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Can structural grading of foveal hypoplasia predict future vision in infantile nystagmus? A longitudinal study

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**Conflict of Interest:** No conflicting relationship exists for any author.

**Running head:** Predicting Future Vision in Infantile Nystagmus

**Abstract**

**PURPOSE**: To evaluate structural grading and quantitative segmentation of foveal hypoplasia using handheld optical coherence tomography (HH-OCT), versus preferential looking, as predictors of future vision in preverbal children with infantile nystagmus.

**DESIGN**: Longitudinal cohort study

**PARTICIPANTS**: 81 eyes from 42 patients with infantile nystagmus (albinism, n=19; idiopathic infantile nystagmus (IIN), n=17; achromatopsia, n=6) were examined.

**METHODS**: A 10×10mm foveal area was sampled using a 3-dimensional raster scan program (500×100, A scans×B scans) with ultra-high resolution spectral-domain HH-OCT (Leica Microsystems Envisu C2300, <4 μm axial resolution) in preverbal children aged up to 36 months. Foveal tomograms were graded using our six-point grading system for foveal hypoplasia and segmented for quantitative analysis: photoreceptor (PR) length, outer segment (OS) length and foveal developmental index (FDI, a ratio of inner layers versus total foveal thickness). Patients were followed up until they could perform chart visual acuity (VA) testing. Data was analysed using linear mixed regression models. VA predicted by foveal grading was compared to prediction by preferential looking (PL) – the current gold standard for visual assessment in infants and young children.

**MAIN OUTCOME MEASURES**: Grade of foveal hypoplasia, quantitative parameters (PR length, OS length, FDI) and preferential looking VA were obtained in preverbal children for comparison with future chart VA outcomes.

**RESULTS**: We imaged 81 eyes from 42 patients with infantile nystagmus of mean age 19.8 months (range: 0.9-33.4; S.D. 9.4) at their first HH-OCT scan. Mean follow-up was 44.1 months (range: 18.4-63.2; S.D. 12.0). Structural grading was the strongest predictor of future visual acuity (grading: r=0.80, F=67.49, p<0.0001) compared to quantitative measures (FDI: r=0.74, F=28.81, p<0.001; OS length: r=0.65; F=7.94, p=0.008; PR length: r=0.65; F=7.94, p=0.008). PL was inferior to VA prediction by foveal grading (PL: r=0.42; F=3.12, p<0.03).

**CONCLUSIONS**: Infantile nystagmus can be an alarming condition with variable impact on vision. HH-OCT can predict future VA in infantile nystagmus. Structural grading is a better predictor of future VA than quantitative segmentation and PL testing. Predicting future vision could avert parental anxiety and optimise childhood development.

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**Introduction**

Nystagmus is a condition of constant, involuntary to-and-fro movements of the eyes occurring in 24 per 10,000 people.1 Onset is usually in early infancy, which can be alarming for parents and families especially because the pre-verbal child is unable to communicate their level of vision. Parents may initially believe the child is blind or has severely impaired vision and their reaction can include fear, anxiety and uncertainty over their child’s future.2 As there is great variation in visual prognosis, predicting future vision could avert anxiety and/or help parents plan adjustments to support the child, particularly to optimise development and educational attainment. Targeted interventions may include accessible learning materials and toys, as well as support with safe mobility and daily living skills.2

Optical coherence tomography (OCT) is a non-invasive imaging technique that provides ultra-high resolution cross-sectional scans of the retina and optic nerve within seconds. Recently, a handheld spectral-domain OCT (HH-OCT) has been developed for clinical use in the paediatric population. It has overcome the limitations of the conventional adult OCT system and is demonstrably reliable, including in nystagmus.3-5 The normal retinal6 and optic nerve development7 have been recently described *in vivo* using HH-OCT. Diseases investigated with HH-OCT include retinopathy of prematurity and other retinal disorders, nystagmus, trauma, optic nerve disease, intraocular tumours and central nervous diseases.3,5,8

