Presence and development of strabismus in children with telecanthus, epicanthus and hypertelorism

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Purpose: To study the presence and development of strabismus in children with telecanthus, epicanthus, and hypertelorism. Methods: This is a prospective, longitudinal, and observational study. Sixty children aged between 6 months and 18 years with telecanthus, epicanthus, and hypertelorism in isolation or in combination were recruited. A detailed analysis of the history, determination of best corrected visual acuity, complete evaluation of strabismus, and ocular examination were carried out. The presence of telecanthus, epicanthus, and hypertelorism and associated strabismus, if any, was noted. All children were followed up for a minimum and maximum period of 12 and 18 months, respectively, to analyze the strabismus (previously present) and for detection of strabismus in those who did not have. The data were analyzed descriptively with mean and standard deviation. Chi square test and Fishers exact test were used to analyze the data between the groups. A P value less than 0.05 was considered to be statistically significant. Results: Telecanthus was the most common lid feature (55%). At baseline, ten (16.66%) children had strabismus (six: exotropia; four: esotropia). Two (3.33%) children underwent surgery. One child developed exotropia at the third follow-up (18 months). At the end of the study, 11 (18.33%) children had strabismus. No significant association was seen between lid characteristics and the type of strabismus. Conclusion: Children with telecanthus, epicanthus, and hypertelorism in isolation or in combination may or may not have associated strabismus. These features can pose difficulty in strabismus diagnosis, which mandates a careful examination, especially in younger age groups and small-angle strabismus. On the other hand, children without strabismus need longer follow-up to detect the development of strabismus and to initiate further management at the earliest.

Key words: Epicanthus, follow-up, hypertelorism, pseudo-strabismus, strabismus, telecanthus

Methods

This was a longitudinal, prospective, and observational study carried out at a tertiary eye hospital in Karnataka between September 2018 and May 2020. The study was approved by the Institutional Review Board and adhered to the principles mentioned in the declaration of Helsinki 2000. Sample size was calculated considering 80% power and 5% level of significance and assuming that 12% of children with pseudo-strabismus develop true strabismus over 18 months as reported previously[4] and considering that 10% lost to follow-up; the sample size required was 53. Children aged between 6 months and 18 years, who visited the pediatric ophthalmology out-patient department, were evaluated by a single senior pediatric ophthalmologist. Those children having features similar to that seen in pseudo-strabismus, such as telecanthus/epicanthus/hypertelorism or the combination, were recruited for the study (recruitment phase: September 2018 to February 2019 – 6 months). Telecanthus was diagnosed if the inner inter canthal distance (ICD) was greater than the palpebral

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fissure width (PFW). [6,7] ICD and PFW were measured by using a digital vernier caliper (SAFESEED carbon fiber electronic vernier digital caliper; manufacturer: SAFESEED; Country: China) graduated in millimeters (0–150 mm): Fig. 1. All measurements were taken by the same person in order to avoid inter-observer variation. ICD was measured between two medial canthi (where the upper lid meets the lower lid medially) and not from any point on the lacrimal caruncle. PFW was measured between medial and lateral canthi.

