

## Ultrasound diagnosis in two cases of severe craniofacial anomalies

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### Abstract

Abstract: Holoprosencephaly (HPE) is a rare anomaly of the brain consisting of an absent or incomplete separation of the forebrain in early gestation. We present 2 variants of HPE, diagnosed by ultrasound, which combined with the clinical features led to HPE subtypes differentiation.

**Keywords:** holoprosencephaly, head ultrasound, infant, preterm.

### Introduction

Holoprosencephaly (HPE) represents the failure of septation of the midline forebrain structures occurring between 18-28 gestational days, commonly associated with midfacial defects [1]. The correlation between the facial anomalies and HPE subtypes was pointed out by DeMeyer in a paper entitled “*The face predicts the brain*” [2]. HPE is frequently associated with a poor fetal and early postnatal outcome [3]. Although nowadays brain CT or MRI are considered the gold standard in HPS complete diagnostic characterization, head ultrasound (HUS) is referred to as the best choice equally for pre and post-natal screening [4,5].

### Cases report

#### Case 1

A baby girl born after an uninvestigated pregnancy was admitted at 2 days old to the M.S. Curie Hospital

for a plurimalformative syndrome. Both parents were young and apparently healthy. A marked cranio-facial dysmorphism with cebocephaly, microcephaly, proptosis and low set ears was noticed (fig 1). The HUS evidenced a monoventricular cavity with absent interhemispheric fissure and midline structures: *falx cerebri*, *septum pellucidum*, and *corpus callosum*, together with a posterior fossa cyst (fig 2). Based on the clinical data, along with the ultrasound features described above, a diagnosis of alobar holoprosencephaly was established. The karyotype was normal, as well as the heart and abdominal ultrasound. The outcome was rapidly unfavorable, with severe neurologic deterioration, despite the complex anti-epileptic treatment.

#### Case 2

A premature boy, delivered after a 36 weeks uninvestigated pregnancy, was admitted to the Institute for Mother and Child Care at the age of 18 days. The mother, aged 23 was apparently healthy and the father unknown. The physical examination revealed multiple craniofacial abnormalities: cleft lip and palate, depressed nasal bridge, proptosis, hypotelorism, low set ears, microcephaly, along with episodes of apnea and cyanosis, bradycardia, hypertonia, nystagmus, and recurrent seizures (fig 3a).

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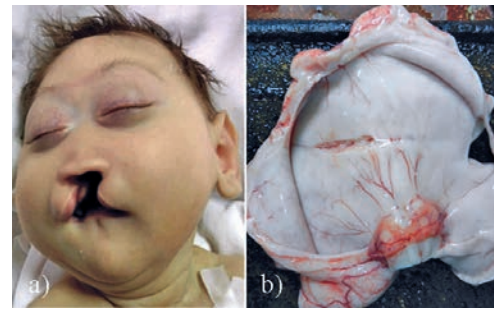
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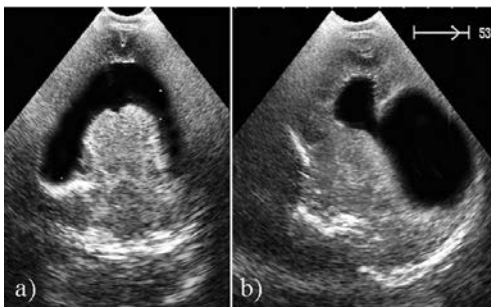
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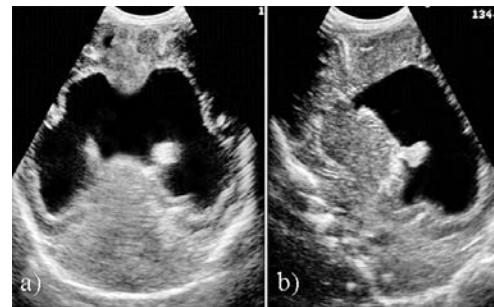
**Fig 1.** Cebocephaly or “monkey-like head” (flattened nose, mononostril, hypotelorism, and proptosis) and low set ears.



**Fig 3.** a) Microcephaly and midfacial defects: hypotelorism cleft lip and palate, depressed nasal bridge, proptosis, low set ears; b) Necropsy: a common ventricle with absent midline structures.



**Fig 2.** Head ultrasonography: a) coronal view: a monoventricular cavity with absent interhemispheric fissure and midline structures: falx cerebri, septum pellucidum, corpus callosum; b) sagittal view: a monoventricular cavity with absent interhemispheric fissure and midline structures and the posterior fossa cyst.



**Fig 4.** Head ultrasonography: a) coronal view: anteriorly fused cerebral hemispheres, complete fusion of the thalami, partially developed occipital and temporal horns. Incompletely formed interhemispheric fissure and falx cerebri, septum pellucidum and callosal agenesis; b) sagittal view: a common ventricle, absent septum pellucidum, absent corpus callosum

HUS demonstrated fusion of the anterior horns of the lateral ventricles, *septum pellucidum* and *callosal* agenesis and fused thalamic nuclei (fig 4). Based on this data, along with the typical facial abnormalities we established a diagnosis of semilobar HPE. The karyotype was normal, and no other malformation were present. During the admission he progressively deteriorated, developing hard to treat epilepsy and died at the age of 2 months. The necropsy was consistent with the HUS data (fig 3b).

