How Can We Prevent Birth of Fetus With Holoprosencephaly? Anatomical and Embryological Aspects of Holoprosencephaly.

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Abstract: Objectives: Holoprosencephaly is a rare condition characterized by different degrees of fused ventricles of the brain resulting from impaired midline cleavage of the embryonic forebrain. The present study aimed to identify cases of holoprosencephaly over a period of three years, to assess the incidence of this malformation, and if possible, prevention of birth of such malformed fetus or infant through genetic counseling. Methods: Diverse features of holoprosencephalic fetus or infant and incidence of holoprosencephaly were studied at GSL Medical College, Rajahmundry; Andhra Pradesh. Results: Incidence found for holoprosencephaly is 2.58 per 10,000 births. Out of total four cases of holoprosencephaly two cases were of alobar and there was each case of semilobar and lobar holoprosencephaly. In two cases there was association between holoprosencephaly and gestational diabetes and in another two cases; there was a familial distribution of holoprosencephaly. Conclusion: Prenatal diagnosis of this rare disorder and genetic counseling has immense importance to prevent holoprosencephaly. [Astik R et al NJIRM 2011; 2(4) : 56-59]

Key-words: Cyclopia, gestational diabetes, holoprosencephaly, prosencephalon

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Introduction: Holoprosencephaly (HPE) refers to a spectrum of abnormalities in which a loss of midline structures results in malformations of the brain and face. In severe cases, the lateral ventricles merge into a single telencephalic vesicle (alobar HPE), the eyes are fused, and there is a single nasal chamber along with other midline facial defects. In less severe cases, some division of the prosencephalon into two cerebral hemispheres occurs, but there is incomplete development of midline structures. Usually, the olfactory bulbs and tracts, and the corpus callosum are hypoplastic or absent. In very mild cases, sometimes the only indication that some degree of HPE has occurred is the presence of a single central incisor. Normally the forebrain is formed and the face begins to develop in the fifth and sixth weeks of pregnancy. Mutations in SHH gene, that regulates establishment of the ventral midline in the CNS, result in some forms of HPE[1].

Holoprosencephaly can be detected prenatally by ultrasound examination at as early as nine weeks of gestation[2,3].The present study aimed to identify cases of HPE over a period of three years, to assess the incidence of this malformation and if possible, prevention of birth of such malformed fetus or infant through genetic counseling.

Material And Methods: We studied the diverse features of HPE over a period of three years at GSL Medical College, Rajahmundry, Andhra Pradesh, India.

All deliveries including live births, stillbirths and abortions were recorded for three years. Antenatal ultrasonography was carried out in reported mother. Fetus or infant with forebrain anomalies was recorded. Parents of fetus with HPE have been advised for termination of pregnancy. Fetus or infant with HPE was embalmed immediately after delivered and later autopsy examination was conducted to know different types of HPE, with consent of parents.

For the radiological investigations and autopsy of study subjects, required permissions were taken from respective offices and departments of the institute as well as from the parents of study subjects. All the methods were followed in-line with international ethics and values.

Results: There were 15,500 births including live births, still births and aborted fetuses. Total four babies with HPE were found, amongst, one was live born, two babies were found to be still born and in one case termination of pregnancy was carried out.

Details of the cases are as follows: Case 1: Ultrasound examination of a 29 year old second gravida, conducted at 18th week of gestation, revealed cyclops, alobar HPE and proboscis. The pregnancy was terminated at 19th week. Autopsy findings showed a 400 gm female fetus with alobar HPE with cyclops; both lungs hypoplastic; absent left kidney and suprarenal gland. The brain showed a single lateral ventricle. The mother had delivered a stillborn male baby with semilobar HPE at 40th week of gestation three years back and had insulin dependent gestational diabetes mellitus during both pregnancies.