Normal development of the human fovea has been traced from 22 weeks gestation to 45 months postpartum using ex vivo histological specimens.9 This is characterised by three developmental processes occurring at the fovea: i) centrifugal displacement of inner retinal layers, ii) cone photoreceptor specialisation, and iii) centripetal migration of cone photoreceptors.9 These stages are seen on OCT morphology as the following features of the fovea, respectively: i) formation and deepening of foveal pit with outward displacement, termed “extrusion”, of the plexiform layers, ii) outer segment (OS) lengthening and iii) outer nuclear layer (ONL) widening.10 Failure of any of these processes results in foveal under-development called “foveal hypoplasia”, causing reduced visual acuity (VA). Foveal hypoplasia is often associated with infantile nystagmus.10 Infantile nystagmus is associated with conditions including albinism and aniridia (mutations of the *PAX*6 gene), or may be idiopathic. “Typical” foveal hypoplasia is characterised by an underdeveloped fovea wherein the lining of individual retinal layers is intact.10 Early onset degeneration of the outer retina as in achromatopsia also causes abnormal persisting inner retinal layers, but since the underlying photoreceptors are disrupted this has been termed “atypical” foveal hypoplasia.10,11

Structural grading of OCT morphology can enable classification of foveal hypoplasia based on severity. Thomas *et al*10 proposed a structural grading scheme for foveal hypoplasia based on OCT data from adults and older children, which has become a widely used scheme with Grades 1 to 4 representing the most to least developed fovea, whilst the atypical grade represents disruption of the photoreceptors seen in achromatopsia. Each of the grades corresponded to statistically distinct VA levels. A key recommendation was validation of the scheme using an independent dataset. More recently, Wilk *et al*12 identified two subsets of Grade 1 hypoplasia and proposed to subdivide these into Grade 1a, in which nearly normal pit metrics (depth, diameter, and/or volume within 2 S.D. of the normal average) are observed, and Grade 1b, in which the pit is only a shallow indent (see Methods: Figure 1 for structural grading scheme employed by the present study and Figure 2 for accompanying grading algorithm).

An alternative method of evaluating foveal hypoplasia is quantitative segmentation. This involves measuring the thickness of different foveal layers. Mohammad *et al*13 demonstrated that total photoreceptor thickness and outer segment length are highly correlated with VA in adults with albinism. The ratio of inner layer versus total foveal thickness, termed the foveal developmental index (FDI), correlated with VA in albinism.14

The gold standard test for VA assessment in older children is logMAR chart VA testing, beginning at four years of age.15 From ages 0-3 years, the gold standard test to assess VA is preferential looking, based on the principle that young children tend to fixate to a pattern stimulus in preference to a plain field.16 However, it can be difficult to assess young children with nystagmus using preferential looking due to constant eye movements17, hence it would be of great value to identify a better tolerated and easier office-based method for VA prediction such as using HH-OCT. Visual evoked potentials (VEP) may represent another option for estimating VA in infantile nystagmus18, but this is time consuming and difficult to perform, requiring specialist diagnostic services.

In this longitudinal cohort study, we harness the potential of HH-OCT for the diagnosis and prognosis of foveal hypoplasia in young children. The primary aim was to validate a structural grading system for foveal hypoplasia in infants and young children with infantile nystagmus to predict future vision. Secondary aims were: i) to assess whether structural grading is comparable to quantitative segmentation in predicting future vision; ii) to compare the predictive power of the grading system with preferential looking VA results taken on first examination; iii) to determine whether the grade remains stable over time.

**Materials and Methods**

**Study design and participants**

This was a prospective longitudinal cohort study of patients with infantile nystagmus recruited in a quaternary referral centre in Leicester, United Kingdom. Longitudinal data were collected between 20th February 2012 and 30th January 2018. This study is reported according to the *Strengthening the Reporting of Observational Studies in Epidemiology* (STROBE) statement.

The study adhered to the tenets of the Declaration of Helsinki and ethics committee approval was granted by the East Midlands - Nottingham 2 Research Ethics Committee. Consent was obtained by all parents or guardians of study participants.

