Refractive development in individuals with ocular and oculocutaneous albinism

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Abstract

Purpose
Albinism is known to disrupt emmetropisation in animal models. However, it is not clear if the same effect is seen in humans. This study aimed to investigate the refractive profile in individuals diagnosed with ocular albinism (OA) and oculocutaneous albinism (OCA) based on a large dataset.

Methods
Required data from 618 individuals (61% males and 39% females) diagnosed with albinism were exported from the eyeSmart electronic medical records of L V Prasad Eye Institute. Overall, there were 112 (18%) individuals diagnosed with OA and 506 (82%) with OCA. Based on the spherical equivalent refraction (SER), individuals were classified as emmetropes, myopes, and hyperopes.

Results
The overall spherical equivalent refraction of the individuals ranged from −25.00D to +12.00D with a median +0.25D (−2.00 to +2.25 D). The proportion of individuals with albinism (combined OA, OCA) having hyperopia and myopia (overall: \(N = 282;45.6\%\) vs. \(N = 245;39.6\%\)) were similar (\(p = 0.18\)), and the least were with emmetropia (overall: \(N = 91;14.7\%\)). Across all the age groups (0–10, 11–20, 21–30, > 30 years), the frequency of hyperopes and myopes was significantly higher (\(p < 0.05\)) compared to emmetropes. Both high degrees of hyperopia and myopia were found in individuals diagnosed with OA and OCA. Irrespective of the albinism type, with-the-rule (70%) astigmatism was the most prevalent compared to other types of astigmatism. The frequency of with-the-rule astigmatism was significantly high in the presence of nystagmus compared to individuals with no nystagmus in both OA (75% vs 25%, \(p = 0.01\)) and OCA (77% vs 23%, \(p = 0.014\)) groups.

Conclusion
The presence of both high hyperopia and high myopia and very few numbers with emmetropia across all age groups indicates disrupted normal refractive development in individuals with albinism. With-the-rule astigmatism and nystagmus may result in meridional degradation of the retinal image leading to impairment of normal emmetropisation process in individuals with albinism.

Keywords
Refractive error · Albinism · Astigmatism · Emmetropisation · Myopia

Introduction

Albinism is a group of inherited disorders characterized by either reduced or complete absence of melanin...
pigment due to mutation of the Tyrosinase (TYR) gene that codes for the TYR enzyme. Reduction in melanin biosynthesis results in hypopigmentation of structures such as skin, hair, iris, ciliary body, choroid, retinal pigment epithelium, and a decrease in grey matter volume [1–3]. Broadly, albinism is classified into two types: ocular albinism (OA) which affects only pigmented part of the eye without cutaneous involvement, and oculocutaneous albinism (OCA) which affects both eye and other body parts such as skin and hair [1]. Poor development of fovea and neurological deficit (abnormal decussation of nerve fiber) in albinos accounts for reduced visual acuity [4], stereoacuity [5], nystagmus,[6, 7], and strabismus [8].

Myopia was reported as the common refractive error type in animals with albinism [9–11]. However, the studies investigating the refractive error profile in humans with albinism have found a skewed distribution of refractive error towards hyperopia, with mean spherical equivalent refraction (SER) ranging from +0.46 D [12] to +2.81 D [13] and with-the-rule astigmatism (WTR) being more prevalent among all types of refractive errors [13–17]. The only exceptions were findings by Edmunds [12] (N = 16) and Perez–Carpi nell et al.[18] (N = 7) that showed the equal distribution of refractive error type and a skewed distribution of myopia (mean: −3.50 ± 6.16 D), respectively. Schweigert et al.[19] studied the longitudinal change in refractive error in 75 children with albinism over ten years and observed no significant change in the mean refractive error in three visits spread across a decade (+2.81 ± 2.40 D vs. +2.53 ± 3.40 D vs. +2.15 ± 4.00 D).

Previous research on the refractive profile of individuals with albinism had a limitation of smaller sample size (N = 7 to 75 overall, and fewer than 10 with a high degree of refractive error). As a result, a small variation in distribution across the emmetropic, myopia, or hyperopic cohorts might skew the result towards one side thereby falsely increasing the prevalence of particular refractive error. Given the possibility that albinism may interfere with emmetropisation [16], it is critical to establish the association between refractive error and albinism based on a large sample of individuals distributed across different age groups and albinism types. This study aimed to investigate the refractive error profile in individuals with OA and OCA across different age groups based on a sample of 618 individuals with albinism.

