Holoprosencephaly With False Median Facial Cleft: A Case Report and Literature Review

***Babalola OF, Salawu AI, Okunlola AI, Orewole OT**

ABSTRACT

Holoprosencephaly is a rare intracranial congenital anomaly that may present to the Plastic Surgeon with Median Facial Cleft. These are unique disorders of forebrain development resulting from an accident early in embryogenesis with the degree of the associated median facial malformation correlating with the severity of the holoprosencephaly. We present a case report of a 4-week-old male referred to our unit with a false median facial cleft, recurrent seizures and underlying holoprosencephaly who had surgical correction of the cosmetic deformity created by the false median cleft.

Keywords: Holoprosencephaly, False Median Facial Cleft, Cosmetic Deformity

Key Messages: *Holoprosencephaly is a rare condition with varying severity that may present to the Plastic Surgeon with median facial cleft. While surgical operation is not immediately advised in Meyers 1-4 groups due to poor prognosis, consideration of sociocultural factors may allow for careful surgical intervention in selected cases*

INTRODUCTION

The face is key to the recognition and differentiation of an individual hence congenital craniofacial abnormalities are usually distressing to the parents of the newborn who request urgent remedy. However, in certain rare craniofacial defects, the problems seen on the face represent an underlying associated brain anomaly and this is exemplified by false median cleft associated with Holoprosencephaly. Incidence of Holoprosencephaly has been put at between 1 in 16,000 and 1 in 53,394 live births.[1] This report aims to highlight the challenges and peculiarities of a case seen in our practice.

Department of Surgery,[1] Federal Teaching Hospital, PMB 201, Ido – Ekiti, Ekiti – State, Nigeria

*Corresponding Author: olakunlebabs@yahoo.com
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CASE HISTORY

A 4-week 5-day old male infant was referred from a private hospital with a defect in the upper lip noticed from birth. The child had developed generalized tonic-clonic seizures before presentation. The mother had a history of febrile illness in the first trimester of pregnancy. She consumed unknown herbal medications during the first 5 months of pregnancy. The child's feeding was supplemented with infant formula feeds due to suckling difficulty during breastfeeding. The father's age at the time of conception of the child was 55years and mother's age was 35years. There was no family history of similar health issues in the past, the other siblings were 14years, 12years, 8years and 2years respectively. The child's weight at admission was 3kg (60% of expected) and occipitofrontal circumference was 30cm (expected was 37+/-2cm).

Examination revealed a pink active male infant with craniofacial disproportion in favour of the face and a cleft of the upper lip. He had patent normotensive anterior fontanelle, closed posterior fontanelle and fusion of the lambdoid sutures. There was a midline cleft of the upper lip, alveolus and premaxilla. There was absence of columella, flattened nasal tip and bilateral proptosis. The examination of the other systems was normal.

A clinical diagnosis of syndromic atypical cleft of the upper lip with craniosynostosis was made. He was commenced on anticonvulsant with initial good seizure control while temperature control with antipyretic and broad-spectrum antibiotic coverage was also initiated. Cranial Computed tomographic scan (CT scan) showed fused metopic and coronal sutures, patent sagittal suture, symmetrically dilated body of the lateral ventricles, slit-like third ventricle with normal fourth ventricle. It was then concluded that this is a case of holoprosencephaly with false median cleft. Echocardiography showed no congenital heart malformation. At the age of three month, he had surgical repair of the median cleft lip but the craniosynostosis surgery was deferred.

The median cleft was repaired in three layers vis a vis the muscle layer, the skin and the mucosa in that order while Z-plasty was incorporated into the vermillion repair to prevent a straight-line scar. The richness of the upper lip tissue allowed for easy apposition without tension. A neo-columella was fashioned from the skin lining the tip and dorsum of the nose and then tabularized. This was anchored to a de-epithelialized area of the repaired upper lip.

He was discharged 2-week postoperatively, to be followed up at a nearby tertiary care institution because of proximity to home. The result of genetic karyotyping sent abroad was untraceable as the parents continued care in another facility due to proximity to their place of residence. However, the child passed away seven months post-operatively.