Children with previous orbito-facial trauma, previous strabismus surgery, or orbital surgeries; those with lid abnormalities (entropion, ectropion, ptosis, coloboma, lagophthalmos), media opacities, pupil abnormalities, and retinal pathologies; and children who could not come for follow-up were excluded. Children in whom there was one or more features of pseudo-strabismus but ICD and PFW measurements and/or evaluation of strabismus (alternate cover test) were not possible were excluded from the study. Details regarding antenatal history, birth history, developmental history, parental consanguinity, family history of strabismus, and other ocular and systemic conditions were noted. Stereopsis and binocular single vision (BSV) were assessed with refractive error correction wherever possible using titmus fly test (for near) and worth four dot test (for distance and near). The uncorrected visual acuity (UCVA) and best corrected visual acuity (BCVA) for distance and near were recorded in each eye separately wherever possible; vision charts were used according to the age of the child: fixating and following objects/fixating and following light in children less than 2 years, kay symbol matching cards in pre-verbal children, and kay symbols and Snellen charts in verbal children. The reduced Snellen chart was used for near vision at 33 cm in verbal children. Values of Kay symbol charts were converted to Snellen equivalent. Abnormalities in the head posture if any were noted. Ocular alignment was tested using Hirschberg test, cover test, cover–uncover test, alternate cover test (to detect phorias), and alternate prism cover test to measure the amount of deviation with a 6 meter fixation target (target being a toy or visible letter of the Snellen chart) and at near with 33 cm fixation target (toy or letter in reduced Snellen), with and without optical correction. Hirschberg and Krimsky tests were considered in children who did not cooperate for the above-mentioned tests. All tests to detect and assess strabismus were performed by the same pediatric ophthalmologist. Following these tests, children in whom either latent or manifest deviation was detected were considered to have associated strabismus. The number of children with features similar to that seen in pseudo-strabismus (telecanthus, epicantus, and hypertelorism) and diagnosed to have had associated strabismus at the first visit was noted down. In the remaining children, who did not have strabismus, a diagnosis of pseudo-strabismus was made. Torch light examination was carried out in all, and slit lamp examination was performed wherever feasible to assess the anterior segment. Cycloplegic refraction with age-appropriate drugs (homatropine 2% three times daily for 3 days in children below 5 years and cyclopentolate hydrochloride 1% two times 10 minutes apart for children above 5 years) was performed in all children. Cycloplegic refraction was evaluated by retinoscopy and/or automated refractometry; subjective correction was carried out wherever possible. The type of refractive error was determined by the post-cycloplegic spherical equivalent refraction (SER), calculated as sphere +½ cylinder. In our study, significant refractive error was defined as follows: for myopia, SER of ≥–0.5 D in one or both eyes; for pathological myopia, SER of ≥–6 D in one or both eyes; for hypermetropia, SER of ≥+0.5 in one or both eyes; for astigmatism, SER of ≥±1.00 D in one or both eyes; and for emmetropia, SER between –0.5 and +0.5 in one or both eyes. Dilated fundus examination was performed in all children, especially to look for macular scars, fibro-vascular proliferation, and macular drag, which can cause strabismus. These cases were excluded from the study. Spectacles were prescribed in children with significant refractive errors. In children with esotropia (ET), full cycloplegic correction was given; a diagnosis of fully accommodative ET was made if the child was orthotropic or corrected within eight to ten prism diopters after spectacle wear for 4–6 weeks. On the other hand, if there was residual ET of more than ten prism diopters after 4–6 weeks with spectacles, a diagnosis of partially accommodative ET was made.

Amblyopia was defined as the difference of two lines or more in visual acuity between the two eyes or a visual acuity worse than or equal to 6/9 with the best optical correction or a lack of central, steady, and maintained fixation. [9] Children with amblyopia were treated with part time occlusion therapy and followed up every 2–3 months. All children were followed up every 6 months for a minimum period of 12 months (two follow-ups) and a maximum period of 18 months (three follow-ups). Those children who missed their follow-up because of coronavirus disease 19 (COVID-19) lockdown (April 2020) came during the last week of May 2020. COVID-19 protocols were followed while these children with their parents were in hospital. Children with strabismus at presentation were followed up with BCVA, stereopsis test, and all tests for ocular deviation as in the first visit to understand the status of stereopsis, strabismus, and amblyopia and hence the need for further intervention. Children without strabismus at the first visit (pseudo-strabismus) were evaluated to detect its development at each follow-up visit. Children who had or
developed strabismus were managed with spectacles and/or amblyopia treatment and/or surgery. The data were analyzed descriptively with mean and standard deviation. Chi square test and Fishers exact test were used to analyze the data between the groups. A P value less than 0.05 was considered to be statistically significant. All statistical analyses were carried out by using the SPSS 25.0 version (SPSS, Chicago, IL, USA) software for windows.

