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Case Report

The Neonate Was Born with Holoprosencephaly

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ABSTRACT

Holoprosencephaly is a rare congenital brain malformation resulting from failure of diverticulation and cleavage of primitive prosencephalon which occurs at 4 - 8th week of gestation and is usually associated with multiple midline facial anomalies. it is the most common forebrain developmental anomaly in humans with prevalence of 1/16,000 in live borns, an incidence as high as 1:250 in conceptuses, and a worldwide distribution. The etiology of HPE is very heterogeneous. First, this pathology can be caused by environmental or metabolic factors. The only formally recognized environmental factors are insulin-dependent diabetes mellitus (1% risk of HPE) and maternal alcoholism with a risk that cumulates with smoking . Clinical expression is variable, extending in unbroken sequence from a small brain with a single cerebral ventricle and cyclopia to clinically unaffected carriers in familial holoprosencephalyHere. we report a boy 39 weeks neonatal case of holoprosencephaly with Antenatal ultrasonographic diagnosis, with microcephaly, hypotelorism, flat nose, a single nostril, midline cleft lip and palate microcephaly.

Keywords: Holoprosencephaly, Midline facial anomalies, Ultrasonographic diagnosis

Introduction

The boy was born at 39 weeks weighting 2.6 kg by NVD. The mother was primy, 28 years and she received good prenatal care during the pregnancy, had no history of infection.

There is no history of smoking or alcohol consumption. Antenatal complication like diabetes mellitus or other problem was absent. The family history was negative.

Serologic tests were undertaken during prenatal examination and were negative for syphilis, HIV, hepatitis B and C, and rubella. Antenatal ultra sonographic examination of the fetus at 31 weeks of gestation showed holoprosencephaly and microcephaly.

After birth, the neonate had spontaneous respirations, normal heart rate with gross hypotonia and poor reflex activity. The Apgar scores were 8at 1 min and 9 at 5 min. She was admitted to the neonatal intensive care unit of emamreza hospital - mashad. Physical examinations showed, microcephaly (less than the 3rd percentile), short stature (less than the3rd percentile).

Premaxillary agenesis was recognized: hypotelorism, flat nose, and median cleft lip and palate. The prolabium, premaxillary bone, and septalcartilage and columella were absent, and nasal bone was hypoplastic. The postnatal sonography of the brain revealed hydrocephaly and brain (CT) scan demonstrated holoprosencephaly. echocardiography revealed anatrial septal defect of no hemodynamic significance. The chromosomal analysisshowed a 46,xy, normal karyotype biochemical and hormonal lab test was at normal ranges and after he tolerated full breast milk discharged after 10 days.

Discussion

During the third week of embryonic life, the prechordal mesoderm migrates into the area prior to the notochord and affects midline facial development; hence, before 4 weeks of embryonic age, the varying degrees of loss or disruption in the development to prechordal mesoderm cause abnormal for brain development and midfacial defects. Patau et al (1).

First recognized the relationship between the trisomy of chromosome 13 and a clinical syndrome in 1960. About 80% of Patau's syndrome cases are regular trisomies arising from nondisjunction at the first or second meiotic division. A small proportion of cases have a translocation either arising *de novo* or inherited from a parent who carries a balanced translocation (2). The newborn's prognosis is often poor mainly because of the neurological and cardiac malformations.

Trisomy 13 accounts for up to 75% of cases of

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patients with holoprosencephaly (HPE) 3 due to all chromosomal anomalies (including cryptic rearrangements). Up to 20% of those cases also have triploidy (4).

Figure 1.

HPE refers to a spectrum of central nervous system (CNS) malformations that result from a primary defect in the normal inducing and molding of the rostral neural tube during early embryogenesis. It is usually considered to be the result of prosencephalon cleavage failure, which usually occurs during the fifth or sixth week of gestation (3,5). In 1882, Kundrat (6,7) reported the first description of neuropathological HPE, recognizing the aplasia of bulbs and olfactory tracts as a common denominator in this group of malformations, which he named arhinencephaly. In 1959, after Yakovlev's8 studies, the term arhinencephaly was considered erroneous. In 1963, DeMyer and Zeman,9followed by DeMyer et al.10 in 1964, named this malformation as presented with orbital hypotelorism, flat nose, bilateral cleft lip, and cleft palate. They believed holoprosencephaly, studying two patients who and Gross (1973) (12). introduced the concept of the defects of the midline (6,12,13). Based on the gross examination of the degree of non-hemispherical separation, DeMyer and Zeman (1963) (9). Also proposed a classification of HPE into three types, namely a lobar, semi lobar, and lobar. This classification is based on the presence or absence of the inter-hemispheric fissure and the extent of separation of both hemispheres. In 1993, Barkovich and Quint14 identified a mild variant of HPE, called syntelencephaly or middle interhemispheric variant, indicating that the HPE apparently represents a continuum of cerebral malformations without a cutting point that makes a clear distinction between the different subcategories.

Because of the interrelated development of the primitive brain and underlying mesodermal structures, patients often exhibit specific craniofacial anomalies, including midline facial clefts, cyclopia, and nasal abnormalities, in addition to brain "holosphere" or the undivided prosencephalic vesicle. Particularly in the severe forms of HPE, the same failure of induction of midline structures may be reflected in midline facial characteristics.

