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CASE REPORT

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Alobar holoprosencephaly: Survival beyond the neonatal period and associated comorbidities: A case report

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Abstract: Holoprosencephaly results from incomplete cleavage of the forebrain during early embryogenesis period. Types of holoprosencephaly include alobar, semi-lobar, lobar and the middle interhemispheric fusion. Holoprosencephaly has been associated with various facial dysmorphism. We report two cases of alobar holoprosencephaly confirmed by magnetic resonance imaging (MRI) of the brain. Both were born at term, from HIV-negative, mothers, with no identifiable risk factors. Both mothers did not have antenatal ultrasound scans. Postnatal comorbidities and complications included feeding difficulties, global developmental delay, hearing and visual impairment, and epilepsy.

Key words: Alobar holoprosencephaly, diagnosis, survival, comorbidities

Résumé: L'holoprosencéphalie résulte d'un clivage incomplet du cerveau antérieur au cours de la période précoce de l'embryogenèse. Les types d'holoprosencéphalie comprennent l'alobar, le semi-lobar, le lobar et la fusion interhémisphérique moyenne. L'holoprosencéphalie a été associée à diverses dysmorphies faciales. Nous rapportons deux cas d'holoprosencéphalie alobaire confirmés par l'imagerie par résonance magnétique (IRM) du cerveau. Tous les deux enfants sont nés à terme, de mères séronégatives pour le VIH, sans facteurs de risque identifiables. Les deux mères n'ont pas bénéficié d'échographie prénatale. Les comorbidités et complications post-natales comprenaient des difficultés d'alimentation, un retard global de développement, des déficiences auditives et visuelles, et l'épilepsie.

Mots clés : Holoprosencéphalie lobaire, diagnostic, survie, comorbidités

Introduction

Holoprosencephaly is the commonest congenital malformation of the forebrain resulting fromits incomplete cleavage during the first fourweeks of embryogenesis with an Online Mendelian Identification (OMIM) number of 236100.[1]In order of decreasing severity, it ranges from alobar holoprosencephaly where there is a complete lack of separation of the brain hemispheres, semilobar form where there is an anterior fusion, lobar form in which there is some continuity between the brain hemispheres across the frontal cortex and the least severe form of the middle interhemispheric fusion which involves fusion of the posterior frontal and parietal lobes.[1]Holoprosencephaly is associated with a range of brain abnormalities and facial dysmorphism including midline defects such as cyclopia, synopthalmia, cleft lip/ palate, ocular hypertelorism, single nostril with a proboscis, and flat nose.[2]

The incidence of holoprosencephaly in resource-limited settings is largely unknown. Most of the available information is obtained from case reports from diverse settings. Globally, it is estimated to occur in1 in 250 conceptions but due to spontaneous abortion or demise of the affected fetus, it is observed in approximately 1 in10,000 live births.[3]The majority of children born with alobar holoprosencephaly succumb during the neonatal period. Death is usually attributed to various complications including respiratory insufficiency and central apnoea due to brain immaturity, dehydration due to diabetes insipidus, seizures, and early onset neonatal sepsis.[4] Survival of alobar holoprosencephaly beyond the neonatal period is rare.[4,5] If it occurs, it is usually accompanied by severe comorbidities such as developmental delay, sensory insufficiency, epilepsy, and malnutrition, all resulting in a poor quality of life. In this case report,

we aim to describe two cases of alobar holoprosencephaly from Tanzania, the associated facial dysmorphism, survival beyond the neonatal period, and the importance of antenatal sonography. Both of them were managed at the Muhimbili National Hospital, the tertiary public health facility in the country. The neonatal unit is located within the maternity block with a total capacity of 130 baby cots. The unit is divided into a level III neonatal intensive care unit (NICU), a high dependency unit (HDU), a prematurity ward, a Kangaroo mother care ward, and a general neonatal ward. The nurse-to-patient ratio in the NICU and HDU ranges between 1:2 - 1:3. The unit is staffed with three specialist neonatologists, neonatology fellows in training, pediatricians, senior pediatric residents, and nurses trained in neonatal care.