Case 2: A 30 year old gravida three para two; gave birth to a stillborn female baby at 39th week. Birth weight was 2.5 kg. She has most severe facial defect: Cyclopia- an abnormality characterized by the development of a single eye located in the area normally occupied by the root of the nose and a missing nose which was in the form of a proboscis (a tubular appendage) located above the single eye (Fig 1). The x-ray skull both AP and lateral views showed single orbit whereas the other features were found to be normal. Plain CT brain showed fusion of both cerebral hemispheres and single lateral ventricle in all slices (Fig 2). Previous two babies were normal and there was no family history of congenital anomalies and the mother was non-diabetic. Further details were not found as parents refused autopsy examination of fetus.

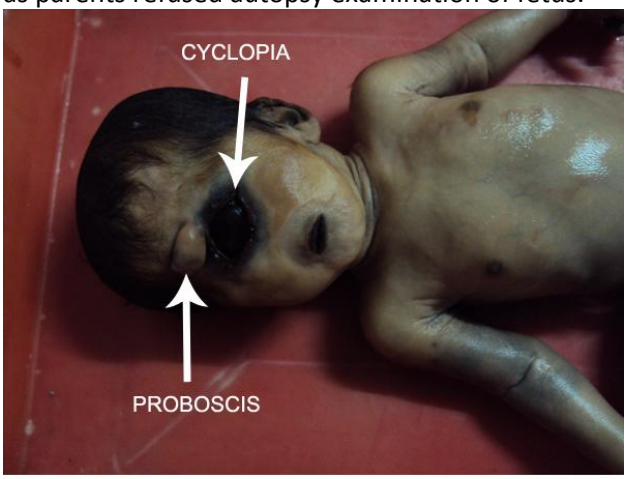

Figure-1 Alobar holoprosencephaly with cyclopia and proboscis

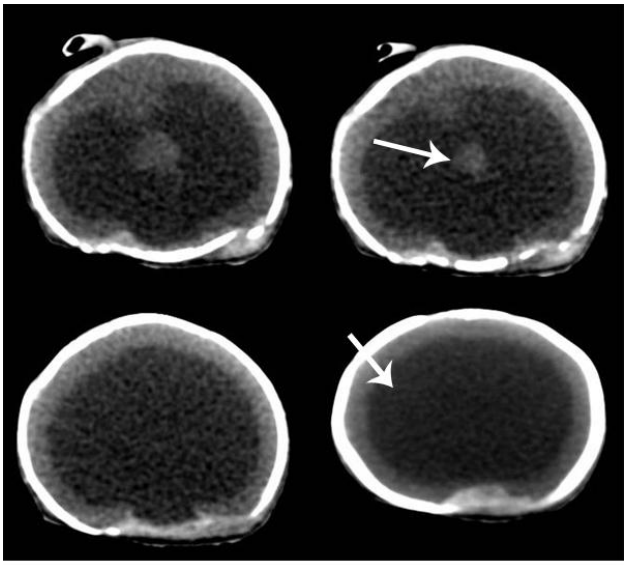

Figure-2 Plain CT brain of case 2 showing fusion of both cerebral hemispheres and single lateral ventricle in all slices

Case 3: A 28 year old second gravida para one; gave birth to a stillborn male baby at 40th week. Birth weight was 2.8 kg. Examination showed microcephaly, a midline cleft lip, hypotelorism. The autopsy examination showed non-division of forebrain and absence of lateral ventricle in rostral part; and in caudal part there were totally separated cerebral hemispheres with two lateral ventricles (Fig 3). The mother had insulin dependent gestational diabetes during both pregnancies. Previous male baby was normal.

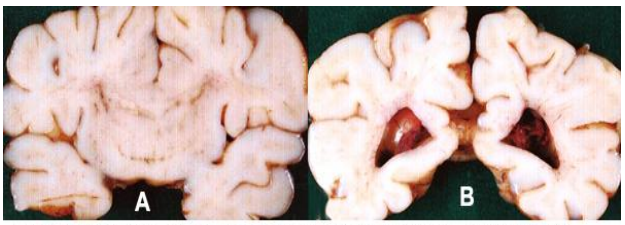

Figure-3 Non-division of forebrain and absence of lateral ventricle in rostral part (A); and in caudal part (B) there was totally separated cerebral hemispheres with two lateral ventricles

Case 4: A 35 year old gravida four para 2; delivered a female fetus with birth weight of 2.4 kg at 39th week of gestation. Except hypotelorism and cleft lip, the facial features were found to be normal. Plain CT brain showed normal separation of the ventricles and thalami but absence of both septum pellucidum and olfactory bulbs gave clear picture of HPE. The baby had temperature instability, poor feeding problem and convulsions in neonatal life and died on 10th day. Parents refused for autopsy

examination. The female sib of the neonate also died at 3rd day after delivery, two years back, due to some congenital anomaly of the brain as per her mother. The exact cause of death was not known. Other two sibs were found to be normal and the mother was non-diabetic.

