Original Article

Phenotypic variations in ocular features among siblings with oculocutaneous albinism

Manjushree Bhate, Sakshi Lalwani, Subhabrata Chakrabarti[1]

Purpose: To assess the clinical profiles, presenting ocular features, and variations in the phenotypic features in siblings with oculocutaneous albinism (OCA). **Methods:** Electronic medical records of consecutive siblings diagnosed with albinism from January 2016 to December 2020 were reviewed to identify the affected siblings. The variations in their phenotypic characteristics were studied. **Results:** Significant variations were observed in the clinical features between the siblings (n = 42). A difference of >2 lines in visual acuity was observed in 50% (n = 21) of the sibling pairs. Compound hyperopic astigmatism was the commonest refractive error. The refractive status was different in 80.95% (n = 34) pairs. Although individually strabismus and abnormal head posture were observed in one-third and one-fourth of individual children, respectively, both siblings with similar strabismus were seen in only 16.67% (n = 7) and with a similar abnormal head posture in 13.33% (n = 5). Nystagmus was the most consistent finding across these siblings with a similar nature of horizontal jerk or pendular in 65% of sibling pairs. **Conclusion:** This study observed significant variations in phenotypic presentations among siblings with OCA. Such differences in clinical manifestations and severity would be helpful in appropriate counseling of these families as the need for rehabilitation services is likely to vary across siblings.

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Oculocutaneous albinism (OCA) is one of the commonly inherited autosomal recessive conditions, which is characterized by reduced or absent melanin affecting the eyes, hair, and skin to varying degrees of severity. The variations in presentation indicate a spectrum from mild to severe forms of visual impairment. The impact of albinism on individuals from a psychosocial and visual impairment perspective is enormous. Marked phenotypic variations have been observed in patients with albinism.[1] There are several reports on the clinical profiles and presentations of OCA patients, but to our knowledge, there are no studies that have looked at siblings with phenotypic variations in OCA.

Herein, we present a detailed clinical profile and phenotypic variations across 42 unrelated pairs of siblings with OCA that presented at the L.V.Prasad Eye institute Hyderabad India , over a period of 5 years (2016–2020).

Methods

The study was approved by the Institutional Review Board and adhered to the tenets of the Declaration by Helsinki. The cases were identified from our electronic medical records (EMR) database using the diagnostic code "ICD E70.3" for OCA. The search was confined to the years from January 2016 to December 2020.

A total of 42 pairs of siblings from unrelated families of OCA (<18 years) were included in the study. Most of the families had two affected children and in the one family with three affected children, the older child who was over 18 years of age was excluded. The siblings were coded as S1 and S2.

The clinical diagnosis of OCA was made on the basis of predefined clinical diagnostic criteria (combination of major and/or minor), which included ocular features of reduced vision, nystagmus, iris transillumination, and the presence of fundus hypopigmentation with foveal hypoplasia. Some patients additionally had a visual evoked potential (VEP) for assessing crossed asymmetry. In addition, marked hypopigmentation of skin and hair as compared with parents and unaffected siblings was noted in the affected children.

An ophthalmic workup was carried out for each participant and comprised of uncorrected and the best-corrected visual acuity recorded as Snellen or Teller Acuity Cards/HOTV (in preverbal children). These were converted to logMAR visual acuity except for five patients whose acuities were recorded in terms of fixing the following light. Visual acuity loss was graded as per the WHO criteria, i.e., mild (20/40 or better, >0.3 LogMAR), moderate (20/50 to 20/160, 0.40–0.90 LogMAR), severe (20/200–20/600, 0.1–1.50 LogMAR), and

Strabismus, Pediatric and Neuro-Ophthalmology, Jasti V. Ramanamma Children's Eye Care Centre, L.V. Prasad Eye Institute, Hyderabad, Telangana, [1]Brien Holden Eye Research Centre, L.V.Prasad Eye Institute Hyderabad, Telangana, India

Correspondence to: Dr. Manjushree Bhate, Strabismus, Pediatric and Neuro-Ophthalmology, Jasti V Ramanamma Children's Eye Care Centre, L. V. Prasad Eye Institute, Hyderabad - 500 034, Telangana, India. E-mail: manjubhate@lvpei.org

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profound (worse than 20/600, 1.60–2.40 LogMAR). Cycloplegic refraction with Homide 2% eye drops or Cyclogyl 1% eye drops (cyclophosphamide) was performed and converted to spherical equivalent for statistical analysis. Evaluation of extraocular motility in the nine cardinal positions of gaze was carried out. The evaluation of ocular alignment and strabismus by cover-uncover test and assessment of anomalous/abnormal head posture (AHP) by asking the child to read the visual acuity chart till the smallest possible letter/picture was performed. The nature and characteristics of nystagmus were documented. A detailed anterior segment evaluation with a slit lamp was performed to look for the presence of iris transillumination defects and the posterior segment was assessed for the presence and the degree of fundus pigmentation, optic disc size, color, and the presence or absence of optic disc hypoplasia. The macular area was visualized for the presence of a blunted foveal reflex and foveal hypoplasia.

