In the face of alobar holoprosencephaly: A case report

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Holoprosencephaly (HPE) is a rare congenital brain malformation caused by incomplete forebrain cleavage during embryogenesis. Alobar HPE, the most severe form, is characterised by a single cerebral hemisphere and absent midline structures, accompanied by severe facial anomalies. We present the case of a neonate with alobar HPE, diagnosed postnatally, displaying facial dysmorphism, seizures and global hypertonia. Genetic testing revealed no chromosomal or significant genetic anomalies. Neuroimaging confirmed characteristic findings, including a mono ventricle and fused thalami. This report highlights the diagnostic challenges, multifactorial aetiology and the need for multidisciplinary care in managing this complex condition, emphasising its poor prognosis and associated complications.

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Holoprosencephaly (HPE) is a rare structural brain abnormality involving incomplete cleavage of the forebrain (prosencephalon) into the two cerebral hemispheres.[1] It can be partial or complete and can present with different grades of severity. It is a rare malformation, occurring in approximately 1 in 16 000 live births and is thought to be multifactorial in aetiology.[2]

In 1964, DeMyer *et al.*[3] provided the most widely recognised classification of HPE,[3] dividing HPE into three subtypes: lobar, semilobar and alobar. The subtypes are outlined by the presence or absence of an interhemispheric fissure and the degree of cleavage of the cerebral hemispheres.

HPE is associated with chromosomal abnormalities, the most common being trisomy 13 or trisomy 18.[4] It is also associated with facial dysmorphism, often predictive of the so-called 'holoprosencephaly sequence' of brain anomalies. The most common facial defects in alobar HPE include a proboscis-like nasal structure, ocular hypotelorism, cyclopia, cebocephaly, median cleft lip/palate, and midface hypoplasia.[3]

Case presentation

We present a case of a neonate at day 1 of life, referred to an academic hospital from a community healthcare centre. The neonate was born during an uneventful natural vaginal delivery and was referred owing to the presence of dysmorphic facial features. On initial examination, a median cleft lip and palate was noted. Further examination revealed that the patient was also microcephalic (head circumference of 31 cm, *Z*-score –2.4, <3rd percentile), had a single nostril and exhibited hypotelorism (Fig. 1). The cardiovascular and respiratory systems examined normally. Owing to the cleft lip and palate, the patient required nasogastric feeds and later underwent placement of a percutaneous endoscopic gastrostomy feeding tube. Neurologically the patient was noted to have decreased tone globally.

Blood investigations included a quantitative fluorescent polymerase chain reaction (QF-PCR) analysis, which revealed XX chromosomes, with no aneuploidy detected on chromosomes 13, 18 or 21. Microarray testing was conducted to exclude chromosome abnormalities not detected by a QF-PCR. It showed a female profile with no clinically significant copy number variants.

Radiological investigations included an initial cranial ultrasound, which showed the presence of alobar HPE with no midline structures visible. This was confirmed by a computerised tomography (CT) brain scan, showing a mantle of peripheral cerebral parenchyma, fused thalami and an absent corpus callosum and interhemispheric fissure. No cavum septum pellucidum was noted and a mono ventricle was seen (Fig. 2).

During the hospital stay, the patient developed global hypertonia and seizures, which were controlled with antiepileptics. The patient also developed hypernatremia, which resolved with fluid management. Both these complications were thought to be secondary to the underlying neurological abnormalities.

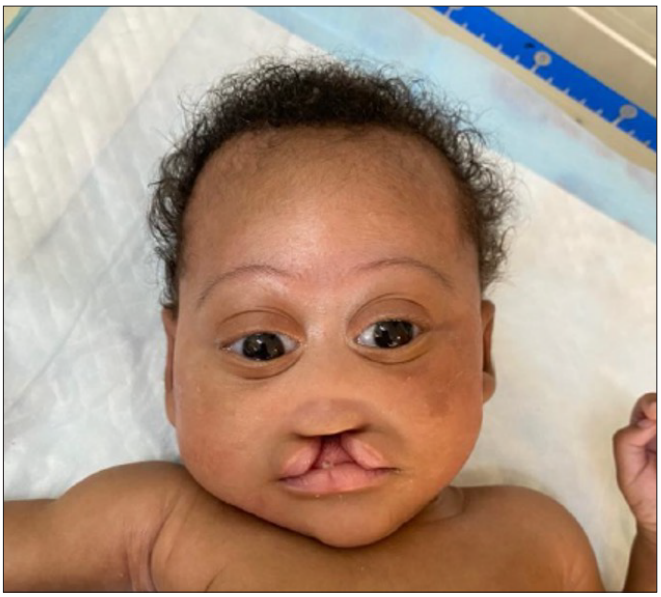

Fig. 1. Facial dysmorphism, including microcephaly, single nostril, hypotelorism and cleft lip and palate.

