

Visual Deprivation and Foveation Characteristics Both Underlie Visual Acuity Deficits in Idiopathic Infantile Nystagmus

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PURPOSE. Children with idiopathic infantile nystagmus (IIN) exhibit visual acuity deficits that have been modeled in terms of foveation characteristics of the nystagmus waveform. Here we present evidence for an additional component of acuity loss associated with the deprivation experienced during the sensitive period of visual development.

METHODS. Binocular grating visual acuity and eye movement recordings were obtained from 56 children with IIN (age 4.8 ± 3.2 years) and documented waveform history from longitudinal visits. Visual acuity was modeled in terms of foveation characteristics (Nystagmus Optimal Fixation Function, NOFF) and of each child's time course of pendular nystagmus during the sensitive period.

RESULTS. Mean visual acuity was 0.25 ± 0.19 logMAR below age norms, and the mean foveation fraction was 0.28 (NOFF = -0.9 ± 2.3 logits). Nystagmus had a median onset at age 3 months and transitioned to waveforms with extended foveation at age 35 months. The best fit of the model showed the following: Poor foveation (0.01 foveation fraction) was associated with 0.60 logMAR acuity deficit; this deficit gradually reduced to zero for increasingly better foveation; pendular nystagmus during each decile of the sensitive period was associated with an additional 0.022 logMAR deficit. The model accounted for 57% of the variance in visual acuity and provided a better fit than either component alone.

CONCLUSIONS. Visual acuity in IIN is explained better if, besides the child's foveation characteristics, an additional component is taken into account representing the nystagmus-induced visual deprivation during the sensitive period. These findings may have implications for the timing of treatment decisions in children with IIN.

Keywords: infantile nystagmus, visual deprivation, visual acuity

Infantile nystagmus (incidence approximately 1 in 1000–6000)^{1,2} typically has an onset before the age of 6 months and occurs either in idiopathic form or in combination with other ocular conditions, such as albinism, bilateral optic nerve hypoplasia, congenital cataract, or various types of inherited retinal degenerations. The incessant movement of the eyes in patients with infantile nystagmus causes a smeared image of the outside world on the retinas, which encumbers visual performance and reduces visual acuity. In children with idiopathic infantile nystagmus (IIN), visual acuity tends to be mild to moderately reduced from early in life,^{3,4} while infantile nystagmus associated with albinism or optic nerve hypoplasia results in more profound visual acuity deficits,^{5–6} with nystagmus possibly adding to the acuity deficit caused by the underdeveloped retina and/or optic nerve. Presently no cure for infantile nystagmus exists, but a number of treatment options are available to reduce the amount of fixation instability. In particular, improvements in both eye movement characteristics^{7–10} and visual acuity^{11–15} have been reported after surgery to all four horizontal rectus muscles, both in adults and in young children.¹⁴

For IIN, it is currently unknown to what extent the visual acuity deficits are the direct result of the motion smear induced

by the continuously moving eyes and would resolve if the nystagmus were to be eliminated. Since motion smear presumably causes (partial) binocular visual deprivation from an early age, it is plausible that at least part of the visual deficit is the result of bilateral amblyopia.^{16,17} With the advent of treatment options this has become an interesting issue because, if indeed bilateral amblyopia plays a significant role, the timing of intervention may be important. Lessening of the deprivation within the sensitive period of visual development may yield better outcomes than when intervention takes place after the visual system loses its plasticity.

Previously, the attained level of visual acuity has been modeled in terms of foveation characteristics of the nystagmus waveform,^{18–20} that is, the patient's fixation stability at the time of testing. Here we present evidence for an additional component of visual acuity loss associated with the (partial) binocular visual deprivation experienced during the sensitive period of visual development. The premise of our approach is that pendular nystagmus waveforms are typically associated with poor foveation characteristics and thus may lead to binocular visual deprivation, whereas jerk-like waveforms with extended foveation periods usually have much better foveation

and allow for relatively normal vision and normal visual development.