DISCUSSION

The term Median facial dysplasia describes craniofacial defects comprising lack of cupid bow, short prolabium, absence of frenulum labii, hypoplasia of premaxilla, absent upper central and lateral incisors, deficient septal cartilage, absent nasal spine with the addition of unilateral or bilateral cleft deformity in the absence of gross brain abnormalities.[2] Mid-face hypoplasia is characterized by underdevelopment or posterior positioning of the inferior portions of the orbits, nasal bones and maxilla only hence mid face hypoplasia can be a component of median facial dysplasia, which clinically has associated features of cleft lip/palate without clinically detectable abnormalities of the brain (constitute 2% of cleft lip/palate patients).[2,3,4] All the abnormalities described above are exhibited by patients with varying degrees of holoprosencephaly sequence which is characterized by gross abnormalities of the forebrain.[1,2]

Mid-face and forebrain development are closely related due to the unique involvement of the precordial mesoderm and specialized neural crest cells in their organogenesis at the 3rd week of intrauterine life. The precordial mesoderm stimulates downward growth to form the median facial skeletal components. It also stimulates the rostral neuroectoderm to initiate differentiation of the forebrain, errors during this phase of embryogenesis initiate holoprosencephaly.[2,4] The degree of median facial malformation correlates with the degree of holoprosencephaly of the brain**.** Median facial anomalies are of two varieties namely; True median cleft (hyperteloristic): It is due to lack of midline fusion of the two medial nasal swellings from the frontonasal process. It occurs late in organogenesis hence it is rarely associated with brain malformation. Severity

ranges from vermilion notch to coloboma of nasal ala. False median cleft (hypoteloristic): it is caused by incomplete division of the cerebral hemispheres associated with inhibited development of the frontonasal process which occurs early in organogenesis.

De Mayer and Zeman[4] classified facial cleft holoprosencephaly into 5 groups. Groups 1-4 are incompatible with life and are not expected to live beyond the first year of life while group 5 has normal or near normal brain development and are candidates for surgical intervention by a multidisciplinary team. The index patient belonged to group 4. He had a false median cleft with Semilobar holoprosencephaly along with several complications ranging from problems of recurrent seizures despite high doses of anticonvulsants, to feeding and temperature regulation problems. Many authors have also reported that the management of patients in groups 1-4 is complicated by convulsions, difficulty in feeding, endocrine deficiency, electrolyte imbalance and abnormal temperature control.[3,5,6,7,8] Genetic karyotyping is recommended for the family of this group. The underlying aetiological factors of the disease in our patient were also difficult to ascertain as there was neither family history nor history of chronic maternal illness like diabetes mellitus, however positive history of maternal febrile illness and consumption of unprescribed herbs in the first trimester may have contributed to the expression of the disease.

Holoprosencephaly is a gross abnormality of the fore-brain that results from incomplete division of the prosencephalon usually between the 18th and 28th day of gestation with an incidence of 1:250 in utero and 1:16,000 per live birth.[1,7,9,10,11] Holoprosencephaly is classified into 4 subtypes; Alobar, Semilobar, Lobar and Middle interhemispheric fusion in decreasing order of severity.[7,10] The genetic abnormalities associated with this disorder include Trisomy 13 and Trisomy 18, accounting for 40% of cases. Mutation in SSh gene is the commonest cause of familial and syndromic holoprosencephaly, other genes implicated include IC2, SIX3, TGIF, PTCH, GL12, TDGF1.[7,9,11] In 70% of cases, the molecular basis of the disease is unknown despite gene sequencing. Consequently, a multi-hit hypothesis of genetic and environmental factors has been proposed as the cause of the disease and the extreme clinical variability of presentation.[9,10]

The radiological findings in our patient were in keeping with the classical description of previous authors[10] however, the ultrasonography done during antenatal visits in early pregnancy did not reveal the presence of the condition in the fetus. Ultrasonography is highly observer-dependent while the sonological skills are enhanced by the quality of the equipment. Our patient's parents being rural dwellers were not privileged to access such advantage hence the lack of prenatal diagnosis of the condition in this case. Many authors have emphasized the need for our healthcare facilities to improve the quality of antenatal care with special attention given to mothers considered to be high risk.[11,12.13]

The index patient's median facial cleft had a poor prognosis and the parents were sufficiently counseled on the seeming futility of surgical adventure. They however insisted on having the median cleft lip repaired before being discharged home due to the sociocultural pressure and stigmatization of the facial appearance. A multidisciplinary approach comprising of a team of Plastic Surgeons, Anaesthetists, Pediatricians, Dieticians and Clinical Social Workers prepared, operated and managed the index patient as advised by previous authors[14,15] bearing in mind the challenges of our resource limited clinical setting. A midline vertical closure with simultaneous neo-columella fashioned from local flap satisfied the primary aesthetic concern in our patient. However, Yauchi et al[16]

currently advocate skin graft philtrum reconstruction to compensate for soft tissue defect and second stage tissue transplant for columella reconstruction in their case report.

