RESEARCH PAPER | Medical Science | Volume : 3 | Issue : 11 | Nov 2013 | ISSN - 2249-555X

Holoprosencephaly-A rare case report

KEYWORDS: alobar holoprosencephaly, polydactyly, polysplenia

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ABSTRACT *Holoprosencephaly, a disorder resulting from failure of cleavage or incomplete differentiation of the forebrain structures at various levels or to various degrees, is related to hereditary factors, chromosomal anomalies, cytogenetic abnormalities, and environmental teratogenic factors. We report a case of alobar holoprosencephaly, with similar physical findings, including microcephaly, microphthalmia, cebocephalus, choanal atresia, pseudo cleft palate, distended abdomen, and acrocyanosis.*

In 1963, Demyer and Zeman(1) proposed the term holoprosencephaly which is a disorder resulting from failure of septation, cleavage, or differentiation of the midline forebrain structures at various levels or to various degrees. Defects in development of the midfacial region frequently coexist. The disease affects both components of the forebrain: the telencephalon and the diencephalon. Demyer et al. Divided the pathological characteristics of the forebrain into 4 categories: lobar (presence of an interhemispheric fissure but the cingulate gyrus and the lateral ventricles are fused, and there is no septum pellucidum),

semilobar (posterior partial formation of the interhemispheric fissure, with only a single ventricle), variant (heterotopic gray matter), and alobar (absence of the interhemispheric fissure, falx cerebri, the third ventricle, and fused thalami, and often absence of neurohypophysis and olfactory tracts) ones according to the graded degrees of failed differentiation.(1) The various holoprosencephalic abnormalities of the face include cyclopia, proboscis, ethmocephalus, cebocephaly, premaxilla agenesis, median cleft palate/lip, and other less-severe facial dysmorphism.

Case Report.

This female baby was born to 34- and 31-yearold, non-consanguineous parents who had suffered from infertility for 3 years. The primigravida was transferred to our obstetric department for confirmation of hydrocephalus which was suspected during the last month of pregnancy by local medical clinics. Fetal ultrasonography at 37 weeks of gestation revealed oligohydramnios, microcephaly, a single large ventricle, a fused thalamus, and hypotelorism. A tentative prenatal diagnosis of alobar holoprosencephaly was made. A child weighing 3500 g was born at 38 weeks of gestation by cesarean section due to breech presentation. A delay of initial crying was found after delivery. The Apgar scores were 4 at 1 min and 6 at 5 min. There were abnormal physical findings, including microcephaly, microphalmia, hypotelorism, cebocephalus, a pseudo cleft palate, and choanal atresia; preaxial polydactyly of the left hand was an additional finding. The results of a postnatal brain echogram were the same as those of the prenatal stage. She died at 30 hours of age. The karyotype of the patient was 46,XX. The abnormal findings by autopsy included: (1) a single large ventricle with an opening to the posterior part of the brain and a fused thalamus, (2) the absence of olfactory and optic nerves, (3) dysgenesis of the hypopituitary, thyroid, and adrenal glands, (4) choanal atresia, and (5) polydactyly.

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 of prechordal mesoderm cause abnormal forebrain development and midfacial defects.(2) Holoprosencephaly, the most common structural anomaly of the developing forebrain and midface in humans, is a disorder in which the cephalic neural tube fails to develop and does not divide into right and left lobes. Holoprosencephalon is the term used to describe a single, unpaired forebrain. The epidemiology of holoprosencephaly was poorly described before, partly due to the inclusion of only small case numbers and there being no basal population; on the other hand, there is marked natural loss of the fetus, while milder forms may go unrecognized. Consequently, the prevalence rate differs in various study groups. During early embryogenesis it is about 1 in 250; due to the high rate of spontaneous abortion, the prevalence rate in live births ranges from 1: 14,736 to 1: 26,730.(3) The first population-based survey of holoprosencephaly prevalence provided by Bullen et al. representing the total prevalence (including pregnancy termination) was 1.2 cases per 10,000 registered births, and the birth prevalence (affected live births and stillbirths at > 24 weeks' gestation) was 0.49 cases per 10,000 births. The etiology of holoprosencephaly indicates interactions with both genetic and environmental factors, including chromosomal anomalies, gene rearrangements, mendelian mutations, and teratogens, and it can usually be determined. Although it is extremely heterogeneous, there may be a common final pathway for the abnormal development of the forebrain and face. The majority of holoprosencephaly cases are sporadic; cases of familial holoprosencephaly are reported to be autosomal dominant, autosomal recessive, or X-linked in inheritance. Nearly 50% of all holoprosencephaly cases have cytogenetic abnormalities, and approximately 18%-25% of patients of holoprosencephaly have a documented monogenic syndrome.(4,5) To the present, there are at least 12 known loci which may contain genes critical for normal brain development on 11 chromosomes. Trisomy 13 is the most commonly identified cause; others include trisomy 18, HPE1(21q22.3), HPE2(2p21,SIX3), HPE3(7q36, SHH,SonicHedgehog), HPE4(18p11.3,TGIF),(6) HPE5(13q32,ZIC2), HPE6(3p24-pter), HPE7

(13q12-q14), HPE8(14q13), HPE9(20p13), HPE10 (1q42-qter), HPE11(5p), HPE12(6q26-qter),(7) t(7;13)(q21.2;q33), 3q22 deletion,13q33, q34 or 35- qter deletion, 7q36-qter deletion, and 14q22 deletion, del(14) (q11.1q13).(8) Environmental teratogens reported to induce holoprosencephaly include maternal diabetics (with a reported 200-fold increase in the incidence of holoprosencephaly in infants of diabetic mothers over infants of non-diabetic mothers),(9) steroid alkaloids, thanol, and retinoic acid.(10) Syndromatic associations include Martin syndrome, Steinfeld syndrome, CHARGE association, Meckel- Gruber syndrome, Kallmann syndrome, Hall- Pallister syndrome, Vasidi syndrome,(11) Smith-Lemli-

Volume : 3 | Issue : 11 | Nov 2013 | ISSN - 2249-555X

Opitz syndrome, holoprosencephaly-polydactyly syndrome,(12) and Rubenstein-Taybi syndrome. Associated abnormalities include microcephaly, hydrocephalus, agenesis of the corpus callosum, posterior fossa abnormality, cerebellar vermis aplasia, myelomingocele, absence of an olfactory bulb, a cleft lip/palate, adrenal hypoplasia, renal dysplasia, renal cysts, omphalocele, cardiovascular malformations, intestinal abnormalities, club foot, sirenomelia,(13) spina bifida, and endocrinopathies (pituitary gland dysplasia, growth hormone deficiency, and diabetes insipidus).(14) Knowing the etiologies of holoprosencephaly is important for establishing the risk of recurrence.

Early detection by sonography offers a better and earlier diagnostic procedure than amniocentesis. The earliest gestational age at the time of diagnosis was 14 weeks. Because of the short life span and ominous outcome in all patients with alobar holoprosencephaly, genetic counseling and prenatal diagnosis by ultrasound (transabdominal or transvaginal scanning) are of great importance for early detection and allows earlier termination of the pregnancy.(15)

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