

# Holoprosencephaly: Two Case Reports

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## ABSTRACT

*Holoprosencephaly is a rare malformation encountered in newborns. It refers to the absent or incomplete division of the prosencephalon.*

*Case no. 1: a fetus was diagnosed by ultrasonogram at 29 weeks of gestation with alobar holoprosencephaly, proboscis and cyclopia. The premature infant was delivered by cesarean section at 32 weeks of gestation, confirming antenatal diagnosis.*

*Case no. 2: a premature newborn at 29 weeks of gestation, who presented posterior pole of cranial cavity occupied by a translucent, asymmetrically disposed structure, with anatomically normal cerebellum, compressing the posterior horn of the left cerebral hemisphere. Lateral ventricles, had also a large communication in their middle with incomplete fused thalami. The diagnosis of lobar holoprosencephaly with arachnoid cyst was confirmed by the autopsy.*

**Keywords:** holoprosencephaly, arachnoid cyst, middle interhemispheric variant of holoprosencephaly

**H**oloprosencephaly (HPE) is the most frequent malformation of the prosencephalon. It represents the absence or incomplete division of the prosencephalon during the 4<sup>th</sup> and 8<sup>th</sup> week of gestation. Its incidence is estimated to be 1 in 16000 live births and 1 in 250 spontaneous abortions (1). It is cla-

ssified in 3 types, according to the degree of cerebral involvement: alobar, semilobar and lobar. The clinical features vary very much, depending on the severity of holoprosencephaly. We present in this paper two cases of newborns diagnosed with holoprosencephaly and a brief discussion on the pathogenesis, clinical features, management and prognosis of holoprosencephaly.

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**Case no. 1:** a preterm male sex infant was born at 32 weeks gestational age by a 26 year old mother. The birth weight was 1800 grams. The infant died immediately after birth. The pregnancy, which was partially investigated, had an apparently uncomplicated course. The mother had a previous cesarean section in 2002, her first child having a normal neurologic development until now.

At 29 weeks of gestation **alobar holoprosencephaly** was diagnosed by brain scan. The sonography showed: fused cerebral hemispheres in their anterior and middle regions, major dilatation of the cerebral ventricles, proboscis, microcephaly, bilateral microftalmia and hypotelorism; the orbits were situated between the mouth and the proboscis. At birth, the infant presented with: cyclopia, proboscis and macroglossia. The autopsy showed, besides the facial malformations, fused cerebral hemisphe-



FIGURE 3. Proboscis, cyclopia



FIGURE 4. Single ventricle, choroid plexuses - coronal section



FIGURE 5. Single ventricle, fused thalamic nuclei - coronal section



FIGURE 1. Proboscis, cyclopia, macroglossia

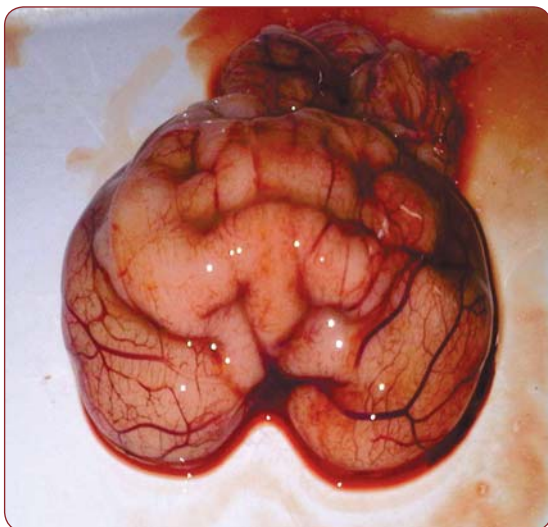


FIGURE 2. Fused cerebral hemispheres

res, a single ventricle, and fused thalamic nuclei in their caudal portion and suprarenal glands agenesis (Figures 1-5).