Methods

This is a retrospective study, conducted at the L V Prasad Eye Institute (LVPEI), Hyderabad, India. The individuals who presented to any of the centers of LVPEI for the first-time during August 2010 to August 2018 for a comprehensive ocular examination and were diagnosed with the condition of “albinism” were included in the study. A standard informed general consent was obtained from every individual or the parent/guardian of the minors prior to their clinical examination permitting the use of their electronic medical records information for research purposes. This study was approved by the ethical institutional review board of LVPEI, Hyderabad, and adhered to the tenets of the declaration of Helsinki.

Overall, 618 individuals met the inclusion criteria, of which 18.0% (N = 112) were diagnosed with OA, and 82% (N = 506) with OCA. Additionally, congenital nystagmus was noticed in 73% (N = 451) of all the individuals with albinism. The diagnosis of OCA was made when the individuals had both ocular and cutaneous findings (decreased melanin synthesis in skin, hair follicle, and eye), and as OA when the findings were confined only to the eye and no cutaneous findings.

The required variables such as demographic details, uncorrected visual acuity (UCVA), best-corrected visual acuity (BCVA), spherical, cylindrical, axis values of objective refraction, retinal findings, and the diagnosis of each eye were extracted from the eyeSmart electronic medical records (EMR) of LVPEI. Further analysis was performed only on right eye data as the spherical equivalent refraction was not significantly different between right and left eye (p = 0.74). The individuals with missing data or with any of the other ocular conditions that could influence the refractive error were not included in the study (for example cataract, aphakic, psuedophakic, post-refractive surgeries, keratoconus, silicone oil insertions, and pterygium).

Based on the age at the baseline visit, all individuals were categorized into 4 groups in 10-year intervals, i.e., 0–10, 11–20, 21–30, > 30 years. The UCVA and BCVA were estimated under normal room
illumination with high contrast Snellen visual acuity chart at 20 feet, and conversion to logMAR notation was done for data analyses. Out of 618 individuals with albinism, recording BCVA in both eyes was possible in 458 (74.1%) individuals. Vision was assessed qualitatively based on fixing and following (FFL) techniques in 29 preverbal children (< 3 years), and in two children (> 3 years) who were non-cooperative for either logMAR visual acuity and Lea symbols. When the individuals were not able to read any letter at any distance, visual acuity was recorded using the counting fingers (CF) technique where they were asked to count fingers at progressive shorter distances (distance was recorded when the tasks were performed reliably by the individual). If CF was not applicable, then the examiner used hand movement (HM), and positive perception and projection of torchlight (PR & PL). Poor visual acuity was defined as the combination of CF, HM, and PR & PL.

The objective refraction using retinoscope and subjective refractions were performed by trained optometrists. Cycloplegic refraction was performed 30 min after the instillation of 1% cyclopentolate eye drops in 50% (N = 312) of the individuals per age (< 16 years) and clinical requirements. The SER was defined as the sum of the spherical and half of the cylindrical power. Myopia was defined as SER less than -0.50 diopters (D). Based on degree of myopia, individuals were categorized into mild (< -0.50D to -3.00D), moderate (< -3.00D to -6.00D), high myopia (< -6.00D) [20]. Hyperopia was defined as spherical equivalent refraction more than + 0.50 D. Based on the degree of hyperopia, individuals were categorized into mild (> + 0.50D to + 3.00D), moderate (> + 3.00D to + 6.00D), and high hyperopia (> + 6.00D). Emmetropia was defined as spherical equivalent between -0.50 to +0.50 D. Based on the cylindrical component of the eye, astigmatism was classified as with-the-rule (WTR) if the axis meridian was between 15 degrees on either side of the horizontal meridian (N = 412; 77%), against-the-rule (ATR) if the axis meridian was between 15 degrees on either side of the vertical meridian (N = 27; 5%) and oblique astigmatism if the axis was from 15 to 75 degrees or 105 to 165 degrees (N = 98; 18%) [21].