Case reports

Case 1

History: A female neonate born to a primiparous, HIV-negative woman in her early 30s, who had no history of diabetes, smoking, or alcohol use during pregnancy. The pregnancy course was uneventful with no history of consanguinity, previous history of abortions, or intrauterine fetal death. Ultrasonographic scan was not done throughout pregnancy. She delivered at a primary health care facility, by emergency cesarean section due to fetal distress which was diagnosed during monitoring of labor that had a spontaneous onset at 38 weeks of gestation. A female neonate, weighing 3.5 kg, with an APGAR score of four and seven at the first and fifth minutes respectively was born. Resuscitation by tactile stimulation and suction was done at birth. She was noted to have multiple congenital malformations at birth, which necessitated same-day referral to the tertiary national health facility for specialized neonatal care.

Examination: Upon arrival examination findings revealed sagittal suture diastasis, ocular hypertelorism, cleft lip and palate, low-set ears, and a small flat nose with a single nostril and an absent nasal septum (Image 1). Both eyes phenotypically appeared fully formed. She had a phenotypically normal spine, normal female external genitalia, and normal extremities.

Investigation: On imaging, a cranial ultrasound (*Image 2*)revealed absent the midline brain structures, absent corpus callosum, absent cavumseptum pellucidum, a large mono-ventricle CSF-filledstructure, and a fused central thalamus. Brain MRI (*Image 3*) was then done which revealed a thin rim of cerebral tissue anteriorly without evidence of a midline cleft, with a large CSF dense space in the anterior fossa. There was no evidence of falx cerebri. The cerebellum was preserved. The brain MRI concluded features of alobar holoprosencephaly. An echocardiogram revealed a structurally and functionally normal heart with situs solitus, levocardia, with no valvular dysfunction. The abdominal ultrasonography was normal. On blood workup, the complete blood count was essentially normal leucocyte count of 9.4Kcells/microlitre with normal white blood cell differential counts, haemoglobin of 20g/dl, and a normal c-reactive protein of 5.6mg/l. Serum electrolytes were normal. Screening for Immunoglobin G and Immunoglobin M against Toxoplasmosis, Cytomegalovirus, and Rubella were negative.

Care and treatment: A nasogastric tube was inserted from the first day of life and the neonate was kept on expressed breast milk and supplemental intravenousdextrosesaline. She was also kept on oral phenobarbitone due to frequent episodes of seizures and ceftriaxone for ten days. The family was counseled on the condition of her baby and accepted.

Differential diagnosis: Due to the presenting features, Patau syndrome and Smith-Lemli-Opitz syndrome were the differential diagnoses considered.

Post-discharge care and readmission: She was discharged home with a feeding nasogastric tube in situ at two weeks of age, and kept attending the outpatient department for growth and clinical monitoring. The mother opted to continue feeding by using a cup and saucer from one month of age. She was re-admitted at six months of age due to severe acutemalnutrition. Her anthropometric measurements at six months were; weight of 3.1 kg and length of 56 centimetres corresponding to World Health Organisation (WHO) weight-for-length and length-for-age of Z-scores below -3 Standard Deviations indicating severe wasting. Occipital frontal circumference was 43 centimetres which was normal for age. She was also diagnosed with aspiration pneumonia attributed to difficulty feeding due to oromotor dysfunction and cleft lip and palate. On developmental milestones, she could not fix and follow objects, she could not turn her head to sound, and she had not attained any gross motor milestones. A detailed ophthalmologic examination revealed cortical visual impairment secondary to brain malformation. She was kept on outpatient monitoring for physiotherapy and growth and development, until the age of nine months when the mother relocated to another region.

Case 2

History: A male neonate, born to a woman in her early 20s, primiparous, from a non-consanguineous relationship, HIV negative, with no history of smoking, alcohol use, diabetes during pregnancy, or previous history of pregnancy loss. He was born via a cesarean section, at 37 weeks of gestation, with a birth weight of 3.8kg, by caesarean section at a regional referral facility in Dar es Salaam, Tanzania. He cried immediately with an APGAR score of 8 and 10 at the first and fifth minute respectively, and did not require any form of resuscitation at birth. Upon delivery, he was clinically diagnosed with hydrocephalus with cleft lip and palate which necessitated referral to the tertiary facility for specialized neonatal care where he arrived at day two of life.