The pathogenesis of this disorder has been elucidated in a number of recent experimental studies on the neural tube and the identification of various gene mutations. Four genes, related to brain development, were detected and their chromosomal regions have been studied: HPE1, HPE2, HPE3, and HPE4 (15). The cases used in each of these chromosomal mapping studies, although few, exhibit a broad spectrum of HPE phenotypes, reflecting the complexity and heterogeneity involved in its etiology.

This malformation occurs in families, although the degree of involvement among affected individuals can vary widely within the same family. The incidence of HPE is about 0.48-0.88 per 10,000 live births with normal chromosomes (3).
However, there is a high rate of fetal wastage, with the incidence of HPE in intrauterine demise estimated at 40 per 10,000 (3).

Several maternal/environmental factors, including diabetes and ethanol consumption have been associated with HPE sequence (3,5). Experimental ethanol exposure in rats and

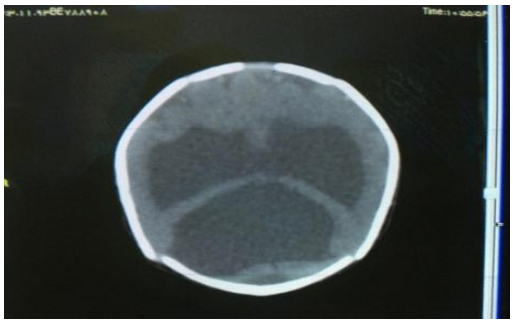

Figure 2.

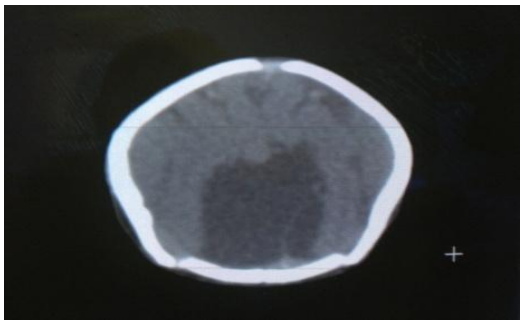

Figure 3.

monkeys can produce facial and CNS abnormalities similar to HPE (3).

In human cases of HPE, when there is no maternal diabetes or fetal alcohol exposure, a genetic cause in conjunction with other systemic abnormalities has been recognized. The most common chromosomal abnormality in patients with HPE is trisomy of chromosome 13, as in this case report, which is reported in 24-45% of newborns with this trisomy. In addition to trisomy 13, several other chromosomal abnormalities, including trisomy 18, trisomy 13-15, trisomy 13-15 mosaicism, ring chromosome 13 or 18, and chromosomal deletion 13 or 18, have been identified in patients with HPE. This malformation was also reported in Klinefelter syndrome16 and trisomy 10 (17).

The most serious expression of classic HPE occurs in alobar HPE. In this form, the brain is usually smaller than normal and consists of one holosphere without interhemispheric fissure, sagittal sinus, or falxcerebri, exhibiting the shape of pancake, cup, or ball.13,18In the upper posterior view of the brain, the telencephalon is not divided, usually shows as a horseshoe shape, with a single ventricle in its lower portion.

Prognosis

HPE is not a condition in which the brain deteriorates over time. Although serious seizure disorders, autonomic dysfunction, complicated endocrine disorders and other life-threatening conditions may sometimes be associated with HPE, the mere presence of HPE does not mean that these serious problems will occur or develop over time without any previous indication or warning. These abnormalities are usually recognized shortly after birth or early in life and only occur if areas of the brain controlling those functions are fused, malformed or absent.

Prognosis is dependent upon the degree of fusion and malformation of the brain, as well as other health complications that may be present.

The more severe forms of encephalopathy are usually fatal. This disorder consists of a spectrum of defects, malformations and associated abnormalities. Disability is based upon the degree in which the brain is affected. Moderate to severe defects may cause mental retardation, spasticquadriparesis, at hetoid movements, endocrine disorders, epilepsy and other serious conditions; mild brain defects may only cause learning or behavior problems with few motor impairments.

Seizures may develop over time with the highest risk before 2 years of age and the onset of puberty. Most are managed with one medication or a combination of medications. Typically, seizures that are difficult to control appear soon after birth, requiring more aggressive medication combinations/doses.

Most children with HPE are at risk of having elevated blood sodium levels during moderate-severe illnesses, that alter fluid intake/output, even if they have no previous diagnosis of diabetes insipidus or hypernatremia.

Conclusion

Several neuropathological studies have shown that malformations of the holoprosencephalic sequence can be multiple and complex, involving multiple anatomic sites. Therefore a thorough morphological examination is required to better delineate underlying diseases as well as pathophysiological mechanisms. It is also essential that genetic counseling be improved, given the wide phenotypic variability, genetic heterogeneity, and risk of recurrence even in apparently sporadic cases. Recent advances in the study of the pathogenesis and genetics of HPE have shown that it is a continuous spectrum of lesions. These advances may contribute to further reclassification of these cerebral lesions and enable HPE to be better understood.

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