Investigative Ophthalmology & Visual Science

Nystagmus Characteristics in Albinism: Unveiling the Link to Foveal Hypoplasia and Visual Acuity

Herman E. Talsma,[1] Charlotte C. Kruijt,[1,2] Gerard C. de Wit,[1] Stefan H. L. Zwerver,[1,3] and Maria M. van Genderen[1,4]

[1]Bartiméus Diagnostic Center for Complex Visual Disorders, Zeist, The Netherlands
[2]Department of Ophthalmology, Leiden University Medical Center, Leiden, The Netherlands
[3]Department of Cognitive Neuroscience, Donders Institute for Brain, Cognition and Behaviour, Radboudumc, Nijmegen, The Netherlands
[4]Department of Ophthalmology, University Medical Center Utrecht, Utrecht, The Netherlands

Correspondence: Herman E. Talsma, Bartiméus Diagnostic Center for Complex Visual Disorders, Van Renesselaan 30a, Zeist 3703 AJ, The Netherlands;
htalsma@bartimeus.nl.

Received: September 15, 2023
Accepted: November 21, 2023
Published: December 22, 2023

Citation: Talsma HE, Kruijt CC, de Wit GC, Zwerver SHL, van Genderen MM. Nystagmus characteristics in albinism: Unveiling the link to foveal hypoplasia and visual acuity. *Invest Ophthalmol Vis Sci.* 2023;64(15):30. https://doi.org/10.1167/iovs.64.15.30

Purpose. The purpose of this study was to describe the association among nystagmus characteristics, foveal hypoplasia, and visual acuity in patients with albinism.

Methods. We studied nystagmus recordings of 50 patients with albinism. The nystagmus waveform was decomposed into two types: dominantly pendular and dominantly jerk. We correlated the nystagmus type, amplitude, frequency, and percentage of low velocity (PLOV) to Snellen visual acuity and foveal hypoplasia grades.

Results. The grade of foveal hypoplasia and visual acuity showed a strong correlation ($r = 0.87$, $P < 0.0001$). Nystagmus type and PLOV had the strongest significant ($P < 0.0001$) correlation with visual acuity ($r = 0.70$ and $r = -0.56$, respectively) and with foveal hypoplasia ($r = 0.76$ and $r = -0.60$, respectively). Patients with pendular nystagmus type had the lowest PLOV, and the highest grade of foveal hypoplasia ($P < 0.0001$). Severe foveal hypoplasia (grade 4), was almost invariably associated with pendular nystagmus (86%).

Conclusions. Foveal hypoplasia grade 4 is associated with pendular nystagmus, lower PLOV, and worse visual acuity. Based on these results, nystagmus recordings at a young age may contribute to predicting visual outcomes.

Keywords: nystagmus, foveal hypoplasia, visual acuity

Albinism is a genetically determined disorder in which either the synthesis of melanin or the maturation of melanosomes is impaired.[1] In oculocutaneous albinism, which is autosomal recessively inherited, the eyes, skin, and hair are affected, whereas in ocular albinism, an X-linked condition, only the eyes are affected. Albinism is associated with reduced visual acuity. Kruijt and colleagues described the phenotypic spectrum of a large cohort of patients with albinism and investigated the relationship between ocular abnormalities and visual acuity.[2] They found that visual acuity only significantly correlated with two characteristics: the grade of foveal hypoplasia, as first described by Thomas et al.[3] (see Fig. 1), and the presence of nystagmus. Foveal hypoplasia can be graded from 0 (normal fovea) to grade 4 (no inner and outer retina differentiation). Based on molecular diagnosis, there is a significant difference in the spectrum of foveal hypoplasia grades.[4,5] In contrast to foveal hypoplasia, nystagmus characteristics in albinism have not yet been graded or differentiated.

Congenital nystagmus occurs in more than 90% of patients with albinism.[2] Nystagmus has different appearances. Dell'Osso[6] described 12 different types of nystagmus waveforms. These waveforms can be decomposed into two main components: "Pendular" and "Jerk."[7] Nystagmus varies, besides waveform, in amplitude, frequency, and direction. By using an eye-tracker, eye movements can be measured and all of the parameters of the nystagmus can be determined. In addition, foveation periods, that is, brief intervals in the nystagmus waveform during which the image is on or near the fovea and eye velocity is relatively low, can be determined this way. Foveation periods depend on the type of nystagmus waveform, and the duration of the foveation periods correlates with visual acuity. Dell'Osso et al. described this relationship in a function called the nystagmus acuity function (NAF) and later in the expanded NAF (NAFX).[8] However, in the case of an underdeveloped fovea, there is often no stable eye position.[9] In these cases, methods using the "foveation period," like "NAFX" and the newer "nystagmus optimal fixation function" (NOFF),[10] are ineffective at predicting visual acuity. Weiss investigated the relationship between the slow-phase velocity of nystagmus and visual acuity in children with albinism and dropped the position criterium. In the absence of a stable eye position, they found that visual acuity in individuals with albinism and pendular nystagmus is more likely to be correlated with eye velocity.[9,10]

