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Longitudinal study of spherical refractive error in infantile nystagmus syndrome

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Abstract

Purpose: To explore the onset and progression of spherical refractive error in a population with infantile nystagmus syndrome.
Methods: Retrospective refractive error data were obtained from 147 medical records of children with infantile nystagmus syndrome (albinism $n = 98$; idiopathic infantile nystagmus $n = 49$), attending a low vision clinic in Northern Ireland, over a 24 year period (1986–2010). Data were categorised by age to allow for comparisons with published studies. A prospective group of participants with Infantile nystagmus syndrome (INS) [$n = 22$ (albinism $n = 18$, idiopathic infantile nystagmus $n = 4$)] (aged 0–4) were also recruited. Cycloplegic streak retinoscopy was performed biannually, over a 3 year period. Spherical equivalent refractive error and most ametropic meridian were analysed.
Results: The mean spherical equivalent refractive errors for albinism and idiopathic infantile nystagmus groups (across all age categories) were hypermetropic, with highest levels demonstrated by the participants with albinism aged $1 \leq 4$ years (Mann-Whitney U test, $p = 0.013$). Mean most ametropic meridian was highest in the albinism group aged $1 \leq 12$ years (Mann-Whitney U test, $p < 0.05$). Individual data demonstrated relatively static spherical equivalent refractive errors over time. Prospective participants were hypermetropic at all visits and those with albinism had, on average, higher refractive errors than those with idiopathic infantile nystagmus (IIN). No significant correlations were noted between visual acuity and spherical equivalent refractive errors or most ametropic meridian.
Conclusions: Hypermetropia is the most prevalent spherical refractive error in the INS population, irrespective of level of visual acuity. Individuals with infantile nystagmus syndrome fail to demonstrate typical patterns of emmetropisation, particularly in the presence of albinism.

Introduction

Infantile nystagmus syndrome (INS) is an ocular motor condition, consisting of involuntary, rhythmical oscillations of the eyes.[1] Nystagmus may occur in isolation, known as idiopathic infantile nystagmus (IIN), or in association with other conditions such as albinism. INS is often associated with reduced vision and ametropia. It has been well documented that individuals with INS typically display high levels of astigmatism that are with-the-rule in nature.[2–5] However discrepancy still exists between reports relating to the most prevalent form of spherical refractive component, and little is known regarding onset and progression of spherical refractive error in INS populations. Yahalom *et al.*[6] recently attempted to isolate spherical refractive error in INS (albinism) avoiding the use of

spherical equivalent, and demonstrated a high prevalence (43%) of significant hypermetropia. Investigations of the spherical component using the more conventional spherical equivalent refractive error (SER) or most ametropic meridian (MAM) will allow a more complete description of the spherical errors present in this population and permit direct comparisons with other populations. Additionally, Yahalom *et al.*[6] presented combined data from participants aged from 6 months to 35 years. As refractive error changes significantly in typically developing populations from infancy to adulthood, it may be useful to explore spherical refractive error in INS within narrower age bands, in order to allow for the effects of normal emmetropisation.

Aims

The present study aims to retrospectively analyse the spherical refractive profile of individuals with INS (albinism and IIN) attending a low vision clinic over a 24 year period. In addition, a small group of infants and young children with INS have been recruited to provide prospective longitudinal data.

