AFRICAN JOURNAL OF MEDICINE and medical sciences

Volume 36 Number 3 September 2007

ISSN 1116—4077

Afr J Med Med Sci (2007) 36, 283-287

Holoprosencephaly in Ibadan, Nigeria: a report of three cases and review of literature

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Summary
Holoprosencephaly is a rare congenital malformation resulting from failure of cleavage of midline structures of the forebrain and face. It affects 0.49 – 1.2 in 10,000 births around the world. The nature of this condition in African children is not well documented in literature. We present a cluster of three cases of holoprosencephaly with varying degrees of facial and intracranial malformations seen within a 6 month period at the University College Hospital, Ibadan, Nigeria.

Keywords; *Holoprosencephaly, rare, congenital, malformation, brain, face.*

Résumé
L'holoprosencephalie est une malformation congénitale rare résultant du manque de la partition des structures média ire de l'avant carrure et de la face ; cette maladie affecte 0.49-1.2°% pour 1000 naissance globalement ; la nature de cette condition chez les enfants n'est pas proprement documenté en littérature. Nous présenterons 3 cas d'holoprosencephalie avec des dégrées variées des malformations faciales et intracrânien vu entre une période de 6 mois au centre universitaire hospitalier de l'université d'Ibadan, Nigeria.

Introduction

Holoprosencephaly (HPE) refers to a spectrum of congenital malformation of median structures of the brain and face as a result of incomplete cleavage of the developing forebrain. The resulting median facial malformations can range from mild to severe, but when combined in definite patterns like cyclopia, ethmocephaly or cebocephaly always indicate the presence of a holoprosencephalic brain [1,2]. The most severe form of cerebral malformation is the alobar type found in close to 50% of cases. Prevalence of HPE is said to be approximately 0.49 - 1.2 in 10, 000 births and girls are more commonly affected. The exact cause of holoprosencephaly is largely unknown but genetic and environmental/toxic factors (operating singly or together) have been implicated. There is a well known association between cytogenetic anomalies and HPE in 38 – 50% of cases, of which trisomy 13 accounts for 50 – 75% [2-7]. Most affected babies are stillborn or have very short lifespan depending on the severity [6]. We present the clinicopathologic features in three cases seen at the University college hospital, Ibadan, Nigeria between March and September 2005.

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Case Reports

Case A

A 27-year-old primigravid teacher who received antenatal care in a peripheral hospital from 16weeks of gestation presented at 36 weeks of gestation on account of obstetric ultrasound finding at 35 weeks of fetal hydrocephalus, a single ventricle and thin cerebral mantle. That was her first sonogram. She had essentially uneventful pregnancy. She took a certain non alcoholic herbal preparation (exact components unknown) and calcium lactate tablets from the 5th week, as well as ferrous sulphate and folic acid from the 16th week of her last menstrual period. She was neither hypertensive nor diabetic, and early pregnancy was uneventful however she had fever at 33 weeks of gestation for which she was treated with oral chloroquine. She had no obvious facial anomalies neither did her husband. A live male infant was delivered at 38 weeks gestation by caesarian section. Apgar scores were 4 and 5 at 1 and 5 minutes respectively. Birth weight was 2.0 kg. He had multiple craniofacial abnormalities including a single central orbit of 5cm in diameter (cyclopia), without eyelids, containing two small fused globes (synophthalmia) and a 3 cm long proboscis above the orbit. There were no nasal structures, the maxilla was hypoplastic with flat palate. The pinnae were well formed but low set. Occipitofrontal circumference was 29 cm, and fontanelles were absent. He was lethargic, floopy and neonatal

reflexes were absent. The fingers were short and stubby with normal palmar creases, but no overriding fingers. The chest was barrel shaped but he had no cardiac murmurs. He died after 7hours of life.