Although the relationship between nystagmus and visual acuity has been extensively studied,[8–15] the relationship between nystagmus and foveal hypoplasia has yet to be elucidated. Children with idiopathic infantile nystagmus (IIN), who usually have normal foveae or at most grade 1 foveal hypoplasia,[16] have a mild to moderate reduction in visual acuity.[10] However, when nystagmus is linked to albinism the visual acuity deficits can be more pronounced.[10,14] The nystagmus might further exacerbate the already reduced acuity due to an underdeveloped fovea.

This research investigated how different nystagmus characteristics in patients with albinism correlate with visual acuity and the grade of foveal hypoplasia.

Methods

Study Population

We invited 51 patients from a larger group of 522 patients with albinism[2] for additional eye-tracker tests. A diagnosis of albinism was made according to the diagnostic criteria proposed by Kruijt et al.[2] In the case of genetic confirmation, at least one major criterion or two minor criteria were required for the diagnosis. For genetically unconfirmed cases, at least three major criteria or a combination of two major and two minor criteria were required. Supplementary Table S1 shows the genetic diagnosis in 16 patients; the remaining patients had a clinical diagnosis of albinism, We selected the 51 patients for this study based on their visual acuity: they had either relatively good visual acuity (logMAR ≤ 0.3, $n = 21$) or poor visual acuity (logMAR ≥ 0.6, $n = 30$).

The median age of the patients was 29.1 years (range = 12–69 years). Thirty patients were women, and 21 patients were men. The study was approved by the Medical Ethics Committee of Leiden University Medical Center and adhered to the tenets of the Declaration of Helsinki. Informed consent was obtained from the subjects after explaining the nature and possible consequences of the study.

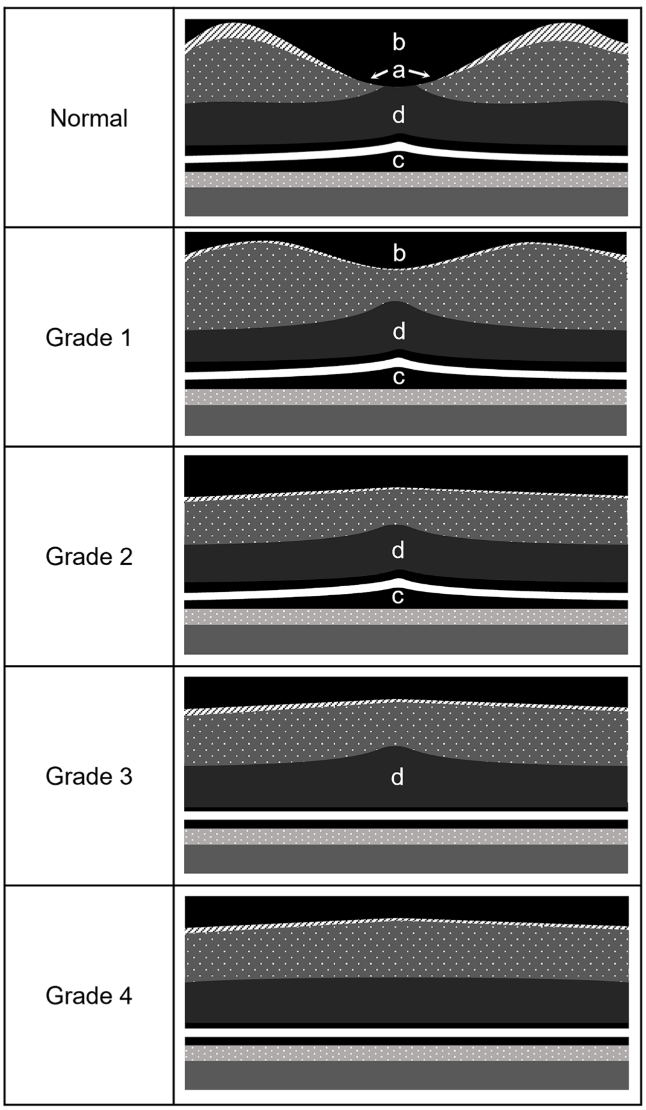

Figure 1. Foveal structural features, detectable using optical coherence tomography (OCT): simplified and adapted from Thomas et al.[3] (**A**) Extrusion of plexiform layers, (**B**) foveal pit, (**C**) outer segment lengthening, (**D**) outer nuclear layer widening.

Visual Acuity and Foveal Hypoplasia Grading

Using the SLOAN optotype, we measured visual acuity with a digital optotype chart (Vision Testing Software; Good-lite LLC, Elgin, IL, USA) based on the Early Treatment Diabetic Retinopathy Study (ETDRS) principle.

