CASE REPORT

RJME
Romanian Journal of Morphology & Embryology
http://www.rjme.ro/

Holoprosencephaly sequence

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Abstract

Holoprosencephaly (HPE) sequence is a rare spectrum of cerebral and facial malformations resulting from incomplete division of the embryonic forebrain into distinct lateral cerebral hemisphere. Three ranges of increasing severity are described: lobar, semi-lobar and alobar HPE. A subtype of HPE called middle inter-hemispheric variant (MIHF) has been also reported. The etiology is heterogeneous: teratogens, chromosomal abnormalities and single gene mutations can be involved. Holoprosencephaly results in early morbidity and mortality with a reduced survival beyond neonatal period. The disorder is estimated to occur in 1/16 000 live births. This case report presents a male new born diagnosed with holoprosencephaly, accompanied by median cleft palate, absent nasal bones and chromosomal abnormalities.

Keywords: holoprosencephaly, absent nasal bones, cleft palate, chromosomal abnormalities, male.

Introduction

Holoprosencephaly denotes a failure in the division of the embryonic forebrain (prosencephalon) into distinct lateral cerebral hemisphere. A series of facial anomalies are frequently associated, due to the common origin of embryonic forebrain and midface from pre-chordal mesoderm [1–3]. The disorder occurs between 4th to 8th week of pregnancy.

According to severity, holoprosencephaly is categorized in three forms: (1) alobar holo-prosencephaly, or complete absence of midline forebrain division resulting in a monoventricle and fused cerebral hemispheres; (2) semilobar holo-prosencephaly, or incomplete forebrain division resulting in partial separation of the cerebral hemispheres; and (3) lobar holoprosencephaly, or complete ventricular separation with focal areas of incomplete cortical division [1, 5]. A milder form of inter-hemispheric fusion or middle inter-hemispheric variant (MIHF) has been described.

Environmental, genetic, multi-factorial, and unknown causes can be involved in the genesis of this condition.

The disorder is associated with morbidity and mortality with a significantly reduced survival beyond neonatal period. Treatment is symptomatic and supportive, and requires a multidisciplinary management. Child outcome depends on the HPE severity and the medical and neurological complications associated.

Holoprosencephaly is estimated to occur in 1/10 000–20 000 live births [1, 6].

Patient, Methods and Results

We present a case of low birth weight male newborn, referred to our Unit by a level I hospital for microcephaly and cleft palate.

The newborn came from an unplanned pregnancy of a teenage mother with no prenatal care. At the admission, the baby presented with respiratory difficulties, microcephaly, facial deformities, hypotonia and poor reflexes.

The baby was admitted in the Neonatal Intensive Care Unit (NICU) and received supportive and symptomatic treatment according to his status. A series of imaging studies and laboratory tests were performed.

During his stay in the NICU clinical course of the baby was unfavorable with persisting hypotonia, and seizures, temperature instability, prolonged jaundice, feeding difficulties, failure to thrive, and death at 37 days of life.

Clinical examination

The physical examination revealed a low birth weight male newborn W=2450 g, L=47 cm, with a dysmorphic appearance (Figure 1):

- microcephaly (cranial perimeter 27.5 cm; 10% percentile on growth chart);
- small anterior fontanelle 0.6 cm/0.5 cm;
- abnormal scalp and upper facial hair growth pattern;
- large and asymmetric ears;
- facial anomalies: ocular hypotelorism (inner cantal distance 1.4 cm);
- absent nasal bones and nasal septum (Figure 2); midline clefting (keilognatopalatoskysis – Figure 3);
- abnormal neurological status: hypotonia, diminished/absent archaic reflexes, recurrent seizures.

Cranial ultrasonography

A head ultrasonography was performed using a low frequency transducer. With the limitations due to the very small anterior fontanelle, it showed a unique large ventricle and fused cerebral hemispheres (Figure 4). Single monoventricle, partially fused frontal inter-

hemispheric fissure consistent with semilobar HPE. No magnetic resonance imaging (MRI) or a cranial computed tomography (CT) could be done at that time.

Chromosomal analysis

A chromosomal analysis was performed and showed a normal male karyotype 46, XY, with an inversion on the long arm of chromosome 5: 5q14→5qter (Figure 5).

Necroptic examination

Necroptic examination showed the partially fused cerebral hemispheres with a thin brain mantle and lacked sulcal pattern) and a large unique ventricle (Figure 6).

