# Alobar Holoprosencephaly Associated with Cebocephaly and Craniosynostosis

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**Abstract-** Cebocephaly is a very rare congenital midline facial anomaly characterized by a blind-ended single nostril and ocular hypotelorism, and is usually combined with alobar holoprosencephaly. We report here a case of alobar holoprosencephaly with cebocephaly and craniosynostosis. Chromosomal analysis revealed normal karyotyping. The facial dysmorphism was characterized by the single nostril, hypotelorism, absence of philtrum and small head girth. The failure of cleavage of the prosencephalon and the fusion of all cranial sutures except for the sagittal suture were documented by computed tomography (CT) and magnetic resonance image (MRI). Early detection by the prenatal ultrasound examination is important because of poor prognosis of alobar holoprosencephaly.

**Key Words:** Cebocephaly, Holoprosencephaly, Craniosynostosis

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## INTRODUCTION

Holoprosencephaly, categorized into alobar, semilobar, and lobar types, is a rare developmental abnormality of the brain resulting from the failure of separation of the embryonic forebrain, or prosencephalon, into symmetrical cerebral hemispheres(1). It is frequently accompanied by midline facial abnormalities, such as cyclopia, ethmocephaly, cebocephaly and pre-maxillary agenesis. In cebocephaly, the facial features include orbital hypotelorism and a proboscis with a single midline nasal opening. Craniosynostosis is premature closure of the cranial sutures and the sagittal suture is the most commonly affected. In patients with holoprosencephaly, premature closure of the metopic suture may be found. We present on a patient with alobar holoprosencephaly with cebocephaly and craniosynostosis.

## CASE REPORT

A 1930-gram baby girl was born with gestational age of 33 weeks to non-consanguineous parents. The primigravid mother had gestational diabetes by the end of the third trimester. However, she did not receive regu-

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lar pre-natal examination, including ultrasonography, during the entire course of the pregnancy. There was no history of exposure to alcohol, teratogens, or ionizing radiation during pregnancy. The APGAR scores were 6 at 1 min and 8 at 5 min. A delay of initial crying with general cyanosis was found after delivery and the baby was admitted to the neonatal intensive care unit immediately.

Physical examination revealed a small head girth (head circumference 26cm, < 10th percentile) with midline facial defects, including a single midline nostril, choanal atresia, eyeball protruding and pronounced hypotelorism (Fig. 1). On neurologic examination, she manifested as generalized hypotonia. Primary reflexes were absent. Echocardiography showed a patent foramen ovale. indings except for a patent foramen ovale. The karyotype of the patient was 46, XX. The studies of perinatal TORCH infection (Toxoplasmosis, other [syphilis, varicella-zoster, parvovirus B19], Rubella, Cytomegalovirus, and Herpes infections) were all negative. Three-dimensional CT showed a single narrow nostril, and craniosynostosis (Fig. 2). Cranial MRI showed that (1) the frontal lobes were undivided, (2) the interhemispheric fissure and the corpus callosum were absent with fused thalami and (3), a large anterior mono-ventricle was incorporated into the third ventricle (Fig. 3).

The patient had frequent seizures 6 hours after birth. She also suffered from intermittent respiratory distress because of airway stenosis and recurrent aspiration pneumonia during hospitalization. The parents asked for 31 days after birth against medical advice and despite explanations of poor prognosis. She expired within 3 days after discharge.

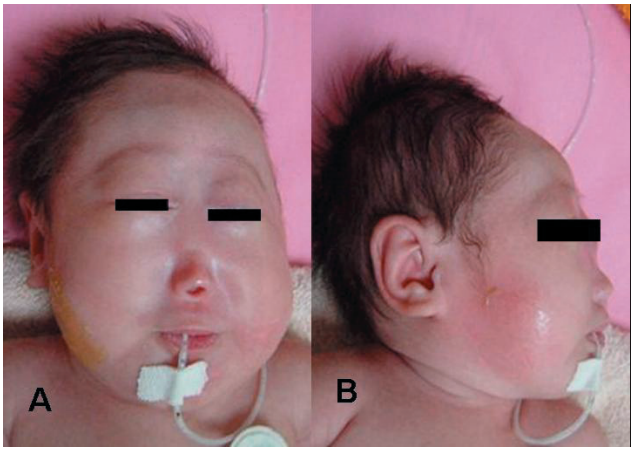


**Figure 1.** Anterior (A) and lateral (B) views of the face showed the small head girth with a single nostril, hypotelorism and absence of philtrum.

## DISSCUSSION

Holoprosencephaly was coined by DeMyer and Zeman in 1857 for the complex congenital brain malformation characterized by failure of the forebrain to bifur-

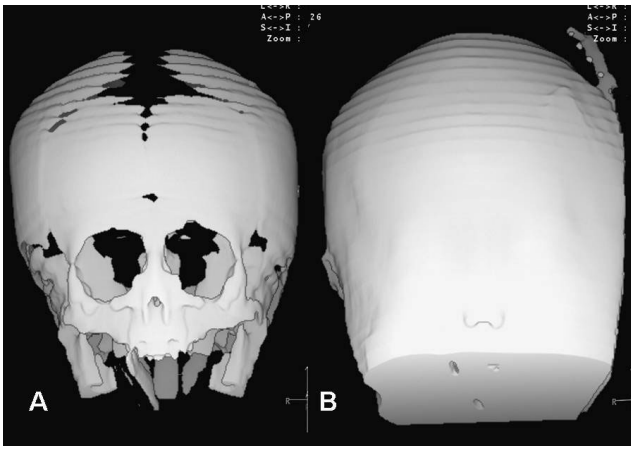


**Figure 2.** Three-dimensional CT of the anterior (A) and posterior (B) skull showed hypotelorism and premature synostosis of all of the cranial sutures except for the sagittal suture.

