Abstract:

**Background:** Holoprosencephaly (HPE) is a rare congenital malformation of the brain, resulting from interrupted forebrain bifurcation. The most common and severe form of HPE is alobar HPE, which is associated with severe facial malformations like cyclopia, ethmocephaly, cebrocephaly and premaxillary agenesis. Various syndromic malformations (like trisomy 13,18) can lead to HPE, the most frequent being trisomy 13. Combination of postaxial polydactyly and alobar HPE is seen in trisomy 13. Case report: A 35 weeker male neonate was antenatally diagnosed with alobar Holoprosencephaly, Ethmocephaly and Postaxial Polydactyly. MRI brain showed pancake type of thin cortical rim anteriorly, absent corpus callosum and fused thalami with single monoventricle, suggestive of alobar HPE. MRI face was suggestive of ethmocephaly. This rare co-existence of polydactyly and alobar HPE is a hallmark of trisomy 13. As the karyotyping was normal, pseudotrisomy 13 was considered in this case. Conclusion: We report a preterm male neonate with antenatally detected alobar holoprosencephal and ethmocephaly, which were confirmed by postnatal MRI brain. The rare combination of postaxial polydactyly and alobar holoprosencephaly with normal karyotyping is suggestive of pseudotrisomy 13, a rare entity.

**Key words:** Holoprosencephaly, ethmocephaly, neonate, polydactyly, pseudotrisomy13, alobar, cyclopia

Introduction

Holoprosencephaly (HPE) is a rare congenital, structural malformation of the brain, resulting from incomplete separation of the forebrain into two hemispheres. This embryological event is usually completed by fifth week of gestation (between 4th to 8weeks) [1]. Classic HPE has a spectrum of brain malformations ranging from severe life threatening alobar HPE (often associated with facial malformations) to milder forms like semilobar, lobar and middle interhemispheric variant (MIHV).
type HPE [2,3,4]. A rarer septopreoptic HPE is also described [2]. It can also be associated with other CNS abnormalities. Alobar HPE, the most common and severe form of HPE is associated with characteristic craniofacial anomalies like cyclopia, ethmocephaly, cebocephaly and premaxillary agenesis in 80% of cases [2,3]. Various syndromic, chromosomal malformations (like trisomy 13, 18) and gene mutations can lead to HPE [5], coupled with environmental teratogenic exposure before eight weeks of gestation. Combination of postaxial polydactyly and alobar holoprosencephaly are seen in trisomy13 [5]. The incidence of HPE is 1 in 250 pregnancies and the survival rate of fetuses with this disorder is only 3% [6,7]. Hence the true live birth prevalence is 1 in 10,000 live births [5].

Case report:
A male neonate was born at 35 weeks of gestation by cesarean section to a 24 year old second gravida. This was a product of non consanguineous marriage and the mother conceived spontaneously. There is no history of febrile exanthema, use of anti hyperlipidemic drugs and retinoids during the first trimester. Similarly, there is no history of smoking or alcohol consumption. Antenatal complication like diabetes mellitus was absent. The antenatal ultrasound (at 27 weeks of gestation) showed alobar holoprosencephaly along with facial abnormalities. As the gestation was beyond 20 weeks, medical termination of pregnancy could not be performed. After birth, the neonate had spontaneous respirations, normal heart rate with gross hypotonia and poor reflex activity. This neonate had major life threatening congenital anomalies. There was ethmocephaly with a rudimentary nasal structure-the proboscis, located between the eyes in the midline (as shown in figure 1A, white arrow), poorly formed philtrum along with other malformations like central incisor teeth, ankyloglossia and arhinia. The neonate also had postaxial polydactyly of both upper and lower limbs (as shown in the figure 1A & 1C, black arrows) and bilateral undescended testes. There was no cleft lip, cleft palate or bifid uvula. However, the palate was high arched. The neonate was subjected to magnetic resonance imaging (MRI) of the brain soon after birth, which showed absent corpus callosum, fused thalami (figure-2A, black arrow) with single monoventricle and thin cortical rim (as shown in figure-2B&2C as shown with arrows). MRI of the face revealed two orbits which were fused on the medial side (figure-2A, white arrow) with single proboscis (figure-2D, as shown with arrow) and absent nasal bones, suggestive of ethmocephaly. Due to these life threatening malformations, the neonate died within 24 hours of life, despite life saving measures. The previous sibling was normal and there is no similar history in the family. Polydactyly in association with alobar holoprosencephaly is a manifestation of trisomy 13. However, the karyotyping was normal in the index case, hence pseudotrisomy 13 was considered. Specific genetic mutations could not be done, due to financial constraints.