We used optical coherence tomography (OCT) scans (RT-Vue; Optovue, Fremont, CA, USA), to grade foveal hypoplasia. Besides line scans, radial MM6 scans were available to ensure that the center of the foveal region was captured. As shown in Figure 1, we graded foveal hypoplasia from grade 1 to 4, according to the grading scheme of Thomas et al.[3]

Nystagmus Analysis With Eye-Tracking

We used a Tobii T60 XL eye-tracker with a 24-inch TFT widescreen monitor (Tobii Inc., Stockholm, Sweden), which records the gaze direction of the eyes with a sample rate of 60 Hz without the need for a chinrest or other apparatus. The stimulus consisted of a black dot on a grey background with an average luminance of 50 cd/m2 presented for 25 seconds, with the patient sitting approximately 60 cm away from the display. The tests took place in undisturbed conditions in an office room. Tobii Studio software version 3.3.2. was used to collect the nystagmus data of the albinism patients, after an initial standard 5-point calibration procedure.

Data Analysis Nystagmus

Using Theodorou's method,[7] we decomposed the nystagmus waveform into two classes: dominantly pendular and dominantly jerk. Nearly all nystagmus waveforms with normalized amplitude can be considered a linear combination of a jerk and a pendular form, as illustrated in Figure 2. We classified waveforms with a factor a above 0.5 as pendular and below 0.5 as a jerk. The only nystagmus that cannot be classified this way is the bidirectional jerk, which we classified manually.

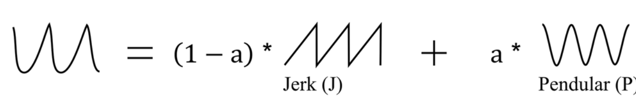

Figure 2. Nystagmus waveforms decomposition.[7]

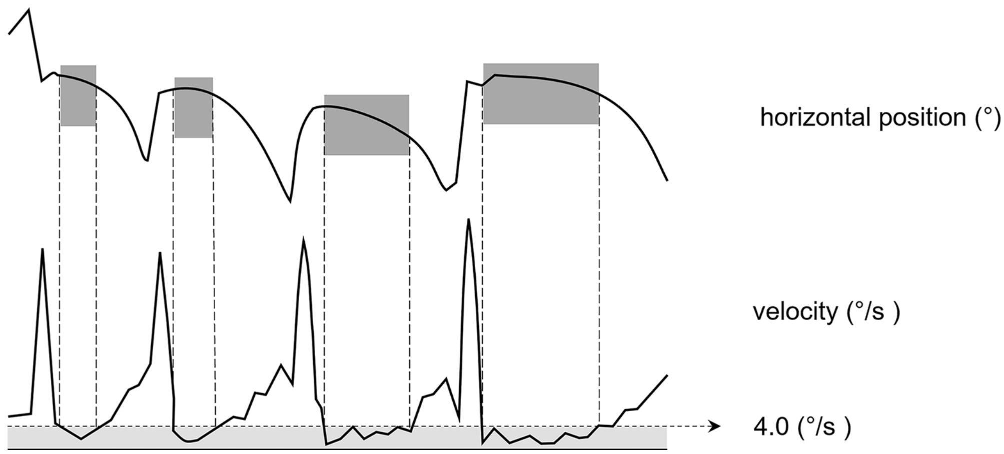

Figure 3. Example of the horizontal position of a jerk-type nystagmus (*top graph*) and corresponding eye velocities (*bottom graph*). The slow phases are indicated by the *top dark grey boxes*. For this 1-second measurement interval, the percentage of low velocity (PLOV), defined as the proportion of time during which the velocity remains below 4 degrees/second, is approximately 40%.

In equation form, the linear combination of a jerk and pendular nystagmus looks as follows:

$$f = (1 - a)\,\mathrm{sawtooth}\,(2\pi t, 1 - w) + a(\cos 2\pi t) \quad (1)$$

with parameter t as the time. Parameter a, between 0 and 1, represents the amplitude of the pendular term, and (1-a) the amplitude of the jerk term. Parameter w is the width of the rising ramp of the sawtooth function.[17] The width of the rising ramp is a proportion of the total cycle. The default is 1, producing a rising ramp, whereas 0 produces a falling ramp. The width = 0.5 produces a triangle wave. Only the two extreme ranges for w were considered: between 0.0 and 0.1, representing a right jerk, and between 0.9 and 1.0, representing a left jerk. We determined parameter a as follows: first, with a Python program, we identified the different cycles of the measured nystagmus and for each cycle, the peaks and troughs were superposed by scaling the time axis. Subsequently, we discarded the outliers – cycles with log amplitudes that fell outside two times the standard deviation – and constructed an averaged and normalized waveform cycle. We then used Python's scipy.optimize.curve_fit,[18] nonlinear least squares to best fit the function, f, to the data by varying parameters a and w (a and w only in the ranges specified above).