Ancillary investigations included optical coherence tomography (OCT) macula, A-scan biometry for axial length evaluation, and slit-lamp and fundus photography were deemed necessary. Families were also advised genetic counseling and a systemic workup by a pediatrician to rule out bleeding disorders, chest infections, and associated syndromes.

Results

A total of 42 pairs of siblings (n = 84) were studied and there was a higher male preponderance (57 males: 27 females). The mean age of this cohort was 8 ± 5 years (range: 3 months–18 years). Parental consanguinity was noted in 13/42 sibling pairs (31%).

Visual acuity

The variations in visual acuity ranged from 20/30 (logMAR 0.17) to 20/1400 (logMAR1.84). Collectively, best-corrected visual acuity in the better eye demonstrated a mild vision loss in six (7%), moderate vision loss in 34 (41%), severe vision loss in 32 (38%), and profound vision impairment in the remaining seven (8%) patients. Differences in logMAR vision were seen in 76% of the sibling pairs, whereas the remaining siblings, either showed similar visual acuities or it could not be compared as one of the siblings did not have Snellen/logMAR vision [Fig. 1]. In addition, the best-corrected visual acuity in each eye also showed differences as compared with the fellow eye.

Refractive status

The refractive errors range included myopia (range: −0.50 D to −6.00 D), hyperopia (range: +0.50 D to +10.00 D), and astigmatism (range: −0.50 to −7.00 D). The most common refractive errors were compound hyperopic astigmatism in (n = 58; 68%), compound myopic astigmatism in (n = 10; 11.90%), whereas simple hyperopia and simple myopia were seen in five (5.95%) and four (4.76%) patients, respectively. Seven of 84 children (8.33%) had no refractive error [Fig. 2a]. A wide variation in the refractive status was observed between the sibling pairs. Of the 42 pairs, the refractive status was observed to be dissimilar or different in 34 pairs (80.95%). Eight pairs (19.04%) had similar refractive status across both the siblings of whom, seven pairs (16.67%) presented with compound hyperopic astigmatism while one pair (2.38%) had hyperopia [Fig. 2b].

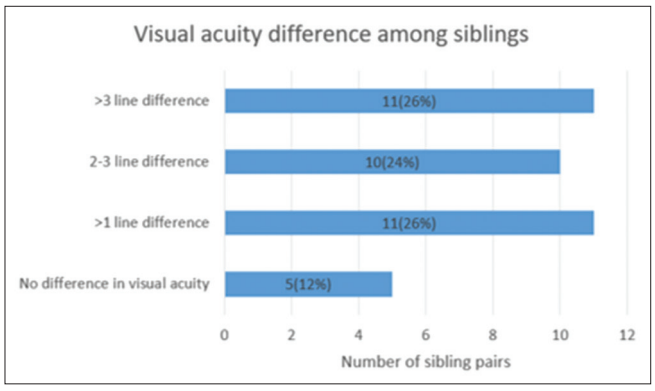

Figure 1: Visual acuity difference among sibling pairs

Strabismus

The presence of strabismus may be linked to the anisometropic amblyopia or to the nystagmus/AHP. Individually, it was observed in 30.95% (n = 26/84) of patients. Exotropia was the more common presentation (10 PD to 55 PD); 11/26 (42%) had manifest exotropia, and 3/26 (12%) presented with intermittent exotropia (X (T)- 5–10 PD). The remaining 8/26 patients (31%) had manifest esotropia (14–50 PD) and two (7.5%) had esophoria (16–18 PD), and only 2/26 (7.5%) had hypertropia (8–10 PD) [Fig. 3a].

Among the sibling pairs, seven (16.67%) presented with strabismus [Fig. 3b]. None of the patients underwent correction for strabismus as well as for AHP.

Abnormal head posture (AHP)

Overall abnormal head posture was observed in 22 patients (26.19%). Face turn was more common (15/22; 68%) followed by head tilt (4/22; 18%), whereas chin down (2/22; 9%) and chin up (1/22; 4.5%) were less prevalent. Among the sibling pairs, 5/42 (13.33%) had an abnormal head posture. The degree of face turn was within the range of 5 to 30 degrees. Head tilt was between 0 and 10 degrees and a chin elevation/depression was 15–20 degrees.