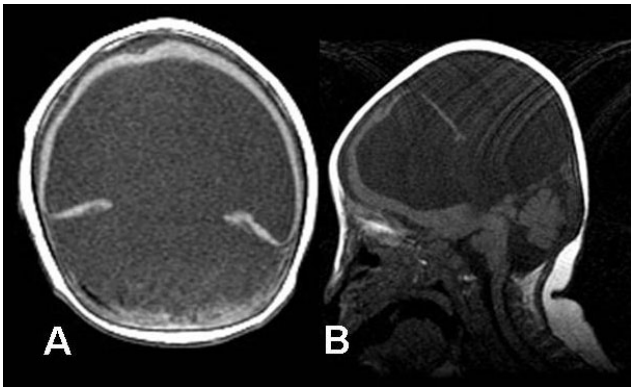


**Figure 3.** The axial T1-weighted axial (A) and sagittal images (B) showed a “pancake” hemisphere and mono-ventricle.

cate into two hemispheres, a process normally complete by the fifth week of gestation[1]. It is the most common congenital malformation of the developing forebrain and midface in humans[2]. Its prevalence rate is difficult to determine due to spontaneous abortion, marked natural loss of the fetus, and various study groups, although its clinical incidence is estimated to be 1 in 13,000 to 18, 000 live births, with female predominance[2,3]. Commonly associated anomalies are microcephaly, hydrocephalus, intestinal abnormalities, cleft lip/palate, post-axial polydactyly, congenital heart defects, renal dysplasias, and encephalocele[4]. A considerable overlap is common between many of the individual features of each syndrome, such as Martin syndrome, Steinfeld syndrome, CHARCE syndrome, Smith-Lemli-Opitz syndrome, and Rubenstein-Taybi syndrome[5].

The etiologies of holoprosencephaly are heterogeneous, including genetic and environmental factors. Almost half of all cases have cytogenetic abnormalities and much as 25% have a documented monogenic syndrome[6]. Approximately 70% of patients with trisomy 13 have holoprosencephaly and about 75% of cytogenetically abnormal cases of holoprosencephaly are associated with trisomy 13[7]. Based on non-random chromosomal re-arrangement, at least 12 different loci on 11 different chromosomes have been implicated in the pathogenesis of holoprosencephaly[8]. To date, seven genes have been associated with holoprosencephaly in humans: SHH, PATCHED1 (PTCH), TGIF, TDGF1, ZIC2, SIX3, and GLI2[9]. Therefore, high-resolution chromosome studies, gene mutation analysis, and genetic counseling are recommended for children with holoprosencephaly.

Multiple environmental factors have also been reported in the pathogenesis of holoprosencephaly, including maternal diabetes, radiation or toxin exposure during pregnancy, TORCH infection, cigarette smoking, and retinoic acid[10]. Muenke reported that there is a 200-fold increase in the incidence of holoprosencephaly in infants of diabetic mothers in comparison with those of non-diabetic mothers[11]. Our patient had a normal karyotype and had no obvious risk factors of holoprosencephaly except for the maternal diabetes.

There are three classifications of holoprosencephaly: alobar, semi-lobar, and lobar types. Alobar holoprosencephaly, as in our patient, is the most serious form and is usually associated with severe facial anomalies[12]. The holoprosencephalic facies, characterized by hypotelorism, are grouped into five major categories: 1) cyclopia: a single eye or partially divided eyes in a single orbit with a proboscis above the eye; 2) ethmocephaly: severe hypotelorism and a proboscis between the eyes; 3) cebocephaly: hypotelorism with a single nostril and a blind-ended nose; 4) absent inter-maxillary segment with central defect and hypotelorism; 5) inter-maxillary rudiment with hypotelorism[13]. Our patient had the same features as described for cebocephaly.

Craniosynostosis, the premature closure of one or several cranial sutures, can be seen in holoprosencephaly, cranio-facial anomalies and many syndromes. The most common form is scaphocephaly, which presents as a premature closure of the sagittal suture and is more common in males[14]. However, our patient presented with a premature closure of all cranial sutures except for the sagittal suture.

Landmark imaging findings of holoprosencephaly are mono-ventricle and fused frontal lobes. Advances in neuroimaging studies have shown telencephalon, deep-gray structures, ventricular system, cerebral cortex, white matter maturation, and other malformations[15].

Patients with alobar holoprosencephaly usually expire during the first year of life because of impaired brain stem function[16]. The less severe semi-lobar or lobar holoprosencephaly without life-threatening abnormalities may have longer life spans. Prognosis and outcome is correlated with the severity of neurologic deficits. Of the 104 children with holoprosencephaly evaluated at the Carter Center, the mean age was 4 years, with 15% between 10 and 19 years of age[16]. However, most survivors have development delays, profound mental retardation, inability to smell, and seizures[16,17].

Holoprosencephaly can be detected as early as the first trimester by prenatal sonography, which is less sensitive for milder forms[18,19]. In the Carter Center study of 104 holoprosencephaly cases, prenatal diagnosis was made in only 22%[19]. Early detection is important for early termination of pregnancy because of the short life

span and ominous outcome of alobar holoprosencephaly[18,19]. Unfortunately, in our case, the patient did not have regular prenatal ultrasound examination and prenatal diagnosis was not made.

In summary, holoprosencephaly is a complex developmental brain malformation commonly associated with facial anomalies. Careful ante-natal screening to detect associated anomalies is essential for an early diagnosis.

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