Results

Seventy-four children in the age group of 6 months to 18 years with features as seen in pseudo-strabismus such as telecanthus/epicanthus/hypertelorism or the combination were recruited from September 2018 to February 2019. All were followed up for a minimum period of 12 months and a maximum period of 18 months. Fourteen children were lost to follow-up; therefore, 60 children were analyzed, of which 33 (55%) were males and 27 (45%) were females. The mean age at the first visit was 6.659 ± 3.565 years (range 6 months to 14 years). The mean length of follow-up was 17.4 months. The majority (96.66%) of the children had no family history of strabismus. Two children had a family history of strabismus, of whom one child (1.7%) had a history of exotropia (XT) in the mother and the other child (1.7%) had a history of ET in the grandmother; neither of these two children had or developed strabismus. Parental consanguinity was present in 14 children (23.33%), out of whom three children (5%) had strabismus. The history of pre-term birth and a low birth weight (<2.5 kg) was observed in four (6.66%) and six (10%) children, respectively. One child with pre-term birth and a low birth weight who did not have strabismus at the first visit developed so (exotropia) at the third follow-up (18 months). The mean ICD was 29.94 mm and 30.76 mm, respectively, in males and females. The mean PFW was 29.98 mm (both eyes) in males, and in females, it was 27.75 mm (right eye) and 27.78 mm (left eye). Various features similar to that seen in pseudo-strabismus and its association with strabismus are given in Table 1 and Fig. 2. At the first visit, ten (16.66%) children had strabismus at a mean age of 7 years (range: 3–12 years); six (60%) had ET [five (83.33%) with accommodative ET and one (16.66%) with infantile ET] and four (40%) had XT. The mean age of diagnosis of ET was 7.16 years (range: 3–12 years), and that of XT was 6.75 years (range: 3 years to 10 years). The remaining 50 children were diagnosed as pseudo-strabismus. Table 2 depicts the presence and development of strabismus and ophthalmological characteristics of each child with strabismus. Among the five children with accommodative ET, the average hypermetropic value was + 3.8D (range: +2.5D to +5.0D) and the average amount of deviation was 33 prism diopter (PD) (maximum 60 PD and minimum 20PD). None of the children had a high AC/A (accommodative convergence/accommodation) ratio. Four children with XT at the first visit had a mean deviation of 40PD (maximum 65PD, minimum 20 PD). Two children with strabismus underwent surgery [Table 2]. Fifty-eight (96.66%) children were followed up to analyze for the status of strabismus (eight children) and to detect the development of strabismus in the remaining pseudo-strabismic children. All 58 children completed two follow-ups (12 months), whereas 18 children (31.03%) were able to complete three follow-ups (18 months), Table 2. Five children who had their third follow-up due in April 2020 completed the same in the last week of May 2020 after COVID-19 lockdown was lifted; COVID-19 protocols were followed while the five children along with parents were in the hospital. Among the 50 children who were diagnosed as pseudo-strabismus at the first visit, one child developed XT at the third follow-up (18 months) at the age of 4 years [Table 2] with a deviation 15 PD. This child had compound hyperopic astigmatism (CHA) and was prescribed spectacles.

At the end of the study, 11 (18.33%) children had strabismus (ten at first visit and one at the third follow-up). The mean age at the diagnosis of strabismus was 6.77 years (range: 3 years to 12 years). No significant association was seen between lid characteristics (telecanthus, epicanthus, and hypertelorism) and the type of strabismus (p value 0.241). Fifty children (83.33%) had a refractive error, and ten children (16.66%) were emetropic. The most common type was CHA in 14 children (28%). Ten (20%) had compound myopic astigmatism (CMA), nine (18%) had mixed astigmatism (MA), 11 (22%) had simple myopic astigmatism (SMA), two (4%) had simple hyperopic astigmatism (SHA), three (6%) had simple hyperopia (HM), and one (2%) had simple myopia (M). The relation between refractive error and features seen in pseudo-strabismus (telecanthus, epicanthus, and hypertelorism) was found to be statistically insignificant (p = 0.098). Fifty-nine eyes (49.16%) of 33 children (55%) had amblyopia at the first visit, among which eight children (24.24%) had strabismus (five had ET and three had XT). The remaining 25 (75.75%) children had a refractive error only. Fischer’s exact test was performed, and the relation between amblyopia and the presence of strabismus was not found to be statistically significant (p value 0.315).

| Characteristic features | Frequency | Esotropia | Exotropia | Total |
|-------------------------|-----------|-----------|-----------|-------|
| Telecanthus             | 33 (55%)  | 3 (50%)   | 2 (40%)   | 5 (45.45%) |
| Telecanthus + Epicanthus| 17 (28.33%)| 1 (16.6%) | 2 (40%)   | 3 (27.27%) |
| Epicanthus              | 05 (8.33%)| 0 (0%)    | 0 (0%)    | 0 (0%) |
| Hypertelorism           | 2 (3.33%) | 1 (16.6%) | 0 (0%)    | 1 (9.09%) |
| BPES                    | 1 (1.66%) | 0 (0%)    | 0 (0%)    | 0 (0%) |
| Epicanthal fold with anti mongolian slant | 1 (1.66%) | 1 (16.6%) | 0 (0%) | 1 (9.09%) |
| Telecanthus with anti-mongolian slant | 1 (1.66%) | 0 (0%) | 1 (20%) | 1 (9.09%) |
| Total                   | 60 (100%) | 6 (100%)  | 5 (100%)  | 11 (100%) |

