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CC –BY **Holoprosencephaly sequence with a constellation of anomalies in Yenagoa, a Niger Delta Region: report of two cases**

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**Abstract:** This report is on holoprosencephaly (HPE) sequence with other clinical and radiographic anomalies of other organs. This condition which has never been reported in Yenagoa, an oil rich Niger Delta Region was observed simultaneously in two neonates within a period of two months at different hospitals in this area. The inhabitants who include pregnant mothers with their fetuses are predisposed to health challenges associated with the exposure to toxic chemicals derived from environmental degradation and pollution due to oil spillage/processing. This report is therefore aimed at providing a description of HPE associated with varying multi-systemic conditions in order to motivate researches on prevalence of congenital anomalies and induce support in ensuring appropriate health care services. The approach to clinical evaluation and experience on diagnostic evidence is discussed. The importance of karyotyping which could not be carried out cannot be overlooked. However, the clinical and radiological

features suggested the diagnoses of HPE Sequence. Holoprosencephaly (HPE) occurs due to a primary defect in prechordal mesoderm, resulting in fusion anomaly of the forebrain with also varying degrees of midline facial development anomalies. Although, HPE could be isolated, in certain conditions, it may occur in combination with other anomalies of the central nervous system and other organs. The causes of HPE are generally unknown but genetic and environmental factors have been implicated. Recognizing the prognosis in management, considerations vary from being conservative to reconstructive surgeries. The first neonate died on the 13<sup>th</sup> day of life, while the second neonate is still alive on supportive management of anticonvulsants and nutritional support on the 11<sup>th</sup> week of life at the time of writing this report.

**Key words:** Congenital malformations, Craniofacial malformations, Dysmorphism, Holoprosencephaly sequence, Niger Delta region

## Introduction

Holoprosencephaly (HPE) sequence is a rare series of cerebral and facial structural malformations due to failure in the division of the embryonic forebrain (prosencephalon) into lateral cerebral hemispheres from the fourth to eighth week of gestation.<sup>1-3</sup> Holoprosencephaly poses important health challenges because of the high mortality rate, chronic disability issues, psychosocial disruptions as well as the financial burden on the family and the society.<sup>1-4</sup> There are also reported adverse effects of this exposure on fetal development and outcomes of pregnancy from paternal and maternal associated factors.<sup>5,6</sup> Since Yenagoa is a city in an oil producing area, there is a need to report for the first time HPE in order to encourage more researches and highlight

challenging issues associated with its management in the area.

The WHO estimated that neonatal deaths from congenital anomalies worldwide increased from 260,000 (7% of all neonatal deaths) in 2004 to 303 000 (11.6% of all neonatal deaths) in 2016.<sup>7,8</sup> This may be on account of improved diagnostic facilities. However, in Nigeria a collaborative study using verbal/social autopsy (VASA) interviews reported in 2017 that out of 723 neonatal deaths, congenital malformations were responsible for only 0.9-1.1%.<sup>9</sup> Studies emanating from Nigeria had reported varying prevalence of congenital anomalies to be 4.15, 5.51 and 15.84 in the South East, North East and South West regions of Nigeria respectively.<sup>10-12</sup> A higher prevalence of 20.73 per 1,000 live births was reported in Port Harcourt a Niger Delta/South South

region in 2017.<sup>5</sup> This higher prevalence could be due to the peculiarities of an oil producing environment. HPE accounts for the most common malformation of the embryonic forebrain.<sup>1,3,4</sup> The HPE prevalence rate reported by Orioli and Castilla in their review of 21 epidemiologic studies and data obtained from the West Midlands Congenital Anomaly Register (WMCAR) was 1 to 1.7 per 10,000 of live and stillbirths.<sup>13,14</sup> However, this increased to about 50 per 10,000 in aborted embryos.<sup>13</sup> There is apparently no Nigerian National birth defects surveillance network and data on congenital anomalies with special emphasis on HPE is sparse. However, there have been Case Reports from Port Harcourt and Ibadan (South-south and South-west regions of Nigeria respectively) describing the condition.<sup>15,16</sup> The females to males ratio at birth is reported as 2:1 and increases with worsening severity of HPE.<sup>13</sup> The cause of this gender disparity is said to be on account of a greater male death.<sup>13</sup>

There are different types of HPE consisting of alobar, semilobar, lobar and middle inter-hemispheric variant (in order of reducing severity).<sup>1,3,4,17</sup> The etiologies of HPE vary ranging from the unknown to multifactorial factors with MRI preferably used to confirm the diagnosis, while Chromosomal microarray (CMA) identifies those with genetic involvement.<sup>13</sup> The treatment is supportive, and requires a multidisciplinary management depending on the degree of forebrain defect.<sup>2-4</sup> The midline facial anomalies are pointers to severe brain malformations and functions with significantly reduced survival beyond neonatal period in babies with severely malformed forebrain.<sup>1-3</sup> We hereby report two cases of HPE in order to highlight the health challenges in an oil producing area and to draw attention to the financial and socio-cultural issues associated with the management of congenital malformations.