Discussion: Holoprosencephaly is classified into four stages according to severity of symptoms: alobar HPE is the most serious form in which the brain fails to separate and is usually associated with severe facial anomalies; semilobar HPE in which the brain's hemispheres have a slight tendency to separate; lobar HPE is the least severe form in which there is considerable evidence of separate brain hemispheres; the middle interhemispheric variant (MIH) in which the cerebral hemispheres fail to divide in the posterior frontal and parietal regions [4,5].
Croen et al.[6] found 46% HPE of alobar type, 20% of semilobar and 5% lobar type in the Californian study. We found 50% HPE of alobar type; and semilobar and lobar types were 25% each.

The facial anomalies in HPE are usually categorized into four main types: 1 cyclopia with a single eye or various degrees of doubling of the eye anlage, with or without a proboscis; 2 ethmocephaly with ocular hypotelorism and proboscis located between the eyes; 3 cebocephaly with ocular hypotelorism and a single-nostril nose; and 4 median cleft lip and palate (premaxillary agenesis) and ocular hypotelorism. Less severe facial dysmorphism, microsigns such as a single central incisor and/or ocular hypotelorism, and HPE without facial malformations are also found[7]. In present study cyclops and proboscis were found in both cases of alobar holoprosencephaly. Less severe degree of facial anomalies were present in semilobar and lobar type of HPE; however hypotelorism was present in both cases.

Holoprosencephaly occurs in 1 per 15,000 live births but is present in 1 per 250 pregnancies that end in early miscarriage[1]. In contrast, the rate among human abortuses was estimated at 40 per 10,000, indicating a very high rate of embryonic and fetal loss[8]. In a large epidemiologic study in a Californian population, Croen et al.[6] observed an overall prevalence of 1.2 per 10,000 live births and fetal deaths, whereas the prevalence for live births was 0.88 per 10,000. In another perinatal study from Scotland, Whiteford and Tolmie[9] found a prevalence of 0.7 per 10,000. In present study the incidence of holoprosencephaly is 2.58 per 10,000 births, little higher than earlier literature.

Whiteford and Tolmie[9] found higher incidence of HPE in female. As a result an X-linked mode of inheritance has been proposed[10]. In present study the sex ratio for HPE was 3 females: 1 male.
Although the majority of holoprosencephaly cases are sporadic, familial HPE has been described in pedigrees, suggesting autosomal dominant, autosomal recessive and possibly X-linked inheritance[11]. The recurrence rate for non-chromosomal HPE was 12%[9] and 6%[10]. The present study showed positive family history of HPE in case 1 and case 4.

Among the chromosomal causes of HPE, Taylor[12] found trisomy 13 in 70% of cases. Maternal illness, especially maternal insulin dependent diabetes mellitus, may predispose to HPE[13,14]. In present study there is an association of insulin dependent diabetic mother and HPE in case 1 and case 3.

In holoprosencephaly developing forebrain is too narrow, showing a lack of outgrowth of the ventral neuroectoderm during early embryogenesis[15]. As a result the interplacodal area is either absent (resulting in agenesis of the eyes and orbits, cyclopia, synophthalmia, hypotelorism) or too narrow[16]. SHH and SIX3 genes in ventral neuroectoderm, and ZIC2 in the dorsal neuroectoderm affect the outgrowth and differentiation of the forebrain. Mutations of genes expressed dorsally in the neural tube give rise to inappropriate division of the prosencephalon into cerebral hemispheres with agenesis of the telencephalic roof plate, resulting in HPE with variable midfacial dimension[17].