Examination: upon arrival, examination findings re

Image 1: Facial dysmorphic features of the first case

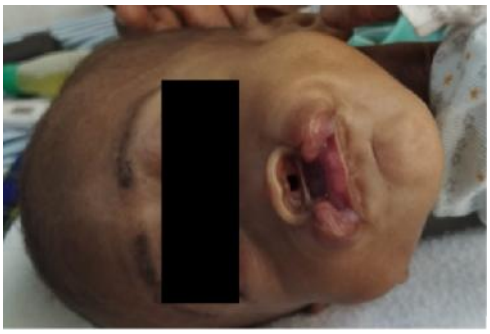


Image 2: Brain USS of the first

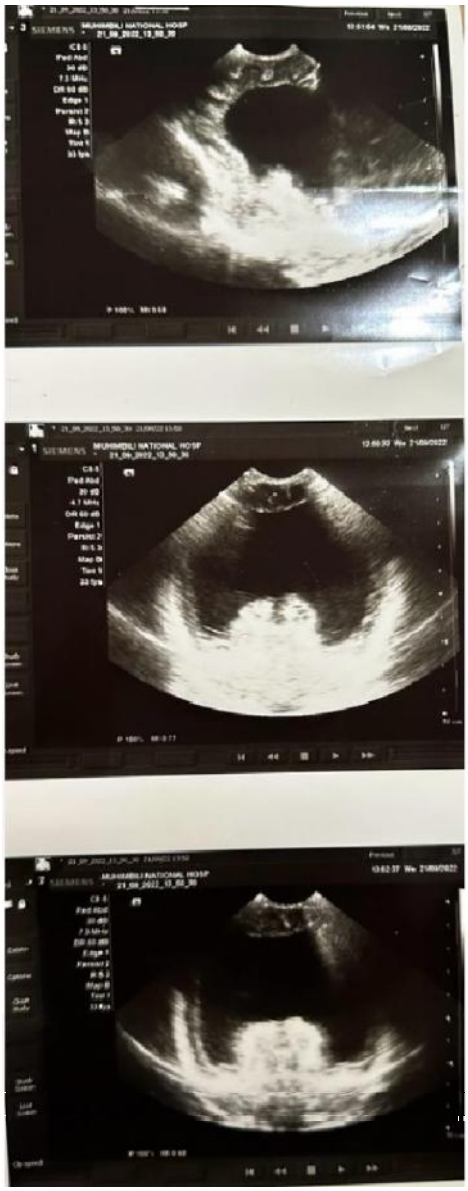


Image 3: Brain MRI of the first case

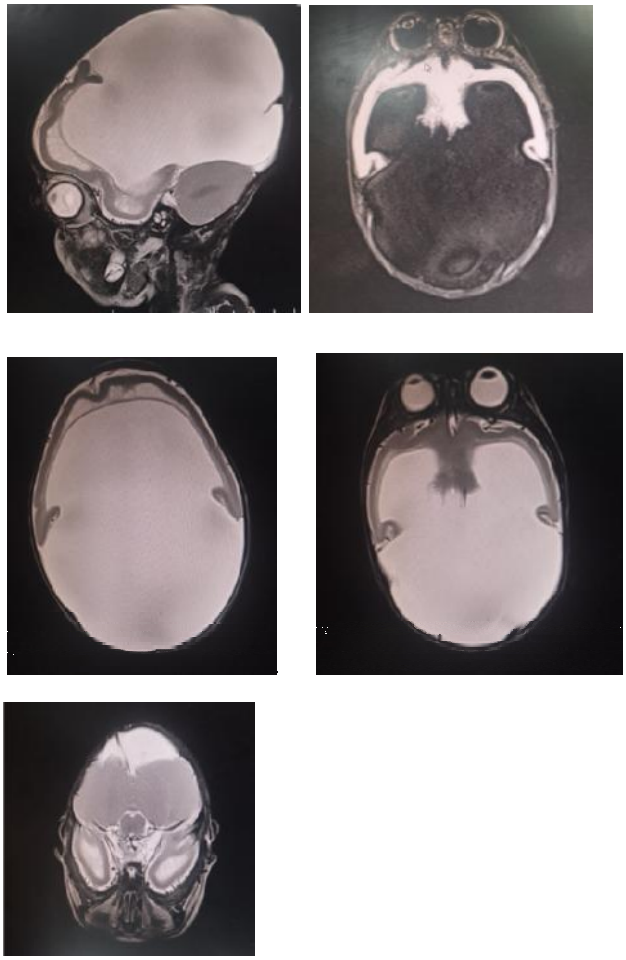
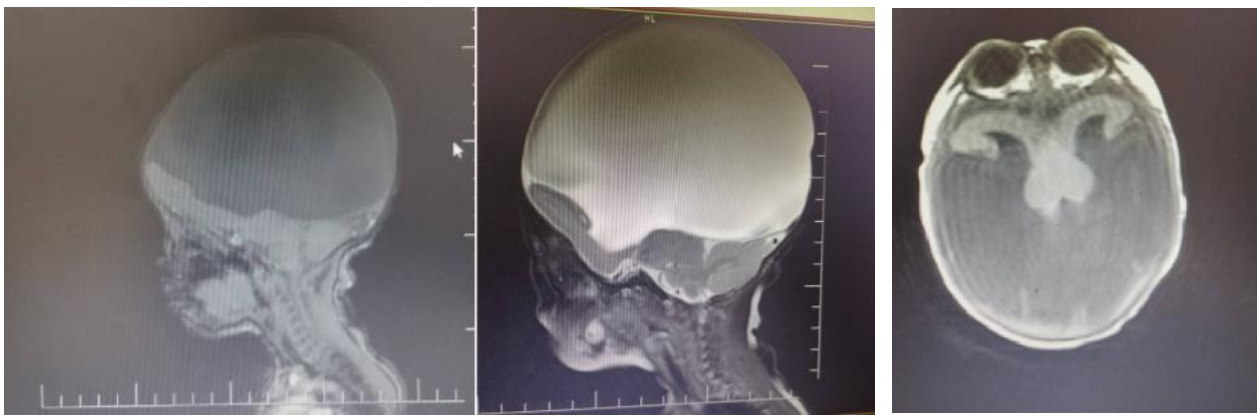