Autopsy findings were; single cerebrum partially surrounding a single midline dilated ventricle without any falx or interhemispheric fissure, with abnormal sulci and gyri, absent olfactory bulb, no third ventricle (pancake type of alobar holoprosencephaly). The cerebellum appeared well formed (Figures 1 and 2). There was atrial septal defect. Other organs were not remarkable, however facilities were not available for genetic analysis

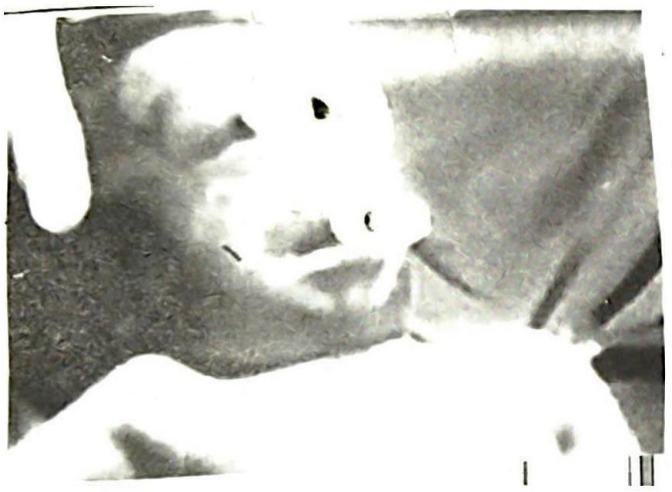

Fig. 1a: Cyclopic face of Case A showing single orbit, synophthalmia and absence of nasal structure

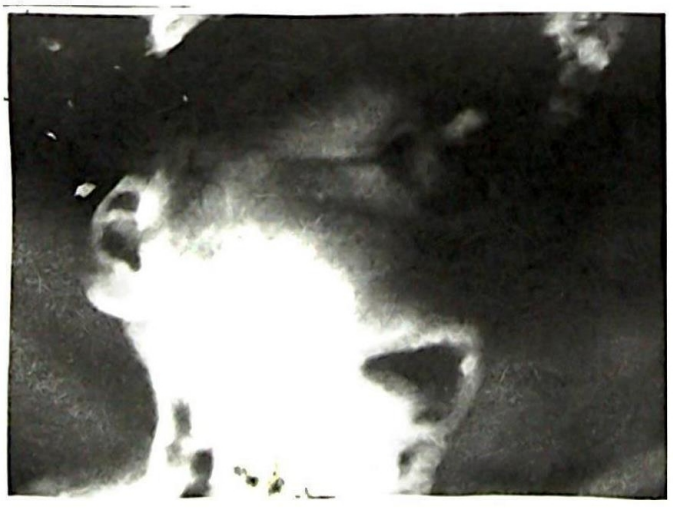

Fig. 1b: Side view of the cyclopic face demonstrating the proboscis above the orbit.

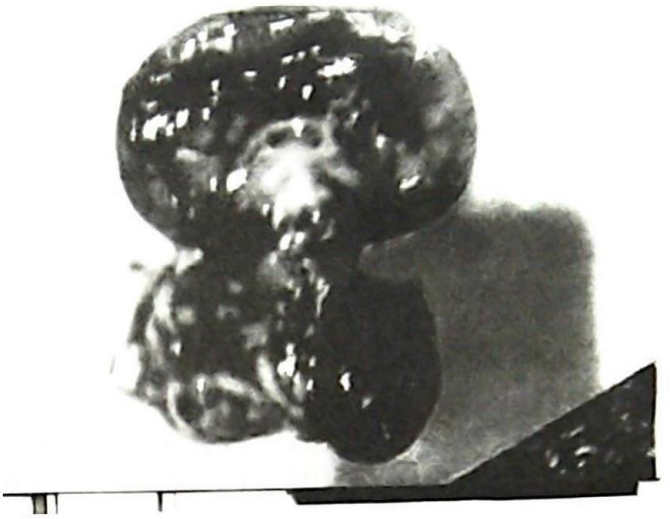

Fig. 2: The pancake brain type of alobar HPE in case A showing the undivided cerebral tissue partially surrounding the ventricle.

