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EDITORIAL ON THE SPECIAL EDITION OF ANNALS OF IBADAN POSTGRADUATE JOURNAL OF MEDICINE ON MANAGEMENT OF CLEFT LIP

This special edition contains nine articles covering various aspects of cleft lip and palate. It's a rich contribution from several specialties that highlights the collaborative nature of the management of the disease. From this, one can conclude that research in cleft lip and palate is rapidly evolving in our sub-region. There is an unusual insertion of crossword and diagrammatic puzzles designed to ease the tension of learning.

The first article: Antenatal events amongst mothers of babies with orofacial clefts was an observational cross-sectional study using questionnaires. This came up with the finding of the use of certain medications in pregnancy amongst 72 mothers. There was an interesting finding of herbal medication in about 20% of them. However no antenatal predisposing factors were are identified. Because the mean age of mothers in the series was about 35 years, the authors indicated that the role of advanced parental age on the prevalence of congenital anomaly was not consistent in literature. This aspect therefore requires further investigation.

The second paper is an interesting electronic search bordering on systematic review through PubMed and Google Scholar on the subject of Hemifacial Microsomia (HM). This literature review on the second most common craniofacial birth defect is pertinent here. The author described methods of classification of HM and came up with Vento and associates' proposed classification called by the acronym OMENS which mirrors UICC and TNM systems of classification of cancers. They also discussed that the new classifications of HM deformities failed to galvanize broad acceptability since its introduction about 20 years ago. This is the kind of vagary that occurs when several classification methods are brought to view. The popularity of such methods of classification depends on the acceptability and the way such can be applied to day-to-day use in clinical practice.

There was only one case report. This was on a missed diagnosis of an isolated transverse facial cleft presenting as a delayed case due not to the caregivers but to Healthcare workers failure to diagnose. Repair of such anomaly is usually gratifying of course made a lot of difference in the psyche of the patient concerned.

In the molecular genetics review paper by Oboli *et al.* it is gratifying to note that genetic studies of cleft lip and palate are gradually increasingly becoming popular in our environment. The next review, Orofacial clefts and cardiovascular risk and diseases discussed the causal association of the two. It has been known for a long time that congenital cardiac anomalies are common with cleft lip and palate and this comprehensive review spells out common syndromes with congenital cardiac anomalies and the role of the paediatric cardiologist in the management of such patients.

Onah *et al.'s* Orthodontic needs of patients with cleft lip and palate is a longitudinal study that shows that there is a need for long-term follow-up of these patients. In another cohort study of 115 surgeries the authors' outcomes of a high incidence rate of 39%, a little over half of these developing fistula. Also, a little over half of the patients were considered to have to have near normal speech. This kind of review is encouraged.

In the article of speech articulation errors in Nigerian individuals with cleft lip following repair Olusanya *et al.*, in bringing up this preliminary overview indicated that at the present infancy level of care, five centres in Nigeria provided speech therapy services under the Smile Train partnership.

The last of the broadly distributed publications is a review of perioperative antibiotic therapy in orofacial clefts surgery by Olawoye *et al.* Their reporting on a large retrospective series comprising 3,108 patients from India in which there was no difference in the wound infection rates between the group which had postoperative antibiotics and the group which did not is instructive.

There is certainly an improvement in the science compared to research of 20 years ago when the investigations were largely epidemiological. The time has come to emphasize the importance of translational research which should dovetail to improved management of these patients and provide a good avenue for comparison with management in other climes especially those with more advanced technology.

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ORIGINAL ARTICLES

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ANTENATAL EVENTS AMONGST MOTHERS OF BABIES WITH OROFACIAL CLEFTS

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ABSTRACT

Background: **Exogenous factors occurring in the antenatal period could be contributory to the formation of orofacial cleft. This study sought to determine the antenatal events in mothers that may have contributed to orofacial cleft deformity of their children.**

Methodology: **It was a prospective observational cross sectional study of consenting mothers of babies with orofacial cleft who met the inclusion criteria. The study instrument was a questionnaire.**

Results: **Seventy-two mothers participated in the study. Most of these mothers were below 35 years of age and more than half, 43 (59.7%) were of the low-intermediate socioeconomic status. Although majority, 70 (97.2) of the mothers had antenatal care, the mean gestational age at commencement of antenatal care was 4 months. Almost all, 69 (95.8%) mothers had ultrasound scans however the detection of the orofacial cleft was in only 2 (2.8%) mothers. The commonest medication taken was haematinics, 26 (36.1%). Herbal medication, 15 (20.8%) and antimalarial, 12 (16.7%) were the other drugs more frequently taken. The mean age of pregnancy at commencement of these medications was 3.6 months.**

Conclusion: **Although uptake of antenatal service was common practice among mothers of babies with orofacial clefts in this study, no antenatal predisposing factors were identified.**

Keywords: Cleft lip and palate, Antenatal events, Mothers

INTRODUCTION

Orofacial cleft is the commonest craniofacial congenital anomaly, which occurs approximately one in every 700 – 1,000 births[1,2]. The precise aetiology is unknown possibly due to the heterogeneous nature of the anomaly.[2,3] However several risk factors have been suggested for this anomaly.[2,4-7], These factors have been reported variously among different populations as predisposition such as family history of cleft, parental tobacco smoking, alcohol intake during pregnancy, increased maternal and paternal age, smoking, exposure to insecticides, nutritional deficiencies, low socioeconomic status and residence in particular locations/geographical locations.[4,6-8] This study was undertaken to describe the antenatal events in a Nigerian population of mothers with babies with orofacial clefts. Knowledge of practices among mothers of babies with cleft anomalies may aid in the identification of possible aetiological factors and steps that could be taken to reduce the incidence of these anomalies in our environment.

MATERIALS AND METHODS

This was a prospective observational cross-sectional study of consenting mothers of babies with orofacial cleft who presented to the cleft clinic of the hospital from 2014 to 2015. Antenatal events in this study were defined as health related events both experienced and performed by the mothers in the antenatal period. Mothers with babies older than six months of age were excluded from the study because of the reliability of being able to recall the prenatal events. Questions pertaining to age of the parents and infants, socioeconomic status of the mothers, uptake of antenatal services, use of medications and traditional concoctions during pregnancy, occurrence of illness and trauma during pregnancy were asked. Documentations of the anomalies were also recorded regarding the type of orofacial cleft, laterality and extent of cleft anomalies as well as the frequency of other associated congenital anomalies. The socioeconomic status (SES) was categorized according to a modification of the classification by Ogunlesi, which described five classes.[9] These classes were re-

categorized as in Table 1; high-intermediate SES (Classes 1 and 2), intermediate SES (Classes 3) low-intermediate SES (Class 4) and low (Class 5). An addition class of High SES was introduced and dependents were not categorized into a particular class (Table 1). The type of cleft was described as cleft lip with or without cleft palate (CL±P), cleft palate only (CP) (Bell) and rare craniofacial clefts. Categorical variables were compared using Chi square and multiple means were compared using ANOVA. Significance was set at $p \leq 0.05$.

RESULTS

Within the two-year study period, 72 mothers of infants with clefts anomalies participated in the study. More than half, 43 (59.7%) of these mothers were from the low-intermediate SES (Figure 1). The mean ages of the mothers and fathers were 29.2 years and 37.5 years respectively (Table 2). Majority (79.2%) of the mothers were younger than 35 years of age. Cleft of primary palate with or without secondary palate (CL±P) was the most common, 56, (77.8%) and the rare craniofacial cleft was the least observed, 4(5.6%),

Table 1: Modified socioeconomic class (SES) classification

SES	By Ogunlesi	Components
High		Director of Oil companies, Senior politicians, Multinational company directors, Industrial and Bank Directors.
High-intermediate	Classes I and II	Executive managers, Senior civil servants, Professionals (doctors, lawyers), Senior Clergy, High Scale Traders, University lecturer
Intermediate	Class III	Intermediate grade civil servants, nurses, lab scientist, Photographers, junior clergy, secondary school teachers
Low-intermediate	Class IV	Semi-skilled workers; Tailors, Bricklayer, Traders, Artisans, Drivers, Farmers, Mechanics, Market trader (shop owners), Auxiliary nurses, Hair dressers
Low	Class 5	Unskilled; Messengers, Roadside traders, Cleaners, Laborers, petty trader
Dependents		Students, housewives, Unemployed

Table 2: Ages of the infants, mothers and fathers

	Infants	Mothers	Fathers
Mean age	1.5 (SD±1.3) months	29.2 (SD±5.8) years	37.5 (SD±6.8) years
Median	1 year	29 years	37 years
Range	3 days to 5 months	18 to 41 years	23 to 56 years

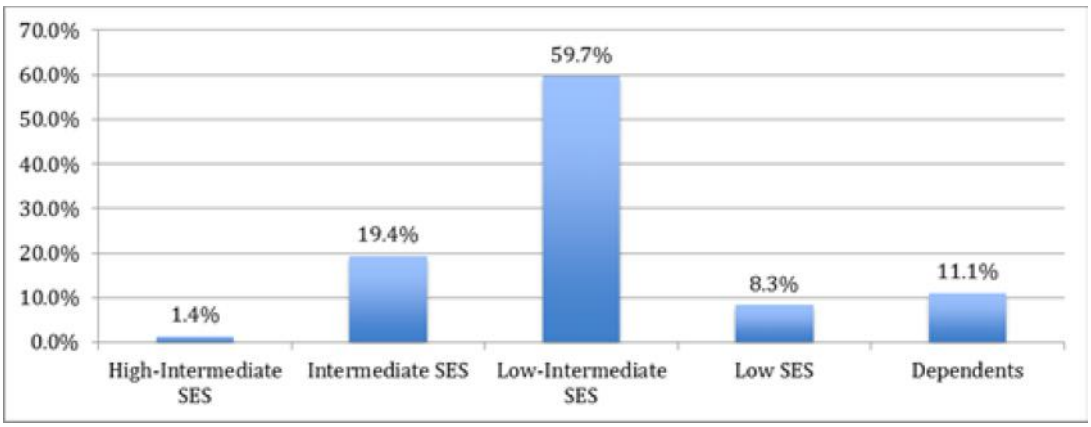

Figure 1: Frequency distribution of socioeconomic status (SES) amongst mothers

Table 3: Characteristics of the cleft anomalies

Type of cleft:	Cleft of primary palate with or without secondary palate (CL±P)	77.8% (56)
	Cleft of secondary palate (CP)	16.7% (12)
	Rare craniofacial clefts	5.6% (4)
Laterality	Left	36.1% (26)
	Right	30.6% (22)
	Bilateral	20.8% (15)
	Midline	6.9% (5)
	NA	5.6% (4)
Extent	Complete	69.4% (50)
	Incomplete	25.0% (18)
	NA	5.6% (4)
Cases with Associated anomalies	Yes	18.1% (13)
	No	81.9% (59)

Table 4: Pattern of antenatal practices

Antenatal Practices		**Frequency in percentage (number)**
Antenatal consultation	Yes	97.2% (70)
	No	2.8% (2)
Age of pregnancy at commencement of antenatal	Mean	4.1 (SD±1.6) months
	Range	1 to 7 months
Ultrasound during pregnancy	Yes	95.8% (69)
	No	4.2% (3)
When ultrasound was done	First ultrasound	5.1 (SD±1.9) months
	Second ultrasound	6.9 (SD±2.0) months
	Third ultrasound	7.5 (SD±2.7) months
Identification of the cleft anomaly at ultrasound*	Yes	2.8% (2)
	No	93.1% (67)
	NA	4.2% (3)
Smoking during pregnancy	Yes	0.0%
	No	100.0%
Alcohol consumption during pregnancy	Yes	0.0%
	No	100.0%
Drugs taken during pregnancy	None	8.3% (6)
	Haematinics alone	36.1% (26)
	'Abiwere'	20.8% (15)
	Antimalaria	16.7% (12)
	Analgesics	8.3% (6)
	Others	9.7% (7)
Age of pregnancy when drug was taken		3.6 (SD±1.4) months
Trauma	Fall (3)	5.6% (4)
	Motorbike accident (1)	
Illness	Febrile illness (24)	38.8% (28)
	Diabetes (1)	
	Hypertension (1)	
	GIT disturbances (2)	
Mean age of pregnancy when other events occurred	Illness	3.9 (SD±1.4) months
	Trauma	4.9 (SD±0.4) months

(Table 3). The clefts were commoner on the left side, 26 (36.1%), majorly 50, (69.4%) complete in extent and less than a quarter was associated with other congenital anomalies,13 (18.1%).

Majority, 70 (97.2%) of the mothers gave positive history of attending antenatal clinics, which commenced when the pregnancies were at a mean age of four months (Table 4). Almost all (95.8%) the

Table 5: Comparison SES of mothers to the characteristics of the craniofacial clefts

		Socioeconomic status						Mothers age ≥ 35		
		High-intermediate	Intermediate	Low-intermediate	Low	Dependent	P-value	Yes	No	P-value
Type of cleft	CL±P*	0.0%	23.2% (13)	632.5% (35)	7.1% (4)	7.1% (4)	0.002!	12.5% (7)	85.7% (48)	0.059
	CP	8.3% (1)	8.3% (1)	58.3% (7)	16.7% (2)	8.3% (1)		50.0% (6)	50.0% (6)	
	Rare clefts	0.0%	0.0%	25.0% (1)	0.0%	75.0% (3)		25.0% (1)	75.0% (3)	
Extent	Incomplete	5.6% (1)	0.0%	72.2% (13)	11.1% (2)	11.1% (2)	0.001!	16.7% (3)	77.8% (14)	0.531
	Complete	0.0%	28.0% (14)	58.0% (29)	8.0% (4)	6.0% (3)		20.0% (10)	80.0% (40)	
	NA	0.0%	0.0%	25.0% (1)	0.0%	75.0 (8)		25.0% (1)	75.0% (3)	

**Age was not available for one mother, ! 73.3% had less than the required cell count.*

mothers had ultrasonographic scanning done, first of which was at pregnancy age of 5.1 months and only in 2.8% was the cleft anomaly detected (Table 4). None of the mothers gave a positive history of either smoking or alcohol intake but 91.7% gave positive history of some form of drug intake during pregnancy, majority (36.1%) of which were haematinics alone (Table 4). The mean age of pregnancy at which these drugs were taken was 3.6 months. Traumatic events were reported in 5.6% at a mean pregnancy age of 4.9 months and 38.8% gave a positive history of illness at a mean pregnancy age of 3.9 months (Table 4).

Table 6: Comparison of antenatal practices of mothers to the characteristics of the craniofacial clefts

		Use of medication			Trauma			Illness		
		Yes	No	P-value	Yes	No	P-value	Yes	No	P-value
Type of cleft	CL±P	91.1% (51)	8.9% (5)	0.823	5.4% (3)	94.6% (53)	0.812	46.4% (26)	53.6% (30)	0.534
	CP	91.7% (11)	8.3% (1)		8.3% (1)	91.7% (11)		33.3% (4)	66.7% (8)	
	Rare clefts	100.0% (4)	0.0%		0.0% (0)	100.0% (4)		25.0% (1)	75.0% (3)	
Extent	Incomplete	88.9% (16)	11.1%(2)	0.759	5.6% (1)	94.4% (17)	0.881	33.3% (6)	66.7% (12)	0.422
	Complete	92.0% (46)	8.0% (4)		6.0% (3)	94.0% (47)		48.0% (24)	52.0% (26)	
	NA	100.0% (4)	0.0% (0)		0.0% (0)	100.0% (4)		25.0% (1)	75.0% (3)	

Comparison of the mother's age, use of medication, history of trauma and illness with the type and extent of the cleft anomaly did not reveal any significant differences between the younger and older mothers and between those who gave a positive history and those who did not (Table 4). However, there were significant differences between the SES classes in terms of the type and extent of cleft anomaly (Table 5).