Image 4: Brain MRI of the second case



revealed multiple dysmorphic features including a single nostril, cleft lip, and palate with an occipital-frontal circumference of 42 cm which corresponded to severe macrocephaly.

Investigation: Brain MRI *(Image 4)*revealed fused thalami, with a thin rim of agyric cortex, absent interhemispheric fissure, falx cerebri, and septum pellucidum, findings suggestive of alobarholoprosencephaly. On blood workup, the complete blood countrevealed a leukocyte count of 8.58kcells/microlitre, with relative neutrophilia of 74%, normal haemoglobin of 18.7g/dl, and thrombocytopenia of 14.7Kcells/microlitre, with an elevated C-reactive protein was of37.8mg/l. Serum electrolytes assessment revealed hypernatremia of 161mmol/l which was attributed to dehydration hypernatremia which could be due to diabetes inspidus, a common complication in alobar holoprosencephaly. other electrolytes were normal.

Care and treatment: A nasogastric tube was inserted and he was kept on three hourly expressed breast milk, supplemental intravenous dextrose saline, and intravenous ceftriaxone for ten days which was then changed to intravenous ciprofloxacin after eight doses due to a persistent high C-reactive protein level. He was reviewed by maxillofacial and neurosurgery surgery specialists, and he was planned for palliative ventriculoperitoneal shunt but the patient died on his 14th day of life. The clinically identified underlying cause of death was sepsis with electrolyte imbalance.

Discussion

We present two cases of alobar holoprosencephaly confirmed by brain MRI attended at a tertiary facility in Tanzania. This adds to a previous case report of a neonate with alobar holoprosencephaly that was reported from a referral facility in the northern part of Tanzania, who succumbed to respiratory failure at the 6th day of life.[6]Similar to our cases, the previously described case was of a term neonate, born from a mother who did not have any identifiable risk factors and did not have ultrasonography throughout her pregnancy.[6]
Holoprosencephaly can occur sporadically, as described in the case reports from Tanzania. Familial cases have also been described.

One-third of children born with holoprosencephaly have been found to have chromosomal abnormalities. The commonest associated syndrome is Trisomy 13, which occurs in up to 39% of patients diagnosed with holoprosencephaly.[7] Other associated syndromes include, but not limited to Smith- Lemli-Opitz syndrome, CHARGE syndrome and Meckel syndrome.[1,7]Single-gene mutations have also been associated with holoprosencephaly. These include dysregulation of *SHH, SIX3, TGIF1,* and *ZIC2* genes on chromosomes 7,2,18 and 13 respectively.[8] Both our cases were suspected of having Patau syndrome (Trisomy 13), although genetic studies could not be done due to limited resources and the unavailability of these services locally. Genetic evaluation is mainly useful for counseling the parents about the risk of recurrence in subsequent pregnancies rather than altering the course of treatment and outcome of the affected infants.