Case B

A Male infant was delivered by caesarian section to a 30 year old primiparous teacher at 36 weeks gestational age following prenatal ultrasound diagnosis of hydrocephalus at 30 and 34 weeks of gestation. Mother was not known to be diabetic, had three episodes of febrile illnesses at 8, 21 and 28 weeks of pregnancy treated as malaria with oral chloroquine, sulphadoxine and pyrimethamine and artesunate respectively. She took a non alcoholic herbal medication with the same local name as in the first case in addition to ferrous sulphate and folic acid during pregnancy. There was no history of median cleft lip or central incisor teeth in the parents. The birth weight was 4.1kg, apgar scores were 8 and 10 at 1 and 5 minutes respectively. He had a length of 52cm, occipitofrontal circumference of 51cm and craniofacial disproportion in favour of the cranium otherwise the face appeared normal. He was active. He had a normal cry. The neonatal reflexes were normal. Muscle tone was normal in all the limbs. The child had feeding difficulties and respiratory distress and died on the 11th day of life. Autopsy revealed total lack of cleavage of the cerebral structure, thinning of the cortex, a single ventricular cavity (containing 1200mls of CSF, brain weight without CSF was 155 gm) partially surrounded by the cerebral tissue (pancake type of alobar HPE). The optic and occulomotor nerves were present. The

cerebellum and brain stem appeared well formed (Figures 3a, and b). There were no other abnormalities. The mother had a normal baby 15 months after.

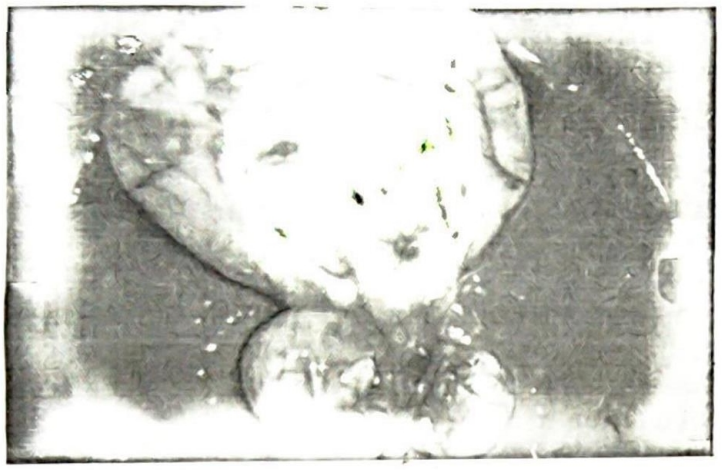

Fig.3: Ventral surface of the brain in Case B showing the undifferentiated cerebrum partially surrounding the enlarged univentricle.

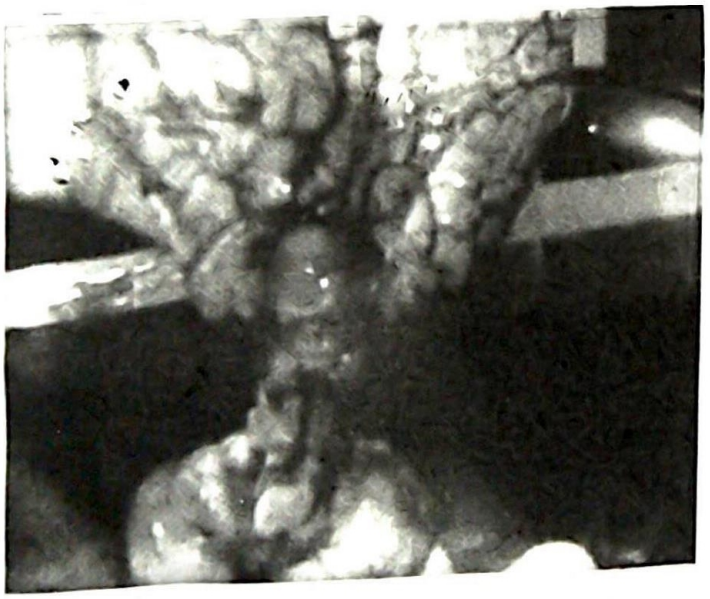

Fig. 4: The dorsal surface of the brain in Case B. The cerebellum appears normal.