DISCUSSION

This study has described the events and practices of a population of Nigerian mothers of babies with orofacial cleft anomalies during the antenatal period. The commonest anomaly type was the CL±P and CP had the least frequency. The anomaly was more on the left side, a larger proportion of the cases were complete in extent and majority were isolated cases without associated anomalies. Thus, the population of babies in this report is similar to the pattern of previously reported for orofacial cleft populations.[6,10,11] Therefore the participants of this study are considered to be representative of mothers of the population of babies with orofacial cleft anomalies. On this background, the antenatal events and practices were assessed.

The uptake of antenatal services was common among the mothers however the age of pregnancy at the time of commencement of antenatal services was delayed to the second trimester; a stage at which the anomaly would have occurred. This precludes any form of preventive measures against congenital anomalies (such as the use of folic acid especially preconception) during antenatal period as the formation of the face occurs between the 4th and 8th week of intra-uterine life.[6]

The birth of a child with congenital anomaly can be devastating to parents.[12] A prenatal diagnosis is helpful in the acceptance of a baby born with congenital anomaly as it provides the time for the would-be parents to prepare for the arrival of such a child.[12] Perinatal ultrasound scanning has been a routine component of antenatal care in many countries.[13] A prenatal diagnosis of cleft anomaly using ultrasonography was first described in 1981.[12] Over ninety percent of pregnant women usually take up this service.[13] The first ultrasound has been documented to be done in less than four months of gestational age in about seventy percent of the cases.[13] The detection

rate for cleft anomaly appears to be low but higher when the cleft anomaly occurs with other congenital malformations.[13,14] As far back as 1995 in a study of over 180,000 pregnancies of known outcomes, 178 were cleft anomalies and only 17.5% were detected prenatally by ultrasound scanning.[13] In the year 2000, from the analysis of 20 European registries of congenital anomalies, the detection rates for orofacial clefts in general, CL±P and CP were 21.4%, 26.8% and 6.6% respectively.[15] However, the detection rate for orofacial clefts has improved over the years to about 85% since the introduction of the routine transabdominal 20-week fetal anomaly scan in 2007 in the Netherlands.[16] This notwithstanding, the detection of cleft palate alone still remains a considerable challenge.[17] Ultrasound scanning was also found to be a common practice among the mothers in this study. This was usually done once, when the pregnancy was just over 5 months. However the reported detection rate was extremely poor as only a very small percentage of the anomaly was detected before birth. The reason for this was not explored in this study but may be due to lack of available expertise in the field of radiological prenatal diagnosis[13,17] and/or lack of adequate facilities.[18]

The socioeconomic status (SES) stratification employed for this study was a modification of the SES classification by Oyedeji as described by Ogunlesi.[9,19] The Ogunlesi's classification considered in addition the income of the individual. However, some modifications were made to this classification as individuals considered in our society to belong to very high socioeconomic class (as identified in Table 1) do not appear to be represented under the Ogunlesi's classification and were therefore included as 'High' SES in this study. Also, it was challenging to place dependants in a particular class, as they do not necessarily belong to the class of the individual on whom they were dependent. For instance a housewife may be married to a father in Intermediate SES but may not have the full benefits of that class as access to these benefits are assumed to be dependent on the judgment of whom she is depending on. The conventional middle class was split into three categories; the high-intermediate, intermediate and the low-intermediate as there exist significant income disparity between these categories of middle classes.[9] Majority of the mothers were in the Low-Intermediate SES class in this study. The possibility of nutritional deficiency as an aetiological factor in the occurrence of orofacial cleft in our environment is entertained because of the predominance of low-intermediate SES class in this category of mothers. However further investigation will be required to analyze the effect of nutrition on the prevalence of cleft anomalies in our environment as the distribution of the classes of SES observed in the study may be a reflection of what obtains in our general population.

The role of advanced parental age on the prevalence of congenital anomalies is not consistent in literature.[11,20] The influence of maternal age on pregnancy outcomes has been documented severally, while data on the effect of paternal age is sparse.[20] Some studies found associations between advanced parental age[20] while some did not.[21] Some found associations between advanced maternal age and CLP[6], some found between increasing paternal age and CLP[22] while some reported increased incidence with both maternal and paternal ages.[23] Hay *et al* reported higher prevalence of cleft palate in mothers older than 35 years and fathers older than 40 years.[24] The mean ages of the fathers and mothers were both lower than these (29 years for mothers and 37 years for fathers). These age values were strikingly similar to the findings of a similar study in a different part of the country that reported mean age of 37.1 years for fathers and 29.2 years for the mothers.[25] The role of parental age on the prevalence of orofacial clefts is not clear in literature and therefore requires further investigation.

Maternal smoking has been found to be associated with increased risk of having babies with orofacial clefts.[6] Relationship between maternal alcohol consumption and orofacial clefts on the other hand is not well understood.[26] A number of studies have found no relationship (Bell) while some have documented increased risk of having babies with orofacial clefts with consumption of high quantities of alcohol.[5,27] This risk was observed for CL±P and syndromic clefts in women who consumed 5 or more drinks at a time on at least a weekly basis.[6,27] However the roles of these possible teratogens are uncertain.[6,26] In our study smoking and alcohol consumption do not appear to be a practice among mothers having babies with cleft lip and palate anomalies in our environment. This negative history of smoking was similarly reported from some other part of our country.[25]

Medication during pregnancy does not appear to be a common practice in this report including the use of herbal concoctions locally termed 'abiwere'. Abiwere, literally translated from the local Yoruba language means to be delivered of a baby without complications. Less than a quarter, 15 (20.8%) of the participants in this study gave a positive history of taking this concoction during pregnancy. This number of respondents was also similar to a previous study that

reported 22.1% of the mothers gave a positive history of taking herbal concoctions during pregnancy.[25] Admittance to taking any form of medications; orthodox or traditional was at the beginning of the second trimester a period at which the face was expected to have been formed.[6] Thus the practice of taking medication during pregnancy in this study does not appear to have influenced the occurrence of the cleft anomaly.

Fever during the first trimester of pregnancy has been associated with increased risk of orofacial clefts when antipyretic is not taken to alleviate the fever.[28] The prevalence of trauma was low and almost one third was ill during pregnancy, majorly febrile illness. These were similar to the findings of a previous study although the age of pregnancy at the time of occurrence of the events were not stated.[25] However the age of pregnancy at the time of occurrence of these events was reported to be within the second semester therefore is not considered to be influential in the occurrence of the cleft.

CONCLUSION

Although uptake of antenatal service was common practice among mothers of babies with orafacial clefts in this study, detection of orofacial cleft anomaly via ultrasound was very low. No antenatal aetiological predisposing factor was identified in this study.

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CLASSIFICATION AND MANAGEMENT OF HEMIFACIAL MICROSOMIA: A LITERATURE REVIEW

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ABSTRACT

Hemifacial microsomia (HFM) is the 2nd most common craniofacial birth defect after cleft lip and palate. It is said to arise from the 1st & 2nd intrauterine branchial arches. HFM is believed by many experts to be congenital but not inherited as most patients afflicted have no previous family history. It also known as craniofacial microstomia with cranial involvement. The real cause is unknown but largely blamed on hemorrhage of the stapaedial artery. The phenotypic expression is variable from mild to severe involving many structures such as bone, nerve, muscular tissues and soft tissue. Facial structures commonly affected include the ears, the mouth and the mandible. Mostly unilateral but bilateral have been reported. However, not much is known about this condition in sub-Saharan Africa. Multidisciplinary team management is the general consensus for optimal care. Awareness in sub-Saharan Africa of this disorder is still evolving

This review identifies various classifications, diagnoses, investigations, treatment and timelines for management of HFM. The aim of the current review was to discuss the diverse controversies, classification, diagnosis and treatment of HFM so as to increase the understanding of this condition.

Keywords: Congenital malformation, Syndrome, Hemifacial microsomia, Hypoplasia, Classification, Distraction osteogenesis, Orthognathic surgery

INTRODUCTION

Hemifacial microsomia (HFM) is among over 250 congenital syndromes that cause asymmetrical anomalies of derivatives of the first and second brachial arches.[1,2,3] In 1881, Carl Ferdinand Von Arlt a German physician was the first to describe this malformation.[4] It has attracted sizeable attention in the literature over several decades resulting in conflicting names such as brachial arch syndrome, lateral facial dysplasia, oto-mandibular dystosis and first and second brachial arch syndrome.[4,5,6] Many authors used to consider Goldenhar syndrome as a different entity from HFM until current evidence proved that it is actually a variant of HFM.[1, 3,4,6] Goldenhar syndrome which Gorlin and associates formerly referred to as oculo-auriculo-vertebra dysplasia/spectrum is also associated with cardiac and renal defects in addition to vertebral malformation and epibulbar dermoids.[1,7,8] 'Craniofacial microsomia' as coined by Converse and associates involves the presence of cranial defects with other characteristic features of HFM.[5]

According to several studies across the globe, HFM is the second most common congenital craniofacial birth defect after cleft of the lip and palate.[1,5,6] Cohen *et al* (1989) put the incidence of this anomaly as 1 in every 5600 newborn.[1] However, recent finding of a higher figure of 1 in 3000 have been reported.[7,8] Predilection for males with a male-female ratio of 3:2 has been demonstrated by many investigators.[1,2,6] HFM occurs sporadically with most people affected possessing no positive family history of this deformity; hence, there is strong consensus that it is genetic but not hereditary.[6,7,8]

The genetic basis of HFM is just gradually being unraveled.[7,9] A recent study in 2018 by Chen and associates found mutation in large host of genes such as OTX2, PLCD3 and MYT1 in people with HFM.[10] Coincidentally, HFM is associated with about 7% to 15% of both typical cleft lip/palate and Tessier;s atypical facial cleft.[6,8] Similar environmental factors and teratogens like maternal diabetes and thalidomide, retinoic acid, triazene, vasoactive medications have been blamed for the occurrence of HFM.[3,4,10] Nevertheless, the controversies persistently engulf the aetiopathogenesis of HFM with three models proposed.[4,9,10,11,12] Experimenting in animals, Poswillo declared that following administration of 10mg/kg of thalidomide to female pregnant mice; resultant hemorrhage from rupture of stapaedial artery led to

complete damage or partial disruption of the development of the first and second brachial arches and localized necrosis of their derivatives.[11,12] The others are the abnormal development of the cranial neural crest cells and Merkel's cartilage due to damage or destruction by teratogens.[10,11,12] Although, Chen and colleagues advocated that the first theory is the most plausible of the lot.[10] However, they insisted that these three mechanisms might have acted in concert during the first 9-8 weeks of gestation to cause the derangements that produce the numerous related features of HFM.[13]

Phenotypic expressions of HFM depend on the extent of this haemorrhage and its effect on these two arches.[11,12,13] Therefore, there is a wide spectrum of presentation of this malformation varying from the mild to the severe spanning the skeletal, neural, muscular tissues and soft tissue. It affects the development of the lower half of the face, most commonly the ears, the mouth and the mandible.[6,8,9,13] There is an assortment of degrees and combinations of underdevelopment and malformations of this region.[6] Several reports observed usual occurrence on one side of the face, but involvement of both sides have been shown.[6,11,13] However, there is paucity of research and knowledge about this complex malformation in Nigeria and the sub-Saharan Africa.

The purpose of this current article is to review the literature and summarize pertinent information about the aetiopathogenesis, classification, clinical presentation, radiological investigations, differential diagnosis and surgical treatment of hemifacial microsomia.

MATERIALS AND METHODS

An electronic search of the literature was performed in PUBMED and google scholar without time restriction for appropriate English papers on hemifacial microsomia based on a series of keywords in different combinations: "craniofacial microsomia", "oto-mandibular dystosis", "auriculo-oculo-vertebra spectrum", "Goldenhar syndrome", "lateral facial dysplasia", "first and second brachial arch syndrome", "OMEN", "distraction osteogenesis", "maxilla", "mandible", "treatment", "Kaban and Pruzansky", and "classification". Prospective, retrospective studies, randomized/nonrandomized clinical trials, meta analysis, cohort studies, case–control studies, and case reports were considered. The reference lists of original and review articles were also sought. In addition, a manual exploration of major oral and maxillofacial surgery textbook was undertaken. Letters to the Editor, historical reviews, and unpublished articles were excluded.

RESULTS

Aetiology

This multifactorial aetiogenesis can be divided into genetic and environmental factors.[6, 13]

Genetics

Continuing research have confirmed the complex genetic mosaic in HFM and demonstrated the constellation of genes involved.[10] X-linked, autosomal dominant and recessive patterns have been discovered in familial cases of HFM. Mutations in OTX2, PLCD3 and MYT1 genes have recently been discovered to play a crucial role in the aetiopathogenesis of HFM.[1,2,3,10,13] In addition, previous genetic studies implicated chromosomal deletion in trisomy 18, 5q and duplication in 7q in HFM.[6,10,13] It was observed that HFM is common with children born through assisted reproduction in the USA.[13,14] The age of the parents and donor might be a cofounder in this situation.[13,14,15] However, there are ongoing attempts to shed more on the exact molecular processes and understand the pathogenesis of HFM through whole gene sequencing in animals and large clinical studies.[10]

Table 1: Pruzansky's classification of HFM

Grade I	Smaller mandible than the preserved normal side
Grade II	on the affected mandible; condyle, ramus, and sigmoid notch identifiable, but grossly distorted in size and shape
Grade III	affected mandible is grossly distorted, loss or agenesis of ramus, condyle and TMJ.

Environmental Factors

Drugs and chemicals such as retinoic acid, triazene, primidone, thalidomide exposure; and use of vasoactive medications have been revealed to be strong risk factors in the aetiology of HFM. Several mothers with diabetes in developed countries have been reported to give birth to HFM children.[2, 3,4,14]

Pathogenesis

It is aetiologically and pathogenetically heterogeneous.[6, 10,13] The pathogenesis of HFM remains highly controversial with three plausible mechanisms suggested.[10,13] Poswillo through his observations in the classic experiment in pregnant mice postulated that thalidomide induce vascular damage with consequent haemorrhage of the stapaedial artery and the resultant haematoma consequently impedes the development of first and second brachial arches.[16] He stated that the bigger the haematoma and the longer it takes to

Table 2: Kaban *et al.* classification of HFM

Type I Normal mandible-Type I
Type IIA The mandible and glenoid fossa are small-
Type IIA Short ramus, glenoid fossa is in anatomically acceptable position
Type II B Short ramus, TMJ is inferiorly, medially and anteriorly displaced with hypoplastic condyle
Type III Complete absence of ramus, glenoid fossa and TMJ

resolve, the more complex and severe the anomalies are. Johnston and Bronsky contradicted these theories with their proposition that teratogenic effect on neural crest cells cause the abnormal development and migration of neural crest cells between 30 and 45 days of gestation.[17] They argued this occurred before the thalidomide induced damage which affects only the second brachial arch.[18] The third hypothesis is the damage to merkel's cartilage with possible retarding factor on the development of these two brachial arches contributing to the occurrence of HFM.[10] Chen and associates, however, assert that the most plausible construct is the first. Pathogenesis of HFM still remains an enigma as many leading researchers in this field conceded that none of the above models fully explained the many variable features of HFM and overlapping characteristic with syndromes like Treacher-Collins, Down and DiGeorge.[10,13]

Classification of HFM

In order to most favorably manage HFM numerous classifications have been developed based on the anatomic and diverse clinical presentations, thus, helping to construct an optimal treatment plan. An extensively adopted and widely applied system for HFM in clinical use was first pioneered by Samuel Pruzansky in 1969[19] (Table 1). He used simple plain posterior-anterior radiographic view of the jaw to grade the affected mandible into three distinct morphologies.