Discussion:
Hypersensephaly (HPE) is the most frequent developmental defect of the forebrain and midface in humans. The most frequent and severe form of HPE is alobar HPE (60% of all HPE) [3]. Less severe manifestations of HPE are being diagnosed as the newer neuroimaging modalities are available, hence the true live birth prevalence of HPE would be higher than the earlier estimates[2,3]. The principal defect that leads to HPE is incomplete cleavage of the forebrain (prosencephalon) into right and left hemispheres, deep brain structures and the olfactory and optic bulbs and tracts[1,2,3]. The degree of interruption in forebrain separation determines the type of HPE, their manifestations and outcome. Various types of HPE have varied range of neurological manifestations, outcomes and survival rates. In the most severe variant of alobar HPE, there is no separation of hemispheres with a single monoventricle, fused thalami and a thin anteriorly placed thin rim of cerebral cortex [2,3], which was seen in the index case. This is associated with absent septum cavum pellucidum and absent corpus callosum, as in the present case. Alobar HPE is invariably associated with characteristic craniofacial malformations like cyclopia (single fused orbit with a proboscis above it), cebocephaly (two orbits, extreme hypotelorism with a normally placed nose and a single nostril) and ethmocephaly (two orbits fused on the medial side with single nostril proboscis). Both cebocephaly and ethmocephaly are associated with dysplastic changes of the ethmoid bone and anterior portion of the sphenoid bone with concomitant hypotelorism and defects of the medial orbital walls [8,9]. Through the latter defects, the eyes were joined in the ethmocephalic fetus (synophthalmia). Other changes of the bone (single optic foramen, approximated maxillae, choanal atresia and thickened palate) and soft tissue (eccentric or fused
extraocular muscles, single optic nerve) are also seen. Both cebocephaly and ethmocephaly were classified as two-orbit variants of cyclopia [8,9]. Index case had ethmocephaly (confirmed by MRI). These fetuses usually die inutero or soon after birth and often have syndromic associations. The index neonate had central incisor teeth, ankyloglossia, arhinia, bilateral postaxial polydactyly of both upper and lower limbs and bilateral undescended testis. However, there was no cleft lip, cleft palate or bifid uvula (other manifestations of trisomy 13).

Milder forms of HPE include semilobar (anteriorly fused frontal and parietal lobes with posteriorly separated cortical matter), lobar HPE (fused frontal lobes, rostral part of telencephalon on the ventral aspect and posteriorly separated right and left cerebral hemispheres and lateral ventricles)[2,3]. Other variants of HPE include Middle interhemispheric fusion variant (MIHF/MIHV or syntelencephaly) [2-4] and septopreoptic variant [2,3]. MIHF/MIHV consists of failure of separation of posterior frontal and parietal lobes with varying degree of cleavage of the basal ganglia and thalami. In this variant, body of the corpus callosum is absent but the genu and splenium are present. In septopreoptic type non-separation is restricted to the septal and/or preoptic regions [2].

Etiological factors that lead to HPE are heterogeneous, which include chromosomal, genetic and teratogenic factors. Chromosomal abnormalities that play a key role in HPE are trisomies, duplications, deletions, and ring arrangements. HPE in 40% of the live births is associated with a chromosomal abnormality, the most frequent being trisomy 13 (around 50% of cases) [5]. HPE is seen in 70% of infants with trisomy 13 (Patau syndrome) and this is often associated with postaxial polydactyly [10]. As the index case had both of these manifestations, trisomy 13 was considered. However, the normal karyotyping in this neonate suggested pseudotrisomy 13 [11]. Presence of cytogenetic abnormalities in HPE carries worst prognosis with survival beyond infancy being only 2%. In contrast, those without chromosomal abnormalities have 30-60% chances of survival beyond infancy [5].

