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Case Report

Anatomy Section

Alobar Holoprosencephaly with Ectrodactyly, Oesophageal Atresia and Other Rare Anomalies: A Case Report

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ABSTRACT

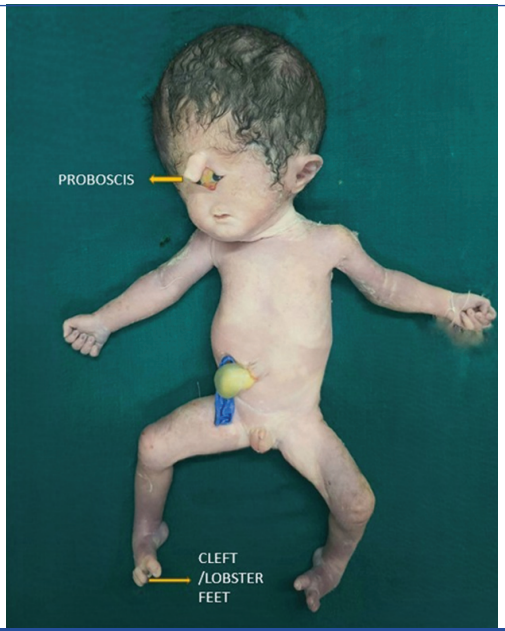
Synophthalmia with severe holoprosencephaly is a rare congenital anomaly, with a prevalence of approximately 1 in 100,000 total births and a female preponderance. It is characterised by a single midline orbit with two fused eyeballs, with or without a proboscis, along with absence of the nose and philtrum. The authors report a case of a 38-week-old male stillborn foetus, delivered vaginally to a 24-year-old healthy, non diabetic, second-gravida mother. On gross examination, the foetus exhibited low-set ears, a single midline orbit with two fused eyes, a proboscis above the orbit, absence of the nose and philtrum, microstomia, micrognathia, peripheral cyanosis and bilateral lobster foot. Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) revealed a single orbit with ill-defined sinuses and alobar holoprosencephaly, characterised by absence of the corpus callosum, septum pellucidum, interhemispheric fissure and uncleaved thalami. Internal examination revealed a type I single umbilical artery, type A oesophageal atresia and valvular pulmonary stenosis. The presence of more than three associated anomalies in the present case underscores the rarity of this association.

Keywords: Lobster foot, Pulmonary stenosis, Synophthalmia

CASE REPORT

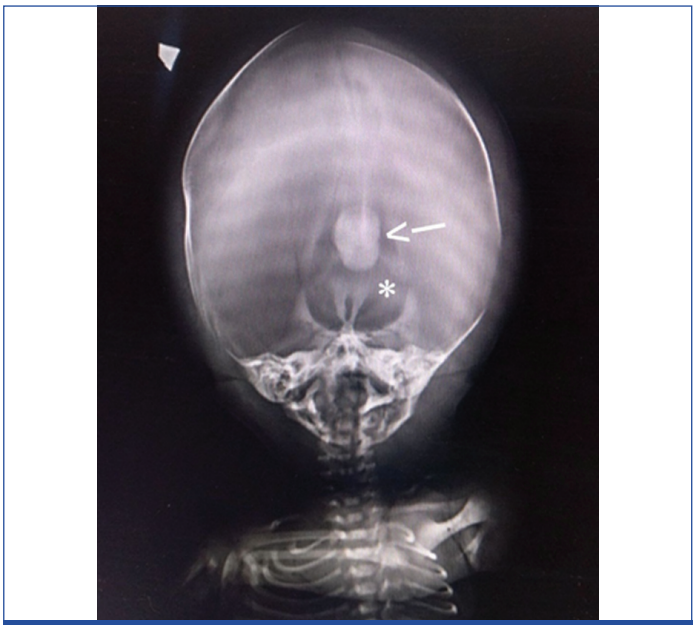
A 38-week-old male stillborn foetus was delivered vaginally to a 24-year-old healthy, non diabetic, second-gravida mother. There was no history of consanguineous marriage, co-morbid illness, or teratogen exposure. The mother had previously delivered a healthy female child.