Methods

Data collection

Refractive error data were obtained from 147 medical records of children with INS [albinism (n = 98), and idiopathic infantile nystagmus (IIN, n = 49)] attending low vision and refraction clinics at The Royal Group of Hospitals (RGH), Belfast (N. Ireland). Data were collected from each individual participant's record from the first appointment, and from subsequent visits thereafter. Time lapses between visits varied but generally were at 3 months (after the initial visit), then every 6 months (for 1–2 years) and then annually, until self-discharge or the data collection period ended. Children were transferred from the 'paediatric low vision clinic' to the 'adult low vision clinic' at 18–19 years of age. The adult and paediatric clinics were held in the same department and staffed by the same practitioners on a different day. Medical files remained the same. Patients were deemed to have self-discharged from the adult low vision clinic after three consecutive non-attendances. The number of visits ranged from one to 15 visits per patient (albinism mean = 6.01 $\pm$ 2.94, range 1–15 visits, IIN mean=4.02 $\pm$ 2.34, range 1–11 visits). Those who attended for three or more visits (albinism n = 83, IIN n = 36) were included in the longitudinal analyses. Retrospective data collection spanned a 24 year period (1986–2010). 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. Individuals with coexisting ocular or neurological conditions were excluded. All eye examinations were performed by experienced paediatric optometrists and refraction techniques included cycloplegia, static distance, and Mohindra retinoscopy.[7] Refractive error was recorded in conventional form (sphere, negative cylinder, & axis) and thereafter converted into spherical equivalent form (SER: sphere +1/2 cylinder) for analysis. Most ametropic meridian [MAM, (meridian furthest away from the retina)] data are also analysed in order to present a full and comprehensive description of spherical refractive error in this population and to ensure that the SER data are not contaminated by high cylindrical errors. For example, the MAM would be +3.00D for the following refractive error; +3.00/ -1.00×180. A summary of astigmatic data is also included. Where available visual acuity measures were noted. During the study period a range of VA tests were employed, including Snellen charts, preferential looking tests and LogMAR acuity tests.

Age group categories

Data were categorised into age group classifications to allow for comparisons with other studies and with normative data.[8,9] The following age groups were used; $\leq$0.5 year, 0.5 $\leq$ 1 years, 1 $\leq$ 4 years, 4 $\leq$ 8 years and 8 $\leq$ 12 years, 12 $\leq$ 16 years, >16 years. Occasionally data were available for some participants more than once within an age band (e.g. participant attended three times whilst they were aged four to 8 years). The data nearest the centre of the age group category were selected for analyses such that individual participants data were represented only once in each age group category.

Prospective data

A group of participants with infantile nystagmus syndrome [n = 22 (albinism n = 18, idiopathic infantile nystagmus n = 4)] (aged zero to 4 years) were recruited from the RGH to explore the early changes in refractive error in INS. Cycloplegic streak retinoscopy was scheduled to occur biannually, over a 3 year period and was performed by the author (NH). A sub-group of participants was randomly selected and refracted a second time (on the same day) by AJJ to confirm the spherical and astigmatic corrections. Both NH and AJJ are Optometrists with extensive experience in clinical optometric assessments of young children with low vision and in particular nystagmus. Informed consent was obtained from each participant's parent. The research followed the tenets of the Declaration of Helsinki.

Results

Retrospective data

Data were normally distributed (Kolmogorov-Smirnov Z test, all $p > 0.05$) however due to the differences in sample size between age groups, non-parametric analyses were used to compare refractive components. Spherical equivalent refractive error (SER) ranged from −13.00DS to +15.00DS in albinism, compared with −6.00DS to +8.00 DS in IIN. Refractive astigmatism ranged from 0 to −7.00DC and 0 to −4.50DC in the albinism and IIN groups respectively. Visual acuity ranged from 0.06 to 1.60 logMAR ($6/7.5^{+2}$–6/240 Snellen). Poorer visual acuity was recorded from the albinism participants [0.20–1.60 logMAR (6/9.5–6/240 Snellen)] than the idiopathic infantile nystagmus (IIN) group [0.06–0.90 logMAR, (6/7.5 + 2–6/48 Snellen]). Regression analyses demonstrated no significant correlations between mean visual acuity and SER or MAM in each age group category for either diagnostic group ($p > 0.05$).

Prevalence of refractive error

The most prevalent form of SER[9,10] was hypermetropia in both albinism (*Table 1*) and IIN groups (*Table 2*).

Spherical equivalent refractive error

The mean SERs for albinism and IIN groups (across all age categories) were hypermetropic. Higher levels of hypermetropia were demonstrated by the albinism participants, with the exception of the >16 year old group (*Table 3*). A statistically significant difference between mean SER in the two diagnostic groups was found in the 1–≤4 year old age group (Mann-Whitney U test, $p = 0.013$) (*Table 3*). In the IIN group the mean SER demonstrated an overall trend towards higher hypermetropia with increasing age. There were no IIN infant data available in the ≤0.5 year old age group for comparison.

Longitudinal analysis of SER

The SER from individual participants were plotted as a function of age for both subject groups (*Figures 1 and 2*). Only those records that detailed attendance on three or more occasions were included (albinism $n = 83$, IIN $n = 36$). Each individual line represents graphical data from one patient's attendance at the low vision clinics.