METHODS

Participants

All 56 participating children (age 4.8 ± 3.2 years at last visit) had a diagnosis of IIN based on eye movement recordings and on comprehensive ophthalmic and fundus examination by the referring ophthalmologist. Infantile nystagmus is characterized by infantile-onset conjugate involuntary eye movements, which are usually uniplanar and predominantly horizontal and which feature an accelerating slow phase.^{21,22} Children enrolled in this study were evaluated for visual function and eye movements at 3- or 6-month intervals until age 2 years and once annually thereafter. The inclusion requirements were diagnosis of IIN with no prior treatment and no treatment (other than optical correction) during the study, and longitudinal follow-up sufficient to estimate the onset of nystagmus and the transition from pendular waveforms to jerk-like waveforms with extended foveation periods.²³ Patients with concurrent eye disease (such as albinism, optic nerve hypoplasia) or other syndromes, systemic disease, or developmental delay were excluded. All participants wore optical correction according to their cycloplegic refraction during all testing if the spherical equivalent refractive error exceeded 2.0 diopters (D) and/or the cylindrical refractive error exceeded 1.0 D.

The age of onset of (pendular) nystagmus was based on eye movement recordings performed in our lab, clinical information provided by the referring physician, and parental report. The age of transitioning to waveforms with extended foveation was based exclusively on eye movement evaluations performed in our lab.

This research followed the tenets of the Declaration of Helsinki. Informed written consent was obtained from a parent or legal guardian of each participating child. The protocol and consent form were approved by the Institutional Review Board at the University of Texas Southwestern Medical Center and were in compliance with the US Health Insurance Portability and Accountability Act (HIPAA).

Eye Movement Recording

Nystagmus eye movements were recorded at a 500-Hz sampling rate using either an infrared limbus reflection goggle system (Ober 2; Permobil Meditech, Woburn, MA)²⁴ controlled by Orbit Eye Trace XY1000 software (version 1.71; IOTA, Sundsvall, Sweden), or a high-speed remote video eye tracker (EyeLink 1000; SR Research, Ltd., Kanata, ON). Bright, steady fixation stimuli (computer-generated 1.5°-diameter cartoon pictures) were presented on a large (>50° diameter) black background using a rear-projection screen and a liquid-crystal display projector in a dimly lit room. Children were seated 1.15 to 1.35 m from the screen and were instructed to attend to the picture; for infants, attention to the pictures was attracted with sound; or, if this was unsuccessful, a small toy was held in front of the infant's face at a distance of approximately 0.5 m. A table with a chinrest and headrest was used for children who were capable of using it, while infants and toddlers usually sat in a parent's lap with the researcher or the parent holding the infant's head. A minimum of 20 seconds of data was recorded from each patient under binocular viewing. For patients who were capable, monocular 5-point calibrations were performed using steady fixation stimuli at 0° and $\pm 10^\circ$ eccentricity horizontally and vertically, with each stimulus presented for 5

seconds. For those infants who did not tolerate monocular occlusion or who did not appear to follow the calibration stimulus, a group-averaged gain factor was used instead, which was obtained from a separate group of normal infants and children who tolerated monocular occlusion for the calibration measurements. (Although individual calibration would be desirable even in the youngest patients, an earlier study showed no significant difference in gain factor between those few young patients in whom calibration was successfully performed and the group of age-similar normals.¹⁹)

Eye movement data were analyzed offline using the Nystagmus Optimal Fixation Function (NOFF),¹⁹ an automated algorithm that searches for the cleanest portion of data based on the "foveation fraction": the fraction of data points that meet simultaneous criteria for eye position and eye velocity. For calculations and statistics, the foveation fraction is converted to logistic units (logits), thus resulting in NOFF values ranging from approximately -5 for very poor fixation (or <0.01 foveation fraction) to approximately +5 for near-perfect fixation (or >0.99 foveation fraction). The simultaneous criteria for position and velocity bear similarity with those of the Expanded Nystagmus Acuity Function (NAFX),¹⁸ but the NOFF's automated algorithm to search for the cleanest portion of the data makes it more feasible in data for children. Earlier we showed very good correlation between NOFF and NAFX results calculated from the same set of eye movement recordings.¹⁹