Elias et al [17] proposed a classification of patients with milder deformity as against those with severe deformity in planning surgical intervention. Following their suggestion, we went through a period of observation, treatment and stabilization before intervening surgically to alleviate the fear of neglect of the child by caregivers and the community due to sociocultural issues that may lead to isolation and stigmatization of the entire family.

CONCLUSION

Holoprosencephaly is a rare condition with variation in the spectrum of severity that may present to the Plastic Surgeon with facial dysmorphic features especially median facial cleft. While surgical operation is not immediately advised in Meyers 1-4 groups due to poor prognosis, consideration of sociocultural factors may allow for careful surgical intervention in selected cases.

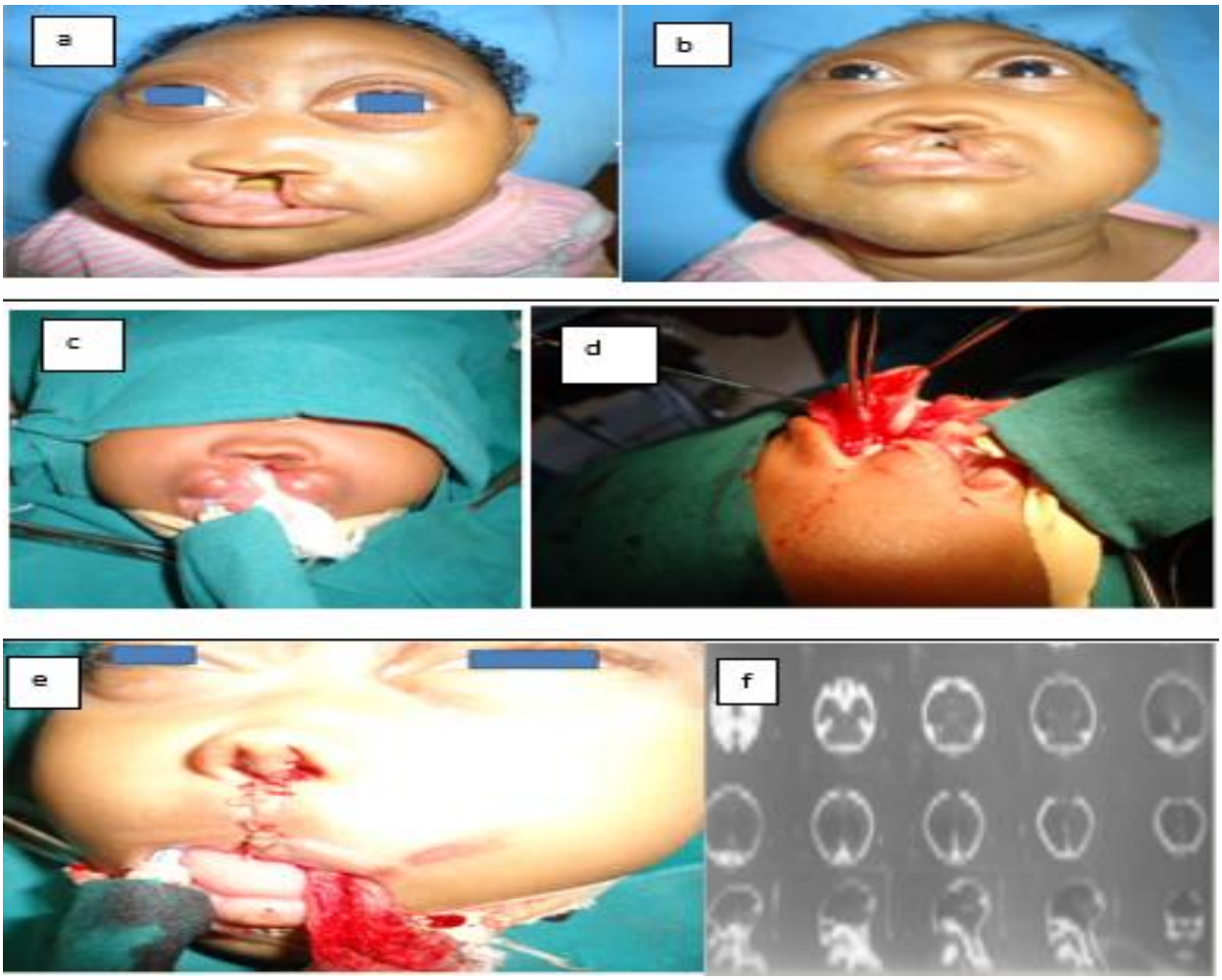

Figure I- Legend- a and b are preoperative pictures showing the false median cleft, c and d are intra-operative pictures. e. Immediate post-operative picture. f is CT scan images of the patient

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