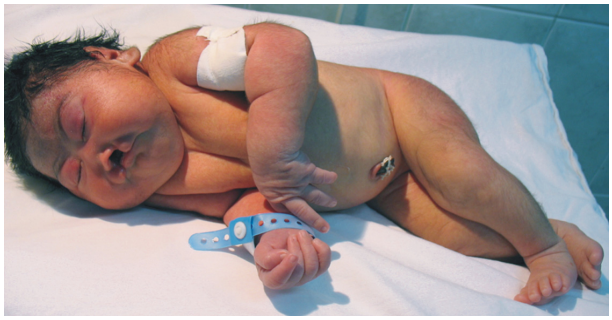

Figure 1 – ***The dysmorphic appearance: microcephaly, abnormal scalp and upper facial hair growth pattern, large ears, hypotelorism.***

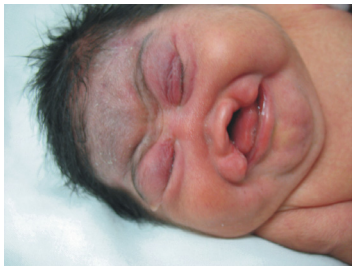

Figure 2 – ***Absent nasal bones and nasal septum.***

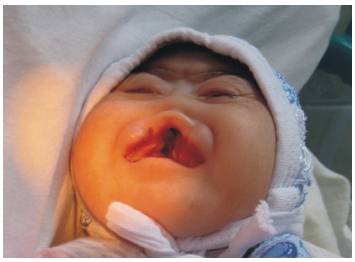

Figure 3 – ***The midline clefting (keilognato-palatoskysis).***

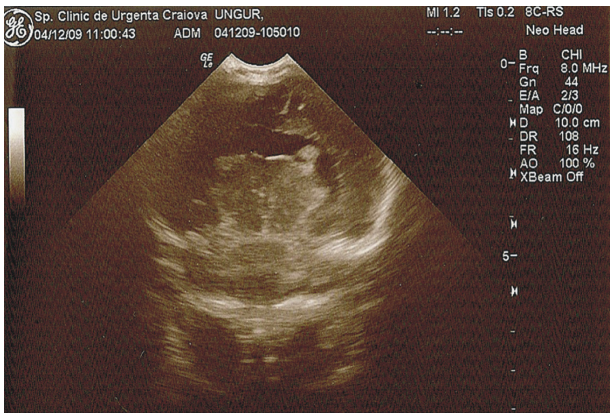

Figure 4 – ***The unique large ventricle and fused hemispheres.***

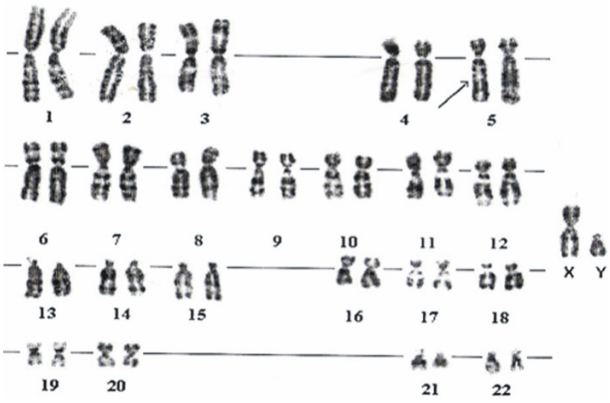

Figure 5 – ***Karyotype 46, XY, with inversion 5q14→ 5qter.***

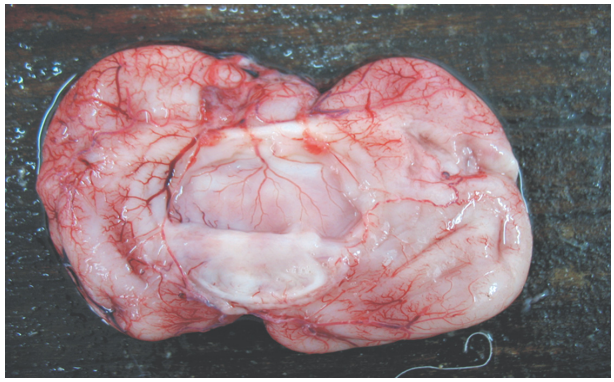

Figure 6 – ***Macroscopic image of the sectional cerebrum: a large unique ventricle.***

Discussion

Holoprosencephaly (HPE) arises from disruption of the normal induction and patterning of the rostral neural tube during early embryogenesis [1, 6].

