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A cebocephaly with holoprosencephaly spectrum: Clinical case and literature review

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ABSTRACT

Holoprosencephaly is a brain defect resulting from incomplete cleavage of the embryonic forebrain. It includes a wide spectrum of presentations with several forebrain and midfacial malformations of various degrees ranging from mild to severe. Here we describe the presentation of a newborn with semilobar holoprosencephaly with a cebocephaly (single nostril) and review literature regarding the various neuroimaging and craniofacial findings associated with the condition.

Keywords: Congenital facial malformation, Holoprosencephaly, Pyriform aperture stenosis

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INTRODUCTION

The term holoprosencephaly (HPE) was first proposed by DeMyer and Zeman. It is a developmental disorder resulting from failure of cleavage of the midline forebrain structures. There are four types of HPE: Lobar (presence of an interhemispheric fissure with a fused cingulate gyrus and lateral ventricles, and absent septum pellucidum); semilobar (partial formation of the interhemispheric fissure, with only a single midline ventricle); interhemispheric variant (interhemispheric fissure is absent only in the parietal region with fusion of the hemispheres); and alobar (absence of the interhemispheric fissure, falx cerebri, the third ventricle, and fused thalami, and often absent neurohypophysis and olfactory tracts) [1]. Holoprosencephaly is associated with several facial malformations such as cyclopia (a single midline eye), hypotelorism (close-set eyes), ethmocephaly (close-set eyes with a tube-like nose and interorbital proboscis), and cebocephaly (a nose with a single nostril) [2].

CASE REPORT

A 7-day-old male neonate born to 39 years old para-V (4 alive, 1 stillbirth, and 3 spontaneous abortions) mother was referred to Tikur Anbessa Specialized hospital after six days of treatment within a primary hospital for neonatal respiratory distress after birth and midline facial anomaly. The mother had antenatal care at a primary care hospital. She had negative results for syphilis, human immunodeficiency virus (HIV), and hepatitis B virus surface antigen. She is a nonsmoker, with no history of pre-gestational diabetes, exposure to alcohol, potential teratogens, or ionizing radiation during pregnancy. The delivery was uneventful and resulted in the delivery of a 4.2 kg male alive neonate with unknown Apgar scores but the mother states her newborn cried soon after birth.

On physical examination the neonate had signs of respiratory distress, with associated subcostal recession and rapid breathing of more than 78 breaths per minute and oxygen saturation under room air of 75% was documented. The child also had a cyanotic appearance with a heart rate of 170. It was not possible to pass a 6 Fr feeding tube into the nasal cavity during routine suction. The patient has a small head circumference [HC = 30 cm (below –3 z score)] with a midline facial deformity of a single midline patent nostril filled with mucoid secretion, pronounced hypotelorism, and protruding eyeballs (Figure 1). The rest of the physical examination was unremarkable.

The patient had hypernatremia reaching up to 170 mEq/L after which the diagnosis of central diabetic insipidus was entertained. Initial complete blood count (CBC) was normal but subsequent CBC profiles showed low platelet count with elevated CRP and persistent high-grade fevers for which the patient was managed for early-onset neonatal sepsis. Echocardiography and abdominal ultrasound were normal. Computed tomography (CT) scan showed absent falx cerebri anteriorly, fused frontal lobes, midline single lateral ventricle, fused basal ganglia, absent septum pellucidum, rudimentary interhemispheric fissure fused thalami and absent frontal and occipital horns of the lateral ventricles, rudimentary 3rd ventricle, and absent corpus callosum (Figures 2–4). Additionally, pyriform aperture stenosis (5.08 mm) (Figure 5), ocular hypotelorism (1.21 cm) (Figure 6), and an absent cartilaginous portion of the nasal septum was found on the axial CT scan imaging.

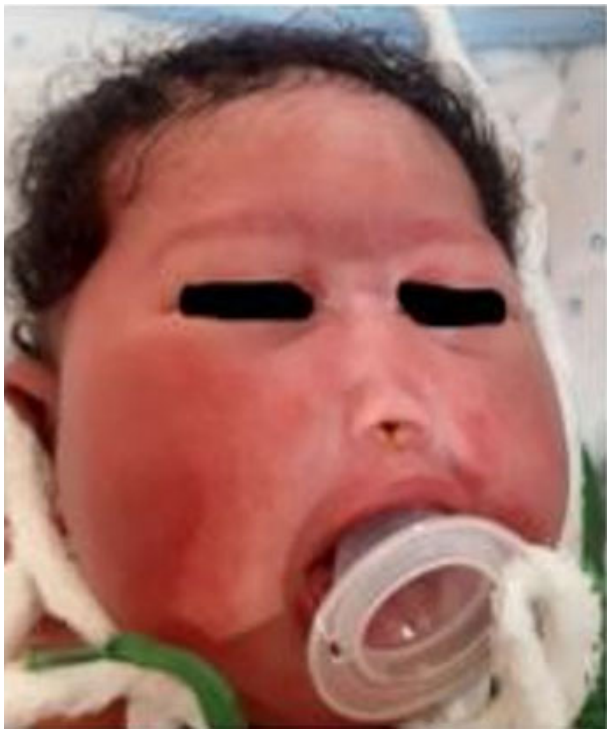

Figure 1: Clinical photograph showing a single nostril (cebocephaly).