Nystagmus

Out of 84 individuals, 74 (88%) had clinically appreciable nystagmus and 10 (12%) did not show clinically apparent nystagmus. Half of these cases had horizontal jerky nystagmus and the remaining had pendular or dissimilar nystagmus [Fig. 4].

Among the sibling pairs, 20/42 (47.6%) presented with nystagmus, 7/20 (35%) had horizontal jerky nystagmus, 7/20 pairs (35%) had dissimilar nystagmus, and 6/20 (30%) had pendular nystagmus.

Fundus photography and OCT

Hypopigmentation of the fundus and ill-defined foveal reflex was documented in all the patients. The degree of foveal hypopigmentation was documented as marked foveal hypopigmentation with visibility of the underlying choroidal vasculature. The optic nerve size was documented as a small grayish appearance of the optic discs.

An OCT of the macula was performed in 21 children and was suggestive of foveal hypoplasia.

Correlation between visual acuity and age

With regards to age, severe to profound vision impairment in the better eye (<20/200; log MAR <1.0) was overall observed in 19 individual children, of which seven children were ≤6 years

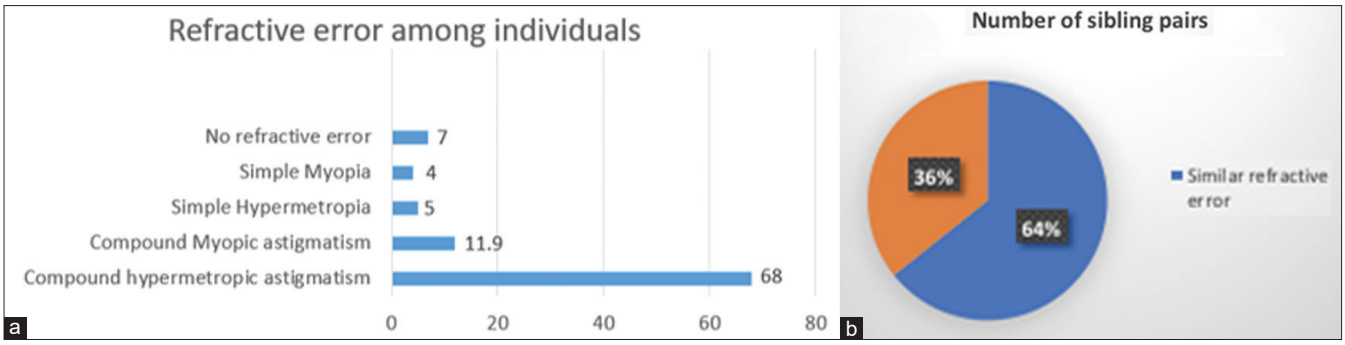

Figure 2: (a) Refractive errors in individual patients (b) : Refractive error in siblings

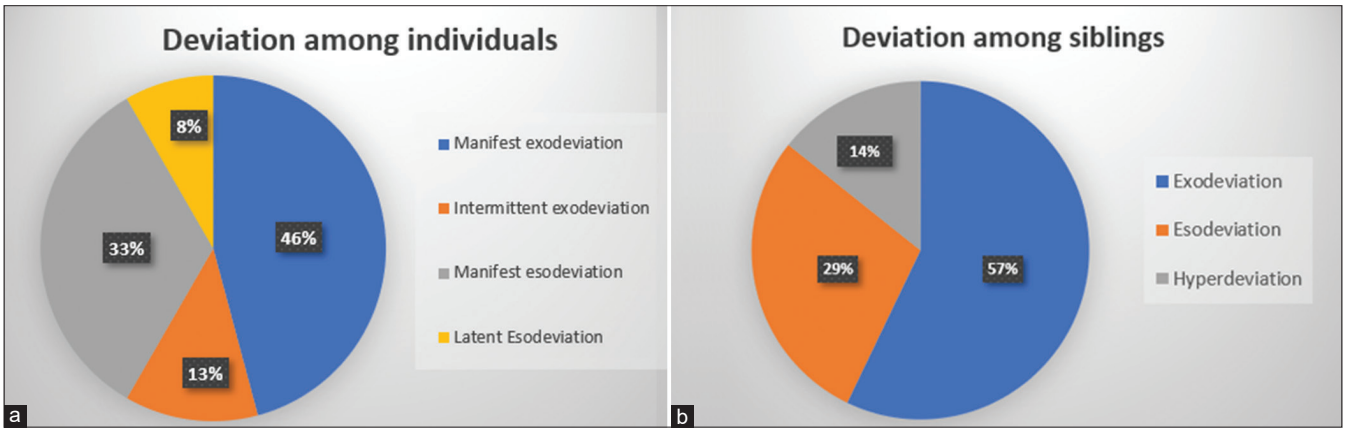

Figure 3: (a) Nature of strabismus in individual patients. (b) Nature of strabismus in sibling pairs