We defined the percentage of low velocity (PLOV) by calculating the horizontal eye rotation velocity during the nystagmus and determining the percentage of time within a specific interval during which the absolute velocity was less than 4.0 degrees/second.[9] For illustration see Figure 3. A typical interval was around 20 seconds and was selected based on the quality of the measurement.

Statistical Data Analysis

All analyses were performed using GraphPad Prism version 6.0.7 for Windows (GraphPad Software, San Diego, CA, USA, www.graphpad.com). We tested the normality of the data with the Anderson-Darling normality test. We correlated different nystagmus parameters to visual acuity and foveal hypoplasia: nystagmus type (jerk/pendular), log amplitude, frequency, and PLOV. Due to the non-normal distribution of visual acuity and foveal hypoplasia, we performed the non-parametric Spearman test for every correlation analysis with the nystagmus parameters. We calculated the statistical differences between the group of patients with pendular and jerk nystagmus with the Mann-Whitney U statistical test. A P value of ≤ 0.05 was considered statistically significant.

Results

The nystagmus recording from one patient was not readable and therefore not considered for shape analysis. Of the 50 remaining patients with albinism, 28 (56%) had dominant jerk and 22 (44%) dominant pendular nystagmus.

The average PLOV of the pendular type (7.4%) was significantly lower than that of the jerk type (21.0%, $P = 0.0001$). Figure 4A shows that patients with pendular nystagmus had worse visual acuity (median 0.90 logMAR,) than patients with jerk nystagmus (median 0.22 LogMAR). This difference was statistically significant ($P < 0.0001$).

All patients had foveal hypoplasia (i.e. $\geq$ grade 1). The patients with pendular nystagmus had a significantly higher grade of foveal hypoplasia than patients with jerk nystagmus ($P < 0.0001$). Figure 4B shows that 86% of patients with pendular nystagmus had grade 4 foveal hypoplasia versus 11% of patients with jerk nystagmus.

All nystagmus parameters correlated significantly with visual acuity except for nystagmus frequency (Fig. 5). From the highest absolute correlation with visual acuity to the lowest, we found: nystagmus type ($r = 0.70$, $P < 0.0001$):

$$PLOV\left(r = -0.56,\, p < 0.0001\right),$$

$$\text{and log nystagmus amplitude}\left(r = 0.50,\, p < 0.0006\right)$$

We also compared the same nystagmus parameters with foveal hypoplasia (Fig. 6). Again, all nystagmus parameters correlated significantly with foveal hypoplasia except for nystagmus frequency. From the highest absolute correlation with foveal hypoplasia to the lowest, we found: nystagmus type ($r = 0.76$, $P < 0.0001$):

$$PLOV\left(r = -0.60,\, p < 0.0001\right),$$

$$\text{and log nystagmus amplitude}\left(r = 0.36,\, p = 0.02\right).$$

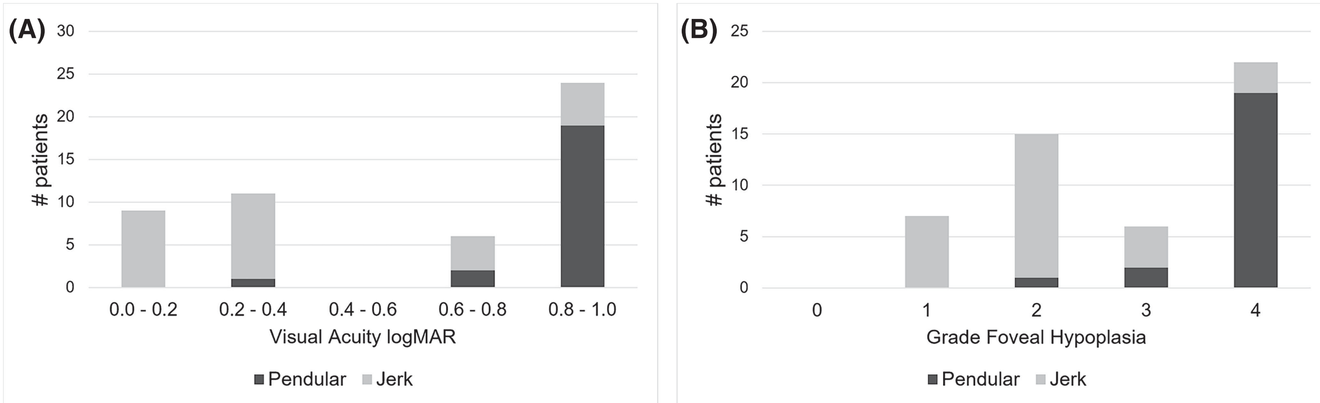

Figure 4. (**A**) Histogram visual acuity (logMAR). (**B**) Histogram foveal hypoplasia.