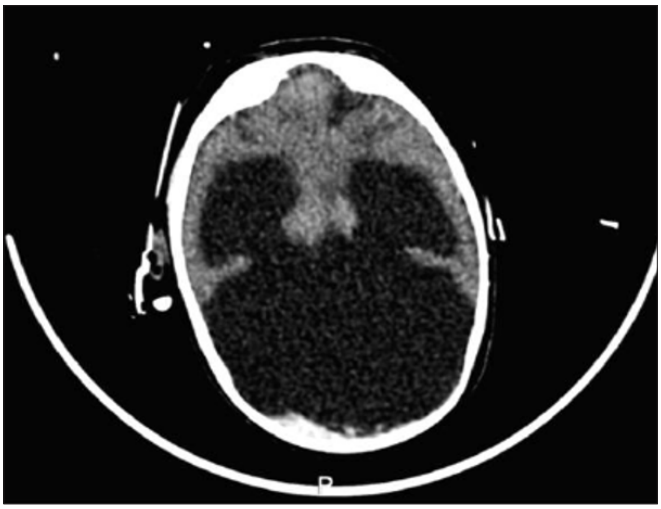

Fig. 2. Computerised tomography brain scan showing mantle of peripheral parenchyma with absent midline structures.

Discussion

HPE is the translation of disordered prosencephalon ventral induction between days 18 and 28 of embryonic life. There is absent or partial cleavage of the forebrain into the telencephalon and diencephalon owing to abnormal signalling. HPE, if not picked up prenatally, classically presents with pathognomonic facial defects, correlating with the degree of separation of the cerebral hemispheres.[5]

HPE is a rare abnormality that is seen more often with other chromosomal abnormalities. It is noted that there may be a small female predominance owing to the increased lethality in affected male embryos. Recurrence risk is unpredictable owing to the multifactorial aetiology of the condition. Chromosomal, genetic, environmental or teratogenic exposure and syndromic associations have all been described.[2]

Trisomy 13 is the most common chromosomal abnormality associated with HPE, with up to 70% of patients presenting with the alobar form. HPE may also occur with trisomy 18, trisomy 21, deletion 13q syndrome, monosomy 18p and triploidy, but these presentations are rare.[2] Mutations involving the gene encoding sonic hedgehog protein, which is responsible for ventralising signals in forebrain development, have been identified as a cause of HPE. Other implicated gene mutations in the development of HPE include *SIX3*, *ZIC2* and *TGIF*. A 'multiple-hit hypothesis' has been accepted. Currently, the exact cause of HPE is yet to be discovered, with approximately 75% of cases with normal chromosomes having no identifiable genetic mutations on screening.[1]

Our patient had a normal chromosomal analysis (XX; no trisomy 13, 18 or 21) and had no genetic mutations identified on microarray testing. In almost all cases of alobar HPE, thalamic nuclei are fused and midline structures are absent (corpus callosum, interhemispheric fissure and cavum septum pellucidum). Absent cleavage into separate hemispheres results in a single forebrain and a primitive mono ventricle with or without the presence of a dorsal cyst, which were noted on CT scan in our patient. The most associated facial defects in alobar HPE include a proboscis-like nasal structure, ocular hypotelorism, cyclopia, cebocephaly, median cleft lip/palate and midface hypoplasia.[1] Our patient had a median cleft lip and palate, hypotelorism, a single nostril and microcephaly (Fig. 1). The most sensitive ultrasound finding postnatally, as was used for the diagnosis in our patient, is a mono ventricle and fused thalami.

HPE should be screened for in all first-trimester prenatal ultrasounds (between 10 and 14 weeks' gestation). The hallmark feature of alobar HPE on prenatal ultrasound is the absence of the cavum septum pellucidum as visualised by the absence of the 'butterfly sign'.[4] Early ultrasound screening may be difficult in lower middle-income countries with poorer resources as many patients are managed at local clinics that may not offer these services and are referred to larger facilities only in case of emergency.[6]

If identified, prenatal management should include a microarray test, karyotyping and counselling for consideration of the option to terminate the pregnancy. Multiple complications contribute to the mortality of patients with HPE, including hydrocephalus requiring shunts, seizures requiring anticonvulsant therapy, cerebral palsy, swallowing problems, gastroesophageal reflux disease, constipation, and hypothalamic and endocrine dysfunction. Half (50%) of patients with alobar HPE die before 5 months of age, with only 30% surviving beyond the first year of life.[4]

Conclusion

Alobar HPE is the most severe form of HPE, which is characterised by the failure of the embryonic forebrain (prosencephalon) to divide into the normal cerebral hemispheres. It can result in significant brain malformations and associated facial anomalies. Prognosis is typically poor, with most cases resulting in stillbirth or early neonatal death.

This case highlights that isolated HPE can occur without chromosomal abnormalities and is possibly secondary to other genetic, environmental or maternal factors, which are poorly understood. HPE is the backbone of many other complications that arise secondary to the structural abnormalities of the brain. These often require a multidisciplinary approach to providing comprehensive care and support to the affected family and patient.

Declaration. None.

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