To determine the annual progression of refractive error, a sub-analysis was performed on the subset (N = 67) of individuals who had come for two visits with a gap of 365–400 days after the baseline visit. The annual progression was calculated as the difference between spherical equivalent refractive error at 1-year follow-up visit and baseline.

**Statistical analysis**

IBM SPSS statistics 23.0.0 (SPSS, Inc, Chicago, IL) was used to perform all the statistical tests, and the inbuilt features of MS-Excel 2016 (Microsoft Corporation) were used to plot the graphs. Descriptive statistics of the variables such as age, gender, nystagmus, types of refractive error, astigmatism, and types of albinism were provided in the form of frequencies. The Shapiro–Wilk test indicated that SER, age, and BCVA were not normally distributed. Median and interquartile range (IQR) were calculated for age, SER, BCVA, and astigmatism. Mean ± standard error (SE) was calculated for the spherical equivalent at baseline visit and annual refractive error progression. Chi-square test/Contingency table was used to identify the significance of the difference in proportions of hyperopia, myopia, and emmetropia and the individuals with and without nystagmus in WTR, ATR, and oblique astigmatism in both albino groups. The Mann–Whitney test was used to see if the median SER differed by gender. The same test was applied to evaluate the difference in BCVA between two albino groups. Kruskal–Wallis test was performed to test the significance level of SER in different age groups. ‘P’ value of < 0.05 was considered statistically significant.

**Results**

The distribution of individuals based on age, gender, and refractive error is summarized in Table 1. Overall, the median (IQR) age of all the individuals with albinism was 10 (5–18) years. Individuals with OA were slightly older than the individuals with OCA individuals (14 (7–24) vs. 9 (5–16) years, p = 0.001). Overall, there were 376 (61.0%) males and 242 (39.1%) females combining both the albinism groups. The median SER of males and females in both OA and OCA groups was similar (p = 0.96 and p = 0.30, respectively). No significant difference (p = 0.903) in SER was observed between different
Table 1  Participant details based on age, gender, spherical equivalent, and refractive error type in individuals diagnosed with ocular and oculocutaneous albinism

| (IQR)       | Overall       | Ocular albinism | Oculocutaneous albinism |
|-------------|---------------|-----------------|-------------------------|
|             | Median age    | Median SER      | Median age              | Median SER      | Median age | Median SER       |
|             | (IQR) in years| (IQR) in D      | (IQR) in years          | (IQR) in D      | in years   | (IQR) in D       |
| Overall     | 10 (5–18)     | 618             | 14 (7–24)               | 112             | 9 (5–16)   | 506             |
| 0–10        | 6 (3–8)       | 328 (53.0)      | 6 (2–8)                 | 39 (34.8)       | 6 (3–8)    | 289 (57.1)      |
| 11–20       | 15 (13–18)    | 177 (28.6)      | 14.5 (14–17)            | 37 (33.0)       | 15 (13–18) | 140 (27.6)      |
| 21–30       | 24 (22–27)    | 69 (11.1)       | 26 (23–27)              | 17 (15.1)       | 24 (22–26) | 52 (10.2)       |
| > 30        | 38 (33–43)    | 44 (7.1)        | 40 (34–44)              | 19 (16.9)       | 35 (33–42) | 25 (4.9)        |
| Gender      |               |                 |                         |                 |            |                 |
| Males       | 376 (61.0)    | 0.50 (–2.00     | 65 (58.0)               | –0.25 (–2.50    | 311 (61.4) | 0.50 (–2.00     |
|             |               | to + 2.38)      |                          | to + 2.00)      |              | to + 2.50)      |
| Females     | 242 (39.1)    | 0.25 (–2.06     | 47 (41.9)               | 0.25 (–2.00     | 195 (38.5) | 0.00 (–2.25     |
|             |               | to + 1.75)      |                          | to + 1.38)      |              | to + 2.00)      |
| Refractive error |            |                 |                         |                 |            |                 |
| Overall SER | 0.25 (–2.00   | 0.13 (–2.22     | 0.50 (–2.00             |                 |            |                 |
|             | to + 2.25)    | to + 1.75)      |                          | to + 2.38)      |              |                 |
| Emmetropia  | 91 (14.7)     | 0.00 (–0.25     | 21 (18.8)               | 0.25 (–0.25     | 70 (13.8)  | 0.00 (–0.25     |
|             |               | to + 0.38)      |                          | to + 0.50)      |              | to + 0.25)      |
| Myopia      | 245 (39.6)    | –2.75 (–7.25 to| 48 (42.9)               | –2.75 (–6.16 to| 197 (39.0) | –3.00 (–7.50 to|
|             |               | –1.50)          |                          | 1.50)           |              | –1.50)          |
| Hyperopia   | 282 (45.6)    | 2.44 (1.50–4.25)| 43 (38.3)               | 2.00 (1.25–4.00)| 239 (47.2) | 2.50 (1.50–4.38)|
| Astigmatism | 535 (86.6)    | –2.50 (–3.13 to| 86 (76.7)               | –1.50 (–2.25 to| 449 (88.7) | –2.50 (–3.44 to|
|             |               | –1.38)          |                          | –1.00)          |              | –1.56)          |
age groups (0–10, 11–20, 21–30, > 30 years) in individuals diagnosed with OA. However, there was a statistically significant difference in SER between age groups in OCA as determined by the Kruskal–Wallis test ($p = 0.013$). Overall, there was a significant difference in median SER in different age groups in individuals with albinism ($p < 0.009$) with median SER showing overall myopic shift with increasing age.