Visual Acuity

Binocular grating visual acuity was assessed with the Teller Acuity Cards II (Stereo Optical, Chicago, IL) using a forced-choice paradigm. Children under age 3 years were tested using forced-choice preferential looking, while older children were asked to point to the location of the gratings. Visual acuity was defined as the mean of the last six reversals of a 2-down-1-up staircase procedure with eight reversals on a logMAR scale.²⁵ Since the normal limits of visual acuity vary considerably with age, especially in the younger patients tested, all measurements were converted to visual acuity deficits, that is, logMAR units relative to published age-corrected mean normal values.²⁶⁻²⁸

Model Fitting

The data from each child's most recent visit were first fit by a simple exponential model describing the visual acuity deficit as a function of the NOFF.¹⁹ Subsequently, a second component was added in order to account for the visual deprivation, thus establishing a two-component model. The first term corresponds to the child's nystagmus characteristics at the time of the last visit (as quantified by the NOFF), and the second term describes the child's history of pendular nystagmus:

$$\text{Visual Acuity Deficit} = a \exp(-\text{NOFF}/b) + cD \quad (1)$$

where NOFF is in logit units; $D = D(\text{onset, transition})$ is a deprivation parameter determined by the age at onset of pendular nystagmus and the age at transition to waveforms with extended foveation; and a , b , and c are the model parameters. For each child, the deprivation parameter D corresponded to the individual proportion of the sensitive period during which the child experienced pendular nystagmus (Fig. 1). The shape of the sensitivity profile was described mathematically by the difference of two exponentials for ease of computing. This function is a simplified version of the one proposed by Banks et al.,²⁹ which has been used for modeling the sensitive period for binocular vision.^{29,30} The parameters of the profile were set such that it had an onset at age 1.5 months,

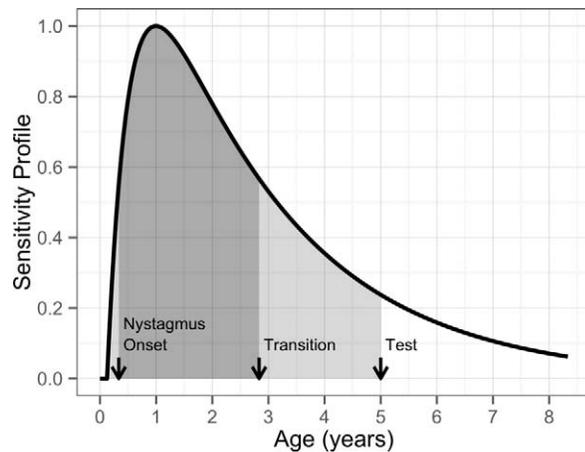


FIGURE 1. Profile of the sensitive period for spatial vision (solid line), set to begin at age 1.5 months, peak at age 12 months, then drop off gradually toward zero after age 8 years. The gray areas under the curve illustrate a typical example of the time course of IIN: From birth until onset at age 3 months there is no nystagmus (small light gray area), followed by pendular nystagmus causing visual deprivation from onset until transition at age 35 months (dark gray area), then jerk-like nystagmus with extended foveation periods until the age at testing (larger light gray area). The ages of 3 months and 35 months in this example correspond to the median ages of onset and transition, respectively, in this cohort.

peaked at age 12 months, and diminished to zero after age 8 years (95% of the area under the curve prior to age 8 years). Published data on the actual human sensitivity profile for spatial vision (from vision deprivation) are all derived from monocular deprivation studies, but it seems reasonable to assume an initial “latent period” of less than 3 months (possibly none), a peak between 12 and 24 months of age, and a gradual decline to zero between ages 7 and 10 years.^{31–34} This also corresponds roughly to the sensitive period for spatial vision in rhesus monkeys.³⁵ All data analyses and model fitting were performed in the R Environment for Statistical Computing.³⁶

RESULTS

Mean visual acuity deficit at the last visit was 0.25 ± 0.19 logMAR below age norms, and the mean foveation fraction was 0.28 (NOFF = -0.9 ± 2.3 logits). Pendular nystagmus had a median onset at 3 months of age (interquartile range, 2–6 months) and transitioned to waveforms with extended foveation periods at a median age of 35 months (interquartile range, 18–82 months). Hence, the duration of pendular nystagmus varied considerably in this cohort (interquartile range, 13–68 months; median 29 months).