Inclusion criteria were: 1) Diagnosis of infantile nystagmus; 2) Age of 36 months or younger at first HH-OCT scan; 3) Age of at least 42 months or older and ability to participate in chart logMAR visual acuity test on follow up visit. Exclusion criteria included unsuccessful acquisition of HH-OCT scan at first visit, loss to follow-up, scans of inadequate quality for structural grading and co-existing neurological problems. If the HH-OCT scan was only successful in one eye, then the other eye was excluded from analysis. If the HH-OCT scan was unsuccessful in both eyes, then the participant was excluded from analysis. Examination 1 involved HH-OCT and full ophthalmic examination including refraction. Examination 2 involved full ophthalmic examination and best corrected VA measurement when the participant was old enough to participate in chart logMAR vision testing. This age group was deemed clinically important as it approaches or coincides with primary school education. In addition, longitudinal HH-OCT scans were obtained.

Diagnosis of albinism was made based on abnormal lateralisation on visual evoked potentials (VEP), iris transillumination defects, skin hypopigmentation and, if clinical uncertainty existed, genetic testing.19,20 Diagnosis of achromatopsia was made based on typical features including light sensitivity, small amplitude nystagmus, inner segment ellipsoid (ISe) disruption identified on OCT, as well as confirmatory electrodiagnostic and genetic testing.10 IIN was diagnosed in children with nystagmus and normal ophthalmic examination, normal VEPs and electroretinograms and/or confirmation on genetic testing (i.e. pathogenic *FRMD7* mutation).

HH-OCT image acquisition, grading and segmentation

A noncontact, spectral domain HH-OCT scanner (ENVISU C class 2300; <4 μm axial resolution; Leica Microsystems, Wetzlar, Germany) was used to image the foveae of all participants in an outpatient setting without sedation. Visual fixation devices were employed to minimise movement during imaging; these included toys, books and cartoons. The acquisition protocol used a 10×10mm scanning window. The 3-dimensional raster scan program for both scan sequences comprised 100 B-scans and 500 A-scans per B-scan line. The acquisition time was short (1.9 seconds) to facilitate successful image acquisition with minimal disruption of quality, thereby avoiding measurement bias.

The HH-OCT imaging protocol involved scanning the right eye followed by the left eye. The *en face* view was used to identify the optic nerve as a landmark for identification of the fovea. The region temporal to the optic nerve was navigated frame by frame until the most central foveal B-scan was found. Where a foveal pit was present, the B-scan with the deepest pit was selected for grading and segmentation. Where no pit was present, the B-scan with the highest OS peak or, if absent, that with the highest ONL dome was selected. If no foveal landmarks were present (termed *fovea plana*), a B-scan was selected within the central foveal area. We repeated scans three times per eye, selecting the highest quality scan where the retinal layers were most easily discernible for analysis. If unsuccessful, scans were repeated until an adequate quality image was achieved or until the child ceased to participate. The total examination time typically took up to 10 minutes per child. All OCT scans were graded by two graders (SRR and MGT) to assess inter-grader reliability. All OCT scans from Examination 1 were segmented for quantitative analysis. Segmentation was performed using ImageJ software (National Institutes of Health, released 2011, Version 1.48, Bethesda, Maryland, U.S.)

Structural grading was based on the scheme described by Thomas *et al*10 with Grade 1 subdivided into 1a and 1b as per Wilk *et al*.12 The grading scheme is displayed in Figure 1 - we refer to this as the Leicester Grading System for Foveal Hypoplasia. The accompanying grading algorithm is displayed in Figure 2. Parameters for segmentation are illustrated in Figure 3.

**Visual acuity measurement**

During Examination 1, preferential looking VA testing using Keeler Acuity Cards (Keeler Ltd, Windsor, UK) was performed where possible; cards were held vertically to more easily determine responses in horizontal nystagmus, thereby avoiding measurement bias.17 During Examination 2, the Keeler LogMAR Crowded Acuity Test, which uses crowded letter optotypes on charts, was used as the gold standard VA test provided the child could cooperate.21 For children who could not cooperate, the Crowded Kay LogMAR Picture test was used.21 This test involves matching easily recognisable pictures (house, car, star, apple, boot and duck) and is easier for children who cannot match letters.21 Where possible, cycloplegic refraction was performed prior to Examinations 1 and 2. Mean spherical equivalent for this cohort was +2.38 (range: -8.75 to +8.38; S.D. +3.22).