Table 1. Prevalence of spherical equivalent refractive error (SER) (%) classification in albinism. Note that individuals may be represented more than once in the table but they are only represented once in each age category

		Prevalence of SER (%) in albinism age groups (years) (*n*)						
Refractive error (SER)	**SER Range (D)**	**≤0.5 (*n* = 9)**	**0.5 ≤ 1 (*n* = 14)**	**1 ≤ 4 (*n* = 31)**	**4 ≤ 8 (*n* = 63)**	**8 ≤ 12 (*n* = 60)**	**12 ≤ 16 (*n* = 50)**	**>16 (*n* = 31)**
Emmetropia	−0.50 > D < +0.50	2 (22%)	1 (7%)	4 (13%)	3 (5%)	8 (13%)	7 (14%)	3 (10%)
Low hypermetropia	≥ + 0.50	3 (33%)	4 (29%)	8 (26%)	14 (22%)	6 (10%)	6 (12%)	5 (16%)
Moderate hypermetropia	≥ + 2.00 to < + 6.00	3 (33%)	7 (50%)	14 (45%)	29 (46%)	27 (45%)	23 (46%)	11 (36%)
High hypermetropia	≥ + 6.00	1 (11%)	2 (14%)	4 (13%)	12 (19%)	11 (18%)	5 (10%)	3 (10%)
Myopia	≤ − 0.50	0	0	1 (3%)	5 (8%)	8 (13%)	9 (18%)	9 (29%)

Table 2. Prevalence of spherical equivalent refractive error (SER) (%) classification in idiopathic infantile nystagmus (IIN). Note that individuals may be represented more than once in the table but they are only represented once in each age category. Data were not available for infants aged zero to 6 months with IIN

		Prevalence of SER (%) in IIN age groups (years) (*n*)						
Refractive error (SER)	**SER Range (D)**	**≤0.5 (*n* = 0)**	**0.5 ≤ 1 (*n* = 3)**	**1 ≤ 4 (*n* = 14)**	**4 ≤ 8 (*n* = 31)**	**8 ≤ 12 (*n* = 26)**	**12 ≤ 16 (*n* = 20)**	**>16 (*n* = 13)**
Emmetropia	−0.50 > D < +0.50	_	0	2 (14%)	5 (16%)	4 (15%)	1 (5%)	1 (8%)
Low hypermetropia	≥ +0.50 to < +2.00	_	2 (67%)	4 (29%)	3 (10%)	7 (27%)	7 (35%)	2 (15%)
Moderate hypermetropia	≥ +2.00 to < +6.00	_	1 (33%)	3 (21%)	15 (48%)	11 (42%)	6 (30%)	8 (62%)
High Hypermetropia	≥ +6.00	_	0	1 (7%)	3 (10%)	1 (4%)	1 (5%)	0
Myopia	≤ −0.50	_	0	4 (29%)	5 (16%)	3 (12%)	5 (25%)	2 (15%)

Table 3. Mean spherical equivalent refractive error (SER) in the albinism and idiopathic infantile nystagmus (IIN) groups for all age categories

Age group (years)	SER (D) (±SD)				
	Albinism	***n***	**IIN**	***n***	***p* value**
≤0.5	+2.64 + /−2.42	9	–	0	–
0.5 ≤ 1	+3.00 + /−2.42	14	+1.10 + /−1.32	4	0.13
1 ≤ 4	+2.69 + /−2.32	32	+0.70 + /−3.08	14	0.013*
4 ≤ 8	+2.81 + /−3.72	67	+1.74 + /−2.86	30	0.08
8 ≤ 12	+2.62 + /−3.30	62	+1.61 + /−2.31	25	0.13
12 ≤ 16	+1.91 + /−3.26	52	+1.08 + /−3.24	20	0.40
>16	+1.84 + /−3.45	32	+2.10 + /−2.33	13	0.77

*Indicates significant difference.

