. The functional significance of foveal abnormalities in albinism measured using spectral-domain optical coherence tomography. *Ophthalmology*. 2011;118:1645–1652.