On gross examination, the foetus exhibited a single midline diamond-shaped orbit with fused eyeballs; absence of the nose and philtrum; presence of a midline proboscis above the orbit; low-set ears; microstomia; micrognathia; tongue-tie; and a single umbilical artery. Severe peripheral cyanosis and bilateral lobster foot were also noted [Table/Fig-1].



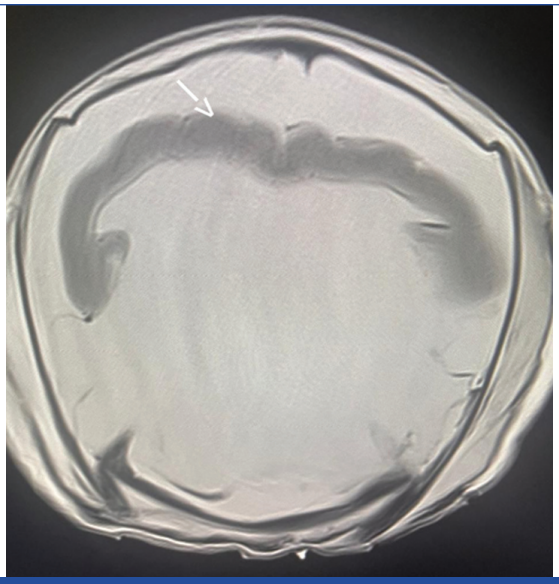
[Table/Fig-1]: Image showing single midline orbit with two fused eyeballs, proboscis above the orbit (arrow), low set ears, absent nose and philtrum, microstomia, lobster foot (arrow), peripheral cyanosis.

A post-mortem radiological examination was performed. An Anteroposterior (AP) view of the skull demonstrated a midline tubular soft-tissue structure consistent with a proboscis, hypoplastic nasal bones and closely spaced orbits, indicating a midline craniofacial anomaly [Table/Fig-2]. MRI of the brain revealed alobar holoprosencephaly with absence of the corpus callosum, septum pellucidum, interhemispheric fissure, uncleaved thalami and deep cerebral nuclei [Table/Fig-3,4]. CT scan of the head showed a proboscis and a single orbit with eyeballs partially fused posteriorly [Table/Fig-5,6].

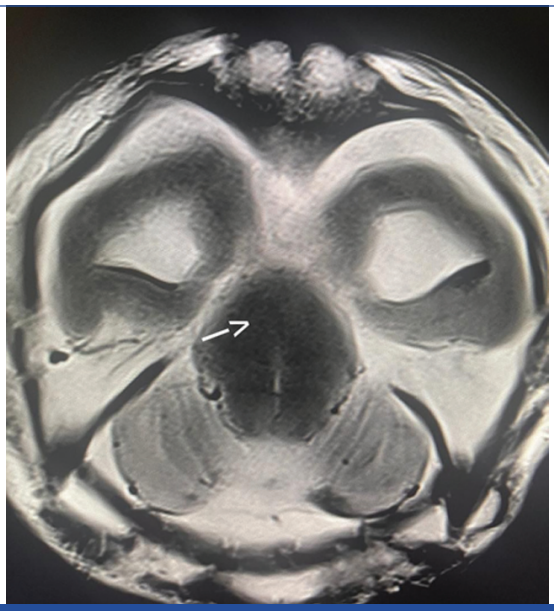


[Table/Fig-2]: Image of plain X-ray of skull AP view showing midline tubular soft tissue structure resembling proboscis (arrow), with associated hypoplasia of nasal bones and closely spaced orbits (star) suggesting a midline craniofacial anomaly.