The individual deprivation parameter D , calculated as the proportion of the area under the sensitivity profile that corresponded to pendular nystagmus, ranged from zero (i.e., no pendular nystagmus) to 1.0 (i.e., pendular nystagmus during the entire sensitive period until the time of testing), with median 0.94 (interquartile range, 0.58–0.99) (Fig. 2). The five children whose deprivation parameter D was zero included three children who, although they showed pendular waveforms, had very small amplitude nystagmus that was deemed visually insignificant, one child whose nystagmus was observed to be intermittent, and one child for whom the earliest eye movement recordings included jerk waveforms with foveation periods. There was a moderate correlation between the deprivation parameter D and the visual acuity

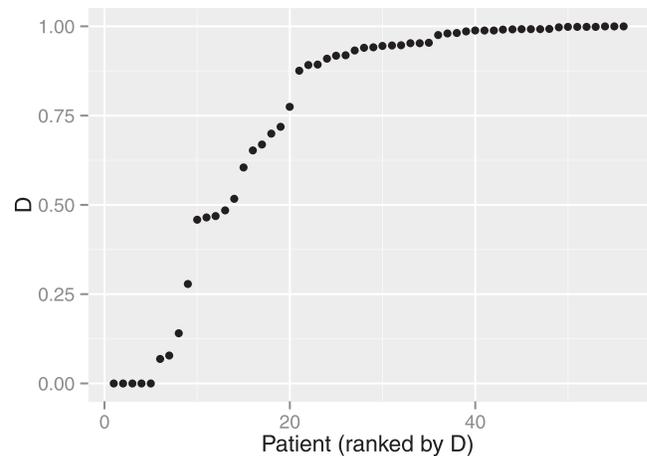


FIGURE 2. In the cohort of 56 patients, the deprivation term D ranged from 0 (no documented pendular nystagmus) to 1.0 (pendular nystagmus during the entire sensitive period).

deficit, with higher values of D associated with more severe visual acuity deficits (Spearman rank correlation $r_s = 0.41$, $P = 0.0018$) (Fig. 3A). There was a slightly weaker correlation between D and fixation stability, with higher values of D associated with lower (poorer) NOFF values ($r_s = -0.32$, $P = 0.015$) (Fig. 3B).

The visual acuity deficit showed an inverse relationship with the child’s nystagmus characteristics at the time of testing, quantified with the NOFF, with larger NOFF values associated with smaller visual acuity deficits (Fig. 4A). By analogy with our previous study, these data were fit with an exponential model, capturing the steeper dependency at the lower range of NOFF values and the asymptotic behavior for higher NOFF values. This model yielded $R^2 = 0.40$ ($P < 0.0001$) for the current data. In order to visualize the latent effect of visual deprivation on the visual acuity deficit data in Figure 4A, the data points were coded by symbol size for the deprivation parameter D . Children with smaller D (i.e., less deprivation; smaller symbols in the figure) tended to have smaller visual acuity deficits, while children with larger D (larger symbols) tended to have larger visual acuity deficits for any given value of the NOFF. The best fit of the two-component model (including the term for the child’s history of pendular nystagmus; Equation 1) resulted in $a = 0.016$ and $b = 1.26$. This implied that poor foveation (0.01 foveation fraction or NOFF ≈ -4.6 logits) was associated with a visual acuity deficit of approximately 0.6 logMAR; the visual acuity deficit gradually reduced to zero for increasingly better foveation. The coefficient c for the deprivation component of the model was 0.22, suggesting that pendular nystagmus for a duration corresponding to one-tenth of the area under the curve of the sensitivity profile (Fig. 1) was associated with an additional 0.022 logMAR visual acuity deficit. The model accounted for 57% of the variance in the visual acuity data, thus providing a better fit ($F_{(1,52)} > 21.1$, $P < 0.0001$) than either component alone (40% for current foveation, 25% for history of pendular nystagmus).