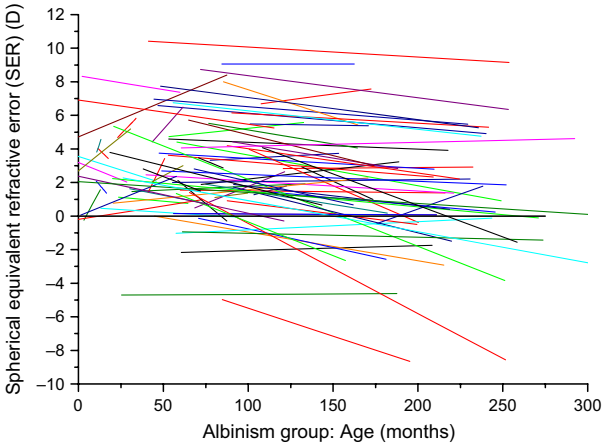

Figure 1. Spherical equivalent refractive error (SER) profile as a function of age in the albinism group. Each line represents graphical data from a single individual attending on three or more occasions (n = 83).

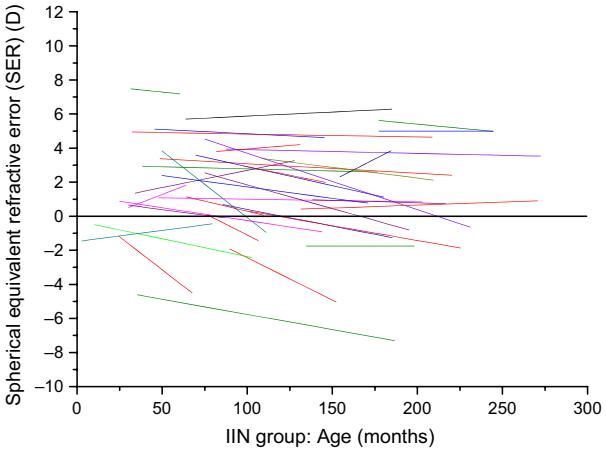

Figure 2. Spherical equivalent refractive error (SER) profile as a function of age in the idiopathic infantile nystagmus (IIN) group. Each line represents graphical data from a single individual attending on three or more occasions (n = 36).

Slope value analyses

Slope values were calculated for each individual participant. Whilst Mann-Whitney analyses demonstrated no significant differences in slope values between the two diagnostic groups (SER p = 0.10, MAM p = 0.15) regression analysis demonstrated that spherical errors had a tendency to decrease over time in the IIN group (SER $p < 0.01$, MAM $p < 0.01$) (IIN slope values SER: −0.01, MAM −0.02) in contrast to the albinism group where slope values were not statisticially significantly different from zero (SER p = 0.94, MAM p = 0.54) (Albinism slope values: SER −0.0003, MAM −0.004).

Figure 3 below compares mean SER found in the different age groups with data from typically developing children.[8,9]

Most ametropic meridian

The mean 'most ametropic meridian' (MAM) or 'non-optimal meridian' is significantly higher in the albinism groups aged 1 ≤ 12 years (*Table 4*).

Astigmatism

Table 5 displays a summary of mean refractive astigmatism values for both groups. In both the albinism and IIN groups mean refractive astigmatism increased with increasing age. Data were not available for infants aged 0–6 months with IIN. Of those participants with clinically significant astigmatism, the majority exhibited with-the-rule (negative cylinder axis from 1 to 15^0 or $165–180^0$)[12] astigmatism (albinism 90%, IIN 78%).

Prospective data

Spherical equivalent refractive error

Figure 4 illustrates spherical equivalent refractive error (SER) as a function of age. Each line represents an individual child who attended on two or more occasions (n = 12). The normative boundary is represented by Mayer *et al.*'s[8] 'upper and lower limits of normal'. The SER data from the children with albinism varied over the study time period [n = 4, 33% (SER remained inside normative boundary); n = 6, 50% (SER remained outside boundary for duration of study); n = 2, 17% (SER started within boundary but fell outside by 10 months of age)]. Data from the children with IIN (n = 3, 100%) remained within the normative boundary throughout the study period (*Figure 4*).