This classification stood for nearly two decades until Kaban and colleagues (1988) utilized teleradiography to modify and increase the earlier classification into four groups based on the TMJ anatomical status. Grade II was further divided into a and b, (Table 2).

Table 3: OMENS classification for HFM

A. Orbit
O0 Normal
O1 Small size
O2 Poor position
O3 Both small size and poor position
B. Mandible (and TMJ)
M0 Normal mandible-Type I
M1 The mandible and glenoid fossa are small-Type IIA
M2A Short ramus, glenoid fossa is in anatomically acceptable position-type IIA
M2B Short ramus, TMJ is inferiorly, medially and anteriorly displaced with hypoplastic condyle-Type II B
M3 Complete absence of ramus, glenoid fossa and TMJ-Type III
C. Ear
Ear anomaly can be classified into external, middle/atresia and presence of branchial arch remnants/sinus tracts.
Max and Meurmen's system is used in OMENS
E0- normal ear
E1- mild hypoplasia and cupping with all structures present
E2- absence of external auditory meatus with variable hypoplasia of the concha
E3-malposition lobule with absent auricle
D. Facial nerve-seventh cranial nerve
N0 No facial nerve involvement
N1 Upper facial nerve involvement (temporal zygomatic)
N2 Lower facial nerve involvement (buccal, mandibular, cervical)
N3 All branches of facial nerve affected
N.B Hypoglossal (N^{12}) and trigeminal (N^{5}) nerves can also be affected.
E. Soft tissue deficiencies
S0 normal-No obvious soft tissue or muscle deficiency
S1 mild-Minimal subcutaneous/muscle deficiency
S2 Moderate–between the two extremes S1 and S3
S3 Severe soft tissue deficiency due to subcutaneous and muscular hypoplasia

Following advancement in medical knowledge and better understanding of the complexities and multisystem nature of this condition, Vento and associates (1999) proposed a more expansive classification called by the acronym 'OMENS' which mirrors UICC 'TNM' system in classification of cancers.[21] (Table 3) This while overcoming the deficiency of earlier classifications of Pruzansky and Kabans' fixation on the mandible. The 'OMENS' acronym include O-Orbit, M-Mandible, E-Ear, N-Nerve and S-Soft tissue. Series of amendments were subsequently made to this classification between 1995 and 2007 to accommodate the discovery of extracranial structures with + added to the OMENS, now OMENS+ and pictorial form to facilitate standardization, transmission, teaching and research. The pictorial form of OMENS+ was further modified in 2011.[21] However, most commentators have expressed misgivings on the laborious and time consuming demands of this classification but admitted the immense advantage of the clinical thoroughness especially for easier and methodical treatment planning.[6,13]

Unlike its predecessors, a new classification for HFM known as craniofacial deformity scoring (CFDS) has failed to galvanize broad acceptability since its introduction in 2001.[6] It is a combination of mandibular scoring deformity and cranial deformity scoring totaling 16 and 19 points for each respectively with heavy reliance on computer tomography to analyze each different bone structures has been found to be challenging with a huge learning curve.[13]

Clinical Presentation

The clinical features of HFM are broad spectrum and vary from one individual to the other. Previous works shows that due to its complex and random expression there is a large range of phenotypic appearance which depends on the constellations of the host genes involved.[3,6,8,13]

Often, the disorder has been found to be unilateral but few report observed that the condition do present bilaterally with the characteristic asymmetry of the cranio-maxillofacial complex.

The more commonly affected structures include ear (external and middle which result in conduction defects between 30-50%), mandible [ascending ramus, condyle and temporomandibular joint (TMJ)], orbit, zygomatic arch and maxilla. Soft tissues majorly involved include facial nerve and muscles such as masseter and temporalis.[6,11,12,13]

This unevenness of the mandible and TMJ result in serious dental consequences such as malocclusion, impaction, delayed eruption, noticeable jaw deviation to the uninvolved side with sometimes presence of ankylosis and velopharyngeal insufficiency.[8, 12]

The positioning of the orbit might be altered (orbital dystopia) with presence of dermoids (epibulbar), retinal or choroidal coloboma, blepharatoptosis, microphthalmia or anophthalmia and others.[6, 8, 13]

Some patients could also present with absent ear (anotia), small ear (microtia), disorders of the middle ear and very bad cases with hearing loss.[6,8,9] Furthermore, the seventh (facial) cranial is frequently affected with different degrees of affectation of the upper or lower branches and in severe cases the fifth (trigeminal) and twelfth (hypoglossal) cranial nerves could also be vulnerable.[6,13]

In addition, findings of abnormal teeth development and eruption such as dental hypoplasia, agenesis, microdontia, malocclusion and delayed teeth eruption have been demonstrated.

Extracranial structures such as kidney, central nervous system (CNS), gastrointestinal tract (GIT), heart, lungs and skeletal could be affected in severe cases.[6,9,15] Hence, the classification of HFM is indispensable to optimally correct and restore the anatomic parts involved to full function.[6]

Imaging for HFM

Plain radiographs of the skull have been generally exploited in the diagnosis of HFM.[6,13] With recent advancement in radiology, advanced imaging tools like cone beam computed tomography (CBCT), spiral multi-slice computed tomography (MSCT), Magnetic resonance imaging (MRI), ultrasound (USS) and three dimensional surgical stimulation models like stereolithographics are gaining popularity.[6, 8,9,22]

Three-D device like stereolithographics has helped to revolutionize the treatment of HFM while simultaneously surmounting the problem of insufficient evaluation and quantification of soft and bony tissues by customary 2-dimension imaging techniques. It also makes pre-operative virtual surgical planning easier with customization of the necessary implants needed to restore the deficient areas.[9,13,22] Cassi and colleague reported the increased use of noninvasive, non-ionizing radiation devise such as laser surface scanner, stereophotogrammetry or ultrasonographic measurements to quantify facial proportion and topography in HFM.[8]

Computer-guided surgical planning and simulation due to increase accuracy, facilitates surgical procedure,

shortens operation time, makes customization of reconstruction plate easier and minimizes complications compared to conventional approach to surgical planning. It is widely utilized by advanced centres in western countries and north Africa.[8,9,13,23] However, the high cost of this technology is sadly out of reach of many centres in developing nations.

Differential Diagnosis

This includes hemimandibular hypoplasia in which there is no soft tissue deficiency, presence of glenoid cavity but chin deviation due to condylar, coronoid and ramus hypoplasia.[6,13] Syndromes such as Treacher-collins, CHARGE, Parry Romberg, Miller-Dierker, branquio-oto-renal, Townes-Brocks and many others that have similarity with HFM. Therefore, a geneticist needs to rule them out.[6, 8,9,13] Pertinently, bilateral presentation of HFM can easily be misdiagnosed as Treacher-Collins but the distinguishing features is that the one side would be more asymmetrical with or without one side slanted than the other. This is in contrast to the almost mirror image of the hypoplasia in both side of the face in Treacher-Collins in addition to micrognathia.[13]

Clinical Presentation

The clinical features of this anomaly vary considerably but commonest dominator is the facial asymmetry associated with mandibular hypoplasia and TMJ incongruity.[8, 9] This is majorly unilateral but occasionally can be bilateral. Maxillary/zygomatic hypoplasia, external/internal ear abnormalities/atresia, coloboma, parotid hypoplasia and microphthalmia. [10, 11] There are also several dental derangements such as oligodontia, malocclusion, open bite and delay eruption. Other congenital anomalies that might be present include vertebral anomalies, cardiac defects, renal defects, mental retardation and host of other soft tissue disorders. [12, 13]

Team Management

Previous studies have consistently documented the importance of multidisciplinary approach in the proper management of HFM. This team is inclusive of large arrays of health professionals spanning paediatric, surgery, medicine, dental and other allied fields. [6,8,9,13] Plastic/maxillofacial surgeons, orthodontists, paedontists, restorative/prosthetic dentist and periodontologists are the major specialists involved in achieving optimal corrective aesthetic, functional restoration of normal occlusion and TMJ function.[8,23] Some workers also highlight the importance of other experts like the cardiothoracic surgeon, orthopaedic/spine surgeons, geneticists and neurosurgeon. [6,8,9,13, 24,25] Unfortunately, in Africa only few countries in northern and southern Africa are able to provide this cohort as it is common found in Asian, Europe and other developed nations. [8, 25, 26]

Treatment

Treatment to correct the dental, skeletal and soft tissues anomalies in HFM can start from childhood even unto early adulthood.[6, 23, 24, 25] Treatments of these disabilities are in phases and can be split into surgical and non-surgical.[8, 9, 13,] According to Cassi et al surgical treatment of HFM patients depend on the extent and severity of deformity with repair of bony, soft tissues and specialized organs like the ear and nerves.[8]

Timing of Surgery

Regarding the timing of surgery there are two rival schools of thought with one advocating that this disorder is not progressive and any major surgical intervention should be delayed until after puberty.[24,25] This they advance would ensure stable and predictable treatment outcome with minimal need for revision surgery; and less health care burden on the family and health system. The divergent view vehemently assert that it is needless to wait for skeletal maturity before commencing surgical intervention as this congenital anomaly is progressive and would get worse over time if early treatment is not instituted.[26,27] They also underline the necessity to circumvent the serious psycho-social cost of stigmatization to the child and family; and to diminish the burden of care on the health system. Many longitudinal studies buttressed the position of the former.[25]

Although few data supports the second point of view with their findings being disputed as a result of short period of follow up.[26, 27] However, recent outcome studies established that the results in both approaches are comparable in terms of outcome and long lasting stability.[24] An investigator, on the other hand, extols the successful integration of the two approaches in their craniofacial centre.[13]

Reconstructive Options

There are arrays of surgical procedures to restore bony loss and soft tissues in HFM which include vascularized and non-vascularized tissue grafts, prosthetic implants, distraction osteogenesis and orthognathic surgery.[6,27,28, 29,30] There has been controversy whether orthognathic surgery was superior to distraction osteogenesis.[6,8,13,29] Although for Kaban I and IIA anomalies distraction osteogenesis have achieved some limited success.[6,12,13] Orthognathic surgery with or without bone grafting is more favoured by surgeons in its ease of wider application.[6,13,29] A recent meta-analysis, nevertheless, concluded that both were comparable in terms of rate of recurrence and surgical outcome.[29]

In Kaban IIB and III with underdeveloped bone and missing TMJ, TMJ reconstructions with costochondral graft were often put into regular use.[24,28] Sternoclavicular, iliac and fibula bones have also been used to successfully reconstruct the TMJ.[6,9,13,28] In richer climes of Europe and America, total TMJ replacement with expensive titanium implant have found acceptance by both patients and surgeon alike.[9,13] Total ear reconstruction with cartilage from the rib has also attracted tremendous attention in the surgical community.[30] Nerve graft from the sural nerve have also been effectively utilized to reconstruct the facial in HFM patients.[6,12,13]

Non-Surgical Treatment

However, removable functional orthodontic appliances like Andresen, Frankel appliance and asymmetrical functional activator (AFA) (hybrid of bite block components of the bionator and the vestibular shield are being employed in early childhood to treat the mandibular deficiency in mild Kaban's type IIA.[8] The disadvantages of this measure are that it is laborious and requires patient's steadfastness and cooperation in order to achieve tangible results.

Early orthopeadic intervention in childhood have been observed to improve aesthetics, function, and reduce psychological trauma and obviate the need for maxillary and mandibular osteotomies in late adolescence.[6,8,19,13] Although some authors have reported successful correction of facial asymmetry in type I and IIa HFM children with functional appliances. Long-term follow up showed that some these children eventually require orthognathic surgery to correct the skeletal and dental malocclusion.

CONCLUSION

In summary, HFM is a complex malformation affecting principally the craniomaxillofacial region. Its pathogenesis is still not well defined and presents with a wide variation of clinical characteristics that affects both hard and soft tissue. Huge resources and long term multidisciplinary team approach are required for optimal management. Surgical and non-surgical treatments have been effectively deployed to achieve optimal aesthetic and functional outcomes.

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MISSED DIAGNOSIS OF ISOLATED BILATERAL TRANSVERSE FACIAL CLEFT: A CASE REPORT

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ABSTRACT

Introduction: **Bilateral transverse facial cleft is the most common of the rare facial clefts and early presentation is a key element for successful management and prevention of possible complications like poor esthetics, speech and eating difficulties. Though several studies have documented reasons for late presentation, none has highlighted non-referral due to missed diagnosis by healthcare workers as a reason.**

Case Report: **A nine-year-old girl was brought by her parents to the Primary Oral Health Clinic on account of "very wide mouth" noticed at birth. The mother noticed the anomaly few hours after she gave birth to her and immediately pointed the attention of the nurses and birth attendants to it but they dismissed her concern. Subsequently, the mother took the girl to the maternity centre for routine immunization appointments, but none of the healthcare workers she encountered recognized the birth defect. The parents further reported that the girl received jests and abuses from her peers. A diagnosis of Isolated Bilateral Tessier number 7 cleft was made based on clinical examination findings. She was referred to a cleft centre where the repair was successfully carried out at no cost to the patient through the Smile-Train® sponsorship program. Subsequent follow-up visits to the primary healthcare clinic in the sixth and ninth month post-surgery revealed remarkable improvement in both patient's and parents' self-reported psycho-social wellbeing.**

Conclusion: **This case report presents a rare presentation of delayed isolated congenital bilateral macrostomia because of healthcare workers failure to diagnose.**

Keywords: Congenital macrostomia, Tessier 7, Rare facial cleft, Missed diagnosis

INTRODUCTION

Congenital macrostomia also described as a Tessier number 7 cleft is a rare facial cleft[1]. It usually occurs from the lack of fusion of the maxillary and mandibular processes resulting in a cleft at the commissures of the lips. While a sulcus at the commissure may be the only finding [1], it typically extends about 1 – 2 cm in length to the anterior border of the masseter [2], while more severe types can extend as far as the ear [3] and beyond[4]. It may either occur in isolation or as part of a syndrome in which case there would be other manifestations [5]. The reported incidence ranges from 1 in 60,000 to 1 in 300,000 live births [1].

Early presentation for treatment is a key element for successful management of clefts[6,7]. However, in developing countries, patients with clefts often present late for treatment with resulting adverse effects on the patients' psycho-social health and treatment outcomes[6,7]. Studies have shown that the reasons for late presentation of these patients for care include poverty, lack of awareness and fear of treatment[6,7]. However, none of the studies reported non-referral by healthcare workers as a reason for late presentation of patients. Hidden clefts such as isolated clefts of the palate are often missed by healthcare personnel[8], but we did not find any report of healthcare personnel missing an external cleft such as this case of congenital macrostomia.

In this case report, we describe a case of bilateral transverse facial cleft, which was noticed by the child's parents at birth but dismissed by healthcare personnel despite repeated attempts by the parents to get treatment for their child.

CASE PROFILE

A nine-year-old shy and withdrawn Yoruba girl, accompanied by her parents, presented at our Primary Oral Health Clinic in a rural community in Oyo State, Southwestern Nigeria on account of "very wide mouth" noticed from birth. The mother who noticed the deformity shortly after birth in a community health centre said she pointed the attention of the midwife and birth attendants to it at the time, but they simply dismissed her observation saying it will heal up or fuse together as the baby grows older. This however was not so as the deformity became wider as the child grew.

The child's perinatal history was uneventful. The mother received regular antenatal care and delivered her uneventfully at the maternity centre. She also recorded normal developmental milestones and received a complete course of the routine immunizations. The child had not had any problems with oral functions (speech, mastication), but aesthetics had been a major challenge. Her peers made unsavory remarks about her especially in her school. Her parents believed this had been a source of psychosocial challenge for her especially as she grew older. She showed an increasing loss of enthusiasm towards going to school and her parents had to change her school at a time. The aesthetic and psychosocial challenges were the primary reasons the parents presented at our primary oral health clinic with her.