Case C

A female infant referred from an outside facility on account of cleft palate at 9 days of age having been delivered at 40 weeks of gestation to a 29 year old primiparous seamstress by spontaneous vaginal delivery. Birth weight was 2.3 kg, no history of perinatal asphyxia. The pregnancy was uneventful, with no exposure to irradiation nor use of alcohol or herbal medications. Prenatal obstetric ultrasound was not done. There was no family history of median cleft or facial dysmorphism. The child was microcephalic (OFC 31.5 cm), with hypotelorism had absent nasal septum, median cleft lip and cleft palate. The upper limbs were normal. She was conscious and alert. She had a normal cry and moderate head lag. Visual fixation was absent in both eyes, neonatal reflexes were present and muscle tone was decreased in all limbs. Family defaulted from follow up but represented the child at $2^{1}/_{2}$ months of age on account of recurrent seizures (infantile spasms) which started at the age of 6 weeks. Electrolytes and urea and blood glucose were within normal limits, cerebrospinal fluid (CSF) analysis was normal. Cranial CT scan revealed widened CSF spaces with brain atrophy, two cerebral hemispheres but a univentricle with partial division and agenesis of the corpus callosum. The 4th ventricle was normal and cisterna magna was dilated. She was diagnosed as semilobar HPE. The seizures remained intractable, despite sodium valproate (30mg/kg/d), nitrazepam (0.5mg/kg/d) and 6 weeks of prednisolone. She was last seen at the age of 11 months by which time there was evidence of severe developmental delay such as absence of social smile and neck control.

Discussion

Cyclopia has been recognized since ancient times and for more than a century, association between abnormalities of midline brain and facial structures in relation to defective embrygenesis have been well described. Several epidemiologic studies have also been done to identify risk factors but it's only in the last decade that breakthroughs have been made in the recognition of the specific gene involved and the molecular basis for these defects.

During embryogenesis, development of the prosencephalon (embryonic forebrain) follows three sequential events; formation from rostral neuroectoderm, cleavage and midline development. The prosencephalon cleaves sagittaly to form the cerebral hemispheres, (including the lateral ventricles and basal ganglia,) transversely into the telencephalon and diencephalon (which ultimately forms the thalamus and hypothalamus) and horizontally to form the optic nerves and olfactory bulbs. Holoprosencephaly occurs when the cleavage fails to take place resulting in a brain that tends to remain as a hollow tube. From about the 5th week of pregnancy, the prechordal mesoderm induces