To illustrate the improvement in the proportion of variance explained by moving from the original exponential model to the two-component model, the visual acuity deficit data from Figure 4A were adjusted individually by the amount $c(D - D_{\text{avg}})$ (where the fit parameter $c = 0.22$, D is the individual deprivation parameter, and $D_{\text{avg}} = 0.747$ is the sample mean of the deprivation parameter) and plotted in Figure 4B. This removed the variability due to individual differences in D , resulting in a slightly tighter clustering of data points around

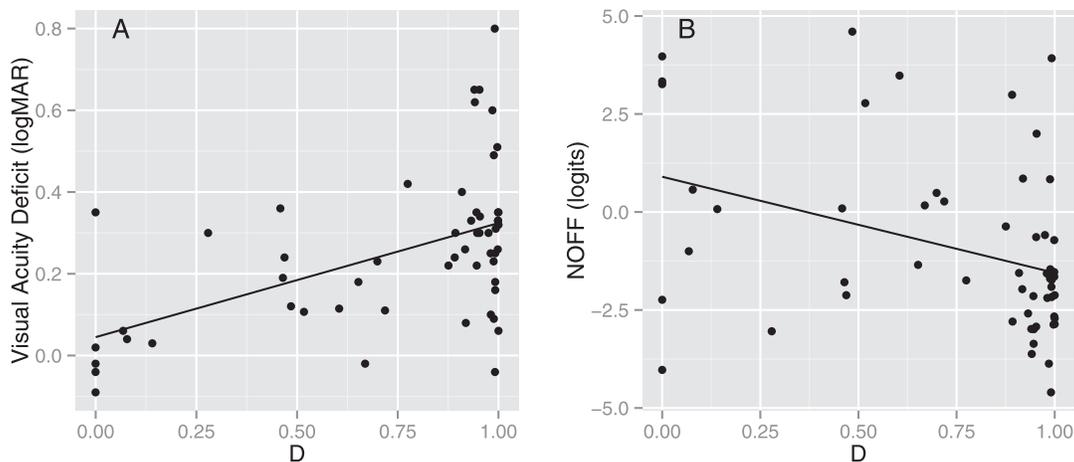


FIGURE 3. (A) The correlation between visual acuity deficit and the deprivation parameter D . Spearman rank correlation $r_s = 0.41$ ($P = 0.0018$). (B) The correlation between NOFF and the deprivation parameter D . Spearman rank correlation $r_s = -0.32$ ($P = 0.015$). The solid lines are the linear regression lines.

the exponential function. This fit converges asymptotically to the value $c^*D_{avg} = 0.168$ logMAR.

DISCUSSION

Using a two-component model to describe visual acuity deficits in children with untreated IIN, we found significant effects of fixation stability (foveation as quantified by NOFF) and of the onset and duration of binocular visual deprivation experienced by the child as a result of pendular nystagmus during the sensitive period of visual development. Similar to observations from previous reports, nystagmus was associated with visual acuity deficits, with the acuity deficit determined, in part, by foveation properties of the nystagmus waveform rather than by nystagmus intensity.^{8,17-20,23,37,38} However, the predictive value of this association is not very strong, as can be seen by the scatter in the data points in Figure 4A. By adding a simple first-order visual deprivation component to the model, the overall portion of explained variance increased (to 57% in the current cohort).

The children in this study all had longitudinal data available that allowed estimating the age of onset of nystagmus and the age at which waveforms with extended foveation periods emerged. Nonetheless, given our typical follow-up regimen, both the age of onset and the age of transition were approximate, thus limiting the accuracy with which the deprivation parameter D could be assessed. Also, the shape of the sensitivity profile (see Fig. 1) was somewhat arbitrary. The exact choice of parameters describing this function, however, did not have a strong effect on the associations (results not shown); a uniform profile (i.e., D determined simply by the duration of the pendular nystagmus between onset and transition) resulted in a weaker association with the visual acuity deficit: $R^2 = 0.20$ (compared to $R^2 = 0.25$ for the profile function shown in Fig. 1).