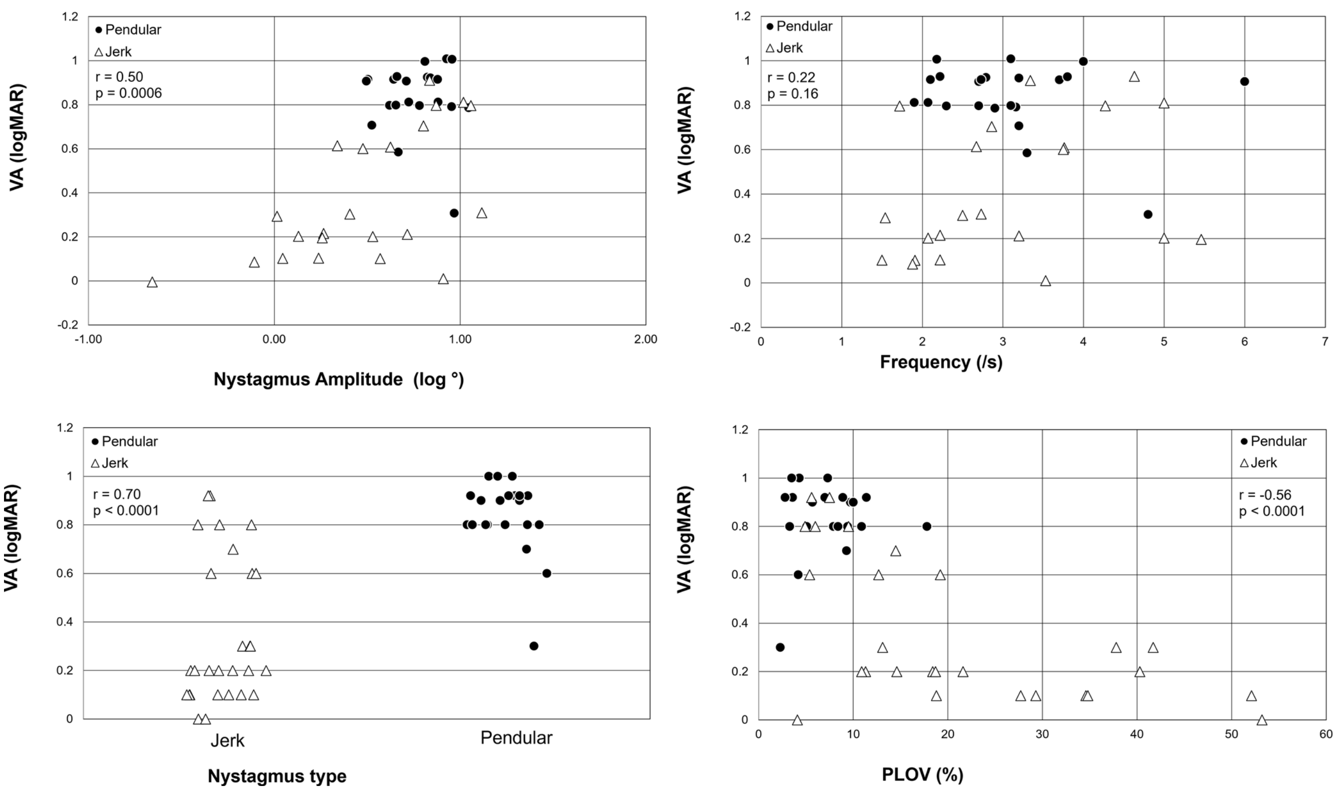

Figure 5. Visual acuity as a function of nystagmus parameters. All nystagmus parameters correlated significantly with visual acuity except for nystagmus frequency. Most significant was the correlation of visual acuity with nystagmus type and PLOV (see also Supplementary Table 2A).

Figures 7A and 7B show a strong correlation between the grade of foveal hypoplasia and visual acuity ($r = 0.86$, $P < 0.0001$).[1] Patients with pendular nystagmus had the highest grade of foveal hypoplasia and the lowest PLOV (see Fig. 7B).

Discussion

This study shows how different nystagmus characteristics in patients with albinism correlate with visual acuity and grade of foveal hypoplasia. Our cohort consisted of 21 patients with relatively good visual acuity and 30 patients with relatively poor visual acuity. We found that approximately an equal number of patients exhibited jerk nystagmus as did pendular nystagmus and that worse visual acuity was significantly associated with pendular nystagmus.