**Case no. 2:** an infant with **lobar holoprosencephaly** and craniosynostosis, born at 29 weeks of gestation. The mother, age 32 years old, had in the past one spontaneous abortion

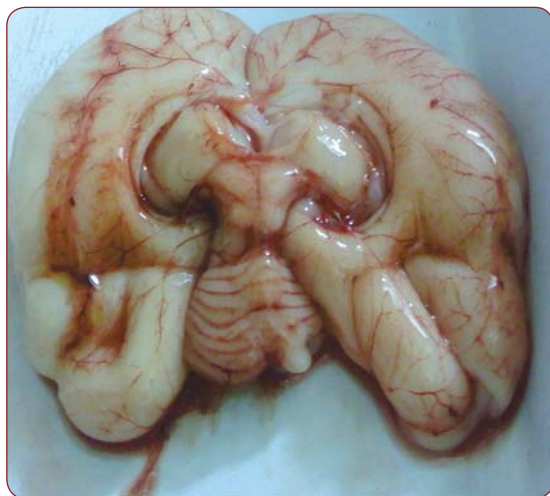
and one spontaneous delivery and she received good prenatal care during this pregnancy. At 19 weeks gestation, the diagnosis of a choroids plexus cyst was made.

At 28 weeks of gestation ultrasound scan revealed posterior pole of cranial cavity occupied by a translucent, asymmetrically disposed structure, with anatomically normal cerebellum, compressing the posterior horn of the left cerebral hemisphere, which was considered to be an arachnoid cyst. Lateral ventricles, had also a large communication in their middle with incomplete fused thalami.

At 29 weeks gestation, following a premature labor, she gave birth to a live baby, female sex, weighting 1350 grams, who died 5 days after birth. Physical findings at birth included



**FIGURE 6.** Arachnoid cyst compressing the occipital lobe of the left cerebral hemisphere, above tentorium cerebelli, intact cerebellum – sagittal section



**FIGURE 7.** Corpus callosum agenesis, midline fusion of cingulate gyrus, lateral ventricles with communication in their middle with incomplete fused thalami

microcephaly and palatoschisis. The autopsy report confirmed ultrasound findings: lobar holoprosencephaly, midline fusion of cingulate gyrus, craniosynostosis, and the remains of the supposed arachnoid cyst (Figures 6-9). □



**FIGURE 8.** Corpus callosum agenesis, midline fusion of cingulate gyrus, lateral ventricles with communication in their middle with incomplete fused thalami – coronal section, ultrasound image



**FIGURE 9.** Arachnoid cyst compressing the occipital lobe of the left cerebral hemisphere, above tentorium cerebelli, intact cerebellum – oblique section through the posterior fossa

### DISCUSSIONS

HPE is classified into three types:

1. Alobar, which means the complete absence of division of the prosencephalon structures, resulting in completely absent inter-hemispheric fissure and corpus callosum, fused thalami, fused cerebral hemispheres with only one cerebral ventricle, and facial dysmorphism which include such abnormalities as cyclopia, proboscis, ethmocephaly and cebocephaly. It is the most severe form.

2. Semilobar, consisting in incomplete separation of the cerebral hemispheres: there are two cerebral hemispheres connected in the frontal area, with a singular ventricular cavity and partially fused thalami.
3. Lobar, in this case interhemispheric fissure is present, septum pellucidum is absent and frontal horns of lateral ventricles communicate freely, corpus callosum is absent hypoplastic or normal, with midline fusion of cingulate gyrus. It is the least severe form.

There is a fourth type described in the literature, the middle interhemispheric variant (MIH), which means a defect of separation of the posterior portions of frontal lobes and the parietal lobes, with varying lack of cleavage of the basal ganglia and thalami and absence of the body of the corpus callosum but presence of the genu and splenium of the corpus callosum. (1)

The etiology of HPE includes genetic and environmental factors. Among the environmental causes there are: maternal diabetes mellitus, maternal alcoholism, in utero infections with CMV, rubella or toxoplasma, some drugs (retinoic acid, cholesterol synthesis inhibitors) (1). HPE can be transmitted in an autosomal dominant way. Mutation of SHH gene is the most frequent cause of familial HPE (2). Also, HPE is associated in 40% of cases with numerical chromosomal anomalies, the most frequent one being trisomy 13 (3).