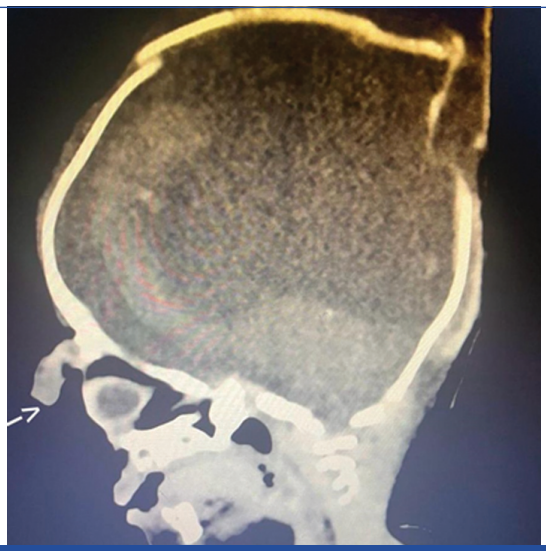
Internal examination revealed an umbilical cord with a Single Umbilical Artery (SUA) arising directly from the right common iliac artery [Table/Fig-7], oesophageal atresia at the level of the diaphragm [Table/Fig-8], right atrial and ventricular hypertrophy with pulmonary outflow tract constriction [Table/Fig-9] and a hypoplastic right lung.



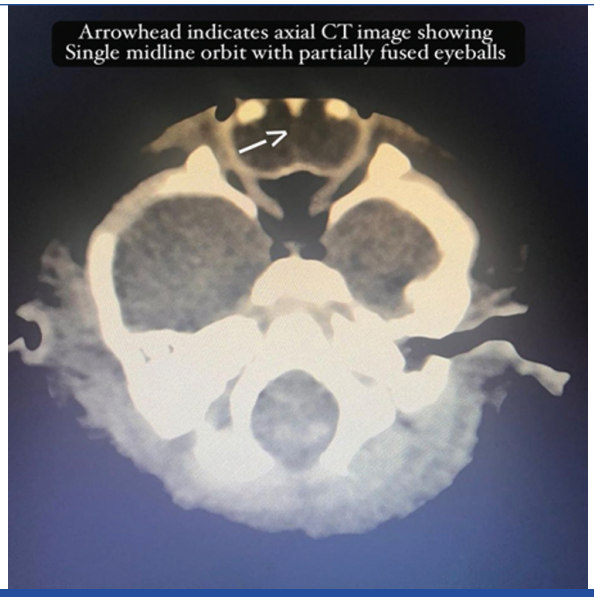
[Table/Fig-3]: Image of MRI Brain T2-weighted axial showing monoventricle in cerebrum (arrow) with pan cake appearance of brain.



[Table/Fig-4]: Image of MRI Brain T2W Axial showing uncleaved thalami (arrow).

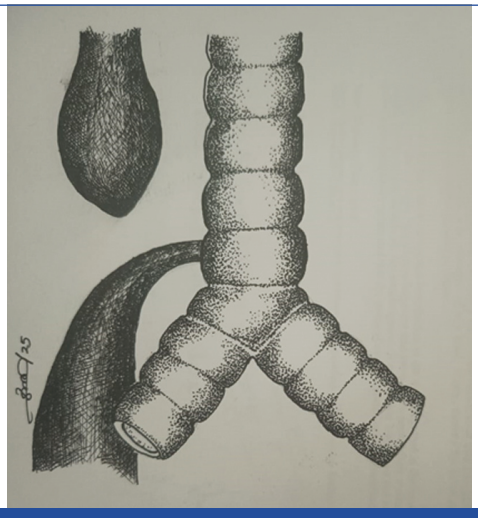


[Table/Fig-5]: Image of CT head sagittal view showing presence of proboscis deformity (arrow).



[Table/Fig-6]: Image of CT head axial view showing single orbit with partially fused eyeballs posteriorly (arrow).

[Table/Fig-7]: Image showing single umbilical artery arising from right common iliac artery (A), median umbilical ligament (U), bifurcation of abdominal aorta (B), right (R) and left (L) common iliac artery.