Worse visual acuity in our study was also correlated with more severe foveal hypoplasia, confirming earlier reports.[2,19] Rufai et al. found that structural grading of foveal hypoplasia using OCT images is a more accurate predictor of future visual acuity in children with infantile nystagmus than quantitative segmentation and preferential-looking testing.[2,19] A remarkable additional finding in our study is that severe foveal hypoplasia (grade 4), was almost invariably asso-

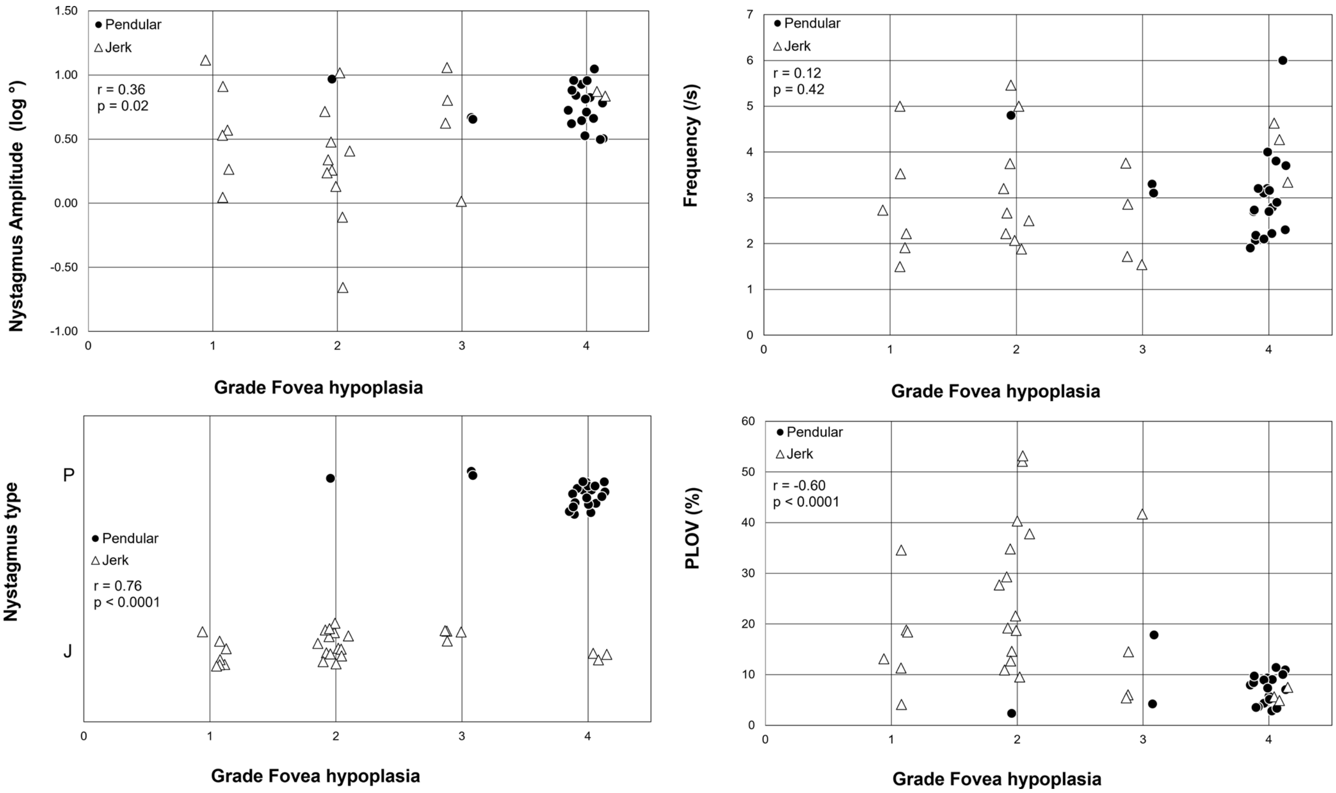

Figure 6. Nystagmus parameters as a function of grade foveal hypoplasia. All nystagmus parameters correlated significantly with foveal hypoplasia except for nystagmus frequency. Most significant was the correlation of foveal hypoplasia with nystagmus type and PLOV (see also Supplementary Table 2B).