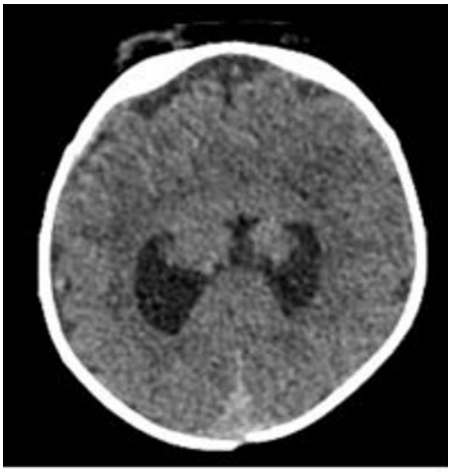

Figure 2: Axial CT image showing partial interhemispheric fissure and midline fused lateral ventricles with absent anterior horns.

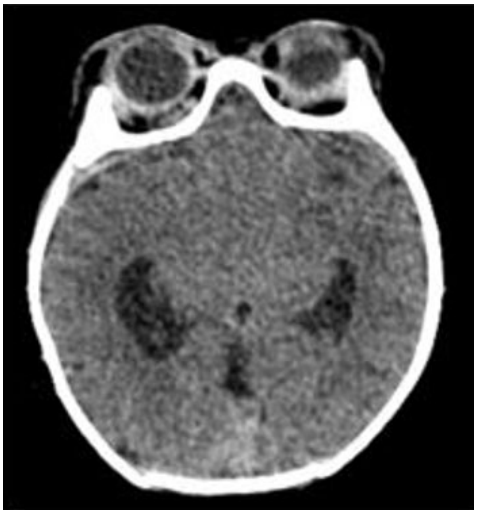

Figure 3: Axial CT image showing rudimentary third ventricle.

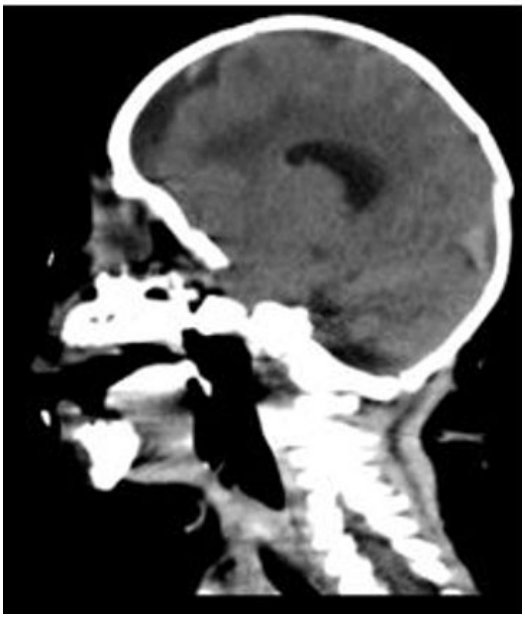

Figure 4: Sagittal CT image showing absent corpus callosum.

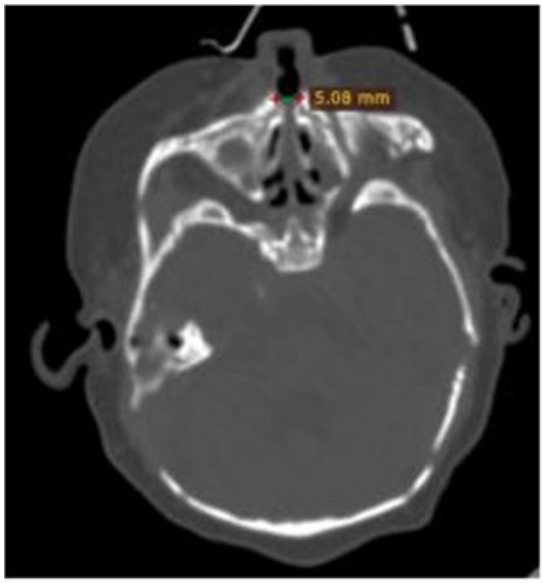

Figure 5: Axial CT image showing pyriform aperture stenosis.