[Table/Fig-8]: Schematic diagram of Type A oesophageal atresia.

DISCUSSION

Synophthalmia is a rare and severe form of holoprosencephaly that occurs due to failure of division of the prosencephalon between the 18th and 28th days of gestation [1]. The stillborn in the present case

[Table/Fig-9]: Image of dissected heart showing pulmonary outflow tract narrowing (C).

was male. Large database analyses have shown a higher number of female infants born with synophthalmia compared to males [1]. However, no sex distinction is observed in cases occurring early in pregnancy. The female preponderance at birth has been attributed to a higher rate of spontaneous abortion of male foetuses during early gestation [1]. The male foetus in the present case may have escaped early pregnancy loss.

Known risk factors for synophthalmia include advanced maternal age, consanguineous marriage, multiple pregnancies, gestational diabetes mellitus, infections {Toxoplasmosis, Rubella Cytomegalovirus, Herpes simplex and Human Immunodeficiency Virus (HIV)-(TORCH)}, drug abuse and exposure to teratogens [2]. The mother in the present case had no history of teratogen exposure or medical co-morbidities during early pregnancy. Trisomy 13 is the most commonly reported chromosomal abnormality associated with this condition [2]; however, genetic testing was not performed in the present case.

The characteristic facial features of synophthalmia include a proboscis—a facial appendage located above the median orbit at the midline—along with microstomia and micrognathia, in the absence of the nose and philtrum. The proboscis represents the anterosuperior part of the normal nasal cavity that develops in the absence of median facial components. It typically contains a single slender midline nostril lined by squamous mucosa with numerous sebaceous glands and connects to a poorly formed nasal cavity that fails to communicate with the nasopharynx [3].

In synophthalmia, the nasal capsule is hypoplastic and positioned higher, with an aberrant nasal septum and absence of nasal conchae, resulting in choanal atresia. Normally, mesenchyme from the frontonasal process invades between the eyes and fuses with the maxillary processes. In synophthalmia, premature fusion of the optic rudiments inhibits this invasion and fusion [4]. The presence of a midline proboscis, absence of the nose and philtrum, microstomia and micrognathia in the present case is likely attributable to failure of downward migration of the frontonasal process to form midline facial structures.

Matalliotakis et al., (2021) reported a similar case of stillbirth with a proboscis, single midline diamond-shaped eye, microstomia and micrognathia [2].

A newborn infant is an obligate nasal breather and congenital bilateral choanal atresia is invariably associated with respiratory distress at or shortly after birth, resulting in cyanosis [5]. The peripheral cyanosis observed in the present case was most likely due to respiratory distress caused by failure of fusion of the nasal cavity above the orbit with the nasopharynx.

The most severe facial phenotypes associated with alobar holoprosencephaly include microcephaly, cyclopia (a single, centrally placed eye), synophthalmia (partial fusion of the two eyes at the midline) and proboscis formation [6]. In synophthalmia, the anterior segment of the eye is usually better differentiated than the posterior segment. Ocular deformities, in association with cerebral and facial malformations, suggest a widespread developmental abnormality of the anterior neural plate [7]. In the present case, the eyeballs were located within a single midline orbit and were partially fused posteriorly, thereby confirming the diagnosis of synophthalmia on radiological examination.

Synophthalmia with proboscis is associated with the most severe form of holoprosencephaly, classified as alobar type [1]. Surveillance and research studies have reported that holoprosencephaly is frequently associated with other congenital anomalies, with one anomaly present in 55% of cases, two anomalies in 24% and three or more anomalies in 21% of cases [1]. In the present case, the foetus with alobar holoprosencephaly also had bilateral lobster foot, oesophageal atresia, a single umbilical artery and pulmonary stenosis. The presence of more than three associated anomalies further highlights the rarity of this association.