BPES - Blepharophimosis ptosis epicanthus syndrome
Discussion

A few features seen in pseudo-strabismus such as telecanthus, epicanthal fold, a small inter-pupillary distance (IPD), a negative angle kappa, euryblepharon, and exophthalmous simulate ET, whereas features such as hypertelorism, a large angle kappa, a large IPD, narrowing of lateral canthi, and exophthalmous simulate XT. Therefore, parents having a child/children with any of the above features can have the visual perception that there is “deviation of the eye” or “eyes not looking normal.” On examination, these children may have associated strabismus or may not have pseudo-strabismus. Pseudo-strabismus is a diagnosis of exclusion, which implies that all tests carried out to detect strabismus are negative. Therefore, one needs to be doubly sure before telling the parents that their child indeed has no strabismus. However, these children can develop strabismus anytime later,[2‑4,11‑16] thus requiring long-term follow-up.

Evaluation to distinguish strabismus from pseudo-strabismus may be difficult because of 1) a younger age, 2) intermittent character of strabismus, 3) poor patient cooperation, and 4) a naive clinician. For these reasons and in doubtful situations, close follow-up is essential in detecting strabismus and amblyopia for early intervention.[2,10] Most previous studies are retrospective. They did not include children with features similar to that seen in pseudo-strabismus. They also did not analyze for the presence of associated strabismus at initial examination but on the other hand included children with pseudo-strabismus and analyzed as to how many developed strabismus later.[2‑4,11‑16] Table 3. In our prospective longitudinal study, we analyzed for the presence of strabismus in children with features similar to that seen in pseudo-strabismus (telecanthus, epicanthus, and hypertelorism) at initial examination as well as during follow-up. Telecanthus was the most common finding in our study: thirty-three (55%) and 17 (28.33%) out of 60 children had isolated telecanthus and telecanthus along with epicanthal fold, respectively, in contrast to the study by Sefi-Yurdakul et al.[2] where epicanthal fold was the most common feature.

In our study, no statistically significant association was found between strabismus and family history (only two children had a family history of strabismus), similar to the studies by Jacob et al.[10] and Prichard and Ellis.[11] However, a few studies found an important association between the diagnosis of true strabismus and a positive family history of strabismus.[2‑14] The history of pre-term birth and a low birth weight (<2.5 kg) was observed in four (6.66%) and six (10%) children, respectively. One child with pre-term birth and a low birth weight who did not have strabismus at the first visit developed so (XT) at the third follow-up (18 months) [Table 3]. We additionally analyzed parental consanguinity, which was present in 14 children (23.33%), out of whom three (5%) had strabismus. At the first visit, we observed ten out of 60 children to have had associated strabismus. During follow-up, only one (1.66%) child aged 4 years developed strabismus at 18 months (third and last follow-up). However, this follow-up period is too short to comment on the development of strabismus in the remaining 49 children. In studies by Anwar et al.,[10] Sefi-Yurdakul et al.[13] and Xu TT et al.,[15] 19%, 12%, and 4.9% of the children with pseudo-strabismus, respectively, developed true strabismus during follow-up [Table 3]. The longest follow-up was 6.9 years,[13] and the shortest was 4.5 months.[12]

In our study, at the first visit, six (60%) children had ET and four (40%) had XT [Table 2]. The mean age at the diagnosis of ET (7.16 years) was higher than that at the diagnosis
of XT (6.75 years), both of which were higher than that observed in Ryu et al.[11] study (ET median age: 3.14 years; XT: 3.83 years). However, we did not find any child with vertical deviation or significant association between features seen in pseudo-strabismus and the type of strabismus.

Detecting the presence of refractive error in these children is equally important as strabismus which has been brought out well in a few of the studies. Jacob et al.[18] found significant association between the magnitude of hypermetropia and development of true deviation. Ryu et al.[3] noticed that 76.4% of children with ET had hypermetropia and 26.3% of children with exotropia had myopia.