HPE can also be associated in about 25% of the cases with several defined multiple malformation syndromes with a normal karyotype, like Smith-Lemli-Opitz, Pallister Hall or velocardio-facial syndrome (1).

In both of the presented cases, no risk factors were identified in the mother's history.

No genetic studies were made on the infants.

We considered the second newborn a case of the middle interhemispheric variant of lobar HPE because of the large communication of lateral ventricles in their middle with incomplete fused thalami, the absence of corpus callosum and the midline fusion of cingulate gyrus.

Antenatal ultrasound diagnosis of middle interhemispheric variant (MIH) is rare. There is a single reference about two fetuses with lateral ventricles communicating only in their middle portion, with normal anterior horns and non-cleavage of the midbrain. These findings were

confirmed by autopsy in only one of the two fetuses (4).

Also the MIH could be hard to identify in infants. After birth the diagnosis is established only when neurologic or cognitive disorders appear. In this cases the diagnosis is obtained through magnetic resonance imaging (MRI) or computerized tomography (TC) (5).

**Clinical findings** are variable and depend on the degree of severity of holoprosencephaly.

- Midfacial defects occur in most cases and have a prognostic significance (2). These include: absence of the eyes, cyclopia, proboscis, cebocephaly (hypotelorism associated with a single nostril), cheilo/palatoschisis, agnathia or micrognathia. Cyclopia, proboscis and cheilo/palatoschisis are associated with severe forms of HPE (6).
- Microcephaly, or, rarely, macrocephaly, suggesting the presence of hydrocephaly (2).
- Mental retardation directly correlated with the severity of HPE.
- Neurologic manifestations are also frequently encountered: seizures, hyper/hypotonia, dysphagia, dysphonia, extrapyramidal disorders, like chorea or dystonia.
- Endocrine dysfunctions: hypopituitarism, diabetes insipidus
- Clinical manifestations of MIH compared with classic subtypes of HPE concluded that MIH is similar to the lobar subtype for functional measures but differs in the absence of endocrine dysfunction (5).

**Prenatal diagnosis** of HPE includes:

- Ultrasonography, which can show: polyhydramnios, hypotelorism, arinia, cyclopia, proboscis, cheilo/palatoschisis, single cerebral ventricle (3). The diagnosis could be made in most cases of alobar and semilobar holoprosencephaly after 17 weeks of gestation, when the production of cerebrospinal fluid starts. In lobar cases diagnosis could be difficult because the antenatal picture of septo-optic dysplasia is almost identical to that of lobar holoprosencephaly (7).
- Fetal MRI
- Cytogenetic analysis.
- Molecular analysis of fetal DNA.

**The treatment** of HPE is supportive and is oriented towards different malformations associated.

**Prognosis** is dependent upon the degree of fusion and malformation of the brain, as well as other health complications that may be present. Alobar and semilobar HPE are lethal. Children born with lobar HPE can survive for years, but encounter a lot of neurologic manifestations and severe mental retardation. □

### CONCLUSIONS

In these case reports are compared two extreme forms of the same pathology.

Middle interhemispheric variant is described by few authors. This is the second case in litera-

ture sustained with ultrasound intrauterine images and confirmed by autopsy.

The incidence of middle interhemispheric variant is not known. There are reported almost 50 cases of MIH in the last 10 years but only three were suspected in pregnancy by ultrasound scanning (4,5,8-10).

In both cases the diagnosis was established before preterm birth, but too late for offering the parents the possibility to decide the opportunity of fetocide. □

### CONSENT

*Written informed consent was obtained from the patient for publication of this case report and accompanying images.*

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