The child is the first of two of her mother in a polygamous family of five children. The family belongs to the lower socioeconomic class; the mother who's the first wife is a petty trader with no formal education, while the father only completed secondary school and works as a roadside mechanic.

On examination, there was an abnormal extension of the lip commissure bilaterally, more marked on the left (about 2cm) than the right (about 0.5cm). Neither extension reached as far as the anterior border of the

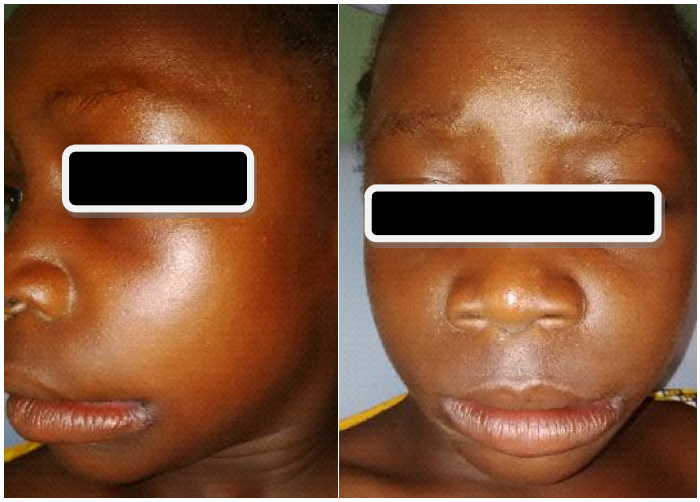

Fig. 1: The Lateral (left) and facial views of the girl at presentation.

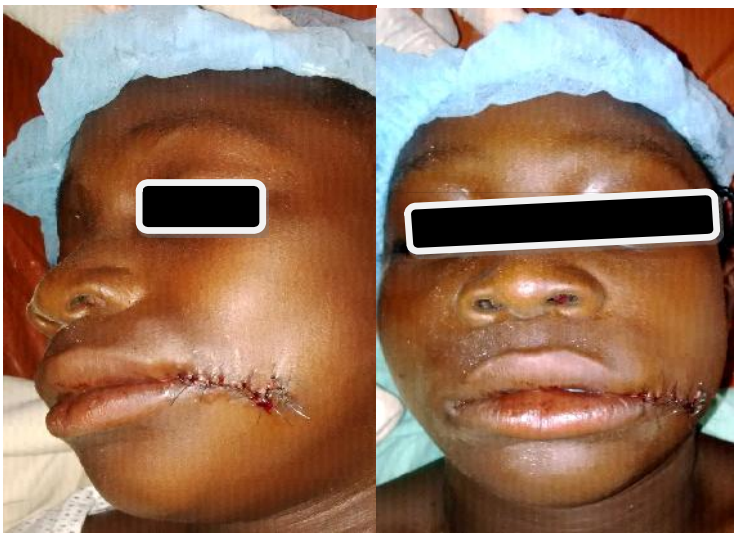

Fig. 2: Immediate post-op facial pictures of the girl.

Fig. 3: The lateral and frontal views of the girl at nine (9) months post-op.

Masseter muscle. However, an abnormally wide mouth opening was present (Figure 1- pre-op photo). No evidence of any associated deformity nor associated syndromes was noticed, hence a diagnosis of Isolated Bilateral Tessier Number 7 cleft (Grade I) was made based on the physical examination findings [9].

The patient and parents were then counseled about the defect. The patient was subsequently referred to a specialist hospital in the capital city of Ibadan, southwest Nigeria for surgical repair of the deformity. The option of repair was readily and happily accepted not only because it would alleviate the attending challenges, but also because it would be at no cost to the parents since it was sponsored by a non-governmental organization (Smile Train). The surgery was successfully carried out (Figure 2- immediate post-op photo). She was reviewed at 1 week, 1 month, 3 months, 6 months, and 9 months post-op, and the reviews were uneventful. At the latest review (Figure 3 – 9 months post-op photo), she was cheerful and reported that she was happy at school. The parents were also satisfied with the outcome of the surgery and expressed their satisfaction with her appearance and newfound enthusiasm for school.

DISCUSSION

This report described a girl in a rural area in Nigeria who was denied access to care for bilateral congenital macrostomia for nine years because the healthcare personnel that she came in contact with up to that point did not recognize congenital macrostomia. This highlights a possible gap in the knowledge of healthcare personnel in rural areas about congenital macrostomia and possibly other rarer facial clefts especially when they are not the severe form. It was disheartening to find that only 5 (less than 20%) of the 26 cases of isolated congenital macrostomia reported in the literature presented for care in the first year of life [1,5,10-13].

The reasons proffered for this late presentation include the fear of stigmatization[10], lack of awareness, poverty, cultural beliefs, lack of access to appropriate health facilities [6,7,14], and poor referral systems [14]. The case of this nine-year-old girl is therefore significant because it highlights a never before reported aspect of "ignorance". The ignorance of healthcare workers. Previous reports show that healthcare workers often miss hidden defects such as clefts of the soft palate [8], but the cleft we report was on the face.

Unfortunately, due to the delay, she was already experiencing some of the reported social complications like "social anxiety"[11]. This was evidenced from the report by her mother that she was becoming increasingly "shy and withdrawn" especially when she is with her peers. All the other associated negative consequences that she was reported to have passed through, like the loss of enthusiasm to go to school, leading to change of schools, poor academic performance, and low self-esteem show that even when the facial cleft did not limit function such as eating and talking, it has the potential of causing devastating social problems if not repaired early enough.

Clefts are managed surgically by specialists in urban areas at prohibitive costs. However, organizations like

Smile Train have provided financial access to cleft services for over ten years [11], and it is therefore tragic that this girl was denied access to treatment for so long.

CONCLUSION

This case report presents a rare presentation of delayed isolated congenital bilateral macrostomia because of healthcare workers failure to diagnose. Therefore, further studies are needed to objectively assess the knowledge of healthcare workers on congenital birth defects. Furthermore**,** continuous medical education for all cadres of healthcare workers on the identification, diagnosis and prompt referral of patients with congenital birth defects should be instituted.

CONFLICT OF INTEREST

The authors declare no conflict of interest exists.

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MOLECULAR GENETICS OF CLEFT LIP AND PALATE: A REVIEW

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INTRODUCTION

Cleft lip with or without cleft palate (CLP) is a common congenital disability. They exist either in combination with one or more other anomalies (syndromic cleft) or in isolation (non-syndromic cleft). Non-syndromic CL/P is more common as it is present in about 70% of cases, out of which 80% are sporadic, and 20% are familial.[1] CLP which is commoner in males, occurs in 1 out of 300 to 2500 births, while isolated cleft palate (CP) which occurs more frequently in females, occurs in 1 out of 1500 births[2,3]. People with cleft lip and palate often require multidisciplinary care involving several surgical repairs commencing in the first year of life, orthodontic interventions for malocclusion, speech therapy, treatment of recurrent middle ear infections, and psychological interventions. These have been noted to contribute a significant burden to the patient, family, and society at large. Thus, an intense effort has been made to unravel its aetiology, which would be important in genetic counselling, risk prediction, and overall prevention of cleft lip and palate[4].

Aetiology of Cleft Lip and Palate

Generally, cleft lip and palate is thought to result from interactions between genetic and environmental factors. Substantial pieces of evidence for the former have arisen from family, and twin studies which revealed high rates of familial aggregation and increased concordance rates in monozygous twins, compared with dizygous twins[5]. For instance, studies by Sivertsen *et al.*[6] and Grosen *et al.*[7] showed that cleft palate has a relative risk of occurrence which is 15 to 56 times higher among first degree relatives. Although environmental factors such as maternal use of alcohol, cigarette and antiepileptic drugs have been identified as risk factors for CLP, recent studies have now revealed important genes either acting alone or within gene networks. Such cases are found as parts of Mendelian monogenic syndromes, chromosomal abnormalities, or otherwise unknown genetic syndromes[8]. These identified genetic risk factors have shed more light on normal craniofacial development with some also implicated in non-syndromic CL/P. As an example of gene-environment interaction, Shaw *et al.*[9] demonstrated a 3 to 8 fold increase in CLP in babies with lack of multivitamins in the first trimester of pregnancy and the TaqI C2 mutation in the *Tgfa* gene. The same mutation was shown to raise the risk of CLP by 6 to 8 times when co-existent with maternal smoking[10], while Jugessur *et al.*[11] found that combined mutations of the *Tgfa* and *Msx1* genes cause an almost ten-fold increase in cleft lip and palate risk as an evidence of gene-gene interaction.

Genetic Regulation of Craniofacial Development

Craniofacial development is a complex event involving several transcription factors and molecular signals. Disruptions in the network of these proteins lead to the development of facial clefts. The diversity in the functions of these genes and their products shows the susceptibility of the craniofacial developmental pathways to form clefts[4].

Facial development in humans begins in the fourth week of intrauterine life with the migration of cranial neural crest cells (CNC) from the rostral part of the neural tube to form the facial primordia and secondary palate[8]. Genes such as *Tgf*b2, *Hoxa2*, *Gli2*, and *Gli3* have been identified to play a role in CNC migration, mutations of which have been shown to contribute to cleft lip and palate in mice[12-14]. Palatal shelves are subsequently derived from the secondary palate and undergo elevation to become horizontally apposed in the midline. Failure of apposition has been linked with mutations in the genes *Msx1*, *Pax9*and *Lhx8* leading to CP[15-17]. Furthermore, epithelial-mesenchymal interactions mediated by interrelated gene networks – sonic hedgehog (*Shh*), bone morphogenetic proteins

Table1: Summary of molecular genetic mechanisms in syndromic cleft lip and palate

Syndrome	Inheritance	Gene	Locus	Function	Gene also implicated in non-syndromic CL/P	References
Cleft lip/palate ectodermal dysplasia syndrome (CLPED)	AR	*Pvrl1*	11q23.3	Encodes nectin-1 which plays a role in cell adhesion	Yes	28-30
Acrofrontofacionasal dysostosis syndrome	AR	*Nbas*	2p24	Skeletal morphogenesis, mediating Golgi-to-endoplasmic reticulum retrograde traffic.	-	31
Popliteal pterygium syndrome (PPS)	AD	*Irf6*	1q32	Mediates TGFβ3 activity in palatal fusion	Yes	25,27
Van der Woude (VDW) syndrome	AD	*Irf6*	1q32	Mediates TGFβ3 activity in palatal fusion	Yes	25,27
Rapp-Hodgkin syndrome (RHS)	AD	*Tp63*	3q28	Apoptosis. Also in establishment of enhancers needed for expression of genes important in craniofacial development such as *Irf6*	Yes	32-24
Roberts syndrome	AR	*Esco2*	8p21	Acetyltransferase activity necessary for sister chromatid cohesion needed for cell proliferation	-	35,36
Hay-Wells syndrome	AD	*Tp63*	3q28	As for RHS	Yes	37
Blepharocheilodontic syndrome	AD	*Cdh1*	16q22	Cell adhesion molecule involved in the maintenance of epithelial cell morphology during embryonic development	-	38-39
Thurston syndrome	AR	*Ddx59*	1q32	Ciliary SHH signaling	-	40
Uvealcoloboma-cleft lip and palate-intellectual disability syndrome	AD	*Yap1*	11q22	Activation of transcription factors important for apoptosis such as p73	-	41,42
Varadi-Papp syndrome	AR	*Cplane1*	5p13	Ciliary SHH signaling	-	43,44
Cleft palate, cardiac defects and mental retardation (CPCMR)	AD	*Meis2*	15q14	Palatal fusion. Repression of SHH/FGF feedback loop.	-	45,46
Vici syndrome	AR	*Epg5*	18q12	Autophagy during embryogenesis	-	47
Ectrodactyly, ectodermal dysplasia, and cleft lip/palate syndrome 3 (EEC3)	AD	*Tp63*	3q28	As for RHS	Yes	48
Branchiooculofacial syndrome (BOFS)	AD	*Tfap2a*	6p24	Transcription activation necessary for formation of neural crest cells during embryogenesis	-	49-51
Cleft palate with ankyloglossia, X-linked (CPX)	X-linked	*Tbx22*	Xq21	Repressor of transcription, with an important role in horizontal elevation of palatal shelves	-	52,53
Holoprosencephaly 2	AD	*Six3*	2p21	Regulation of SHH expression	-	54,55
Opitz-Frias syndrome or (Opitz GBBB syndrome type II)	AD	*Specc1l*	22q11.23	Regulates microtubule and actin organization for proper cell adhesion and migration	-	56,57
Simpson-Golabi-Behmel syndrome type 1	XLR	*Gpc3*	Xq26.2	Regulation of SHH, FGF, and BMP activities	-	58,59
Oral-facial-digital syndrome 1	XLD	*Ofd1*	Xp22.2	Regulation of microtubule function	-	60,61
Gorlin-Goltz syndrome	AD	*Ptch1, Ptch 2, Sufu*	9q22, 1p32, 10q24	Regulation of SHH signaling	-	62-64
Waardenburg syndrome, type 1	AD	*Pax3*	2q36	Transcription factor necessary for skeletal muscle formation	-	65,66
CHARGE syndrome	AD	*Chd7*	8q12	Transcription factor necessary for neural crest cell migration		67,68
DiGeorge syndrome	AD	*Tbx1*	22q11.21	Regulator of BMP signaling	-	69

(*Bmp*), and fibroblast growth factors (*Fgf*) – are essential in normal palatal development[18]. For example, expression of *Shh* in the palatal epithelium is regulated by *Bmp4* in the mesenchyme. *Shh* then regulates *Bmp2* in the mesenchyme, which is essential for mesenchymal proliferation[19,20]. A positive feedback loop also exists

Table 2: Summary of molecular genetic mechanisms in non-syndromic cleft lip and palate

Non-syndromic CLP	Inheritance	Gene	Locus	Function	References
Orofacial cleft 1	AD	*Ofc1*	6p24	-	71
Orofacial cleft 5	-	*Msx1*	4p16	Homeobox gene controlling expression of downstream genes, involved in patterning of the face and palatal midline apposition.	72-73
Orofacial cleft 6	AD	*Irf6*	1q32	As in VDW and PPS	74
Orofacial cleft 8	-	*Tp63*	3q28	Apoptosis. Also in establishment of enhancers needed for expression of genes important in craniofacial development such as *Irf6*	32-34
Orofacial cleft 11	-	*Bmp4*	14q22	Encodes BMP4 which up-regulates MSX1 and SHH for palatal fusion.	19,75,76

between the fibroblast growth factor *Fgf10* and *Shh* expression in the palatal mesenchyme and epithelium, respectively[19,21]. Also, the homeobox gene *Msx1* further modulates the expression of the genes *Bmp4, Shh,* and *Bmp2* above. At week 12, development of the palate is completed in humans.

Genetic Analysis of Cleft Lip and Palate

Almost 500 syndromes have been identified in syndromic cleft lip and palate[22], although not all have been linked to specific genes. Cohen[23] published a review of 154 of these syndromes with their clinical features to aid diagnosis. However, recent molecular genetic analysis has identified the loci of these mutations and functions of the implicated genes. For example, popliteal pterygium and Van der Woude syndromes, the latter being the most common cause of syndromic cleft lip and palate[24], are both autosomal dominant conditions secondary to mutations in the interferon regulatory factor-6 (*Irf6*) gene on chromosome 1q32[25]. Interestingly, mutations in *Irf6* have also been found in non-syndromic cleft lip and palate[26]. The protein product IRF6 is now known to be a transcription factor up-regulated by TGFb3 protein in palatal fusion during embryonic development in humans[27]. In syndromic cleft lip and palate, a given gene may be affected by several different mutations, which accounts for the varied phenotypes that may be observed[4]. For instance, mutations of the C-terminus of the protein TP63 results in cleft lip or cleft palate, whereas mutations of the conserved DNA binding region at the N-terminus results in cleft lip and palate[8].

