

## Study of Holoprosencephaly

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**Key Words:** holoprosencephaly, alobar holoprosencephaly, semilobar holoprosencephaly, lobar holoprosencephaly, neural tube defect

**Abstract:** Holoprosencephaly is a rare congenital brain malformation that occurs during development due to incomplete separation of the cerebral hemispheres. It may be caused due to hereditary factors, chromosomal anomalies, environmental teratogenic factors. Four cases of holoprosencephaly were observed during a period of one year and their features are discussed.

Neonatal brain injury is very important since it predicts subsequent infant mortality and morbidity in the premature infants. The term holoprosencephaly is proposed by De Myer (1963). Holoprosencephaly is a disorder resulting from failure of septation, cleavage, or differentiation of the midline forebrain structures at various levels or to various degrees (De Myer, 1963). It is caused by a primary defect in patterning and induction of the basal forebrain during embryogenesis, causing the improper development of the brain and resulting in incomplete division of the cerebral hemispheres (Stashinkio, 2004). Holoprosencephaly most commonly affects the telencephalon and the diencephalon (De Myer, *et al.* 1963). According to the degrees of failed differentiation of the forebrain, the holoprosencephaly is classified into 4 categories: alobar holoprosencephaly, where

the brain is not divided, semilobar holoprosencephaly in which the cerebral hemispheres is incompletely developed and lobar holoprosencephaly in which the brain has somewhat divided which is the least severe form. Syntelencephaly, or middle interhemispheric variant of holoprosencephaly (Armand Marie Leroi, 2003), in which the posterior parts of the frontal and parietal lobes are improperly separated, but the rostro-basal forebrain properly separates; it is also currently classified as a type of holoprosencephaly (Armand Marie Leroi, 2003).

Holoprosencephaly is associated with facial anomalies including cyclopia, proboscis, ethmocephaly or cebocephaly (Kinsman, *et al.* 2000), microcephaly, midface flattening, hypotelorism, flat nasal bridge and single maxillary central incisor, premaxilla agenesis, median cleft palate and cleft lip and other less-severe facial anomalies (Wallis and Merenke, 2000).

The aim of this study is to increase the understanding and awareness of genetic and clinical manifestations of holoprosencephaly. Therefore a study was carried out to find out the probabilities of occurrence of

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holoprosencephaly among the neural tube defects for a period of one year. 40 cases of neural tube defects were found, among which 4 cases of holoprosencephaly were identified and reported.

## Materials and Methods

About 1500 antenatal scans were done for a period of one year, in the I, II and III trimester; out of which, 40 central nervous system anomalies were found and in turn, 4 of them showed holoprosencephaly.

They were:

Alobar prosencephaly	– 2
Semilobar prosencephaly	– 1
Lobar prosencephaly	– 1

Autopsy was done with the concern of the parents. Autopsy findings were correlated with sonographic findings. CNS anomalies not compatible with life were terminated

## Observations

### *Alobar holoprosencephaly*

The foetuses were 19 weeks & 20 weeks old respectively They were found with alobar holoprosencephaly (Figs.1a & 1b). The parents of both the foetuses were consanguineous and one of the parents suffered from infertility for 5 years. One of the fetuses had cyclops and with proboscis. Their brains showed no separation of cerebral hemispheres; absence of falx cerebri; a large single central ventricle; thin and fused thalami; small third ventricle and the midbrain with a small cerebral aqueduct.

### *Semilobar holoprosencephaly*

The foetus was 22 week old with semilobar holoprosencephaly (Figs.2a & 2b). Its parents were non consanguineous. The foetus was found with median cleft lip. It had a small single central ventricle; fused frontal and parietal lobes bilaterally; inter hemispheric fissure was present only

posteriorly; Lack of cleavage of basal ganglia and thalami; absence of body of corpus callosum but genu and splenium were present.

### *Lobar holoprosencephaly*

The foetus was 20 week old with lobar holoprosencephaly The parents were non consanguineous. The foetus had median cleft lip and cleft palate. The brain was found with right and left cerebral hemispheres but the frontal lobes were fused and the lateral ventricles were separated (Figs.3a,b & 3c).

## Discussion

The holoprosencephaly is a rare congenital malformation and one of the neural tube defects. It is classified into 4 categories: alobar holoprosencephaly, in which nondivision of the brain and with associated facial anomalies. The brain show absence of the interhemispheric fissure, falx cerebri, third ventricle and fused thalami and often absence of neurohypophysis and olfactory tracts (De Myer *et al.*, 1963); semilobar holoprosencephaly in which cerebral hemispheres is incompletely developed with posterior partial formation of the interhemispheric fissure, with only a single ventricle, variant heterotopic gray matter ; lobar holoprosencephaly is the least severe form in which the brain has somewhat divided. The brains are with the presence of an interhemispheric fissure but the cingulate gyrus and fused lateral ventricle and absence of septum pellucidum (De Myer *et al.*, 1963) and syntelencephaly, or middle interhemispheric variant of holoprosencephaly (MIHV), in which the posterior frontal and the parietal lobes are not improperly separated, but the rostro-basal forebrain properly separates. Earlier it is not considered as a variant of HPE at all, but is currently classified as a type of holoprosencephaly (Armand Marie Leori, 2003).