**Statistical analysis**

Our power calculation demonstrated that 38 patients were required to achieve power (α=0.05, β=0.1, r=0.5), based upon the null hypothesis that the correlation is zero. Data was analysed using linear mixed model regression analysis including grade of foveal hypoplasia and eye recorded (right/left) in the model; the dependent variable was chart tested LogMAR VA recorded at Examination 2. Independent variables recorded at Examination 1 included grade of foveal hypoplasia, quantitative segmentation parameters (OS length, ONL length and FDI) and preferential looking VA in LogMAR. Age in months was also included in the model for preferential looking testing because the VA result is expected to improve with age.16 These analyses were computed using SPSS Statistics (IBM Corp. released 2013, Version 22.0. Armonk, NY: IBM Corp.) Agreement between two graders was reported to assess the validity of the grading system. Agreement of grades over time was reported to explore whether grades remain stable over time.22

**Role of the funding source**

The sponsor or funding organisations had no role in the design or conduct of this research.

**Results**

**Baseline characteristics**

Out of 47 patients enrolled to this study, data from 42 (89%) were included: two were lost to follow up and three did not cooperate with HH-OCT scanning. During Examination 1, we obtained OCT scans of 81 eyes from 42 patients of mean age 19.8 months (range: 0.9-33.4; S.D. 9.4); 3 right eye tomograms of 3 patients were of inadequate quality for grading and thus excluded. Adequate power was therefore achieved (n=38, α=0.05, β=0.1, r=0.5). Mean follow-up to Examination 2 was 44.1 months (range: 18.4-63.2; S.D. 12.0). 16 patients were female and 26 were male. In Examination 2, LogMAR VA using letter optotypes (Crowded Keeler’s testing) was successfully obtained in 39 patients (93%) with all children being optimally refracted; 3 patients could not read letter optotypes, hence were tested with Kay’s LogMAR Picture Cards. Baseline characteristics of patients are listed in Table 1.

The cohort included children with albinism (n=19 patients), idiopathic infantile nystagmus (IIN) (n=17) and achromatopsia (n=6).

**Grading of foveal hypoplasia**

Using the grading scheme alone, the inter-grader correlation coefficient was 0.96 when subdividing Grade 1 into 1a and 1b, suggesting the infant grading system is robust. There was disagreement for 3 eyes from 3 patients during the masked grading by the second grader. Each case of disagreement was over what constituted a nearly normal pit as per Grade 1a versus a shallow indent as per Grade 1b, however there was total agreement following discussion and training, which involved studying the treatment algorithm and discussing examples of 1a versus 1b pits. eFigure 1 displays agreement between Graders 1 and 2 prior to training.

Foveal hypoplasia was identified in 57 eyes according to our structural grading scheme, which included Grade 1a (n=17), Grade 1b (n=10), Grade 2 (n=2), Grade 3 (n=10), Grade 4 (n=6) and atypical foveal hypoplasia (n=12). Normal tomograms were seen in 24 eyes.

Figure 4 displays samples of HH-OCT central B-scans per grade. Figure 5 displays a breakdown of diagnoses per grade.

**Prediction of future visual acuity**

Figure 6 is a box and whisker plot displaying the grade of foveal hypoplasia during Examination 1 versus VA during Examination 2. Median (M) and interquartile range (IQR) per grade were as follows: no foveal hypoplasia: M=0.26, IQR=0.27; Grade 1a: M=0.41, IQR=0.32; Grade 1b: M=0.65, IQR=0.16; Grade 2: M=0.60, IQR=0.00; Grade 3: M=0.74, IQR=0.22; Grade 4: M=1.01, IQR=0.23; Atypical: M=0.93; IQR=0.28.

HH-OCT scans of gradable quality were successfully obtained in 81 out of 90 eyes (90.0%). The Leicester Grading System for Foveal Hypoplasia demonstrated strong predictive power for future VA (r=0.80, F=67.49, p<0.0001). This grading system correctly predicted future VA within 0.3 logMAR in 78 out of 81 eyes (96.3%) and within 0.2 logMAR in 60 out of 81 eyes (74.1%).