Ectrodactyly, also known as cleft hand/foot or lobster claw deformity, is a rare congenital anomaly with an incidence of approximately 1 in 90,000 births and no sex predilection [8]. Fibroblast Growth Factor Receptor 1 (FGFR1)–related Hartsfield syndrome comprises two core features: holoprosencephaly spectrum disorder and ectrodactyly spectrum disorder (lobster foot). The diagnosis of FGFR1-related Hartsfield syndrome is established through molecular genetic testing. The combination of ectrodactyly and holoprosencephaly is extremely rare, with only 35 cases reported to date in the English literature [9]. In the present case, molecular testing for FGFR1 gene mutation could not be performed; therefore, the diagnosis of Hartsfield syndrome could not be confirmed, representing a limitation of the present report.

Normally, the umbilical cord contains two arteries and one vein. Initially, both umbilical arteries arise as branches of the vitelline artery, which later undergo remodeling to form a new connection with the dorsal aorta [10]. This connection becomes obliterated during the early fourth week of intrauterine development and by the fifth week, a new connection develops from the fifth pair of lumbar intersegmental arteries, represented by the internal iliac arteries in adults [11]. The incidence of a SUA varies depending on the population studied and the timing of examination, ranging from 0.55% in neonates to 5.9% in high-risk foetuses at 11-14 weeks of gestation [12]. Persutte WH and Hobbins J (1995) proposed three theories explaining SUA: (a) primary agenesis of one artery, (b) secondary atrophy of a previously normal artery and (c) persistence of the original allantoic artery of the body stalk [12]. SUA is broadly classified into four types based on the origin of the artery, with Type I being the most common, in which the artery arises from the right or left common iliac artery [12]. In the present case, a Type I SUA arising directly from the right common iliac artery was observed.

There is a strong association between SUA and congenital anomalies such as gastrointestinal atresia or stenosis, renal agenesis and congenital heart defects [13]. Oesophageal atresia is the most common gastrointestinal malformation, with a prevalence of 1 in 3,000 to 4,500 live births [14]. Based on its relationship with the trachea, Vogt classified oesophageal atresia into five types (Types A-E) in 1929, of which Type C is the most common [Table/Fig-10] [14]. The presence of Vogt Type A oesophageal atresia in the present case further supports the association between gastrointestinal defects and SUA.

Types	Presentation
A	Oesophageal atresia without tracheo-oesophageal fistula
B	Oesophageal atresia with proximal tracheo-oesophageal fistula
C	Oesophageal atresia with distal tracheo-oesophageal fistula
D	Oesophageal atresia with proximal and distal tracheo-oesophageal fistula
E	Tracheo-oesophageal fistula without atresia

[Table/Fig-10]: Classification of oesophageal Atresia based on its relation with trachea [14].

Pulmonary stenosis accounts for approximately 8% of all congenital heart diseases, with a global prevalence of 1 in 2,000 live births [15]. Anatomically, based on the site of obstruction, pulmonary stenosis is classified into three types [Table/Fig-11], of which the subvalvular type is considered a congenital cardiac defect [15]. The presence of subvalvular pulmonary stenosis in this case further confirms the association between congenital cardiac anomalies and single umbilical artery.

Types	Presentation
Valvular	Pulmonary valve is partially fused and the leaflets are thin
Subvalvular	Pulmonary valve obstructed in the infundibular region of the right ventricle
Supravalvular	Obstruction above the pulmonary valve

[Table/Fig-11]: Classification of Pulmonary stenosis based on its site of obstruction [15].

CONCLUSION(S)

Synophthalmia is commonly associated with holoprosencephaly and is rarely associated with single umbilical artery, oesophageal atresia, pulmonary stenosis and ectrodactyly. The coexistence of all these anomalies in a single case has not been reported in the literature to date. Although the presence of ectrodactyly raises the possibility of Hartsfield syndrome, genetic confirmation could not be performed. The present case underscores the importance of a thorough understanding of embryogenesis and highlights the role of early prenatal diagnosis in guiding clinical decision-making and future family planning.

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