### Discussion

HPE results from failure or incompletely cleavage of the forebrain into the right and left hemispheres and into olfactory and optic bulb tracts, occurring in early gestation, and affecting both the brain and the face [3,6]. The most obvious clinical features are represented by the fa-

cial dysmorphism; the severity of the craniofacial malformations being usually parallel to the severity of the brain abnormalities. Other clinical manifestation are: severe developmental and growth delay, seizures, pituitary dysfunction, periodic brainstem and/or hypothalamus dysfunction with irregular breathing, heart rhythm and heat rate and unstable temperature control, usually leading to an early poor outcome [1]. In early embryogenesis the prevalence is 1:250, but at birth it is around 1:16.000, due to a high rate of intrauterine deaths [7].

HPE etiology is heterogenous; chromosomal, monogenic and environmental factors are implicated. Recognized environmental factors are maternal type 1 diabetes mellitus, alcoholism, prenatal exposure to various drugs, or infections (TORCH) [8]. HPE may be associated to trisomy 13, 18, but may also be a solitary manifestation. In about 25% of cases HPE is associated with plurimal formative

syndromes with a normal karyotype, such as Smith-Lemli-Opitz, Pallister Hall or velo-cardio-facial syndrome [8].

In our cases, based on the normal karyotypes we could exclude a chromosomal cause of HPE and presumed as probable etiology environmental factors such as maternal infection or exposure to other teratogens in the first trimester.

Depending on the degree of the forebrain involvement, HPE subtypes, in decreasing order of severity are: alobar, semilobar, lobar HPE, middle interhemispheric fusion variant and septo-optic dysplasia [3,9]. This spectrum of HPE subtypes describes the degree to which the frontal, temporal, parietal and occipital lobes are defined. The midline structures, the *falx*, *corpus callosum* and *septum pellucidum* are either absent or hypoplastic. In both cases a combined work-up using HUS criteria and typical facial features essentially contributed to diagnosis. In case 1, the ultrasound diagnostic features for alobar HPE were: absence of interhemispheric fissure with a monoventricular cavity, absent midline structures (*falx cerebri*, *septum pellucidum*, *corpus callosum*) and a posterior fossa cyst [10]. From the HPE spectrum, the mid facial abnormalities in the alobar form are the most severe: *cebocephaly* “monkey-like head” with small, flattened nose, single nostril, mono-orbit with cyclopia, or just hypotelorism. Except for mono-orbit and cyclopia, all other features were observed in case 1. In semilobar HPE the incomplete separation of the ventricles is revealed on HUS by the anteriorly fused cerebral lobes generating a common ventricle with partially developed occipital and temporal horns, along with thalamic fusion. The interhemispheric fissure and *falx cerebri* are incomplete, *septum pellucidum* is absent and *corpus callosum* is absent or hypoplastic. As observed in case 2, the craniofacial abnormalities are milder compared to the alobar form consisting of cleft lip and palate and hypotelorism.

In both cases, based on the ultrasound data, the main differential diagnosis to be discussed is congenital hydrocephalus, but the associated cranio-facial features were extremely useful in HPE positive diagnosis, and substantially helped with subtype characterization.

Because of the extreme severity of the cerebral malformations, alobar HPE is usually fatal in the neonatal or early infant age, as observed in case 1. Although the survival rate could be slightly higher in semilobar HPE than in the alobar form, in case 2, the severity of the neurological anomalies and the multiple co-morbidities could not prevent the early fatal outcome [11].

**Conclusion:** As the most cases are sporadic, the prenatal diagnosis by routine ultrasound examination is essential and advisable. It is also important to determine the type and to classify the severity of the HPE, because the prognosis strongly depends on the severity of the abnormalities of the central nervous system. In our cases a prenatal diagnosis was not performed due to the fact that both pregnancies were uninvestigated.

**Note:** For facial photos publication the University’s Ethical Committee approval was obtained

## References

1. Barkovich JA, Moore KR, Grant E, et al. Diagnostic Imaging: Pediatric Neuroradiology. 1<sup>st</sup> edition. Amirsys-Elsevier, Salt Lake City, Utah; 2007.
2. Demyer W, Zeman W, Palmer CG. The face predicts the brain: diagnostic significance of median facial anomalies for holoprosencephaly (arhinencephaly). *Pediatrics* 1964; 34: 256-263.
3. Solomon BD, Gropman A, Muenke M. Holoprosencephaly Overview. In: Pagon RA, Adam MP, Bird TD, Dolan CR, Fong CT, Stephens K, editors. GeneReviews™ [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2013.
4. Hahn JS, Barnes PD, Clegg NJ, Stashinko EE. Septopreoptic holoprosencephaly: a mild subtype associated with midline craniofacial anomalies. *AJNR Am J Neuroradiol* 2010; 31: 1596-1601.
5. De Catte L, De Keersmaecker B, Claus F. Prenatal neurologic anomalies: sonographic diagnosis and treatment. *Paediatr Drugs* 2012; 14: 143-155.
6. Gropman AL, Muenke M. Holoprosencephaly. In: Cassidy SB, Allanson JE, eds. Management of Genetic Syndromes. Wiley-Liss, Inc., New York, NY 2005: 279-296.
7. Gupta AO, Leblanc P, Janumpally KC, Tanya P. A preterm infant with semilobar holoprosencephaly and hydrocephalus: a case report. *Cases J* 2010; 3: 35.
8. Ming JE, Muenke M. Multiple hits during early embryonic development: digenic diseases and holoprosencephaly. *Am J Hum Genet* 2002; 71: 1017-1032.
9. Levey EB, Stashinko E, Clegg NJ, Delgado MR. Management of children with holoprosencephaly. *Am J Med Genet C Semin Med Genet* 2010; 154C: 183-190.
10. Paladini D, Volpe P. Ultrasound of Congenital Fetal Anomalies. Informa UK Ltd, London 2007: 22-26.
11. Hahn JS, Plawner LL. Evaluation and management of children with holoprosencephaly. *Pediatr Neurol* 2004; 31:79-88.