We conducted a search on the Online Mendelian Inheritance in Man (OMIM) database with keywords 'cleft lip' and 'cleft palate' which produced over 1500 results. Table 1 summarizes genes implicated in some syndromic cleft lip and palate.

Detection of genes in non-syndromic cleft lip and palate (summarized in Table 2) has been done in recent decades by various methods including linkage analysis, candidate gene approach, and genome-wide association studies (GWAS), with the discovery of shared genetic lesions between syndromic and non-syndromic cleft lip and palate[70].

CONCLUSION

There has been some success in elucidating the genetic basis of cleft lip and palate with the identification of numerous susceptibility genes. However, this number is bound to increase, revealing the overall genetic complexity of craniofacial clefts. Given the role of environmental factors, studies that further explore feto-maternal genetics together with exposure to different environmental factors could aid in the development of a weighted genetic risk assessment for cleft lip and palate which in turn would better inform genetic counselling and prescription of preventive measures.

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OROFACIAL CLEFTS AND CARDIOVASCULAR RISK AND DISEASES: THE CAUSAL RELATIONSHIP AND ASSOCIATIONS

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ABSTRACT

There is a complex interplay between orofacial clefts (OFCs) or cleft of the lip and palate and cardiovascular risk factors and cardiac diseases. The presence of maternal cardiovascular risk factors serves as a potent predisposing factor to the development of OFCs during foetal development in addition to the fact that various congenital anomalies are associated with OFCs either in syndromic or non-syndrome relationship. This article narratively explores this complex interplay, which is not uncommon.

Keywords: Cleft lip and palate, Cardiovascular diseases, Obesity, Hypertension, Natal, Prenatal

INTRODUCTION

Cardiovascular diseases (CVDs) are on the rise globally and cause one-third of deaths worldwide, with 80% of such mortality in developing countries.[1] The burden of CVD is primarily driven by dyslipidemia, hypertension, obesity, diabetes, physical inactivity, poor diet, and smoking.[1] The CVDs burden is anticipated to burgeon in the coming years.[2]

Orofacial clefts (OFCs) or cleft lip and palate defects are the commonest congenital malformation of the head & neck and one of the most frequent congenital disabilities globally.[3,4] The disorder is of enormous medical, surgical, or cosmetic importance in addition to the colossal health care cost. They can occur as syndromic or non-syndromic forms with the latter being the more common.[3, 4]

The estimated prevalence of OFCs in Nigeria is about 0.5:1000 live births.[5-7] It occurs in about 1 in 700 live births globally while it accounted for 3,800 deaths globally in 2017 or 3.8 per 100,000 person death from the Global Burden of Disease (GBD) 2017 estimates.[8,9] Furthermore, the highest prevalence at birth of OFCs is among the native American and Asian (1 in 500 live births), while the lowest prevalence is among the populations of African descent, with approximately 1 in 2,500 live births.[10]

The usual male: female ratio was 2:1 in the various OFC variants such as cleft lip and/or cleft lip and palate.[9] The Nigerian craniofacial anomalies study, Nigeria CRAN, showed a male: female ratio of 1.19:1 of all OFCs.[7]

Furthermore, cardiovascular anomalies are commonly associated with OFCs and these associated cardiovascular defects may require lifelong follow up after corrective surgery for OFCs.[11] Cardiovascular diseases or cardiovascular risk factors and oro-facial defects interplay may be a casual relation or a mere association.

Pre-conceptional, as well as conceptional maternal cardiovascular risk factors (CRFs) may predispose to the development of cleft palate in the offspring. Such increased causality or the CRFs interlink with OFCs may be the strong link to the possibility of reversal of the epidemiological burden for OFCs or just the continuous presence of cases as CVDs/CRFs are on the increase. The key CRFs linked to OFCs includes alcohol use, obesity and smoking with obesity and smoking each having 6% population attributable risk factors.[11] Cardiovascular conditions in the form of congenital heart diseases usually present alongside this condition in newborns.

Cleft lip and/or cleft palate may arise in isolation or association with a syndrome and CRFs, and Congenital heart diseases(CHDs) are associated with both syndromic and non-syndromic OFCs although commoner in the former.[4, 12]

Primordial: Predisposing Cardiovascular Risk Factors

The development of OFCs in offspring is associated with the presence of pre-conceptional maternal cardiovascular risk factors particularly obesity, dietary patterns, maternal hypertension, maternal diabetes mellitus and smoking(passive and non-passive) (See Table 1).[10, 11, 13]

A systematic review and meta-analysis of a collection of data spanning forty-three years from North America, Europe and Australia revealed a significant association between maternal obesity, as measured by the Body Mass Index (BMI), and having a pregnancy complicated by cleft palate.[14] Maternal obesity was noted to lead to the development of foetal cleft palate (OR, 1.23; 95% CI, 1.03-1.47; P=.02) or cleft lip and

Table 1: Table highlighting studies demonstrating the link of cardiovascular risk factors and OFCs

Study	Authors	Year of publication	Type of study	Country /countries	Sample size	Key cardio-vascular risk factors
Association Between Maternal Diabetes Mellitus and Newborn Oral Cleft	Spilson *et al.* [16]	2001	Case control	United States of America	6621 (2,207 cases, 4,414 controls)	Maternal pre-gestational diabetes mellitus
Diabetes mellitus and birth defects	Correa *et al.* [17]	2008	Case-control	United States of America	17,925 (13,030 cases, 4,895 controls)	Maternal pre-gestational diabetes mellitus
Native American Oral clefts, consanguinity, parental tobacco and alcohol use: a case-control study in Rio de Janeiro, Brazil	Leite *et al.* [40]	2009	Case-control	Brazil	822 (274 cases, 548 controls)	Maternal cigarette smoking, Maternal Alcohol Abuse
Risk factors for oral clefts: a population-based case-control study in Shenyang, China	Wang *et al.* [41]	2009	Case-control	China	586 cases 1172 control mothers	Maternal diet
Maternal Factors and Disparities Associated with Oral Clefts	Lebby *et al.* [30]	2010	Cohort	United States of America	3,23(Case 1654 Control 1654)	Maternal cigarette smoking, Pregnancy-associated hypertension
Increased risk of orofacial clefts associated with maternal obesity: a case-control study and Monte Carlo-based bias analysis	Stott-Miller *et al.* [42]	2010	Case-control	United States of America	20,223 (2,153 cases, 18,070 controls)	Maternal pre-pregnancy obesity
Maternal malnutrition, environmental exposure during pregnancy and the risk of nonsyndromic orofacial clefts	Jia *et al.* [43]	2011	Case-Control	China	934 (537 cases, 221 controls)	Maternal (passive) smoking
Orofacial Clefts and Risk Factors in Tehran, Iran: A Case-Control Study	Taghavi *et al.* [44]	2012	Case-control	Saudi-Arabia	600 (300 cases, 300 controls)	Maternal cigarette passive smoking
Maternal Snuff Use and Smoking and the Risk of Oral Cleft Malformations - A Population-Based Cohort Study	Gunnerbeck *et al.* [45]	2014	Registry survey	Sweden	975,866(1761 cases of oral clefts)	Maternal snuff use, Maternal cigarette smoking
Association between maternal smoking, gender, and cleft lip and palate	Martelli *et al.* [46]	2015	Case-control	Brazil	1519 (843 cases, 676 controls)	Maternal smoking
Maternal Risk Factors Associated with the Development of Cleft Lip and Cleft Palate in Mexico: A Case-Control Study	Angulo-Castro *et al.* [47]	2017	Case-control	Mexico	48 (24 cases, 24 controls)	Maternal cigarette smoking, Maternal Alcohol Abuse
Maternal underweight and obesity and risk of orofacial clefts in a large international consortium of population-based studies Hebah	Kutbi *et al.* [13]	2017	Population -based	Northern Europe, United States of America	15,535 (4943 cases and 10,592 controls)	Maternal pre-pregnancy obesity

palate (OR, 1.20; 95% CI, 1.03-1.40;P=.02)[14] Other studies also established the predisposition of maternal diabetes mellitus to OFCs. A large study over a ten-year period, among Swedish women, found a similar result even after adjustment for year of birth, parity, maternal age, and maternal smoking.[15] In this case, however, the presence of another major co-existing anomaly alongside cleft palate showed a stronger association with obesity.[15] Although the reason for this association is unknown, it has been attributed to undetected type 2 diabetes.[15] (Table 1).[16, 17]

Maternal western dietary pattern during the preconception period has also been shown to be a risk factor. A case-control study among a female Dutch population showed that diets rich in meat, pizza, potatoes, legumes, French fries, and low in fruits were shown to correlate with cleft palate in the offspring when compared with diets associated with high intake of fish, vegetables, garlic and nuts.[18] This is unconnected with low maternal serum levels of vitamin B12 and folic acid associated such diet.[18]

[12, 19, 20], which reduces homocysteine level, although data on the use of folic acid as supplement in prevention of OFC is sparse.[12] However, some studies have revealed no association, while others have been inconclusive.[12, 21-23]. Further studies are required to associate hyperhomocysteinamia with coexistence of cardiac diseases and OFC.

Pregestational diabetes mellitus is also a well-known risk factor for cleft palate in the offspring.[24, 25] In a United States Natality database, a population-based case-control study showed that diabetic mothers were almost 1.4 times more likely to develop cleft palate than non-diabetic mothers.[15, 16, 26]

Passive and active cigarette smoking in pregnancy has been associated with the development of cleft palate. The records of 3,891,494 live births from the 1996 U.S. Natality database showed this clear predisposition to OFCs using cases-controls design of maternal smoking even after adjustment of confounding

Table 2: OFCs Syndromes and some congenital cardiac anomalies

Syndromes	Aetiology	Associated cardiovascular disorder	Present congenital heart diseases associations
Loeys–Dietz syndrome[39, 48]	Genetic- autosomal dominant. Mutation in TGFBR1, TGFBR2, SMAD3, TGFB2, and TGFB3	Aortic aneurysm, Aortic dissection, aortic root dilation, arterial tortuosity, mitral valve prolapse	patent ductus arteriosus and atrial septal defect
Malpuech facial clefting syndrome[49]	Genetic autosomal recessive COLLEC11 and MASP1 genes mutation		patent ductus arteriosus and atrial & ventricular septal defect
Treacher Collins syndrome or mandibulofacial dysostosis or Franceschetti-Zwahlen-Klein syndrome[50, 51]	Genetic- autosomal dominant. TCOF1, POLR1C, or POLR1D mutation		Sinus of Valsalva aneurysm
Oculoauriculovertebral spectrum (Goldenhar syndrome)[52]	Autosomal dominant, sporadic		Ventricular septal defect, atrial septal defect, pulmonary stenosis, tetralogy of Fallot
Oculofaciocardiodental syndrome[53]	X-linked dominant		atrial/ventricular septal defect
CHARGE syndrome[54]	Mutation of CHD7 gene		Tetralogy of Fallot, double outlet right ventricle with atrioventricular canal, patent ductus arteriosus, ventricular septal defect and atrial septal defect with or without cleft mitral valve

Hyperhomocysteinemia, which is associated with low levels of folic acid, is a known risk factor for heart disease.[18] Similarly, studies have demonstrated an association between hyperhomocysteinemia and cleft palate[18], while many studies have demonstrated the beneficial effect of maternal folic acid supplementation

variables.[27] There was a demonstrable dose-response smoking risk for OFCs in first trimester especially with combined defect of both lips and palate rather than solitary defects.[27-29] The link with alcohol intake, particularly in the first trimester, may not be unconnected with retinoic acid production.[28, 29] Unlike

the smoking exposure, the association of alcohol intake with OFC is not dose responsive.[28]

Generally, various cardiovascular risk factors are inter-related. Western dietary patterns could predispose to obesity, and obesity may be an early pointer to diabetes mellitus. Therefore, there may be an underlying, undiagnosed impaired glucose tolerance in these populations that were studied, which most studies did not take into account. While some studies identified the role of maternal alcohol intake during pregnancy on OFCs, many are frosted by small sample sizes. Also implicated are hypertension and the usage of antihypertensive drugs[10, 30]

Finally, cardiovascular diseases appear to be more common in the cleft palate than cleft lip,[23,27] but more studies are required to confirm these.

Associations of Orofacial Defects and Cardiovascular Diseases

Congenital heart disease is the most frequent associated anomaly in patients with cleft palate as shown in various studies[3, 6, 31], with atrial septal defect[31, 32] often being cited. Others include patent ductus arteriosus, pulmonary stenosis, tetralogy of Fallot and ventricular septal defect.[33] There is a wide variation of the incidence and prevalence of congenital heart disease among neonates with cleft palate.[7,34] The risk of having a congenital heart disease have been reported to be 23 times that of the general population.[33]

Cardiovascular disease and cleft palate can be present in conditions that can affect multiple organ systems, for example, in chromosomal defects like Edward syndrome (Trisomy 18) and Patau syndrome (Trisomy 13) particularly in the non-isolated cleft palate (Table 3).[25] They can both be significant components in sequences and syndromes, notably Velocardiofacial syndrome,[4, 35] DiGeorge syndrome,[35] and rarely, Van der Woude syndrome.[4] Some genetic mutations like that in *TGFBR1* or *TGFBR2* genes have also been reported to cause combined cleft palate and cardiovascular disease (Table 3).[36]

Orofacial Defects, Paediatric Cardiologist, and the Adult Cardiologist

Even though an affected child may benefit form repair of the defect within a year of birth, such care may not be available in a resource-poor environment like Nigeria especially in situation of non-assess to free treatment intervention such as SMILE programme.[37,38] Furthermore, it may come with a severe attendant implication which is beyond the primary care specialist that may have initially intervened. Those issues associated with OFCs may not be the initial interest of the parents and caregivers, rather the orofacial defect that pose a severe cosmetic problem. Some of the cardiovascular diseases may linger into adulthood with attendant mortality and morbidity which undermine the quality of life. For example, in Loeys-Dietz Syndrome, the OFC may be repaired while leaving a risk of widespread and aggressive arterial aneurysms later in childhood or adulthood.[39]

Table 3: Orofacial clefts and chromosomal anomalies

Chromosomal anomaly	Aetiology	Present congenital heart diseases associations
Velocardiofacial syndrome[55]/DiGeorge syndrome[56] or Chromosome 22q11.2 deletion syndrome[56]	Genetic-autosomal dominant. Deletion in Chromosome 22q11	Interrupted aortic arch type B, truncus arteriosus, tetralogy of Fallot, pulmonary atresia with ventricular septal defect, pulmonary atresia with a ventricular septal defect
Edward syndrome[57]	Sporadic, Trisomy 18	Ventricular septal defect, Patent ductus arteriosus, transposition of great arteries, pulmonary atresia
Patau syndrome[58]	Sporadic, Trisomy 13	Ventricular septal defect, atrial septal defect, Patent ductus arteriosus

Therefore, the excellent prognosis is underpinned not only by the initial management but also care and regular follow-up by an experienced interdisciplinary team from infancy until adulthood.

CONCLUSION

Cardiovascular diseases and cleft palate interrelate in various ways; although the mechanisms are unclear, more studies are required to reveal more associations. There is currently enough evidence that maternal cardiovascular risk factors are potent risk factors for foetal OFCs development in addition to the fact that many congenital heart diseases are associated with OFCs.