HPE in 20-25% of cases is associated with multiple malformation syndromes like pseudotrisomy 13 [10-12], velocardiofacial syndrome, Pallister-Hall and Meckel syndromes [2,3]. Similarly, the deficiency of 7-dehydrocholesterol reductase is also associated with HPE in 5% of cases (as seen in Smith-Lemli-Opitz syndrome) [13]. As cholesterol aids in the activation of sonic hedgehog molecule, defective cholesterol synthesis leads to impaired sonic hedgehog signaling pathway [14]. However, HPE can also occur in familial cases of nonsyndromic malformations.

Minor forms of HPE manifest with developmental delay, seizures and pituitary dysfunction. Majority of the fetuses with this disorder do not survive [2,3,5], those with severe forms do not survive beyond early infancy as it happened with the index case. However, a remarkable proportion of children with milder forms of HPE survive longer than one year. Individuals without major brain abnormalities are described to have microform HPE. The risk of recurrence in HPE is estimated to be 6% [15], which is higher in familial forms. Hence a thorough family history is essential. Prenatal ultrasound, fetal MRI and genetic analysis in subsequent pregnancies aid in the antenatal detection of HPE [5,15]. As HPE is a developmental defect, close screening of the family members for milder forms of HPE like single median incisor, hypotelorism, bifid uvula and pituitary deficiency is vital.

Neonates with alobar prosencephaly are likely to be picked up early in the gestation with widespread screening for antenatal malformations with ultrasound or fetal MRI. Hence, majority of these pregnancies are terminated and it is rare to see live neonates with this malformation in the current era. As HPE was not diagnosed in this neonate till 27 weeks of gestation due to parental ignorance, it refocuses the need for parental education about early screening for life threatening malformations. Pseudotrisomy is an entity associated with high rate of recurrence and hence, this mother needs close monitoring and antenatal screening in the subsequent pregnancies.

Conclusion

A preterm, male neonate presented with antenatally detected unusual malformations of alobar holoprosencephaly, ethmocephaly and postaxial polydactyly which were confirmed by postnatal imaging. This rare combination of postaxial polydactyly with alobar holoprosencephaly is characteristic of trisomy 13. The normal karyotyping in this case suggests pseudotrisomy 13.

Source of Funding: Nil
Conflict of Interest:

This case was solely managed in Princess Esra Hospital, Deccan College Of Medical Sciences
and Authors declare no conflicts of interests with regard to this case.

Acknowledgement:
Sincere thanks to Mr. Mujahed, Dr. Imad and Dr. Naseer. Authors acknowledge the immense help received from the scholars whose articles are cited and included in references of this manuscript. The authors are also grateful to authors/editors/publishers of all those articles, journals and books from where the literature for this article has been reviewed and discussed.

References:

Figure 1A: Gross morphology of the delivered fetus, reveals midline proboscis (as shown with white arrow) with medially fused orbits: Ethmocephaly, postaxial polydactyly in the upper limbs (black arrows)
Figure 1B: 3D SSD of the MRI image revealing ethmocephaly (correlating with the gross morphology)
Figure 1C: Gross morphology of the delivered fetus, reveals post axial polydactyly in lower limbs (as shown with arrows)
**Figure 2A:** T2W Axial image, reveals fused thalami (black arrow) with medially fused orbits (white arrow) and a single proboscis like nostril, suggestive of ethmocephaly.

**Figure 2B:** T2W Axial section through supratentorial compartment, reveals a large monoventricle with absent septum cavum pellucidum, absent interhemispheric fissure and absent falx cerebri, with anteriorly placed thin cortical rim (as shown with arrow), suggestive of alobar holoprosencephaly.

**Figure 2C:** Sagittal T1W image, revealing a thin rim of cerebral tissue, confined to anterior basicranium (as shown with arrow)

**Figure 2D:** 3D SSD reveals craniofacial features as medially fused orbits (ethmocephaly) with midline proboscis (as shown with arrow).

**Abbreviations:** HPE, MRI, MIHF, MIHV