Figure 1 shows the distribution of refractive error in individuals with ocular and oculocutaneous albinism. The overall SER of the individuals (combined OCA and OA) ranged from $-25.00$ D to $+12.00$ D indicating the presence of both high hyperopia and high myopia in individuals diagnosed with albinism.

The most prevalent refractive error type across individuals (combined OA, OCA, with or without congenital nystagmus) were hyperopia (overall: $N = 282$; 45.6%) and myopia (overall: $N = 245$; 39.6%), and the least was emmetropia (overall: $N = 91$; 14.7%). Overall, there was no significant difference in the percentage of individuals in myopic and hyperopic refractive groups ($p = 0.18$). Figure 2 shows the proportion of hyperopes and myopes were significantly higher compared to emmetropes across all age groups ($p < 0.001$).

![Graph A](image1.png)

![Graph B](image2.png)

**Fig. 1** Distribution of individuals based on spherical equivalent refractive error in (A) ocular albinism, (B) oculocutaneous albinism group. ‘Emm’ indicates emmetropia and “Mod” indicates moderate

![Graph A](image3.png)

![Graph B](image4.png)

**Fig. 2** Distribution of individuals based on refractive errors in (A) ocular albinism, and (B) oculocutaneous albinism group

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Considering both the groups, i.e., OA and OCA together, the sub-group analysis of refractive error revealed that the proportion of individuals with mild hyperopia was significantly greater \((N = 174; 61\%)\) compared to mild myopia \((N = 132; 53.8\%\), \(p = 0.016\); the proportion of moderate hyperopia \((N = 73, 25.8\%)\) was significantly higher compared to moderate myopia \((N = 40, 16.3\%), \(p = 0.002\). However, the proportion of high myopia \((N = 73, 29.7\%)\) was significantly high compared to hyperopia \((N = 35, 12.4\%), \(p = 0.001\) when both albinos groups were considered together.

Astigmatism (range: \(-0.25\) D to \(-6.00\) D) was found in 86.6\% \((N = 535)\) of the individuals with the median of \(-2.50\) \((-3.13\text{-}1.38)\) D. Irrespective of the albinism type (OA or OCA), the most prevalent type of astigmatism noted was WTR (70\%), followed by OA (20\%) and the least was ATR (10\%). The proportion of WTR astigmatism was significantly higher in the presence of nystagmus compared to individuals with no nystagmus in both OA (75\% vs 25\%, \(p = 0.01\)) and OCA (77\% vs 23\%, \(p = 0.014\)) group. Likewise, oblique astigmatism was also found to be higher in presence of nystagmus compared to the without nystagmus group in both OA (65\% vs. 35\%, \(p = 0.013\)) and OCA (79\% vs. 21.0\%, \(p = 0.02\)) group (Fig. 3).