Discussion

The present study successfully collected retrospective refractive error data from 147 medical files of children with infantile nystagmus syndrome (INS). A wide spectrum of

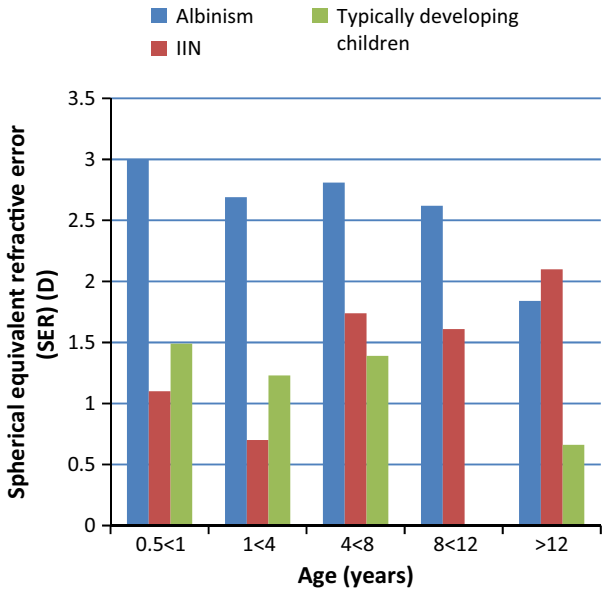

Figure 3. Mean spherical equivalent refractive error (SER) of participants with albinism and IIN compared with typically developing children. 'Visually normal' comparative data were available for children aged 7–12 months, 1–4 years from Mayer *et al.*[8] cited in Wang *et al.*[11] and for 6–7 year olds and 12–13 year olds from O'Donoghue *et al.*[9] Note there are no visually normal data for 8 < 12 year olds.

Table 4. Mean mean most ametropic meridian (MAM) in albinism and idiopathic infantile nystagmus (IIN) groups for all age categories

Age group (years)	MAM (D) (±SD)				
	Albinism	*n*	IIN	*n*	*p* value
≤0.5	+3.50 ± 2.63	9	*n*/A	0	–
0.5 ≤ 1	+3.57 ± 2.53	14	−0.58 ± 0.63	3	0.18
1 ≤ 4	+3.70 ± 2.54	32	+1.32 ± 3.60	14	0.015*
4 ≤ 8	+3.78 ± 4.20	63	+2.45 ± 3.17	31	0.034*
8 ≤ 12	+3.39 ± 4.14	60	+2.14 ± 2.80	26	0.034*
12 ≤ 16	+2.55 ± 4.34	50	+1.46 ± 4.11	20	0.11
>16	+1.65 ± 5.01	31	+3.15 ± 3.26	13	0.44

*Statistically significant.

Table 5. Mean refractive astigmatism in both albinism and idiopathic infantile nystagmus (IIN) groups (across all age categories).

Age group (years)	Refractive astigmatism (±SD) (D)			
	Albinism	*n*	IIN	*n*
≤0.5	−1.72 + /−0.94	9	–	0
0.5 ≤ 1	−1.91 + /−0.97	14	−0.81 + /−0.69	4
1 ≤ 4	−2.26 + /−1.20	32	−1.36 + /−1.27	14
4 ≤ 8	−2.47 + /−1.30	67	−1.48 + /−0.90	30
8 ≤ 12	−2.76 + /−1.30	62	−1.60 + /−0.76	25
12 ≤ 16	−2.73 + /−1.38	52	−2.08 + /−0.94	20
>16	−2.91 + /−1.60	32	−2.67 + /−1.37	13

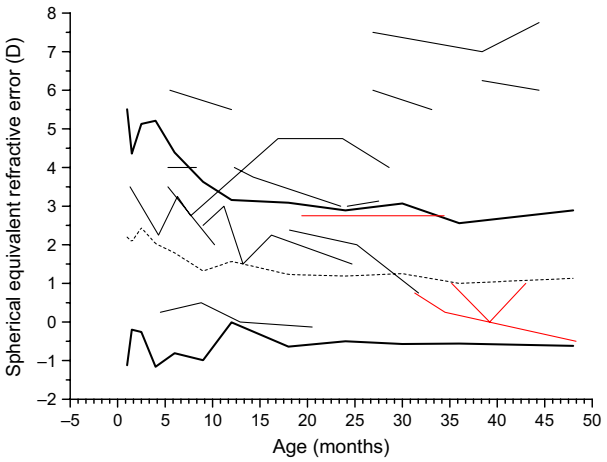

Figure 4. Spherical equivalent refractive error (SER) measured as a function of age (in months) at each visit. Line graph plotted for participants who attended on two or more occasions. Each line represents one individual participant. Only results obtained with cycloplegic refraction are included. The dashed line represents the mean SER from typically developing children and the upper and lower limits of normative data are represented by the darker black lines.[8] Participants with idiopathic infantile nystagmus (IIN) are represented by red lines, and those with albinism by black lines.