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ORTHODONTIC NEEDS OF PATIENTS WITH CLEFT LIP AND PALATE IN ENUGU, FIVE YEARS POST REPAIR

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ABSTRACT

Background: **Orthodontists play an integral role in the management of cleft lip and palate anomaly. This study looks at the frequency of anomalies amenable to orthodontics in patients who have had surgery and the effect of early or late surgical intervention.**

Methodology: **Patients aged 0-5 years with cleft of the lip and/or palate who were operated on by the plastic surgeon at the Good Shepherd Specialist Hospital, Enugu between 1st July 2011 and 30th June 2014, were recalled after a minimum of five years post-surgery and examined to determine the absence or presence of dental anomalies, amenable to orthodontic treatment, which have arisen since surgical repair. Descriptive statistics and t-test were used for data analysis and significance was at 0.05.**

Results: **Thirty-one children were operated upon in the period under review. Seventeen had timely (three months or less) lip repair. Seven had timely palate repair (18 months or less). Thirteen patients were successfully recalled, 12 had cleft lip repair while one had cleft palate repair. Repair was timely in 10 (83.3%) of the 12 that had lip repair with a mean frequency of four dental anomalies, while the two (16.7%) that had late repair had a mean frequency of five dental anomalies and this was not statistically significant (P value=0.711).**

The only isolated cleft palate patient successfully recalled had a late repair. All 13 patients had at least four dental anomalies amenable to orthodontics. Hypoplastic maxilla were the most commonly occurring (eight patients, 61.54%) dental anomaly amenable to orthodontic treatment. None of the patients had a clinically visible supernumerary tooth. Out of 13 patients reviewed, sis were males with a mean frequency of four dental anomalies while seven were females, also with a mean frequency of four dental anomalies. This was not significant (P-value=0.553).

Conclusion: **There is need for the long term Orthodontic follow up of cleft lip and palate patients. The orthodontic management of dental anomaly should, therefore, be central in the planning and treatment of patients with cleft lip and palate.**

Keywords: Cleft lip and palate, Orthodontics

INTRODUCTION

Cleft lip and palate is the 2nd most frequent congenital craniofacial deformity with a mean prevalence in Europe of between 1:500 and 1:700.[1] A lower value is, however, reported among Africans.[2]

A study in Enugu, Nigeria reported an incidence of 1:968[3]. Surgical correction is central to the current team approach to cleft management. An ideal surgical design should proficiently restore functions including speech, mastication, breathing and aesthetics, while at the same time preserving the normal dentofacial growth potential in the involved area. However, surgical repair of cleft lip and palate is fraught with challenges, including those that can be handled by orthodontics. Three principal reasons have been highlighted for carrying out orthodontic treatment in anybody including cleft lip and palate patients:[4] to improve the dento-facial appearance, correct occlusal relationship and to eliminate malocclusions that could damage the long-term health of the teeth and periodontium.

Different cleft lip and palate centers and surgeons around the world have suggested many different treatment protocols including timing of surgical intervention; each claiming superiority of its own approach. In all instances, time is usually the judge in

proving whether the approaches were truly positive on the dentition, jaw growth or other facial structures.[5] It is known that some cleft orthodontic problems are directly related to the cleft deformity itself, such as discontinuity of the alveolar process, missing and malformed teeth, whereas other aspects of the malocclusion are secondary to the surgical intervention performed to repair the lip, nose, alveolar and palatal defects.[5] There is also the issue of inappropriate timing of surgical intervention which may also contribute to the severity of these changes. Too early surgical interventions have been reported to impair maxillary growth, whereas with the converse, teeth eruption and Maxillary growth could be permanently endangered.[6] In Good Shepherd Specialist Hospital, Enugu where the current study was based, the Mohler's modification of Millard technique (for unilateral) and Mulliken's repair (for bilateral) is in common use for lip repair while the intravelarveloplasty is used for palate repair.

OBJECTIVES

To determine the dental anomalies present after a minimum of 5 years in patients surgically treated for cleft lip and palate.

METHODOLOGY

Sequential non-syndromic patients who were operated on, not less than five years ago by the plastic surgeon at the Good Shepherd Specialist Hospital, Enugu from 1st July 2011 to 30th June 2014 and aged 0-5 years as at the time of cleft lip and/or palate repair were selected for review.

From their hospital records they were classified into those who had timely repair and those who did not. Timely lip repair was taken to be repair carried out within three months of birth or less[7] while timely palate repair was taken to be within 18 months of birth or less.[8]

Attempt was made via telephone to reach the parents/guardians of these 31 sequential patients. A recall date and time was scheduled for each patient for re-examination.

On presentation, each presenting patient's case note was brought out from the hospital's record unit. The patients were then examined clinically using cheek retractors under bright light by a single examiner and the features found were recorded. Not more than five patients were recalled per day to prevent examiner's fatigue.

RESULTS

Thirty-one children aged 0-5 years were operated in the period under review. Seventeen had timely lip repair. Seven had timely palate repair. Of the 31 children, only 13 were successfully recalled. Two were said to have died, nine had either relocated out of Enugu town or lived far away and so could not make the appointment, while the remaining seven were not traceable.

Table 1: Timing of lip repair

Timing of lip repair among 12 participants	Number of patients	Mean frequency of dental anomalies
Timely	10 (83.3%)	4
Late	2 (16.7%)	5

Of the successfully recalled 13, 12 had cleft lip repair while one had cleft palate repair. Repair was timely in 10 (83.3%) of the 12 that had lip repair with a mean frequency of four dental anomalies, while the two (16.7%) that had late repair had a mean frequency of five dental anomalies and this was not statistically significant (P value=0.711).

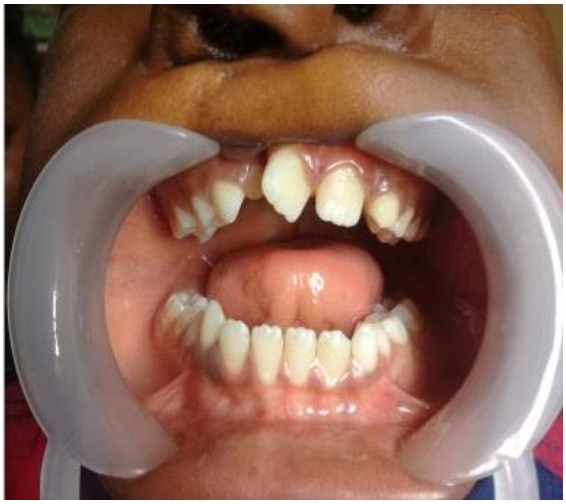

Figure 1: Patient with dental anomaly

In the single patient who had cleft palate, repair was late with a mean of four anomalies. All 13 patients had at least four dental anomalies treatable by orthodontics (Table 1, Figures 1). Hypoplastic maxilla was the most commonly occurring (eight patients, 61.54%) dental anomaly treatable by orthodontic treatment (Table 2).

Table 2: Anomalies seen in the patients

Anomaly	Frequency
Anterior crossbite	5
Anterior openbite	4
Displaced teeth	5
Edge to edge occlusion	2

None of the patients had a clinically visible supernumerary tooth. Out of 13 patients reviewed, six were males with a mean frequency of four dental anomalies while seven were females, also with a mean frequency of four dental anomalies. This was not significant (P-value=0.553).

DISCUSSION

It is generally accepted among clinicians that the management of cleft lip/palate requires the input of multiple specialists[9] including orthodontists (and other dental specialists), because of its usual association and presentation with dentofacial anomalies.[10]

To assess the dentofacial anomalies in this study, 31 patients aged 0-5 years previously operated on were intended for review. Seven (23%) of them had late cleft lip and/or palate repair. A previous study[7] in Enugu with four hundred and ninety-three participants had reported a higher percentage (91.69%) for late repairs. The reason for the relatively small percentage in the present study may be due to the fact that outreach surgeries where older patients are seen more frequently were done but not in our center in the period of the study.

Looking at severity from the point of view of number of anomalies associated with the condition, this study demonstrated an increase in the number of dental anomalies in late repair since there was slightly more number of anomalies seen in the patients who had late repair. This agrees with another study[6] which reported greater severity if repair was "too late".

The dental anomalies, seen in the patients were anterior crossbite, anterior open-bite, displaced teeth, ectopic eruption, edge to edge occlusion, hypoplastic maxilla, impacted teeth, rotated teeth and upper midline shift. Each of the 13 patients had at least four dental anomalies treatable by orthodontics. Indicating more than a 100% chance of a dental anomaly in a cleft patient. This was similar to the finding by Akcam et al[13] in which 96.7% of the participants had a dental anomaly. This, however, largely contrasts with the report of two separate studies[14,15] in South America and Europe with a prevalence of 11.7% and 26% respectively. The reason for this large difference may be attributed to greater awareness and more availability of treatment options than there is in Nigeria.

Hypoplastic maxilla was the most commonly seen anomaly treatable by orthodontics. Souchois et al[14], in their panoramic radiograph assisted study, however, reported that the most prevalent anomalies were missing and supernumerary teeth, occurring at a rate of 4.63% and 3.31%, respectively. No supernumerary teeth were seen in the present study and this maybe as a result of non-use of panoramic radiograph in the assessment.

This difference in gender for those recalled was not statistically significant and this was similar to the study by Akcam et al[13], in which there was no difference in the number of anomalies between males and females.

CONCLUSION

Nearly all cleft lip and palate patients have multiple dental anomalies of which some level of prevention and treatment can be carried out by the orthodontist. There is, therefore a definite need for orthodontic treatment in these patients. The role of the Orthodontist should therefore, be central when planning treatment for persons with cleft lip and palate.

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OUTCOMES OF CLEFT PALATE SURGERIES AT THE NATIONAL ORTHOPAEDIC HOSPITAL, ENUGU, NIGERIA: NOVEMBER 2008 – NOVEMBER 2013

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ABSTRACT

Background: **Despite an increase in the number of palatoplasty procedures at the National Orthopaedic Hospital Enugu (NOHE) sequel to a partnership with Smile Train, no reports on subsequent outcomes have been published. We investigated the speech outcomes and rates of fistula formation, the relationship between introduction of solids and incidence of post-operative oronasal fistulae and the benefits of post-operative honey licks.**

Objective: **To determine the outcome of palatal repairs performed at our center in relation to the timing and nature of post-operative feeds.**

Method: **This was a cohort study of patients who had palatoplasty over a five-year period and were subsequently followed up for a maximum period of 9 years. The patient's present condition, timing of first feeds, onset of solid feeds, honey licks, frequency of wound dehiscence, fistula formation, and speech outcomes were assessed. The evaluation for a fistula was made from two weeks after the surgery by a senior resident in plastic surgery. Analysis was done using SPSS version 21.0 and p value set at <0.05.**

Results: **A total of 115 surgeries: 90 primary cleft palate repairs, 6 combined cleft lip and palate surgeries and 19 secondary cleft palate repairs were done. Male to female ratio was 1:1.3. Age range of patients was 6 weeks to 36 years.**

Timing of introduction of solid meals significantly affected incidence of repair breakdown; and 58% had normal to near-normal speech.

Conclusions: **Licking honey was associated with fewer wound breakdowns. Early return to solid feeds is associated with a higher incidence of wound breakdown following palate repair.**

Keywords: Palatoplasty; Outcomes; Fistula; Speech

INTRODUCTION

Cleft lip and palate is the most common major craniofacial anomaly that presents to the plastic surgeon.[1] Cleft surgery has been on the increase at the National Orthopaedic Hospital Enugu (NOHE) since onset of partnership with the SmileTrain charity in 2006. Data shows an increase in palate repairs but no reports on outcomes of palate repair from NOHE since the inception of this partnership. Increasing volume is expected to translate to better results as the surgeon's experience is an important variable in palate surgery among fit patients. Speech and fistula formation are the most important indicators of success in palate repair. We investigated these outcomes in a nine-year period, as well as the relationship between timing of post-operative introduction of solids and development of oronasal fistulae. We also assessed the potential benefit of post-operative honey licks in reducing wound complication rates following repair.

MATERIALS AND METHODS

This was a cohort study of patients who had palatoplasty over a five-year period and were subsequently followed up for a maximum period of 9 years. Assessors conducted telephone interviews with patients and care-givers. The assessors were not the surgeons who performed the repairs. The patients' present condition, timing of first feeds, onset of solid feeds, post-operative honey licks, wound dehiscence and spontaneous closure, fistula formation, need for revision surgery, and speech outcomes were assessed. Analysis was done using SPSS version 21.0 and p value set at <0.05

Selection of participants

All cleft palate surgeries done at NOHE are routinely uploaded to the SmileTrain Express database. Records from November 2008 to November 2013 were used to retrieve patient data. These included isolated palatal clefts, and cleft lip with cleft palate. Interviews of patients/parents between January 2014 and October 2018 were also used to provide data. Speech quality was assessed by two methods: The parent/care-giver's ability to understand the patient's speech, and (for adults) the interviewer's assessment. There were three

interviewers. One was trained in cleft speech language pathology while the other two were residents in training. Children less than a year at the time of assessment were not assessed.

Surgical technique

Intravenous antibiotics were routinely administered before induction of general anaesthesia and continued for up to five days post operatively.

The patient is laid supine on the operating table and anaesthetised with a cuffed armoured tube placed securely in the midline. Continuous monitoring with non-invasive multiparameter monitors is routine. A sandbag is placed between the shoulders and the patient prepped. A self-retaining mouth gag is inserted and the head of the table turned down in extension until the entire cleft palate is clearly visualised. Oxygen saturation is rechecked and the oral and nasal cavities are cleaned with povidone iodine lotion or ointment paying particular attention to the shelves, cleft and tonsillar regions. A throat pack is inserted. Intra operative infiltration with adrenaline solution is routine. After a seven minute pause the cleft margins are pared on the oral side. Moistened gauze is cut, insinuated and pushed posteriorly and laterally to aid elevation of the shelves, separation of the oral and nasal layers as well as haemostasis. They are removed by the time of closure of the layers. Where the hard palate is involved the nasal layer is separated from the palatine bone. With good visualisation the nasal layer of the soft palate close to the bone is held taut with tissue forceps and the nasal layer teased out with a cleft palate dissector. Every attempt is made to avoid button-holing. The rest of the surgery proceeds depending on the selected technique. Intra-velar veloplasty, von Langenbeck's and Furlow's repairs, in that order of frequency, were the surgical techniques used. The throat pack is removed before extubation which is done when the patient has regained the swallowing reflex and shows spontaneous movement. The patient is turned to the side and routinely given supplemental oxygen briefly before transfer out of the theatre.

The feeding protocol was clear fluids (sugared water) upon recovery from anaesthesia on the day of surgery, and semi-solid diet based on pap for 3 weeks thereafter. Honey was encouraged from the second day. The instruction on commencement of feeds and duration of liquid diet varied between the units. One unit allowed oral intake of clear liquids within 24hours of the repair and routinely prescribed honey licks post operatively. A majority (72%) of the surgeries was done by the surgeon in this unit. Other units allowed oral intake of clear liquids after 48hours and did not recommend honey licks.

Limitations of study

The study is retrospective in nature. Not all patients on the database had traceable contacts. There was no independent assessment by speech therapist for some patients (we report the assessment of the parents/ caregivers, and the interviewer), and neither cephalometrics nor audiology were performed. The relationship of the size of cleft, type of repair, and experience of surgeon to the incidence of fistula formation was not assessed.

RESULTS

There were 115 patients; 49(43%) male and 66(57%) female giving a M: F ratio of 1:1.3. There were 90 primary palate repairs (Figure 1). Age range of surgery was six weeks to 36 years. Twenty-five patients were done at one year, 18 patients were done between one and two years, 29 patients were done between two and 12years, while 18 patients were done between 12 and 36years. We found that very early repair in a fit baby at six weeks did not result in respiratory embarrassment. Reports of such early repairs have been published[1]. Six plastic surgeons were involved in this study. The distribution of patients according to the six surgeons are as follows: 79:4:9:11:4:2 (two patients not identified). Two patients received blood transfusions post-operatively based on the anaesthetist's recommendation.