prosencephalic formation and cleavage and also formation of the face [1,2]. This explains the varying degrees of failure of differentiation of the prosencephalon that occurs when there is a defective prechordal mesoderm and hence the close association of midline facial defects with holoprosencephaly. The timing of the insult to the developing brain which is usually from the first five post menstrual weeks determines the severity of manifestation, with earlier insults tending to result in more severe malformations [1-6]. HPE is subdivided into lobar, semilobar and alobar types depending on the degree of failure of differentiation. The alobar form is the most severe in which there is a single ventricle, absence of the interhemispheric fissure, corpus callosum and septum pellucidum with fusion of the thalami and basal ganglia. They may have a dorsal cyst of varying size from small to large depending on the severity of the malformation. These features were demonstrated in the first two cases. The alobar form is subdivided into pancake, cup or ball types depending on the degree of failure of rotation. In the semilobar form, the occipital horns are partially formed, the posterior portion of the falx and interhemispheric fissures are present, the thalami are fused, the lateral ventricles are fused anteriorly with absence of the corpus callosum. The lobar forms have partial to fully formed but mildly enlarged ventricles, interhemispheric fissures, partial to full development of the corpus callosum and partial to complete separation of the thalami and basal ganglia. The brain stem and cerebellum may be normal or hypoplastic in all types [4]. The third case presented here had incomplete division of the cerebral ventricle consistent with the semilobar type. The intracranial blood vessels are also affected to varying extents depending on the severity of the subtype [4]. The facial features include cyclopia, ethmocephaly (hypotelorism, microphthalmia and absent nasal structure with a proboscis), cebocephaly (ocular hypotelorism and a single-nostril nose as seen in the third case), orbital hypotelorism and median cleft lip and their presence should raise a suspicion as to the presence HPE [1]. Mild facial dysmorphism such as absent or abnormal upper labial frenulum, single central incisor or median cleft palate may be found in the semilobar or lobar holoprosencephaly [8,9]. The third case had hypotelorism, single nostril nose and median cleft lip and palate which suggested the presence of HPE. Hypotelorism in holoprosencephaly is distinguishable from that resulting from other causes of microcrania with hypotelorism by plain radiographs or CT scans. Other facial features of HPE include hypognathia or agnathia but are not pathognomonic [4]. While specific abnormal facies like cyclopia predict the presence of holoprocencephaly, the brain abnormality may not necessarily be associated with facial anomalies as up to 17% of cases of alobar holoprocencephaly have normal facies as seen in case B [10]. The severe forms of holoprosencephaly are incompatible with life and the infants are either stillborn or die very early, whereas the milder forms are compatible with life, but the survivors usually have severe mental retardation [6]. As in case A, the cyclopic appearance with a proboscis and absence of nasal bone structures was consistent with the finding of alobar HPE as described in literature. Cases A and B being of the severe type did not live beyond the neonatal period. Case C was of the semilobar type hence survived but had evidence of severe neorologic impairment.

Apart from chromosomal anormalies, familial forms which may be autosomal dominant or recessive as well as some sporadic cases without any genetic bases have also been reported [11]. The cases associated with trisomy 13 usually present with other extracephalic anomalies. With the exception of case A, none of the babies had extacephalic anormalies, though this does not totally rule out chromosomal abnormalities. Advanced maternal age is not known to play any role. There is a 1% recurrent risk in those with chromosomal anormalies and 6% if sporadic [6,7,12]. These are important in genetic counselling. In the three cases presented, though cytogenetic studies were not available, none had clinical features consistent with trisomy 13. Other important aetiological factors include maternal diabetes which carries a 200-fold increased risk for HPE. Associated prenatal infections include cytomegalovirus, rubella, and toxoplasmosis. Eye abnormalities, including cyclopia have been reported in association with CMV infections. Maternal oral ingestion of alcohol, salicylates, high doses of contraceptives, quinine, retinoic acid and cortisone as well as irradiation have also been implicated [13]. Plant extracts which inhibit cholesterol synthesis have been shown in experimental animals to produce lesions similar to HPE [14] which is why the herbal medication ingested by two of the mothers in early pregnancy is of interest. Prenatal diagnosis by routine ultrasound scans is possible as early as 15 weeks of gestation and in up to 86% of cases [7]. There were sonographic

indications of HPE in antenatal scans in cases A and B however they were reported only as hydrocephalus suggesting the need to increase awareness.

The incidence rate in this environment is unknown and there are no previous reports from this hospital though post mortem rates among still births and neonatal deaths remain low in this environment due to cultural factors [15]. It is difficult to ascertain the aetiology in our cases. However the positive history of utilization of the same herbal medication in two cases suggests a need to evaluate the constituents of this herbal medication, its rate of utilization among pregnant mothers in this environment and determine its relationship to the occurrence of HPE and other congenital malformations.

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Received: 11/05/07
Accepted: 09/07/07