### Case description/presentation

#### Case 1

A 12 hour old male neonate presented in the Tertiary Federal Government Health facility in Yenagoa due to cleft lip and palate, respiratory distress from birth and a high grade fever on the 17<sup>th</sup> of February, 2017. This was the first offspring of a 36 year old bricklayer father and a 27 year old mother who registered late for antenatal care at six months of gestation at a Primary Health Care Centre. The drugs that the mother received were routine antenatal drugs and over the counter medications (names unknown). The mother's only illness during pregnancy was fever in the first trimester which resolved with intake of antimalarial (Artesunate/Lumefantrine). Native body massage was carried out but there was neither use of traditional medications during pregnancy nor exposure to radiation. There was prolonged obstructed labor at 42 weeks gestation and delivery at home assisted by a nurse which resulted in baby not crying at birth. A positive history of a living third degree relative with cleft lip abnormality was obtained. There was no history of consanguinity.

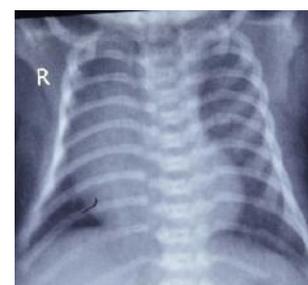
This baby was found to be in respiratory distress with cyanosis and hyperpyrexia (40°C). He had dysmorphic features (Fig 1a) consisting of facial anomalies: flattened nasal bridge; absent nasal philtrum and nasal septum; microphthalmia; micrognathia; midline cleft lip and palate (keilognatopalatoskysis). His weight (2800g) was within the 10<sup>th</sup> percentile while his length (45cm) and occipitofrontal circumference (30cm) were less than 10% percentile. The baby had talipes calcaneo varus deformity; chest hypertelorism, pectus carinatum and low set ears. There were neurologic abnormalities which included: hypotonia, absent primitive reflexes and recurrent seizures. The blood chemistry and complete blood count results were within normal range. The chest radiography revealed cardiomegaly (Fig 2) while the echocardiography: showed mitral and tricuspid valve incompetence; absent shunts (Fig 3). The transfontanelle ultrasound scan through the coronal section and midline sagittal section showed absent midline structures; poorly developed forebrain; well developed posterior fossa and thalami consistent with semilobar HPE (Fig 4). The baby was managed conservatively with antibiotics, anticonvulsants, fluid, calories, electrolytes, oxygen administration and subsequent commencement of gavage feeding. Financial support for care by parents was limited due to poverty and perceived feeling of stigma, rejection and shame despite the intervention of the Social Welfare Unit whose assistance was sought. Logistic reasons peculiar to the facility and financial constraints hindered further diagnostic tests such as karyotype and chromosomal analysis. The fever persisted with subsequent development of apnea which continued until his death on the 13<sup>th</sup> day of life.



**Fig 1a:** Photograph of case 1 showing facial anomalies: flattened nasal bridge; absent nasal philtrum and nasal septum; midline cleft lip and palate.



**Fig 1b:** Photograph of case 2 showing cranio-facial anomalies: flattened nasal bridge, absent nasal philtrum and nasal septum; midline cleft lip and palate; chest hypertelorism



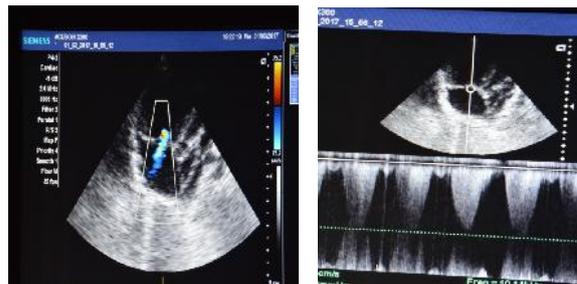
**Fig 2:** Chest Xray of case 1 showing cardiomegaly