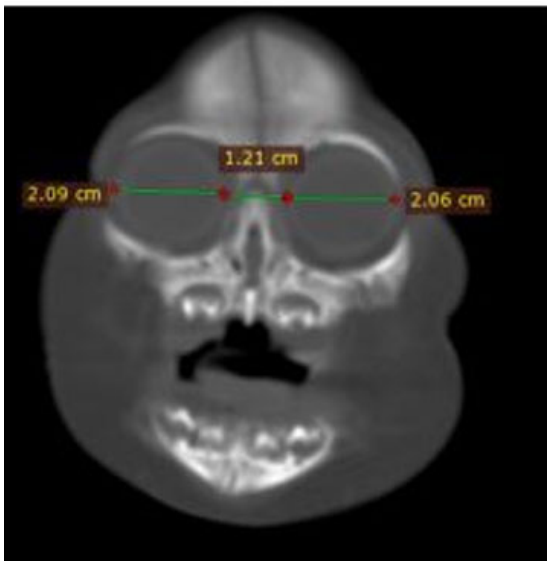

Figure 6: Coronal CT image showing ocular hypotelorism.

The patient was admitted to the neonatal intensive care unit and treated with intravenous antibiotics for neonatal sepsis. The diabetes insipidus was managed by intravenous hypotonic solution. Oxygen saturation gradually improved after the patient was supported with non-invasive oxygen ventilation via face mask and oral airway. The patient was discharged home after one month of hospital stay when he started maintaining normal oxygen saturation levels without oral airway and ventilatory support.

DISCUSSION

Holoprosencephaly (HPE) is a complex congenital brain malformation characterized by incomplete separation of the forebrain into two hemispheres, a process normally complete by the fifth week of gestation [3]. Holoprosencephaly is the most common developmental defect of the forebrain and midface in humans and occurs in 1 in 250 pregnancies, but only 3% of fetuses with HPE survive to delivery, but the overall live birth prevalence in a multicenter study was only 1 in 13,000 to 18,000 [4]. Holoprosencephaly was also found to be more common among females [5].

The etiology of HPE is not clearly known. Holoprosencephaly has a heterogeneous etiology with complex interactions between genetic aberrations and non-genetic exposures [6]. About 25–50% of HPE patients are found to have chromosomal abnormalities and about 18–25% have a mutation in a single gene that causes syndromic HPE [7]. The most common and consistent gene associated with HPE is the sonic hedgehog (SHH) gene [8]. Non-genetic risk factors in human studies include pre-existing diabetes, higher alcohol consumption, aspirin use, lower education level, and use of assisted reproductive technologies. Conversely consistent maternal folic acid use appeared to be protective [9].

Holoprosencephaly is classified into four types depending on the neuroradiologic features: alobar, semi-lobar, lobar, and middle interhemispheric (MIH), each possessing a different clinical outcome and severity.

Alobar HPE is the most severe variant where prosencephalic cleavage fails, resulting in a single midline forebrain with a primitive monoventricle often associated with a large dorsal cyst (Figure 7). The olfactory bulbs and tracts, the corpus callosum and anterior commissure, the septum pellucidum, and the interhemispheric fissure are all absent, while the optic nerves may be normal, fused, or absent. The basal ganglia, hypothalamic, and thalamic nuclei are typically fused in the midline, resulting in absence of the third ventricle [10]. Alobar HPE may also present with a severe craniofacial malformation that can predict the severity of malformation in the brain like cyclopia, ethmocephaly, cebocephaly, midline cleft, and premaxillary dysgenesis [11].

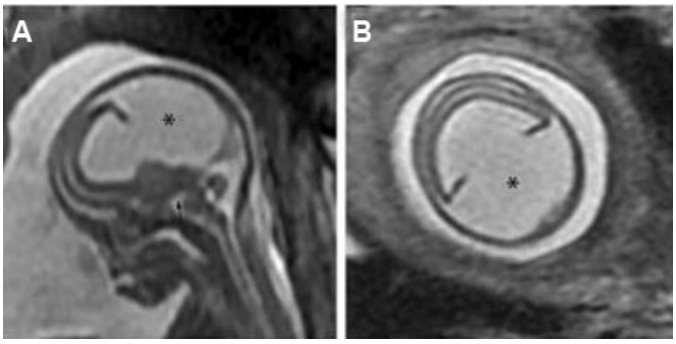

Figure 7: MRI: Alobar holoprosencephaly with cup-shaped holosphere and a dorsal cyst, 17-week fetus. (A) Sagittal T2 and (B) axial T2 images. The monoventricle communicates with the dorsal cyst (*). The thalami and the midbrain form a contiguous mass, consistent with a dysplasia at the diencephalic mesencephalic junction (arrow, A) [24].