Out of 618, the percentage of individuals with poor visual acuity was greater in OCA group (88\%) compared to OA group (13\%). Significant difference \((p = 0.0001)\) was found in median BCVA between individuals with OCA 0.80 (0.60 to 1.00) log MAR and OA 0.50 (0.30 to 0.80) log MAR. BCVA in individuals with congenital nystagmus 0.80 (0.60 to 1.00) log MAR was significantly less \((p = 0.001)\) compared to those without nystagmus 0.60 (0.30 to 0.80) log MAR.

Annual follow-up evaluation was conducted in 11\% (67) of the total study cohort. Out of which, 15\% \((N = 10)\) of the individuals had OA and 85\% \((N = 57)\) had OCA. The most prevalent type of refractive error in this cohort was hyperopia \((N = 30; 45\%)\), followed by myopia \((N = 29; 43\%)\) and emmetropia \((N = 8; 12\%)\). The mean SER \pm standard error of mean [SEM] in myopes was \(-4.0 \pm 0.77\) D and in hyperopes was \(+2.61 \pm 0.41\) D; the corresponding annual progression was \(-0.16 \pm 0.24\) D and \(-0.50 \pm 0.25\) \((p = 0.04)\), respectively, with an overall mean annual progression was \(-0.67 \pm 0.56\) D.

**Discussion**

The current study was conducted to examine the refractive profiles in a large cohort of patients diagnosed with OA or OCA. The main findings that emerged from the present retrospective analysis indicates that both hyperopia and myopia were more prevalent compared to emmetropia in individuals with albinism, which was consistent across all age groups. Furthermore, the myopic shift in mean SER was observed with an increase in age in individuals with...
diagnosed with albinism. High degree of refractive error showed an equal distribution of high myopia and high hyperopia.

In both the OA and OCA groups, a high degree of WTR astigmatism was consistently prevalent compared to ATR astigmatism and oblique astigmatism. WTR astigmatism was more prevalent in the presence of nystagmus compared to individuals with no nystagmus. In addition, the rate of change in mean SER among a subset of the albino group indicated a progression of 0.67 D in a 1-year follow-up.

Previous research studies investigating refractive profile in individuals with albinism had a small sample size (N ≤ 25 in 4 studies with N < 10 with high refractive errors and 1 study had 75 individuals) as compared to the present study [14–19, 22–24]. Therefore, to our knowledge, this is the first study to report refractive profile and distribution in a large cohort of patients with albinism. Based on a large data set, we report a similar proportion of mild, moderate, and high hyperopic and myopic individuals with both OA and OCA groups. The distribution of SER found in this study (−25 D to +12 D) was evident in a related work by Perez-Carpinell et al. [18] (−3.50 ± 6.16, n = 7), while the mean SER was higher compared to our findings which are likely due to the smaller sample size in Perez-Carpinell et al. study. On contrary, other studies have reported relatively hyperopic mean SER in a small sample of albino individuals [12, 13, 16]. Wildsoet et al. [16] reported mean SER +1.07 D (hyperopes > myopes), ranging from −10.50 D to +9.13 D. In the current study, we found a similar percentage of hyperopes and myopes in both OA and OCA (45% vs. 40%, p = 0.18) with median SER of −0.50 D which could be attributed to a large number of individuals with high myopia (> 6D: 75 out of 246 total myopes and > 10 D: 32 of 246) compared to other studies.

In accordance with our findings of 87% of individuals with albinism exhibiting astigmatism ranging from −0.25 D to −6 D, earlier studies have reported mean astigmatic refractive error ranging from −1.07 D to −2.58 D [18, 24], and the WTR astigmatism as the common findings ranging over 50% to 100% [13, 18, 25]. Previous reports have indicated that impaired emmetropisation in albinos was associated with an increasing degree of astigmatism, with no change in spherical equivalent and refractive error [26, 27]. We found a higher percentage of WTR astigmatism among albinos associated with nystagmus, which supports the earlier conclusion of the etiological link of WTR astigmatism with nystagmus among individuals with albinism which needs to be further investigated through prospective study to determine causal relationship [16]. Furthermore, when comparing individuals with and without nystagmus, the percentage of oblique astigmatism was observed to be greater in those with nystagmus. While oblique astigmatism is the least frequent form of astigmatism compared to WTR and ATR in the general population [28–30], it is considerably more common in an individual with albinism. It suggests that in addition to WTR, oblique astigmatism might be one of the clinical characteristics of an individual with albinism.