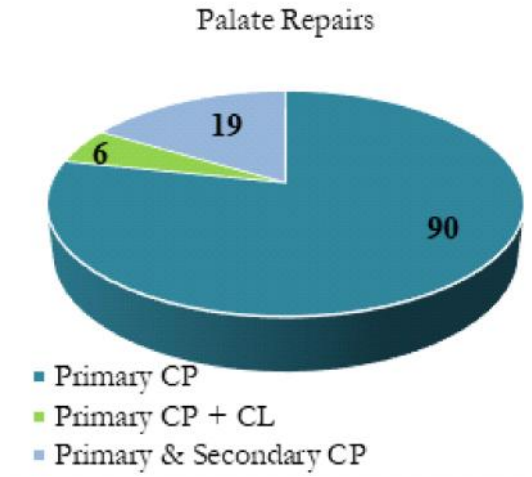

Figure 1: Pie chart of palatoplasties done 2008-2013

Figure 2: Bar chart of time of onset of solid feeds

Three patients had died by the time of evaluation from complications following cardiac anomalies and sepsis up to a year post operatively. The complications were unrelated to the surgery or anesthesia.

Up to 80% commenced oral intake within 48 hours of surgery. Some commenced semisolid/solid diet as early as one week, and over 20% were advised to wait for at least one month before commencing semisolids/solids (Figure 2).

Majority (47.3%) of the patients were considered to have near normal speech. Eleven patients were too young to have developed significant speech and so this could not be assessed (Figure 3).

There were 44 patients (39%) that had wound dehiscence. Of these 24 developed a fistula; giving a

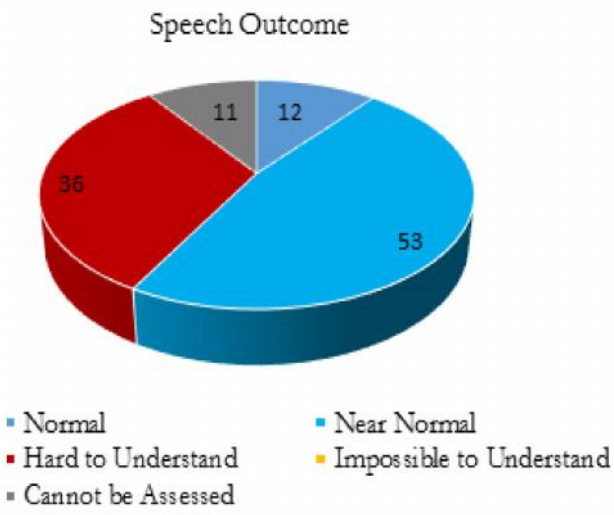

Figure 3: Pie chart of speech outcomes

Table 1: Test of significance feed onset vs breakdown

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	37.356[a]	2	.000
Likelihood Ratio	41.528	2	.000
N of Valid Cases	112		

a. 0 cells (0.0%) have expected countless than 5. The minimum expected count is 9.82

Taking P-value to be 0.05% and confidence interval of 95%, the result showed a chi square value of 37.356, with a significant p-value of <0.001. Therefore, one can say that there is an association/difference between the onset of feeding before and after 3 weeks and after 4 weeks and wound breakdown.

Table 2: significance of honey licks and wound breakdown

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	166.527[a]	4	.000
Likelihood Ratio	82.240	4	.000
N of Valid Cases	115		

a. 5 cells (55.6%) have expected countless than 5. The minimum expected count is .08

THE ABOVE TWO TABLE SHOW THE RELATIONSHIP BETWEEN HONEY LICK AND WOUND BREAKDOWN.
Chi-square value = 116.527, p-value is <0.001, which is significant. Therefore, the occurrence of wound breakdown is not just by chance but also has association with whether a patient licked honey or not.

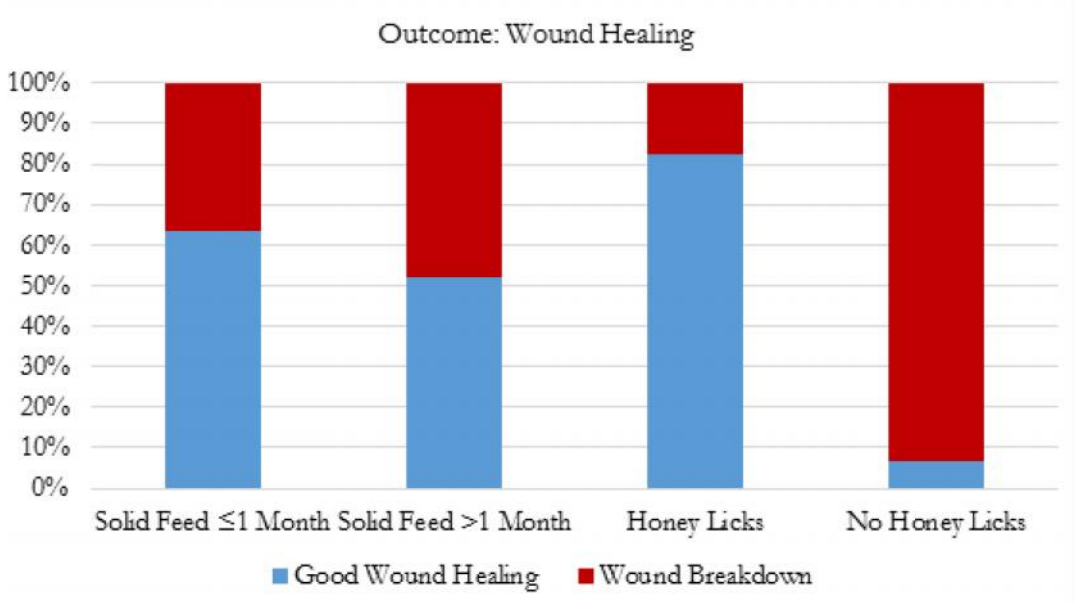

Figure 4: Wound healing and onset of solid feeds/use of honey

fistula rate of 21%. There was a significant association between the time of return to semisolid/solid feeds and wound breakdown (Figure 4, Table 1), and honey licks with wound breakdown (Table 2). Only six revision surgeries had been done at the time of evaluation. Patient compliance with appointments was a continuing challenge.

DISCUSSION

Cleft palate is the third most common major congenital anomaly after club foot and cleft lip.[2] The female sex predilection for cleft palate (isolated and in combination with cleft lip) is in keeping with previous reports from this institution[3] but not from the Nigerian national data[4]. The age range is wide, with an upper age limit similar to reports from outreach surgeries in developing nations,[5] and probably represents a desire for correction once affordability is assured by free treatment. It has previously been noted that 40% to 90% of patients fail to return for palate repair after cheiloplasty.[3] The adult cleft palate patients desire correction and improvement even when it was not done in childhood.

Preoperative intravenous antibiotics are commonly used in cleft surgery. Our routine postoperative use is not new[5] and based on the assumption that presumptive therapy is indicated following their high predilection for recurrent upper airway infection and wound contamination by oral flora. It reduces the incidence of fistulae and other post-operative morbidities.[6]

Palatoplasty aims at successfully separating the nasal and oropharynx, and providing a mobile velum with velopharyngeal competence. Failure of these could result in fistulae and velopharyngeal insufficiency with subsequent speech defects.[7]

Our study showing 39% of patients with wound breakdown is higher than some others[8, 9] but is within the range in literature (0 to 45%).[9, 10, 11] Nutrition may have played a role in our fistula rate. African children, more frequently than their Caucasian counterparts have nutritional challenges which have negative impacts on surgical outcomes. Children with cleft palate are expected to be similarly affected. A higher age at surgery has also been shown to increase the likelihood of wound dehiscence.[8]

Fistula formation depends on the experience of the surgeon,[10] the surgical technique,[2] and the severity of the cleft;[11] a higher incidence being found among less experienced surgeons, using the Veau-Wardill-Kilner technique, and in the more severe Veau cleft types. This association could not be explored in our study. Advancing age at surgery may also increase the wound breakdown and fistula rate from greater difficulty in surgery following repeated infection in the area, fibrosis and resultant increased bleeding.[5] Poorer compliance with post-operative liquid diet protocol in older patients may be contributory. Our series included palate surgery in adults up to 36 years.

Post-operative feeding regimens following cleft palate surgery remain controversial.[12] Studies have suggested that unrestricted feeding with liquid diet is appropriate immediately after surgery[12, 13] Some authors advocate feeding with liquids postoperatively for 10 – 14 days followed by semisolid diet for the next three – four weeks,[14] while others will continue with liquid diets for three weeks, transitioning to a semisolid diet for an additional three weeks.[15] Our study showed a significant increase in wound breakdown in patients commenced early (one-three weeks) on semisolid/solid diets as compared to those commenced on semisolid/solid diet later at one month. Particulate matter from semisolid/solid food gaining access to the repair site could evoke inflammatory changes that impair wound healing and predispose to wound dehiscence, wound breakdown and subsequent fistula formation.

Also, there was a significant reduction in wound breakdown in patients that were given honey to take compared to those that were not. Honey, apart from being nutritive across the age ranges when licked, also serves as wound dressing for the repaired palate and may well promote healing. It contains high levels of glycine, methionine, arginine, and proline, which are all necessary for collagen formation and fibroblast deposition, the essential factors needed for healing.[16] When licked, the honey invariably smears the repair site and serves as wound dressing. Though it is quickly diluted by saliva, dilute honey still exerts antibacterial properties.[17] Its efficacy in promoting healing in cutaneous wounds is well documented; and its efficacy has been suggested to improve by frequent application when used as a dressing agent.[18,19] Frequent licks therefore may be of benefit. A study done in Indonesia showed that honey given as oral drops significantly improved the epithelialization process of the lateral palatal defects post palatoplasty.[20] According to the study, the epithelialization with honey was 2.1 times faster than without it. This study suggests that honey could improve the healing process following palatal surgery resulting in better outcomes as suggested by our study. However since only one unit routinely requested honey licks, the impact of the surgical skill

of that unit may have been important; though some studies have found no significance in outcomes with varying experience of the same operator. Care needs to be taken in advocating the routine use of honey in infants as it has been associated with rare botulism in this age group.[21]

In our study 58% of patients had normal to near normal speech based on assessment given by their caregivers in the absence of an assessment by a speech therapist. This is an assessment by the "end users" rather than by professionals. It is the people in the patient's immediate environment that assess and utilize the speech every day and their evaluation we believe is relevant. It represents a limitation in the study as some languages are less dependent on fricatives which are difficult for the cleft palate patient. However this gives an indication of how well adjusted the patients are post-surgery with regard to speech. Various studies report between 25% - 37% of children that had cleft palate repair with persistent speech problems.[22,23] The age at palate repair also affects the speech outcomes.[24] This would have contributed in part to the over 30% who had difficult to understand speech in our series. However speech improvement still occurred after repair well into adulthood. Studies will be necessary to quantify the benefit patients derive regarding speech improvement when primary cleft palate surgery is performed in adulthood. A particular study reported that two-thirds of these children had significant speech production problems and were enrolled for direct speech therapy.[23] Some speech problems are attributable to impaired hearing which is a possible complication of middle ear disease. They are not as a result of velopharyngeal incompetence. Our lack of audiology makes it impossible to determine what percentage, if any, of our patients had speech problems associated with impaired hearing.

CONCLUSION

In this study, we discovered that very early return to solid feeds is associated with a higher incidence of wound breakdown following palate repair, while introduction of honey licks was associated with reduced incidence of this complication. More studies are indicated to explore a direct cause and effect relationship. More studies also would be needed to define, in this environment, the relationship of fistula formation to the type of cleft palate encountered, the surgical technique used, and the experience of the surgeon. Also more rigorous objective assessment of speech outcomes of cleft palate repairs by a speech pathologist in ourcenter will need to be done.

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Conflict of interest statement

None

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PATTERN OF SPEECH ARTICULATION ERRORS IN NIGERIAN INDIVIDUALS WITH CLEFT LIP AND OR PALATE ANOMALIES FOLLOWING REPAIR.

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ABSTRACT

The occurrence of cleft lip and palate anomaly can impact on an affected individual's quality of life. Cleft of the palate particularly significantly affects the production of speech. This article aims to describe the speech errors following palatoplasty procedures observed from cleft centres within Nigeria. Ability to produce high pressure sounds, frequencies of speech errors and speech intelligibility were analysed from data collated from five cleft centres. The speech services in these centres were provided in partnership with Smile Train, a nongovernmental organization based in the United States of America. Glottal stop was the commonest speech error while the speech intelligibility was considered mild in the majority of cases. This report serves as a form of preliminary overview of the speech pattern of individuals with repaired cleft palate in our environment.

Keywords: Cleft palate, Speech outcome, Nigeria.

INTRODUCTION

Cleft lip and or palate (CL/P) anomaly, the commonest craniofacial congenital anomaly, is an anomaly that can be seen, heard and felt. Its occurrence can, therefore, significantly impact an individual's quality of life. Cleft of the palate especially poses two major challenges to the affected individual; feeding (particularly in the early phase of life) and speech. An affected individual can somewhat adapt to his/her the feeding challenges if the individual survives to adulthood but the speech difficulty remains unless an intervention is done. Speech is a universal means of communication and affectation of this ability can impair the social wellbeing of an affected individual such that integration among peers and into the society as a whole becomes a challenge.

Speech errors associated with individuals with CL/P can be categorized as errors of omission; when a challenging sound is skipped, substitution; when a challenging sound is replaced with a less challenging one such as 'm' sound for 'p' or 'b' sound and distortions; when some other sounds are made in place of challenging sounds such as a glottal or pharyngeal sound for challenging high pressure sound like 'k'[1]. These errors have been known to persist in some individuals even after primary palatoplasty. This study aims to describe the type of speech errors observed in Nigerian individuals with repaired CL/P and compare findings with reports from other parts of the globe.

METHODS

Data of individuals with repaired CL/P receiving sponsored speech therapy in various centres in Nigeria was pooled from February 2015 to May 2019. The sponsorship of the speech therapy services was provided by the centres' partnership with Smile Train, a nongovernmental organization based in the United States of America and the data was pooled with their permission. Frequency distributions of the centres, number of individuals assessed for speech errors and their gender, type and extent of cleft anomaly, ability to make high pressure sounds /p/, /b/, /t/, /d/, /k/, /g/, /s/ and /f/, type of speech errors and speech intelligibility were collated and analyzed. The determination of speech errors and speech intelligibility were based on descriptions by Henningson[2]. For speech intelligibility: normal speech was regarded as speech that was always easy to understand by non-family members, mild speech impairment as speech that was occasionally hard to understand by non-family members, moderate speech impairment as speech that was often hard to understand by non-family members and severe speech impairment as speech that was hard to understand most of the time by non-family members.

The cleft anomalies were classified according to the classification by the American Cleft Palate-Craniofacial Association Classification[3]. The speech intelligibility was cross-tabulated against gender, the type of cleft, presence or absence of fistula and extent of the cleft.

Pearson Chi-Square test was used when the expected cell count was adequate and the Fisher's exact test was used when the expected cell count was less than 5 to test for statistical significance. This was set at $p \leq 0.05$.