**Quantitative segmentation analysis**

All quantitative segmentation parameters demonstrated statistically significant associations with future VA in typical foveal hypoplasia, but none as strongly as structural grading (OS length: r=0.65; F=7.94, p=0.008; PR length: r=0.65, F=6.90, p=0.01; FDI: r=0.74, F=28.81, p<0.001). Scatter plots to show quantitative segmentation analyses for Examination 1 OCT scans versus VA in Examination 2 are shown in eFigure 2.

**Preferential looking**

Preferential looking testing at Examination 1 was successfully assessed in 49 out of 72 eyes (68.1%). Preferential looking was a poorer predictor of future VA (r=0.42; F=3.12; p=0.03) compared to HH-OCT. Age did not have a statistically significant effect (p=0.09). Preferential looking testing correctly predicted future VA within 0.3 logMAR in 19 out of 49 eyes (38.8%) and within 0.2 logMAR in 17 out of 49 eyes (34.7%).

**Longitudinal grading**

Longitudinal OCT scans were obtained in 80 eyes from 40 patients with mean follow-up 40.5 months (range: 10.4-62.3, S.D. 15.7). The longitudinal intra-grade correlation co-efficient was 1.0, as all grades remained the same over time.

**Discussion**

To our knowledge, this is the first longitudinal study in infants and young children using HH-OCT to provide a visual prognosis. In foveal hypoplasia the grading scheme10,12 has been validated and demonstrates the strongest prediction of vision compared to quantitative measures and preferential looking in this cohort. The inter-grader reliability testing demonstrates that this scheme is robust. All grades remained stable throughout the study period. In infants and young children, all typical grades achieved VA approximately 2 lines worse than that predicted by grading in adults and older children10: in whom VA per grade was as follows: Grade 1: median 0.20, IQR=0.12; Grade 2: median 0.44, IQR=0.18; Grade 3: median 0.60, IQR=0.0; Grade 4: median=0.78, IQR=0.11; Atypical: median=1.0, IQR=0.08.10 In infants and young children they were as follows: No foveal hypoplasia: 0.26; Grade 1: 0.41; Grade 2: 0.60; Grade 3: 0.74; Grade 4: 1.01; Atypical: 0.93. As only one patient with grade 2 foveal hypoplasia was recruited in this study, results for grade 2 cannot be generalized. These differences could be due to visual acuity still undergoing development and cooperation/ability for VA testing improving with increasing age.23 The slightly better predicted VA in young children with atypical foveal hypoplasia in our study compared to the study in adults and older children is likely because achromatopsia may be a progressive disease.24

**Grading versus quantitative segmentation**

Our study revealed that grading was a stronger predictor of vision compared to quantitative segmentation. An explanation could be that the grading system incorporates all key elements of foveal development, while measurement of FDI, OS length and PR length only represent individual developmental landmarks. However, quantitative segmentation may give insight into subtle differences within a single grade, which may be particularly useful in achromatopsia, represented solely in one atypical grade. Longitudinal quantitative measurements may also help in the monitoring of patients undergoing emerging therapies. For example, measurements of the ONL in achromatopsia, which changes with increasing age24, are particularly important to determine the degree of cone degeneration in view of gene therapy.

Grading can be performed rapidly in clinic whereas quantitative segmentation requires special training and takes approximately 20 minutes per patient. Furthermore, grading can help clinicians make appropriate decisions regarding management and investigation. For example, if VA is poorer than expected according to grading, there should be raised suspicion of other pathology limiting the VA. This may include other retinal pathology such as retinal dystrophy, cortical/neurological disorders, amblyopia, conditions affecting the anterior segment or sub-optimally corrected refractive errors. Similarly, if a patient has poor vision consistent with a high degree of foveal hypoplasia, it is likely that the limiting factor for poor VA is accounted at the retinal level.