The exact aetiology causing holoprosencephaly is yet to be confirmed. However, various epigenetic interplay of factors has been implicated. Prenatal risk factors include maternal diabetes mellitus, smoking and alcohol use during pregnancy, and exposure to retinoic acid, misoprostol, and cholesterol-lowering drugs.[9]These risk factors were not identified in any of the cases that we report. Holoprosencephaly is associated with a higher risk of pregnancy loss.[3]However, both mothers did not have a history of abortion orintra-uterine foetal death.
Holoprosencephaly, especially severe forms such as the alobar variant can be detected on prenatal ultrasonography.[10,11] Additional to a suggestive prenatal brain imaging, suspicion of holoprosencephaly is significantly supported by a history of an affected family member.[4] Both of our cases had missed the opportunities for prenatal ultrasound scan and they did not have any suggestive history or risk factors. Diagnosis of holoprosencephaly was suspected upon physical examination, and confirmed by brain MRI.[4]Prenatal diagnosis of holoprosencephaly would givean opportunity forearlier commencement of counselling and emotional support for the parents and preparations to deal with a possible pregnancy loss, neonatal death, or taking care of a child with dysmorphic features and associated comorbidities. However, several challenges and ethical dilemmas may arise when counseling parents following an antenatal diagnosis of holoprosencephaly especially in settings like Tanzania where termination of pregnancy may not be justifiable.[6]The diagnosis may increase the risk of peripartum depression, and the possibility of dealing with facing stigma from family and community.[12] It is therefore crucial to ensure adequate psychosocial support for affected families. Furthermore, one of our patients was delivered at a primary healthcare facility with limited access to intensive-care neonatal services. Prenatal diagnosis would justify referral for delivery at a higher health facility where intensive care could be provided if required.

According to DeMyer's maxim of 1964 which suggests that "*the face suggests the brain*", alobar holoprosencephaly would present with severe forms of facial dysmorphism including cyclopia, synopthalmia, and proboscis and a higher risk of mortality.[13,14] This may support the observation of more severe facial dysmorphism in our deceased patient, whose risk of death was further exacerbated by the presence of early-onset neonatal sepsis.

Survival rates for children with alobar holoprosencephaly are low, and among the survivors, a significant proportion exhibits profound global developmental de

delays.[15] This pattern is consistent with our observations of the surviving patient. Other comorbidities may include homeostatic instability, pituitary endocrinopathies, and abnormal sleep-wake patterns.[16] They are also affected with a wide range of nervous system disorders including seizures, hydrocephalus, visual impairment, and hearing impairment.[16,17] Furthermore, patients with holoprosencephaly commonly present with feeding difficulties especially due to cleft lip and palate which is the case for our surviving patient. This increases the risk of malnutrition and failure to thrive. Our case was admitted with marasmus at the age of 6 months despite being kept on exclusive breastfeeding. This was attributed to feeding difficulties due to oromotor dysfunction, and bilateral cleft lip and palate which caused difficulty latching and frequent choking. She also presented with global developmental delay, visual and hearing impairment, and epilepsy. The mainstay of management is supportive treatment of the associated comorbidities.[16]

Alobar holoprosencephaly has been documented among congenital anomalies with the poorest survival even in resource-rich settings. A follow-up study for neonates born with various congenital anomalies in Europe found the lowest survival among those born with holoprosencephaly.[5] Survival of alobar holoprosencephaly beyond the neonatal period is even rarer, although it has been described before. A study conducted in Dublin documented a 95% mortality among cases of alobar holoprosencephaly compared to 22% and 21% mortality among those with semi-lobar and lobar variants respectively.[11] Although with multiple comorbidities, one of our cases survived beyond the neonatal period.

Conclusion

This case report highlights the importance of early diagnosis preferably in the antenatal period, appropriate counseling and management of the affected neonates and their families. Prenatal ultrasonography should be utilized in diagnosis of the condition, and preparation of the parents on possibilities of poor pregnancy outcome including foetal demise, neonatal death or infant with dysmorphic features and multiple associated comorbidities. Healthcare providers should suspect the diagnosis of holoprosencephaly in neonates presenting with typicalfacial dysmorphism at birth.

Mother's perspective (the mother to the surviving infant)

I was frightened on the day of delivery, and I am still learning to care for a baby with unusual facial features. I keep wondering how the family would perceive my baby.

Learning points

From the two reported case reports, we put emphasis to the use of prenatal ultrasonography for the diagnosis of congenital malformations which would necessitate delivery at health facilities with access to neonatal and maternal resuscitation. Although genetic testing services are not available locally, effective supportive care and parental counselling can assist families in navigating the challenges of caring for affected children.

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