On the other hand, Anwar et al.[3] and Prichard and Ellis[12] did not find any association between refractive error and the development of true deviation. However, Anwar et al.[3] noticed failure of the normal myopic shift during the development of eyes as a significant risk factor for the development of esodeviation. In our study, 50 children (83.33%) had a refractive error. All children with strabismus had a refractive error. We observed that ET was common in eyes with hypermetropia and XT was common in eyes with myopia [Table 2]. One child who developed XT in the third follow-up had CHA at the first visit. Therefore, it is essential to follow up children with features similar to that seen in children with pseudo-strabismus (telecanthus, epicanthus, and hypertelorism).

In our study, 33 (55%) children (59 eyes) had amblyopia at the first visit, among which eight children (24.24%) had strabismus (five had ET and three had XT), Table 2. The remaining 25 (75.75%) children had only a refractive error. We also noted that there was no statistically significant relation between amblyopia and the presence of strabismus. However, in Ryu et al.[11] study, 32% of the subjects who developed true strabismus had amblyopia; its incidence was similar for all types of strabismus and was more in the pseudo-strabismus group when compared to the control group, which highlights the importance of follow-up in the former group. In Sefi-Yurdakul[15] study, amblyopia was seen in cases with refractive accommodative ET with hyperopia.

In our study, two children underwent surgery after the first visit: one child had infantile ET (35PD), and the second had XT (63PD); both were orthotropic post-operatively [Table 2].
Table 3: Details of various studies on pseudo-strabismus

| Study author/year | Type of study/sample size | Strabismus | Age group/mean FU | FH/No. of TS | RE/Amblyopia |
|------------------|---------------------------|------------|------------------|-------------|-------------|
| Our study        | Prospective longitudinal/60 with features of PS: telecanthus, epicanthus, and hypertelorism | 10 (16.66%) at first visit 1 (3rd FU) | 6 months - 18 years/17.4 months | 2/nil | +/- |
| Pritchard C et al.[4]/2007 | Retrospective/83 children with PS | 10 (12%) 1 ET 0 XT | 7-119 months/4.5 months | 30/3 | +/- |
| Anwar DS et al.[11]/2012 | Retrospective/31 children with PS | 6 ET (19.35%) | <5 years/8.9 years | 16/6 | +/- |
| Silbert AL et al.[4]/2012 | Retrospective/201 children with PS | 16 ET 3 XT 1 DRS | <3 years/20 months | NA | +/- |
| Silbert AL et al.[4]/2013 | Retrospective/253 children with PS | <36 months: 14 (11%); ≥ 36 months: nil | <36 months ≥ 36 months/2 years | NA | +/- |
| Pritchard C et al.[4]/2013 | Prospective/53 children with PS | 7 (13.20%) 6 ET 1 XT | 4-63 months/11 months | 19/3 | +/- |
| Garrett T et al.[4]/2014 | Retrospective, then prospective/166 children with PS | 4 ET (2.40%) 2 ET 2 XT | <30 months/18-24 months | 70/4 | NA/NA |
| Nazife Sefi-Yurdakul et al.[4]/2016 | Retrospective/65 children with PS | 8 ET (12.30%) 7 ET 1 XT | 4-120 months/25.2±23.28 months | 5/not mentioned | +/- |
| Ryu WY et al.[4]/2019 | Retrospective/17,885 children with PS | 1725 (9.6%); ET 69.7% | <3 years/1.5 years | NA | +/- |
| Xu T et al.[4]/2020 | Retrospective/184 children with PS | 9 ET (4.9%) 7 ET 2 XT | <1 year/3.9 years | 9/not mentioned | NA/NA |

PS - pseudo-strabismus, FU - follow-up, FH - family history, RE - refractive error, ET - ET, XT - exotropia, DRS: Duane retraction syndrome, NA - not assessed

Limitations
This study was performed with a small sample size and short follow-up; hence, it may not be possible to generalize the inferences. We have not compared the study group with that of normal children to understand the course of development of strabismus. We have not analyzed the risk factors for the development of strabismus.

Conclusion
Children with telecanthus, epicanthus, and hypertelorism, which are a few features similar to that seen in pseudo-strabismus, can have associated strabismus. These features can pose difficulties in the diagnosis of strabismus, especially in younger, non-cooperative children and children with small-angle strabismus. This mandates a careful examination. On the other hand, children without strabismus need longer follow-up to understand the conversion of pseudo-strabismus to strabismus. This helps in initiating further management at the earliest.

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Conflicts of interest
There are no conflicts of interest.

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