**Grading versus preferential looking**

Preferential looking was a poor predictor of future VA, tending to underestimate visual potential in nystagmus. Constant eye movement may increase difficulties of assessing whether the child has correctly identified test cards.17 Suboptimal refraction at Examination 1 may have contributed to the poor correlation between preferential looking and chart VA. Mean chart VA predicted by preferential looking in our cohort was 1.0 logMAR, better than a previously published figure in another cohort with infantile nystagmus of mean age 43 months (1.7 logMAR), but still poor.25 Moreover, the success rate in preferential looking was poor (68.1%) compared to HH-OCT (90.0%). Dubowitz *et al*26 achieved a similar success rate of 70% (n=96) for preferential looking in children with retinopathy of prematurity, also associated with foveal hypoplasia, of a similar age to our study. In our study, preferential looking testing correctly predicted future VA within 3 lines in only 38.8% compared to 96.3% for HH-OCT.

**Can the fovea be graded from birth?**

Our grading system involves identifying the presence or absence of intact ISe, foveal pit, OS lengthening and ONL widening. Histological and OCT studies have demonstrated that all of these landmarks can be identified from birth except OS elongation, which continues up to 5 months postnatally.6,27 Hence, it is possible to determine all grades apart from Grade 2 and Grade 3 from birth, as an infant may be inappropriately assigned Grade 3 before OS elongation has occurred. In this study, no patient under 5 months with Grade 2 or 3 foveal hypoplasia was identified. However, we successfully obtained scans from patients aged 1 month and 3 months with Grade 4 and atypical foveal hypoplasia, respectively. Longitudinal OCT scans revealed that all grades remained the same until the end of the study period, hence adding age into the regression model would not impact the correlation between grading and future VA.

**Study strengths and limitations**

To our knowledge, this is the first longitudinal cohort study using HH-OCT to predict future vision in infantile nystagmus. This helps to reassure and/or enable patients and families to optimise the development and educational attainment of the child during this crucial age, as well as helping clinicians in their decision-making process for investigation and management. A powered cohort of infants and young children has been achieved with adequate follow up until the child could participate with chart VA, approaching or coinciding with commencement of primary school education. Our grading system demonstrated an inter-grader coefficient of 0.96, suggesting it is robust. Our grading system shows lower prediction of VA than previously found in older patients.10 This is likely due to less cooperation with logMAR VA testing and an immature visual system.23 Nystagmus characteristics and head posture may influence VA, however, even without taking these factors into account, we found very good correlation between foveal structure and later VA. In the future, a multivariate model including foveal structure and nystagmus could be calculated to investigate whether VA prediction could be refined.

A limitation of our study is that we are currently only able to predict VA in childhood rather than adulthood due to the recent availability HH-OCT. However, it is still of great value to predict an infant’s VA at the time they commence primary education. It is likely that VA will continue to improve based on adult data.10 Another limitation is that only three aetiologies of foveal hypoplasia were represented within this cohort; the grading system was not applied to other conditions associated with foveal hypoplasia such as *PAX-6* mutation28, retinopathy of prematurity29, nanophthalmos30 and other photoreceptor dystrophies. There were only two eyes from one patient that fulfilled the criteria for Grade 2, therefore, median VA predicted from this single patient (0.60) cannot be generalized. With respect to image acquisition, if three scans per eye were unsuccessful, patients could not be included. However, most eyes (90%) were successfully scanned.

**Author Contributions**

SRR: Concept, literature search, figures, study design, data collection, data analysis, data interpretation, writing.

MGT: Concept, literature search, figures, study design, data analysis, data interpretation, writing, critical revision.

RP: Data collection, data interpretation, critical revision.

CB: Study design, data analysis, data interpretation, writing, critical revision.

HL: Literature search, data collection, data interpretation, writing, critical revision.

FAP: Figures, study design, data analysis, data interpretation, writing, critical revision.

IG: Concept, study design, data collection, data interpretation, writing, critical revision, overall supervision.

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Figure 3 is reprinted from *Ophthalmology*, 118(8), Thomas MG, Kumar A, Mohammad S, Proudlock FA, Engle EC, Andrews C, Chan WM, Thomas S, Gottlob I. Structural grading of foveal hypoplasia using spectral-domain optical coherence tomography a predictor of visual acuity? 1653-1660, Copyright (2011), with permission from Elsevier.

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