## Case 2

A female baby was delivered by emergency caesarean section in a private facility in Yenagoa, on account of previous caesarean section in a diabetic mother at 37 weeks gestation. She was the second surviving child among 3 children of a 29 years old mother and 35 years old father. The mother registered late for antenatal care at gestational age of 4 months, received insulin and routine antenatal drugs. She often ingested and drank the juice of fresh bitter-leaf (*vernonia*). The APGAR scores were 1 in 5 minutes; 8 in 5 minutes; 10 in 10 minutes. There is a previous history of sibling death in the first week of life from macrosomia, severe birth asphyxia and birth injury. There is also a family history of profound mental retardation, developmental delay and microcephaly in a second degree relative. There was no history of consanguinity. The baby was admitted into the neonatal intensive care unit (NICU) of the private facility on account of respiratory distress and the multiple congenital abnormalities.

On examination she had dysmorphic features (Fig 1b) consisting of: cranio-facial anomalies: flattened nasal bridge; absent nasal philtrum and nasal septum; midline cleft lip and palate (keilognatopalatoskysis); low set ears and orbital hypotelorism with inner canthal distance of 1.5cm (Normal of 1.6 – 2.5cm).<sup>18</sup> She weighed 3800g (>90% centile); length 45cm (10<sup>th</sup> centile). There was microcephaly with occipitofrontal circumference of 30cm (<10% percentile) and her anterior fontanel size was 2.75 cm<sup>2</sup> (diameters of 2.5 by 3cm). She had talipes calcaneo varus deformity and a dimple at the lumbosacral region. Chest hypertelorism was present with inter-nipple distance of 11cm (normal: 8.6 ±0.5).<sup>19</sup> The baby had neurologic abnormalities consisting of recurrent seizures and the presence of only sucking and grasp primitive reflexes. The blood chemistry was within normal range except for a low calcium result. The complete blood count was normal. The cranial CT scan revealed an absent midline structures; fusion of both lateral ventricle; poorly developed occipital, frontal and parietal lobes; well developed posterior fossa, normal brain stem, fourth ventricle, cerebellum and temporal lobes. This was consistent with semilobar HPE. (Fig 5) The skeletal X-ray, Chest X-ray and abdominal X-ray revealed no abnormalities. The echocardiography that was requested for was not done as the parents authorized the Doctors to stop further investigations and medications. The management comprised of antibiotics, anticonvulsants, oxygen administration, intravenous fluids containing calories and electrolytes then subsequent gavage feeding with infant formula. There was refusal by parents to accept responsibility for the baby and carry out their financial obligations despite intensive counseling. At the time of this report, the baby is 2 months old receiving anticonvulsants, occasional antipyretics and feeding but has been abandoned in the hospital.

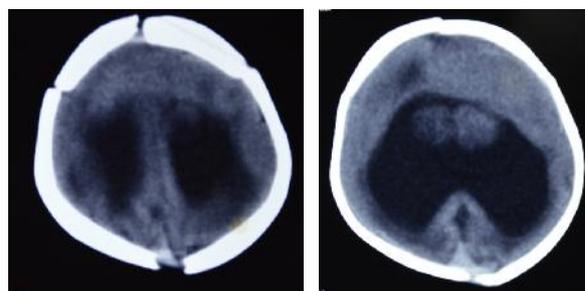
**Fig 3:** Echocardiography of case 1 showing mitral and tricuspid valve incompetence; absent shunts



**Fig 4:** Transfontanelle ultrasound scan of case 1 through coronal section and midline sagittal section showing absent midline structures, poorly developed forebrain, well developed posterior fossa and thalami



**Fig 5:** Cranial CT scan of case 2 showing absent midline structures; fusion of both lateral ventricle; poorly developed occipital, frontal and parietal lobes.



## Discussion

The prosencephalon, mesencephalon, and rhombencephalon, develop by the third embryonic week. At the fifth embryonic week of gestation, the primary brain (prosencephalic) vesicle separate into lateral telencephalic and diencephalic structures.<sup>1,2</sup> HPE occurs as a result of incomplete separation of the prosencephalon, by the 18th to the 28th day of gestation thereby affecting the forebrain and midfacial development.<sup>2,20,21</sup> The abnormalities of forebrain vary from the most severe alobar form to the semilobar, lobar and middle interhemispheric variant.<sup>3,4</sup> Two babies with semilobar HPE have been described whose mothers registered for prenatal care after the first trimester when the forebrain and midfacial development would have taken place.