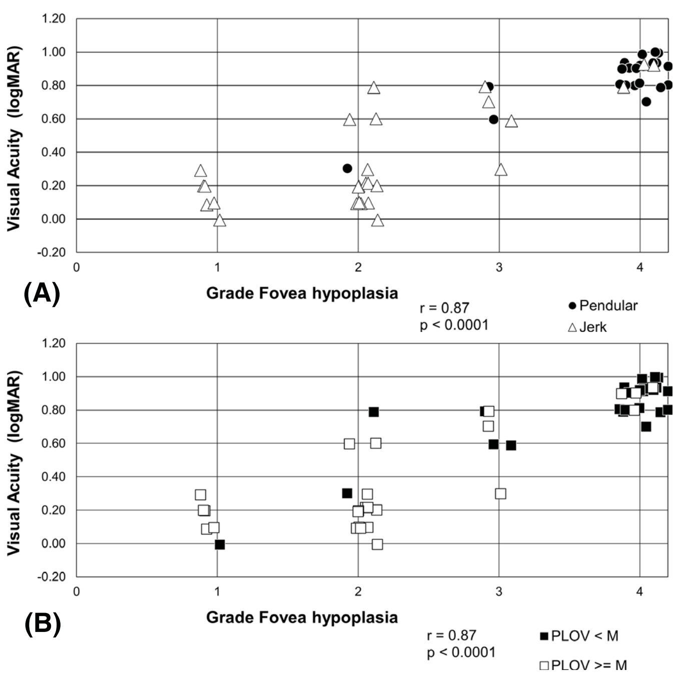

Figure 7. (**A**) Correlation between visual acuity and grade foveal hypoplasia, with patients with pendular and jerk nystagmus displayed separately. Eighty-six percent of patients with pendular nystagmus had grade 4 foveal hypoplasia (see also Supplementary Table 2C). (**B**) Correlation visual acuity – grade foveal hypoplasia. Patients were also divided into two distinct groups: the lower-half patients, characterized by an PLOV < M (M = median(PLOV)), and the upper-half patients, displaying PLOV ≥ M. There is a significant correlation between these two groups and the grade of foveal hypoplasia ($r = 0.53$, $P < 0.0001$; see Supplementary Table 2C).

ciated with pendular nystagmus and low PLOV. In grade 4 foveal hypoplasia, there is a complete absence of cone photoreceptor differentiation, resulting in a central outer retina that resembles a peripheral retina.[3] We hypothesize that the absence of a distinguishable center relative to the more peripheral retina leads to the absence of foveation and to a pendular form of nystagmus. In contrast, milder grades of foveal hypoplasia showing some foveal differentiations are associated with jerk nystagmus. During jerk nystagmus, there is a moment in the cycle where the fast, corrective eye movement directs the gaze to the center.

It is intriguing to speculate on the relative contributions of foveal morphology and nystagmus type to visual acuity. The structural and functional alteration of the fovea in itself can lead to lower visual acuity, but we also demonstrated that a high grade of foveal hypoplasia is significantly associated with a specific type of nystagmus and thus worse visual acuity. The pendular nystagmus associated with the highest grade of foveal hypoplasia has a relatively small percentage of time for the slow phase, i.e., a period with low velocity and a low PLOV. The relationship between nystagmus and visual acuity has been extensively studied.[8,10–15] In all these studies, nystagmus eye velocity plays a role in the correlation with visual acuity.

Theoretically, it might be possible that pendular nystagmus alone can cause the poor visual acuity of patients with albinism with grade 4 foveal hypoplasia. Weiss and coworkers[9] studied the velocity component of nystagmus by comparing the dynamic visual acuity (DVA) of healthy subjects with the visual acuity of patients with albinism based on eye velocity measurements. They concluded that visual acuity in albinism is not limited by retinal image motion alone, but that macular hypoplasia must be a contributing factor.

To our knowledge, no correlation has previously been described between the foveal hypoplasia grade and the type of nystagmus. The fact that we preselected a group of patients with either high or low visual acuity may have contributed to the relatively strong correlation we found between nystagmus parameters and albinism characteristics. For our future research, we plan to investigate these relationships in other patient groups with nystagmus to see if the same correlations hold. Another question of interest pertains to how nystagmus manifests and changes in early childhood, a period in which the fovea is still developing.[20]

Where the degree of foveal hypoplasia can provide insights into visual prognosis, the type of nystagmus may potentially offer similar information as well. Foveal hypoplasia is not always easily determined based on OCT images in very young children. Not every center has access to a handheld OCT, nor the skills and time required to produce a quality OCT scan in young children.[19,21] Registering nystagmus and identifying its type may be more straightforward; it can be assessed by having a child view a monitor while seated on a parent's lap.

This study has some limitations. First of all, calibration can be challenging in patients with congenital nystagmus, because it may be difficult for the eye-tracking system to determine where a person is looking in the presence of nystagmus. If the nystagmus changes when looking in different directions during the calibration, this might lead to a less accurate calibration and, therefore, introduce some error when determining the amplitude of the nystagmus. However, we do not expect this error to be so large to change the results significantly. In addition, no or only minor changes are to be expected in the determination of the frequency and shape of the nystagmus due to this kind of error in the calibration.

Second, the eye-tracker had a sampling rate of only 60 Hz. For the calculation of the amplitude and frequency of the nystagmus, this is not an obstacle as the frequency of the nystagmus itself is only in the order of 3 Hz. The shape might change slightly as with a higher sampling rate accelerations and decelerations might become better sampled. However, we have visually confirmed the different nystagmus waveforms and were able to categorize them successfully into a class described by Dell'Osso.[6] This affirms that the sampling frequency is high enough to make a distinction between pendular and jerk nystagmus waveforms. Furthermore, in our analyses, we use a relative measure. We correlated the relative nystagmus parameters with visual acuity and foveal hypoplasia.