The primary brain vesicles, the prosencephalon, mesencephalon, and rhombencephalon, are formed by the third embryonic week. Separate lateral telencephalic and diencephalic structures develop from a single prosencephalic vesicle, normally beginning by the fifth embryonic week of gestation [6].

Holoprosencephaly (HPE) results from incomplete cleavage of the prosencephalon, occurring between the 18th and the 28th day of gestation and affecting both the forebrain and the face. Deficiencies in embryonic forebrain cleavage range from the most severe or alobar forms to the least severe or lobar forms and middle inter-hemispheric variant [1, 3].

Distinctive midline facial malformations occur in most cases. These malformations are correlated with the degree of holoprosencephaly and have prognostic importance [7, 8].

Typical facial anomalies include the following: (1) cyclopia, in which a single, midline, fused eye exists in a single orbit below a proboscis; (2) ethmocephaly, in which ocular hypotelorism is present with an inter-orbital proboscis; (3) cebocephaly, in which ocular hypotelorism is present with a single-nostril nose; (4) ocular hypotelorism and midline clefting; and (5) ocular hypotelorism and bilateral clefting [1, 3].

Other frequently associated central nervous system (CNS) malformations include arhinencephaly (absent

olfactory bulbs and tracts), absent thalami, hydrocephalus, and neural migration abnormalities. In our case, ocular hypotelorism, midline clefting and other severe facial anomalies, such as absent nasal bones were present (Figures 1 and 2).

The frequency of holoprosencephaly is 1 at 10 000–20 000 live newborn. During early embryonic period, the frequency is 1 at 250 but progressively declines because of high fetal mortality rates [4, 9, 10].

Researches into the etiology of holoprosencephaly has revealed multiple teratogenic and genetic causes (both chromosomal and single gene). The involvement of multiple genes has been implicated in ventral forebrain induction; their products include the Sonic Hedgehog (Shh) protein and the Hedgehog signal transduction proteins patched (Ptc) [11], as well as proteins in the Gli family and cholesterol biosynthesis pathways [12, 13].

A variety of teratogens, chromosomal abnormalities (in 25–50% of cases), and single gene mutations can result in holoprosencephaly. Trisomy 13 (in about 40% of cases) and trisomy 18 are the most frequently identified chromosomal anomalies [14]

A host of chromosomal deletions, duplications, and translocations have been associated with holoprosencephaly [15, 16].

In the case we described, chromosomal analysis showed an inversion on the long arm of fifth chromosome (Figure 4).

Many single-gene disorders (18-25%) can result in syndromes with a variable incidence of holoprosencephaly. Examples include Pallister–Hall, Rubinstein–Taybi, Kallmann, Smith–Lemli–Opitz, Meckel, hydrolethalus, pseudotrisomy 13, and microtia–anotia syndromes [3]. Maternal diabetes has been also implicated [14, 17].

At birth, the ratio of females to males with holoprosencephaly is 2:1 according to some authors [3, 18].

Prenatal diagnosis of holoprosencehaly is based on trans-abdominal or trans-vaginal ultrasonography and magnetic resonance imaging to identify most cases of alobar or semi-lobar holoprosencephaly.

After birth, the preferred imaging study for the diagnosis and classification of holoprosencephaly is cranial magnetic resonance imaging (MRI) [15, 16, 19]. Other imaging modalities are ultrasonography and cranial computed tomography (CT) scanning [1, 20–22]. Ultrasonography can be limited in cases of microcephaly if there is a very small fontanelle.

In our case, diagnosis was based on head ultrasonography, clinical examination and confirmed on necroptic examination.

Treatment in severe forms of HPE is symptomatic and supportive, and requires a multidisciplinary management. Child outcome depends on the HPE severity and the medical and neurological complications associated

Conclusions

Holoprosencephaly (HPE) is a complex brain malformation affecting both the forebrain and the face. HPE has heterogeneous etiologies that can include a teratogenic and/or a genetic basis. It is important to diagnose HPE prenatally and determine the type in order to determine the severity of HPE. Midline facial malformations are strongly correlated with the degree of holoprosencephaly and have prognostic significance. The parents should be counseled about the poor prognosis in cases of severe forms.

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Received: February 10th, 2011

Accepted: May 15th, 2011