Semilobar holoprosencephaly is of intermediate severity with early partial sagittal differentiation and separation. It shows a rudimentary falx, partial interhemispheric fissure, absent septum pellucidum, and partial separation of thalami. The basal ganglia show variable fusion [12]. Additional imaging features include an absent anterior horn of the lateral ventricle and small rudimentary 3rd ventricle, and partial or incomplete formation of the anterior corpus callosum. Additionally, in semilobar HPE the olfactory bulbs are often absent. A craniofacial defect is often present but less severe than the alobar variant [13]. These brain imaging findings of semilobar HPE are consistent with the present case.

The mildest form of HPE is lobar holoprosencephaly characterized by near total cleavage of cerebral hemispheres, presence of falx and interhemispheric fissure. The frontal horns appear squared off or box-like due to the absence of septum pellucidum. The thalami and the basal ganglia are separated. It may be associated with minimal facial dysmorphism like hypotelorism. There is a fourth variant of holoprosencephaly called the middle interhemispheric (MIH) variant. In this condition, the interhemispheric fissure is formed in the frontal and occipital regions and absent in the parietal region with fusion of the hemispheres [14].

Holoprosencephaly is associated with a spectrum of midline facial anomalies whose severity typically corresponds with the severity of the brain malformation. The most severe facial malformations such as cyclopia, ethmocephaly, and cebocephaly are only seen with alobar HPE. Milder facial malformations include findings such as median cleft lip and palate (premaxillary agenesis), midface hypoplasia, congenital nasal pyriform aperture stenosis (CNPAS), and a single maxillary central mega incisor [15]. In our case, the patient had a single nostril with no midline nasal septum, hypotelorism, and CNPAS [16].

Holoprosencephaly is commonly associated with breathing difficulty (including upper airway obstruction due to facial anomalies, aspiration, and central apnea), hydrocephalus, seizure, motor impairment, feeding and swallowing dysfunction, hypothalamic dysfunction (including abnormal sleep–wake cycles, temperature instability), endocrine dysfunction [including central diabetes insipidus that occurs in approximately 70% of patients with HPE, hypothyroidism (11%), hypoadrenocorticism (7%), and growth hormone deficiency (5%)] [12]. In this case, the patient had central diabetic insipidus and upper airway obstruction due to CNPAS.

The diagnosis of CNPAS is established using a CT scan that reveals a narrowed pyriform aperture with a width of less than 11 mm. Congenital nasal pyriform aperture stenosis can occur as part of the holoprosencephaly spectrum and is often associated with a missense mutation in the sonic hedgehog gene (SHH) [17]. Patients with CNPAS can be managed conservatively or with surgery depending on the degree of stenosis [18]. The presence of associated craniofacial anomalies is the main cause of surgical treatment failure. Mild CNPAS is a condition that tends to improve as the child grows with an excellent prognosis [19]. In our case, the respiratory distress from the CNPAS was managed with non-invasive respiratory support with a face mask, oral airway, and regular suctioning. The child responded well to the conservative management and was discharged home after 21 days of admission.

Prenatal diagnosis of holoprosencephaly can be made as early as intrauterine 10th-14th week by using trans-abdominal or trans-vaginal ultrasonography but still the sensitivity of ultrasonography for detection of milder forms of HPE (lobar and MIH) may be low [20]. The prenatal ultrasound finding for alobar HPE include: absence of falx cerebri and interhemispheric fissure, fusion of the thalami, a single ventricle, and absence of cavum septum pellucidum [21]. Other findings include the presence of dorsal cyst or extra-axial fluid collection, abnormal facial morphology like cyclopia, ethmocephaly may be present and, midline facial cleft and hypotelorism being more common sonographic findings [22]. False-positive diagnosis of HPE has been reported in cases of hydrocephalus, arachnoid cysts, and Dandy–Walker malformations with ventriculomegaly [23].

Overall, mortality is high for newborns with HPE. For severe forms of HPE (especially when accompanied with severe craniofacial anomalies or chromosomal abnormalities) early mortality during the first few months of life is common; however, children with milder forms of HPE, that is, lobar and MIH variants of HPE often survive into childhood [24].

CONCLUSION

A cebocephaly (a single midline nostril) is a feature of the holoprosencephaly spectrum and therefore mandates a careful search for an underlying complex congenital brain malformation. Prompt diagnosis and adequate respiratory support at birth are also crucial, as CNPAS might be present. Associated congenital anomalies, morbidities, and prognostic information should be discussed with caregivers depending on the degree of severity of the holoprosencephaly spectrum regarding neurodevelopmental outcomes during counseling.

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Elizabeth T Beyene – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Mehret F Shiferaw – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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Authors declare no conflict of interest.

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All relevant data are within the paper and its Supporting Information files.

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