The two cases reported were of different gender however, previous reports have shown gender disparity with female preponderance in a ratio of 2:1.<sup>3,4,22</sup> The etiology

of HPE are heterogenous consisting of genetic or environmental causes.<sup>1,3,4</sup> Some of the genetic causes that were considered include aneuploidy syndromes such as Trisomy 13 (Patau syndrome) and Trisomy 18 (Edward syndrome).<sup>1,2</sup> Single-gene disorders, mutations in genes and structural chromosomal aberrations including Pallister–Hall, Rubinstein–Taybi, Kallmann, Smith–Lemli–Opitz, and Meckel–Gruber Syndrome have also been associated with HPE.<sup>1-4</sup> Genetic predisposition was identified in both babies through the family history which revealed similar problems in their second and third degree relatives respectively. Infants of diabetic mothers have also been reported to have HPE in addition to other congenital anomalies.<sup>3,4,22</sup> The large for gestational age infant of a diabetic mother with poor glycaemic control who delayed assessing prenatal care suggested the heterogenous aetiology of HPE.

The HPE craniofacial abnormalities consisting of mid facial anomalies: flattened nasal bridge; absent nasal philtrum and nasal septum; midline cleft lip and palate; and microcephaly are classical presentations. ("the face predicts the brain").<sup>3,23,24</sup> Other associated features: limb abnormalities, chest hypertelorism, congenital heart defects occur in genetic conditions and in offsprings of mothers with some medical conditions.<sup>1,4</sup> Medical problems that could be associated include seizures, motor impairment, motor dysfunction, risk of poor nutrition, gastroesophageal reflux, aspiration and constipation.<sup>25,26</sup> Hydrocephalus, chronic lung disease, hypothalamic dysfunction, disturbed sleep–wake cycles and temperature dysregulation, as well as endocrine dysfunction are also some of the associated medical challenges.<sup>21,22</sup>

The diagnosis of the different types of HPE can be done prenatally through trans-abdominal, trans-vaginal ultrasonography and magnetic resonance imaging (MRI).<sup>3,22</sup> However a study reported the need for routine foetal MRI in suspected cases of HPE, and reduction in reliance on ultrasound alone.<sup>22,23,27</sup> In neonates, radiological diagnosis of HPE is best obtained through cranial (MRI).<sup>21,27</sup> However, MRI was not done for any of our patients due to financial constraints. Instead financial support was provided for the cheaper cranial CT scan and transfontanelle ultrasonography which have also been reported to assist in defining the anatomic subtype, and identifying associated CNS anomalies.<sup>22</sup> Determining the karyotype and chromosomal analysis (chromosomal microarray) are important investigations for babies and their parents when genetic causes are considered.<sup>25</sup> This could not be done for the patients, due to non-availability of such laboratory procedures in the State and financial constraints in accessing it outside the state hence abnormal karyotypes or genomic anomalies

could not be identified. This is a pointer to the challenges that exist in the diagnosis and management of congenital abnormalities which could have been mitigated with the availability of improved technological diagnostic facilities and access to a special congenital anomaly group tailor-made health insurance policy. The diagnoses of the two cases reported were made from cranial CT scan, transfontanelle ultrasonography and the clinical manifestations.

Previously, it was reported that majority of children with the severe form of HPE rarely survive beyond early infancy hence the treatment for this was symptomatic and supportive.<sup>2,4,17,20</sup> Considering ethical issues regarding surgical beneficence, intervention when carried out should be done at the earliest possible time.<sup>29</sup> However, where the prognosis is very poor, limiting extraordinary medical assistance aimed towards survival is recommended.<sup>2,4,17,29</sup> In the milder forms, since a large number of the children survive past the first year; a multidisciplinary approach to management consist of interventions by plastic surgeons, neurologists, maxillofacial surgeons and psychologists.<sup>2,4,17,24</sup> Unfortunately, the cultural taboos associated with having a child with dysmorphic features influenced the parents to limit care and in one instance, abandon the baby in the hospital.

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## Conclusion

Holoprosencephaly sequence is a complex spectrum of congenital structural anomaly of the forebrain largely associated with characteristic mid-facial craniofacial anomalies. Considering the heterogenous etiology and challenges associated with stigmatization, it is vital that a diagnosis of HPE is made during the fetal life through ensuring compulsory/routine antenatal congenital anomaly ultrasound scan. This will provide for a well informed medicolegal counseling of families, prognosticating and planning of the HPE management. This report has also created awareness regarding the huge financial burden of management of children with HPE hence the need for subsidized services from the Government and private businesses that have oil-derived wealth from the Niger Delta region.

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## Limitations

These babies would have benefitted from genetic studies, radiological and other specific investigations but were hindered by socio-cultural drawbacks, financial constraints and logistic challenges.

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