Conclusions

Our study on 50 patients with albinism showed a correlation among nystagmus type, visual acuity, and grades of foveal hypoplasia. We demonstrated that foveal hypoplasia grade 4 is associated with pendular nystagmus, a shorter foveation period, and worse visual acuity. Based on these results, nystagmus recordings at a young age may contribute to predicting visual outcomes.

Acknowledgments

Disclosure: **H.E. Talsma**, None; **C.C. Kruijt**, None; **G.C. de Wit**, None; **S.H.L. Zwerver**, None; **M.M. van Genderen**, None

References

1. Neveu MM, Padhy SK, Ramamurthy S, et al. Ophthalmological manifestations of oculocutaneous and ocular albinism: current perspectives. *Clin Ophthalmol*. 2022;16:1569–1587.
2. Kruijt CC, de Wit GC, Bergen AA, Florijn RJ, Schalij-Delfos NE, van Genderen MM. The phenotypic spectrum of albinism. *Ophthalmology*. 2018;125(12):1953–1960.
3. 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(8):1653–1660.
4. Kuht HJ, Maconachie GDE, Han J, et al. Genotypic and phenotypic spectrum of foveal hypoplasia: a multicenter study. *Ophthalmology*. 2022;129(6):708–718.
5. Bakker R, Wagstaff EL, Kruijt CC, et al. The retinal pigmentation pathway in human albinism: not so black and white. *Prog Retin Eye Res*. 2022;91:101091.
6. Dell'osso LF, Daroff RB. Congenital nystagmus waveforms and foveation strategy. *Doc Ophthalmol*. 1975;39(1):155–182.
7. Theodorou M, Clement R. Classification of infantile nystagmus waveforms. *Vision Res*. 2016;123:20–25.
8. Jacobs JB, Dell'Osso LF. Extending the eXpanded nystagmus acuity function for vertical and multiplanar data. *Vision Res*. 2010;50(3):271–278.
9. Weiss AH, Kelly JP, Phillips JO. Relationship of slow-phase velocity to visual acuity in infantile nystagmus associated with albinism. *J AAPOS*. 2011;15(1):33–39.
10. Felius J, Fu VLN, Birch EE, Hertle RW, Jost RM, Subramanian V. Quantifying nystagmus in infants and young chil-

dren: relation between foveation and visual acuity deficit. *Invest Ophthalmol Vis Sci*. 2011;52(12):8724–8731.

11. Dell'Osso LF, Jacobs JB. An expanded nystagmus acuity function: intra- and intersubject prediction of best-corrected visual acuity. *Doc Ophthalmol*. 2002;104(3):249–276.
12. Tai Z, Hertle RW, Bilonick RA, Yang D. A new algorithm for automated nystagmus acuity function analysis. *Br J Ophthalmol*. 2011;95(6):832–836.
13. Demer JL, Amjadi F. Dynamic visual acuity of normal subjects during vertical optotype and head motion. *Invest Ophthalmol Vis Sci*. 1993;34(6):1894–1906.
14. Felius J, Muhanna ZA. Visual deprivation and foveation characteristics both underlie visual acuity deficits in idiopathic infantile nystagmus. *Invest Ophthalmol Vis Sci*. 2013;54(5):3520–3525.
15. Fu VLN, Bilonick RA, Felius J, Hertle RW, Birch EE. Visual acuity development of children with infantile nystagmus syndrome. *Invest Ophthalmol Vis Sci*. 2011;52(3):1404–1411.
16. Thomas MG, Crosier M, Lindsay S, et al. Abnormal retinal development associated with FRMD7 mutations. *Hum Mol Genet*. 2014;23(15):4086–4093.
17. scipy.signal.sawtooth. Copyright 2008–2023, The SciPy community. Available at: https://docs.scipy.org/doc/scipy/reference/generated/scipy.signal.sawtooth.html.
18. scipy.optimize.curve_fit. Copyright 2008–2023, The SciPy community. Available at: https://docs.scipy.org/doc/scipy/reference/generated/scipy.optimize.curve_fit.html.
19. Rufai SR, Thomas MG, Purohit R, et al. Can structural grading of foveal hypoplasia predict future vision in infantile nystagmus?: a longitudinal study. *Ophthalmology*. 2020;127(4):492–500.
20. Provis JM, Dubis AM, Maddess T, Carroll J. Adaptation of the central retina for high acuity vision: cones, the fovea and the a vascular zone. *Prog Retin Eye Res*. 2013;35(1):63–81.
21. Lee H, Purohit R, Patel A, et al. In vivo foveal development using optical coherence tomography. *Invest Ophthalmol Vis Sci*. 2015;56(8):4537–4545.

Investigative Ophthalmology & Visual Science