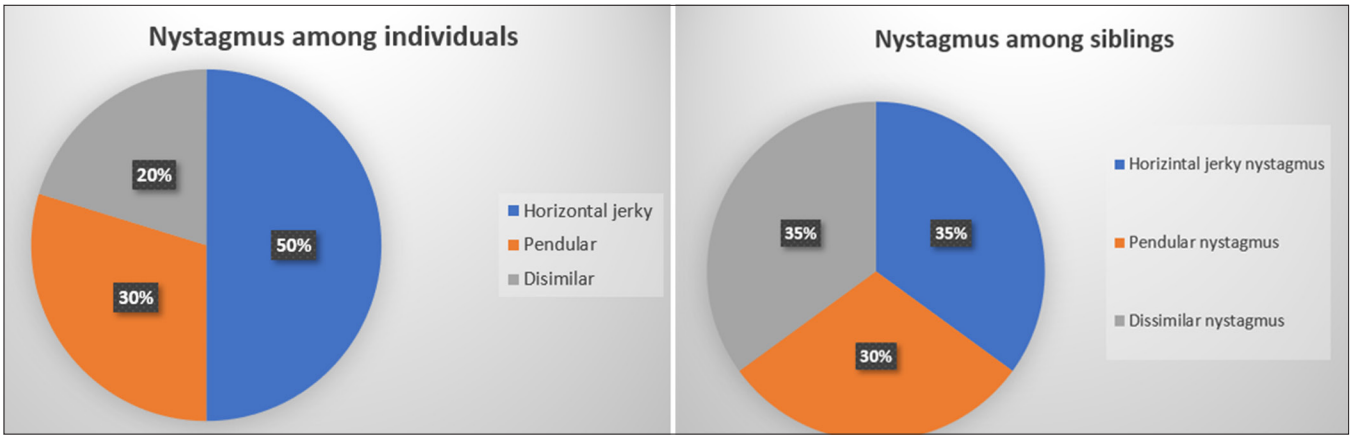

Figure 4: (a) Type of nystagmus in individual patients (b) Type of nystagmus in sibling pairs

of age, eight children were between 6 to 12 years of age, and the remaining were ≥12 years of age.

Correlation between visual acuity, strabismus, abnormal head posture, and refractive error

Among the children with severe to profound vision impairment (better eye), four had an AHP with face turn and none had a head tilt or chin elevation/depression. Strabismus was observed in five children and three of them had both strabismus and AHP.

While among the children with visual acuity of (20/200; logMAR = 1.0) better eye, strabismus was seen in 11 children and AHP was seen in 10. Both strabismus and AHP were observed in six children. Among these, face turn was seen in five, a chin depression was observed in two, and chin elevation in one and two presented with a head tilt.

Furthermore, there was no specific correlation between the age and type or degree of refractive error. Within the group of children with severe to profound vision impairment, hyperopic astigmatism of (>+4.00 D) was noted in 8 children; however, lesser degrees of refractive errors were also observed in this group of children with severe to profound vision impairment.

In children with visual acuity of better than 20/200 (log MAR >1.0), strabismus was seen in ten, AHP in eight (all face turns), while none had both strabismus and AHP.

All children regardless of moderate or severe visual impairment had hypopigmentation of the fundus with foveal hypoplasia.

Discussion

The current study was designed to understand if siblings with oculocutaneous albinism had variable phenotypic presentations. We observed significant variations in the presenting clinical features between the 1st and 2nd siblings within our cohort. The differences in presentations pertained to visual acuity, refractive error, strabismus, and abnormal head posture. Almost half of the sibling pairs had a difference of four Snellen lines or more in their visual acuity. Several factors like strabismus and/or anisometropia leading to amblyopia may be accountable for these differences. The refractive status varied in 80.95% of siblings. It was also observed that one sibling in the pair presented with strabismus in 83.33% and 92.86% had a variation in AHP (either a different or absent AHP) in one of the siblings. This is interesting as the entire cohort exhibited strabismus in a third and AHP in a quarter of all the patients.