The potential explanation by Grosvenor et al. [31] indicated that the development of astigmatism in individuals with albinism is primarily corneal in origin where the presence of nystagmus lowers the corneal rigidity which catalyzes corneal molding under influence of eyelids. Several other factors such as genetics, extra-ocular muscle tension, eyelid pressure, visual feedback have been considered to be the possible link for the development of astigmatism [32]. Among OA and OCA, it was proposed that a severe amount of glare and photosensitivity causes persistent squinting of eyes and therefore could give rise to astigmatism due to corneal molding under influence of eyelid pressure [19]. And, indeed our findings of the higher percentage of WTR astigmatism in the OCA group could be attributed to the same. Wildsoet and colleagues [16] have speculated that the emmetropisation process in albino individuals might follow a different pathway through “meridional emmetropisation”, where the meridional difference in image detail results in an unequal emmetropisation rate in individuals with albinism. Given that emmetropisation is guided by visual feedback guided loop, it seems plausible that large meridional differences in image detail due to astigmatism with nystagmus results in abnormal visual input and thus resulting in impaired emmetropisation in albinos. The rarity of emmetropia across all age groups provides further support for impaired emmetropisation.

We found that individuals with albinism have higher degrees of ametropia both high myopia and high hyperopia ranging from −25 D to +12 D. It potentially suggests that high refractive error (irrespective of the sign) might be indicative of impaired
emmetropisation in an individual with albinism. Furthermore, significant variation in mean SER was found across age groups in those with OCA, but not in OA. The exact reason seems to be unclear why there was no significant difference in mean SER across age groups in OA; however, it could be due to less sample size across the age groups.

In the context of the percentage of type of albinism reporting to the medical service, we found that the higher percentage of albinos reporting to our eye care service were patients with OCA compared to those with OA. Because OCA affects both skin and eye, referrals from general physicians to eye hospitals/institutes may be more prevalent than when an individual suffers from only OA. Because individuals with OCA have a higher risk of skin cancer owing to lack of skin pigment, and because glare and photosensitivity are more common in OCA group might be the reason that they usually require a regular visit to eye care or skincare specialist. The low number of OA patients in our cohort is partly explained by the fact that OA accounts for just 18% of all the albinism cases.

The main strengths of the present study are the inclusion of a large sample of individuals with albinism across different age and refractive error groups. In addition, we were also able to follow up a subset of albinos to determine the longitudinal change in refractive error over time. There were certain limitations in the present study such as we are unable to classify OCA into sub-types, and the absence of biometric data (axial length, anterior chamber depth) which might have provided much detailed analysis of both refractive distribution and biometry among various subtypes of OCA. Secondly, we cannot rule out the presence of corneal astigmatism which could be a potential reason for a higher percentage of WTR in individuals with albinism. Because the study was done in a hospital-based setting, referral bias could not be ruled out, as it would tend to overestimate abnormal refractive findings/underestimate the true rate of emmetropia. Lastly, we were able to follow-up on only a small subset of individuals for a shorter duration to determine the change in refraction over time. However, previous research has found that that a one-year follow-up period is sufficient to detect changes in refractive error [21, 33]. Furthermore, there no control group was used to establish if the progression of refractive error is due to albinism or it is a normal development period.

In conclusion, based on a large data set of individuals with albinism, a large variation in refractive error profile is noted in both OA and OCA, with a similar distribution of both hyperopes and myopia, and with WTR meridional astigmatism being most prevalent. A similar proportion of individuals in high degrees of refractive error indicates impaired emmetropisation in individuals with albinism. Further longitudinal studies are warranted to investigate the potential role of meridional astigmatism on visual input, and especially given the nature of the disease, albinism may improve understanding of the association between melanin, dopamine, and refractive error.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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