Conclusion: Holoprosencephaly is characterized by a failure of transformation of the prosencephalon into cerebral hemispheres with separate ventricles. Holoprosencephaly has many associated anomalies, both of the nervous system and face.

Holoprosencephaly is also associated with malformations in other body systems. The true spectrum of HPE, its clinical manifestations and underlying etiologies require further elucidation. Applying this knowledge to individual and their families is of utmost importance. As holoprosencephaly carries a poor prognosis, detailed ultrasound screening, genetic counseling and termination of abnormal fetuses, may reduce the risk of stillbirth and perinatal mortality.

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References:

1. Sadler TW. Langman's Medical Embryology. 11th edition. Central Nervous System. Lippincott. Williams & Wilkins, London. 2009. 315-316.
2. Kurtz AB, Wapner RJ, Rubin CS, Cole-Beuglet C, Ross D, Goldberg BB. Ultrasound criteria for in utero diagnosis of microcephaly. J Clin Ultrasound. 1980; 8(1): 11-16.
3. Blaas HG, Eik-Nes SH, Vainio T, Isaksen CV. Alobar holoprosencephaly at 9 weeks gestational age visualized by two- and three-dimensional ultrasound. Ultrasound Obstet Gynecol. 2000; 15(1): 62-65.
4. DeMyer WE, Zeman W, Palmer CG. Familial alobar holoprosencephaly (arhinencephaly) with median lip and palate. Report of patients with 46 chromosomes. Neurology. 1963; 13: 913–918.
5. Simon EM, Hevner RF, Pinter JD et al. The middle interhemispheriv variant of holoprosencephaly. AJNR Am J Neuroradiol. 2002; 23(1): 151–156.
6. Croen LA, Shaw GM, Lammer EJ. Holoprosencephaly: epidemiologic and clinical characterists of a California population. Am J Med Genet. 1996; 64(3): 465–472.
7. DeMyer WE, Zeman W, Palmer CG. The face predicts the brain: Diagnostic significance of median facial anomalies for holoprosencephaly (arhinencephaly). Pediatrics. 1964; 34(2): 256-263.
8. Matsunaga E, Shiota K. Holoprosencephaly in human embryos: epidemiologic studies of 150 cases. Teratology. 1977; 16(3): 261–272.
9. Whiteford ML, Tolmie JL. Holoprosencephaly in the west of Scotland 1975-1994. J Med Genet. 1996; 33(7): 578–584.
10. Roach E, DeMyer WE, Conneally PM, Palmer CG, Merritt AD. Holoprosencephaly: birth data, genetic and demographic analyses of 30 families. Birth defects. 1975; 11(2): 294-313.
11. Nanni L, Ming JE, Bocian M et al. The mutational spectrum of the Sonic hedgehog gene in holoprosencephaly: SHH mutations cause a significant proportion of autosomal dominant holoprosencephaly. Hum Mol Genet. 1999; 8(13): 2479-2488.
12. Taylor AI. Autosomal trisomy syndromes: a detailed study of 27 cases of Edward's syndrome and 27 cases of Patau's syndrome. J Med Genet. 1968; 5(3): 227-252.
13. Barr M, Hanson JW, Currey K et al. Holoprosencephaly in infants of diabetic mothers. J Pediatr. 1983; 102(4): 565-568.
14. Kalter H. Case reports of malformations associated with maternal diabetes: history and critique. Clin Genet. 1993; 43(4): 174-179.
15. Muller F, O'Rahilly R. Mediobasal prosencephalic defects, including holoprosencephaly and cyclopia, in relation to the development of the human forebrain. Am J Anat. 1989; 185(4): 391-414.
16. Smits-van Prooije AE, Vermeij-Keers C, Poelmann RE, Mentink MM, Dubbeldam JA. The formation of mesoderm and mesectoderm in 5- to 41-somite rat embryos cultured in vitro, using WGA-Au as a marker. Anat Embryol (Berl). 1988; 177(3): 245-256.
17. Brown SA, Warburton D, Brown LY et al. Holoprosencephaly due to mutation in ZIC2, a homologue of Drosophila odd-paired. Nat Genet. 1998; 20(2): 180-183.