Clinical diagnostic criteria for albinism include reduced vision, nystagmus, iris transillumination, foveal hypoplasia, and ocular hypopigmentation (iris translucency and/or fundus hypopigmentation). When in doubt, visual evoked potentials provide confirmatory information of excessive misrouting of the optic nerve. While these features are generally observed in all patients with oculocutaneous albinism, individual variations have been previously reported in the literature.[1-6] However, for siblings who are expected to have a similar genetic profile, it is expected that the phenotypic variation would be minimal.

Phenotypic variations in a large cohort of siblings with albinism siblings have not been reported previously besides a few isolated case reports. A report by Summers *et al.*[2] described variable expression of vision in siblings with albinism, one brother with a visual acuity of 20/100 while the second has similar cutaneous pigmentation and visual acuity of 20/20. Another case report by Cheong *et al*.[3] described variable expressivity of nystagmus in a sibship.

Krujit and colleagues studied the phenotypic spectrum of albinism in their cohort of 522 patients.[1] They noted variations in visual acuity, foveal hypoplasia, nystagmus, and iris translucency. The variation in visual acuity ranged from −0.1 to 1.3 LogMAR, which was regardless of similar or different genetic profiles. However, the clinical presentations of the patients correlated with the different grades of foveal hypoplasia and nystagmus. Nystagmus, iris transillumination, and fundus hypopigmentation, which was absent in 7.7%, 8.9%, and 3.8% of their cohort, respectively. They concluded that none of the characteristics of albinism were present consistently and hence proposed major and minor criteria pertaining to the Northern and Western European populations.[1]

McCafferty *et al*. reported that in their cohort, the majority (40/41) of the patients with albinism, showed a significant improvement in BCVA during the second decade of life and that extraocular muscle surgery was not a significant factor in BCVA improvement in albinism.[4] They considered this important to guide and counsel parents with regard to the child's ability in the classroom, special educational assistance, driving, and other common parent anxieties. Such a pattern of improved visual acuity in the teenage/older sibling as compared with the child/younger sibling in the first decade of life was not noted in our cohort.

The refractive profile of children with oculocutaneous albinism versus an age-matched non-Albino group was reported by Sayad and colleagues.[5] In their study on 82 albino children and 82 non-albino children, they reported that astigmatism (100%) and hypermetropia (62%), respectively, were the most common refractive errors in the former group. All albino eyes (100%) were high astigmats (≥1.25 D).[4] In our cohort, refractive error was observed in 91.67% of children, and astigmatism was most commonly observed (compound hyperopic and compound myopic astigmatism) in 80.95% of children. In our sibling pairs, variations in terms of the degree and nature of the refractive error were observed with 34 pairs (80.95%) demonstrating a different refractive status and only eight pairs (19.04%) with a similar refractive status. The efficacy of spectacles in persons with albinism was studied by Anderson and colleagues. In their prospectively studied cohort, a significant improvement in visual acuity and some improvement in binocular alignment and AHP was observed in patients compliant with spectacles.[6]

Previous studies have attempted to correlate visual acuity with iris transillumination, degree of foveal hypoplasia, and the relationship between the presence of nystagmus, visual acuity, and ocular abnormalities.[1,7-10] Summers *et al*.[11] in his review concluded that heterogeneity in clinical phenotype indicates that expressivity is variable.

A review by Levin *et al*.[12] addressed the wide variety of phenotypes and limited genotypes in albinism patients. The genetic classification subdivides oculocutaneous albinism into OCA type 1 to 7, OCA type 1A being the tyrosinase negative and the most severely affected phenotype also referred to as the "white albino," whereas in the type 1B or the "yellow variant," vision is moderate to severely affected. Liu *et al*.[13] in their review discussed the current and emerging therapies in albinism.

None of our cohort of siblings underwent genetic testing for the type of OCA, however, we observed a significant variation in the clinical features and hence we may have different types of OCA.

To our knowledge, our study is perhaps the first to describe the ocular phenotypic variations in siblings. This may be beneficial while counseling and advising families of the degree of involvement in affected younger siblings.

The limitations of our study include its retrospective nature. Macular OCT's were not performed in all the patients in our cohort, hence the degree of foveal hypoplasia and its correlation with visual acuity cannot be adequately commented upon, in addition to the details of the degree of consanguineous marriages in the families were not adequately documented.

Conclusion

Significant variations in the ocular phenotypic features were noted in siblings presenting with oculocutaneous albinism. Based on these phenotypic variations while counseling families, it would be imperative to add that the severity of clinical

presentations and the need for rehabilitative services are likely to vary between the siblings.

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Conflicts of interest

There are no conflicts of interest.

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