There are several other factors that may have influenced the amount of residual variance in the data. The visual acuity measurements were likely affected by a number of error sources known to occur in pediatric vision testing: interindividual differences in visual development, small refractive errors that were uncorrected, and the generally larger measurement

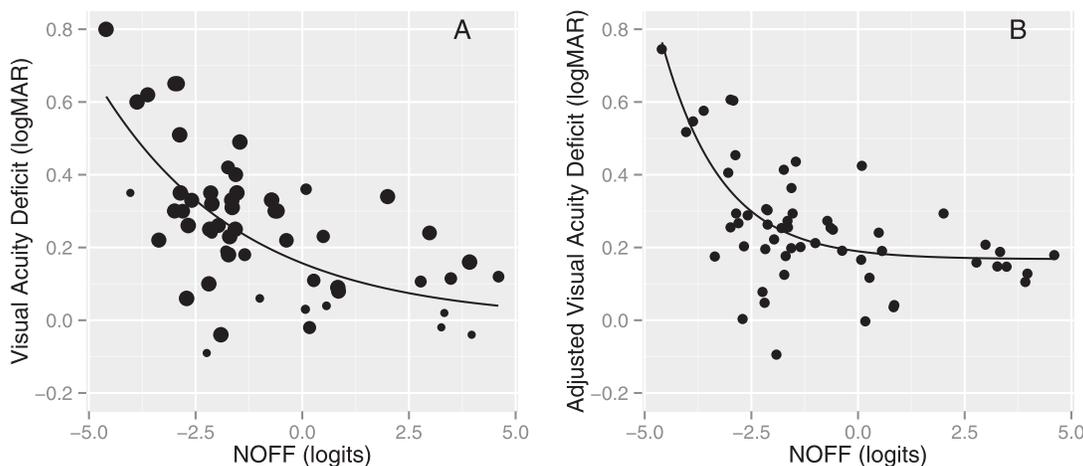


FIGURE 4. (A) Visual acuity deficit plotted as a function of NOFF. Similar to our previous finding,¹⁹ the data were fit reasonably well ($R^2 = 0.40$; $P < 0.001$) by an exponential function. Data points are plotted in symbols of different size according to the individual subjects' deprivation parameter D : Subjects with lower values for D (i.e., a history of less deprivation; smaller symbols) tend to show lower visual acuity deficits than subjects with higher values for D (larger symbols). (B) Visual acuity data adjusted individually by $c(D - D_{avg})$ (i.e., individual vertical shift depending on each child's value of D).

error associated with visual acuity testing in children compared to adults. More importantly perhaps, the assumption that pendular nystagmus causes visual deprivation while jerk-like nystagmus with extended foveation periods does not, is an oversimplification of matters. The amount of visual deprivation due to motion smear likely forms a continuous scale, with high-intensity pendular nystagmus at the severe end and jerk waveforms with long foveation periods at the mild end.

Indeed, our central assumption was that the prolonged motion smear produced by nystagmus eye movements constitutes visual deprivation. We found an association of the visual deprivation parameter *D* with visual acuity deficits. However, it is conceivable that, conversely, any visual acuity deficit somehow contributes to or helps maintain fixation instability. As little is known about the underlying mechanism that leads to the transition from pendular to jerk waveforms in many patients with IIN, we cannot rule out that children with relatively good visual acuity make the transition to jerk waveforms sooner than children with poorer visual acuity, thus establishing a potential two-way interaction between visual function and ocular motor control. Interestingly, our data showed not only associations of visual acuity deficit with *D* and with NOFF, but also an association (albeit weaker) between *D* and NOFF (Fig. 3B). We should therefore emphasize the descriptive nature of the proposed model and warn against inferring causal relationships from it.

Although it remains to be determined if and how the deprivation component resolves over time, our findings have implications for treatment decisions in children with IIN. First, treatment to improve the nystagmus waveform and its foveation characteristics prior to the end of the sensitive period might result in better visual acuity outcome later in life. Second, knowledge about the individual child's time course of the IIN and the various waveforms will be helpful in estimating the potential visual acuity benefit that the child might get from treatment at any age, if the amount of visual deprivation can be estimated.

In conclusion, visual acuity in IIN is explained better if, besides the child's current nystagmus waveforms and the associated foveation characteristics, an additional component is taken into account representing the nystagmus-induced binocular visual deprivation that was experienced during the sensitive period of visual development.

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