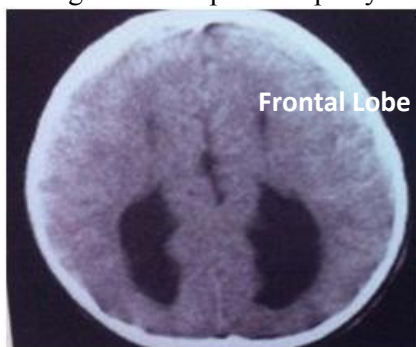
Fig 1a &amp; b Alobar holoprosencephaly

Fig. 2a & b Semilobar holoprosencephaly (22<sup>nd</sup> week of pregnancy)

Fig. 3a &amp; b Lobar holoprosencephaly



Fig. 3c Lobar prosencephaly



The four cases of the holoprosencephaly observed in the present study also showed majority of the malformations reported above.

Apart from the facial anomalies, associated abnormalities include microcephaly, hydrocephalus, agenesis of the corpus callosum, posterior cranial fossa abnormality, cerebellar vermis aplasia, myelomeningocele, absence of an olfactory bulb, hypothalamic and brainstem dysfunction, increased muscle tone, sleep disturbances (Barr and Cohen, 1999), renal

dysplasia, renal cysts, cardiovascular malformations, intestinal abnormalities, omphalocele, gastro oesophageal reflux, choking etc, club foot, sirenomelia, (Chen *et al.* 1997), spina bifida, and endocrinopathies (pituitary gland dysplasia, growth hormone deficiency and diabetes insipidus (Traggiai and Stanhope, 2002), polydactyly (Verloes *et al.* 1991), inability to smell, developmental delay, intellectual impairment, seizures etc. (Bronstein and Wiener, 1991).

### *Development*

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, midfacial defects as well as fusion of lateral ventricles and the 3rd ventricle (Muenke and Beachy, 2000). Division of cerebrum into right and left halves normally occurs at the end of the 5th or the beginning of 6th week of gestation.

### *Birth prevalence rate*

During early embryogenesis, the prevalence rate is about 1 in 250; the prevalence rate in live births ranges from 1: 14,736 to 1: 26,730 due to the high rate of spontaneous abortion, the prevalence rate in live births ranges from (Cohen, 1989); Bullen *et al.* (2001) represented 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. But according to Dubourg *et al.* 2007, holo procencephaly is seen in 1 per 10,000 to 16,000 live births. In most cases of holoprosencephaly, if the malformations are so severe the babies die before birth (Tatori *et al.* 2005).

### *Etiology*

Knowledge of the etiologies of holoprosencephaly is important for establishing the risk of recurrence. The etiology of holoprosencephaly indicates interactions with both genetic and environmental factors which include chromosomal anomalies, gene rearrangements, Mendelian mutations and teratogens.

### *Genetic factors*

The majority of holoprosencephaly cases are autosomal dominant, autosomal recessive, or X-linked in inheritance. Almost 50% of all holoprosencephaly cases have cytogenetic abnormalities and approximately 18% -25% of patients of holoprosencephaly have a documented monogenic syndrome (Croen *et al.* 1996; Olsen *et al.* 1997). Approximately half of all infants or fetuses with holoprosencephaly also have chromosomal abnormalities, most often trisomy 13 (Cohen, 1989; McGahan *et al.* 1990; Muenke, 1994; Rasmussen *et al.* 1996; Ming *et al.* 1998; Bullen *et al.* 2001; Blaas *et al.* 2002).

### *Environmental factors*

Environmental factors are mainly maternal diabetes mellitus which increase holoprosencephaly risk (Ramos-Arroyo *et al.* 1992; Muenke, 1994; Ming and Mueuke, 1998; Peebles, 1998; Croen, 2000; steroid alkaloids, thanol, and retinoic acid (Sulik *et al.* 1995). X-ray exposure, maternal alcohol consumption during early pregnancy (Cohen, 1989; 2002), steroid alkaloids, thanol and retinoic acid (Sulik *et al.* 1995). X-ray exposure, maternal alcohol consumption. Other factors which have teratogenic effects are maternal smoking, respiratory illness medications and salicylate-containing medications, estrogen/progestin, anticonvulsants, weight reduction diets and low maternal weight, previous pregnancy loss and congenital infection with cytomegalovirus, rubella, and

toxoplasmosis (Croen *et al.* 1996). Women with early menarche are more likely to have holoprosencephaly (Croen *et al.* 2000).

## Conclusion

Because of the short life span and ominous outcome in all patients with holoprosencephaly, genetic counseling and prenatal diagnosis is essential. The earliest gestational age at the time of diagnosis is 14 weeks (Bronshtein and Wiener, 1990). Prenatal ultrasound can detect the more severe forms of holoprosencephaly and associated defects such as hydrocephaly (Chervenak, 1985; Vintzileos *et al.* 1987; Peebles, 1998). Therefore prenatal diagnosis and with the consent of the parents, elective termination reduce the birth prevalence of holoprosencephaly (Croen, 1996; Forrester, 2000; Bullen, 2001; Blaas, 2002). Knowledge of the different varieties of holoprosencephaly helps the clinician to arrive at an antenatal diagnosis and to decide about the fetal outcome.

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