refractive errors was demonstrated within the present study group. The greatest range of refractive errors was found in the albinism group. Several studies, using various refractive error assessment methodologies and participant groups of differing ages, had formerly reported contradictory refractive error distributions in populations with albinism. Some studies suggested that myopia was the more prevalent refractive error[3,13,14] whereas others suggested a bias toward hypermetropia.[5,11,15–19] In agreement with the latter studies, results from the present work demonstrated that the most prevalent form of spherical equivalent refractive error (SER) in albinism was hypermetropia. Children with IIN in the present study also had hypermetropic SERs, however these tended to be lower than in the albinism group. Although participant numbers in the IIN group were relatively small, particularly in the youngest age categories, a larger sample size may have been more informative. Children with albinism tended to be assessed in the low vision clinic earlier and more often than those with IIN. This might be because the visual acuities of infants and children with IIN can be relatively good and did not warrant low vision clinic attention. Alternatively referral of children with IIN to the paediatric low vision clinic may have been delayed whilst further investigations were undertaken to confirm a less straightforward diagnosis.

In agreement with previous studies of astigmatism and nystagmus, high levels of astigmatism were present in the current study population. These appeared to increase with age. It has been suggested that these high and increasing

with-the-rule astigmatic errors result from the corneal moulding effects produced by the lids during nystagmus eye movements.[5,20]

It was notable that most ametropic meridian (MAM) results indicated greater significant differences between the groups, than the SER data, perhaps reflecting a truer expression of the spherical element in cases of high astigmatism. Recent work from the authors demonstrates that higher levels of hypermetropia are associated with increasing severity of foveal hypoplasia in albinism using ocular coherence tomography (OCT).[21] As OCT data were not available in the retrospective medical notes it is not possible to draw conclusions on the impact of foveal hypoplasia on SER within the current population.

Emmetropisation

Both the prospective and longitudinal retrospective data explored in the present study, illustrate atypical refractive development profiles in children with infantile nystagmus syndrome (INS). High levels of spherical equivalent refractive error (SER) did not decrease with age as one would expect in typically developing infants. Inspection of the prospective data revealed that 50% ($n = 6$) of prospective participants with albinism fell outside the normal limits for spherical refractive error at each assessment age. Refractive error data from two different prospective participants with albinism fell inside the normal limits until approximately 9 months of age, after which results were observed to be outside the published norms. Prospective participants with a lower SER (<+3.00D) at first visit were more likely to remain within normal limits. These observations reinforce and enhance the findings of previous studies which have explored refractive development in the presence of INS[4,11,22] and support the notion that children with albinism fail to emmetropise. Our work also suggests that children with idiopathic infantile nystagmus (IIN) fail to emmetropise, but additional prospective data with larger participant groups are required to fully explore this.

Analyses of the slope of individual retrospective refractive data over time provide evidence for a failure of emmetropisation in both albinism and IIN groups; with albinism participants displaying a stable spherical refractive error pattern over time and those with IIN demonstrating a more variable profile. These findings are not explained by contamination from the high astigmatic errors also present in this population.

Although visual acuity is likely to have been an important consideration in the failure to emmetropise, the data revealed no correlations between level of visual acuity and SER or MAM. This suggests that visual acuity may have only been one factor in influencing the spherical refractive error outcome and that a combination of the effects of nystagmus, and, in the cases of albinism, poor retinal development and other structural anomalies combined to inhibit emmetropisation. It is important to note that these data are reflective of participants with INS attending low vision clinics, and as such may not fully represent the general INS population.

Conclusion

The current study's findings suggest that emmetropisation is impaired in infantile nystagmus syndrome (INS), with moderate and high levels of hypermetropia being retained beyond infancy well into teenage years, irrespective of visual acuity. Nystagmus oscillations are likely to affect the emmetropisation process as disruption of the visual signal will impact on the visual feedback necessary for accurate emmetropisation. The additional ocular defects associated with albinism (foveal hypoplasia, iris transillumination, fundus hypopigmentation, and visual pathway misrouting) appear to further impact the emmetropisation process, resulting in higher and more complex refractive errors in albinism.

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Disclosure

The authors report no conflicts of interest and have no proprietary interest in any of the materials mentioned in this article.

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