RESULTS

Five centres around the country provided speech therapy services under the Smile Train partnership during the 50-month period under review. Sixty-five individuals with a mean age of 9 years (SD±7.1) and median age of 6.2 years. The minimum age was 2.4 years while the maximum age was 35.8 years. There were 42, 64.6% females and 23, 35.4% males. Cleft of the secondary palate alone was the most common with 37, 56.9% individuals (Figure 1) and 51, 78.5% were complete in extent. Thirteen, 20.0% of all the cleft types, had residual fistulae while 89.2% could produce a high-pressure sound. The /p/ sound was the commonest high-pressure sound that could be produced by 43, 66.0% of individuals (Figure 2) while glottal stop was the commonest compensatory error encountered in 27 individuals, 41.5% (Figure 3). The speech intelligibility was rated as mild in majority, 29, 44.6% of the individuals (Figure 4) while speech therapy was recommended for 60, 92.3% of the individuals. Females, individuals with cleft of both

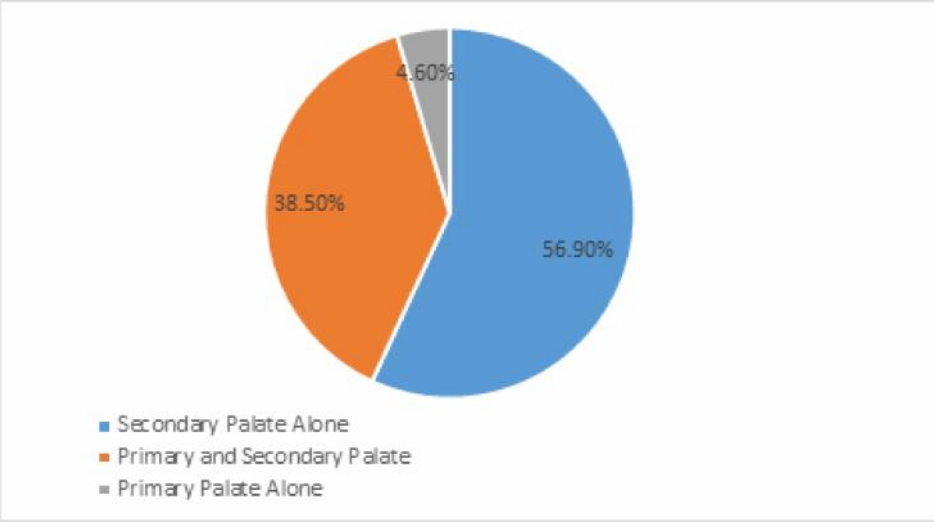

Figure 1: Distribution of types of cleft anomalies

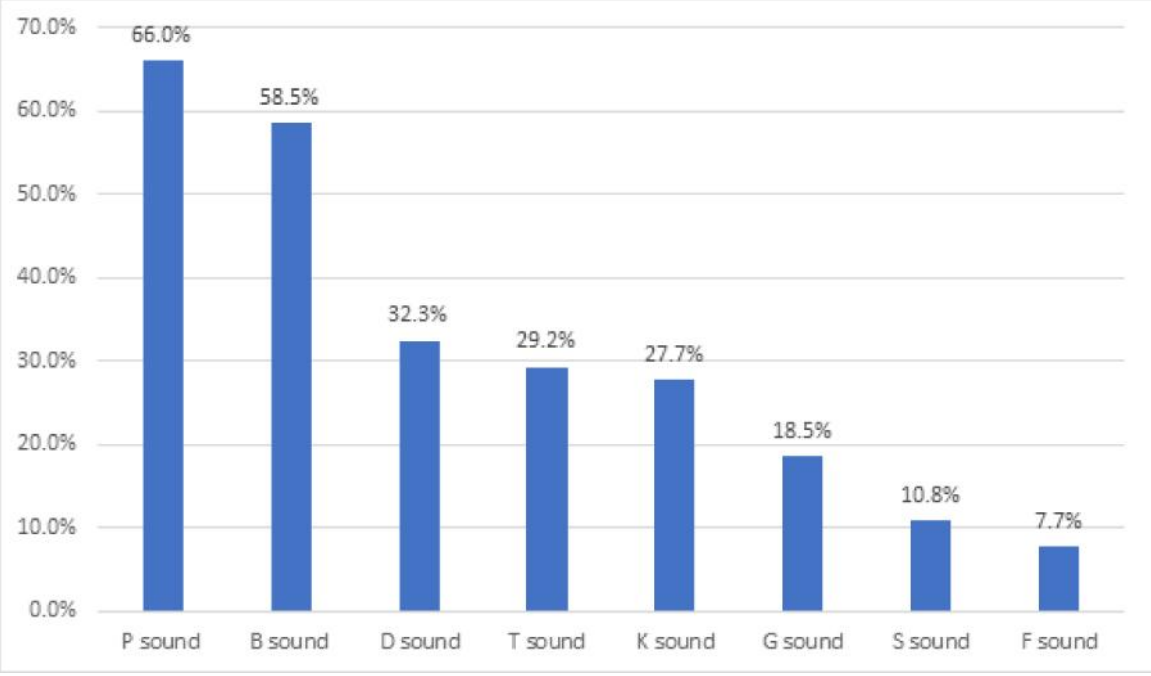

Figure 2: Frequency distribution of the high-pressure sound production

Table 1: Table of speech intelligibility comparisons among gender, type and extent of cleft and the presence or absence of fistula

		Speech Intelligibility						
		Normal	**Mild**	**Moderate**	**Severe**	**NOS**	**Total**	**Fisher' exact test**
Gender	Male	2, 40.0%	12, 41.4%	7, 30.4%	2, 28.6%	0, 0.0%	23, 35.4%	
	Female	3, 60.0%	17, 58.6%	16, 69.6%	5, 71.4%	1, 100.0%	42, 64.6%	0.890
	Total	5, 100.0%	29, 100.0%	23, 100.0%	7, 100.0%	1, 100.0%	65, 100.0%	
Type of Cleft	Primary Palate alone	1, 20.0%	2, 6.9%	0, 0.0%	0, 0.0%	0, 0.0%	3, 4.6%	
	Primary and Secondary Palate	1, 20.0%	9, 31.0%	10, 43.5%	4, 57.1%	1, 100.0%	25, 38.5%	
	Secondary Palate alone	3, 60.0%	18, 62.1%	13, 56.5%	3, 42.9%	0, 0.0%	37, 56.9%	0.391
	Total	5, 100.0%	29, 100.0%	23, 100.0%	7, 100.0%	1, 100.0%	65, 100.0%	
Extent of Cleft	Incomplete	1, 20.0%	7, 24.1%	6, 26.1%	0, 0.0%	0, 0.0%	14, 21.5%	0.647
	Complete	4, 80.0%	22, 75.9%	17, 73.9%	7, 100.0%	1, 100.0%	51, 78.5%	
	Total	5, 100.0%	29, 100.0%	23, 100.0%	7, 100.0%	1, 100.0%	65, 100.0%	
Fistula	Present	1, 20.0%	5, 17.2%	5, 21.7%	1, 14.3%	1, 100.0%	13, 20.0%	
	Absent	4, 80.0%	24, 82.8%	17, 73.9%	6, 85.7%	0, 0.0%	51, 78.5%	
	NOS	0, 0.0%	0, 0.0%	1, 4.3%	0, 0.0%	0, 0.0%	1, 1.5%	0.528
	Total	5, 100.0%	29, 100.0%	23, 100.0%	7, 100.0%	1, 100.0%	65, 100.0%	

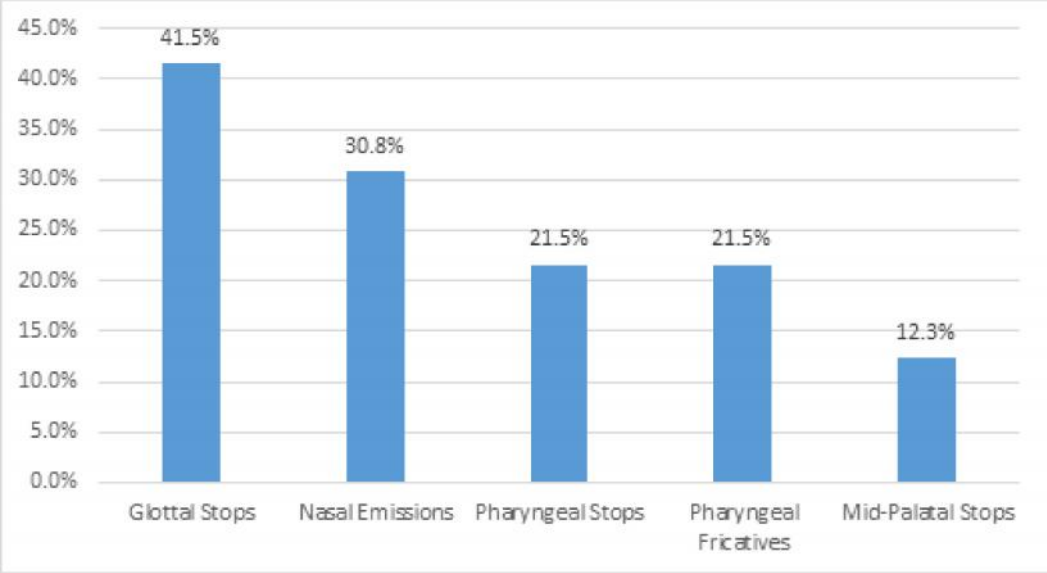

Figure 4: Frequency of the compensatory speech errors observed

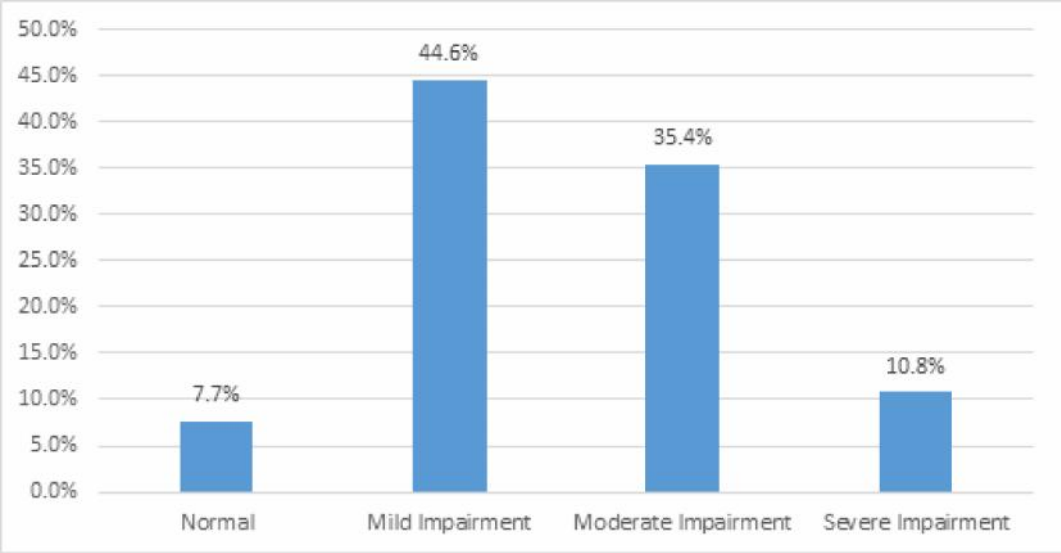

Figure 4: Frequency of speech intelligibility observed

primary and secondary palate and complete clefts appeared to have higher degree of speech impairment (Table 1). Also, the frequency of fistula was higher in those with moderate speech impairment. However, these differences were not statistically significant.

DISCUSSION

This study describes the national distribution of speech therapy centres sponsored by a nongovernmental organization (Smile Train). The number of the centres were limited as the speech therapy programme for cleft anomaly is in its infancy in Nigeria. It only commenced in 2015, four years prior to this study. Before the advent of Smile Train in Nigeria, speech therapy services specifically for individuals with cleft anomalies was scarce[4]. However, since the provision of this special service the pattern of speech errors that have been observed in these Nigerian beneficiaries are reported in this study.

Structurally the production of speech requires proper alignment of teeth, an intact alveolus and palate, especially the soft palate (velum)[5,6]. The velum is required to make contact with the posterior pharyngeal wall thereby preventing nasal air escape during the production of high-pressure sounds. This mechanism is impaired in individuals with unrepaired cleft palate anomaly. Therefore, individuals with cleft palate anomaly find it difficult to make high pressure sounds because of their inability to close the velopharyngeal port[5-7]. As an affected individual grows up without the benefit of a surgical repair (and orthodontic intervention for the linguodental or labiodental sounds), speech is usually produced with errors. These errors in turn impair speech intelligibility[8-11]. Distortions such as glottal stops, pharyngeal stops, mid-palatal stops and pharyngeal fricatives are common compensatory articulation errors that have been associated with the cleft palate speech[12]. These errors do not improve following palatal repair and will require speech therapy to achieve a good speech outcome[13-15]. In fact, it has been suggested that the articulation proficiency of an individual who had had a late primary palatal repair (especially without subsequent speech therapy) may not be ultimately higher than that of an eight-year-old by early adulthood[11]. Surgical repair of a palatal cleft however does not guarantee the production of a normal speech especially if the repair was done late, after the development of speech[1,15-17]. Speech therapy for cleft anomaly is therefore usually necessary after surgical repair to correct the speech errors that are not due to residual velopharyngeal insufficiencies[13].

It has been estimated in literature that about 20% - 75% of individuals with cleft palate still have speech deficits after palatoplasty.[18-20] The frequency of speech errors in individuals who have had cleft palate repair appears to be higher in developing countries; 87% was reported by Bruneel[21] in Ugandan children which was similar to the 92.3% in this study, whereas Bzoch[10] reported 39.8% in European children. The explanation for this difference is not known. More studies are required to ascertain if this observation is a real difference or not. However, the late primary repairs of cleft palate common in our environment may be responsible[22,23].

The plosives /p/ and the /b/ were the least challenging to produce while the fricatives /s/ and /f/ sounds were more severely affected than the plosives as

similarly noted in other studies[9-11,21]. This may be due to the fact that an intraoral pressure will need to be maintained during the production of fricatives unlike the plosives during which the oral pressure is released in an instant manner, a stop as against a continuant such as a fricative. The sound /t/, has also been reported to be frequently misarticulated in similar frequency with the sound /s/[9]. This was however not the case in this study.

The pattern of difficulty with the production of high-pressure sounds may be useful in clinical assessment of the magnitude of the speech problem by asking an affected individual to make the /s/, /f/ or /t/ sound. That is, ability to make any of these notably challenging sounds may suggest the possibility of a less demanding therapy.

Nasal emissions constituted 45% of the indistinct sound errors in the Bzoch[10] study while it constituted 16.1% of the errors in this study. This lower value may not be unrelated to the perceptual nature of detecting this error in this study and could possibly be under reported. In this study the speech intelligibility was rated normal in only 7.7% of the individuals assessed. This is much lower than reports on English and American individuals with 47% normal speech in 12-year-olds[24]. Reasons for this low frequency of normal speech is not known to the authors. However, to improve speech outcomes following palatoplasty and provide a good platform for subsequent speech therapy the following are reiterated: palatal repairs should be done before two years of age (before the commencement of formal speech) and particular attention should be paid to the surgical steps of palatal repairs as it is not enough to restore structure by closing the defect. The surgery should target a functional (good speech) outcome as well. Thus, identification of the speech muscles (especially the levator veli palatini), mobilization of the muscles, proper apposition of the muscle bulk and retro-positioning of the repaired muscle bulk should be integral components of any palatoplasty procedure.

Fistulae rates following palatoplasty has been reported to range from 0-78% in literature[25]. Shankar *et al.*[25] found an early (after primary palatal repair before maxillary expansion) fistula rate of 20% which is similar to this study. Factors such as gender and type of cleft anomaly presence and site of residual fistulae did not appear to affect speech intelligibility. However, this may be due to the insufficient sample size to enable statistical analysis. Future studies will be required to determine site frequency and effect of these residual fistulae on speech outcome following palatoplasty in our environment.

This report serves as a form of preliminary overview of the speech pattern of individuals with repaired cleft palate in our environment. However, there were some limitations observed such as the small sample size. Future studies with larger sample size will be desirable to assess the impact, if any, of factors such as gender, type of cleft, extent of cleft, presence and site of residual fistula on speech intelligibility. Another limitation to this study is the fact that the expertise of the cleft speech service providers in the various centres may differ and can influence the interpretation of their results. In addition, the speech assessments were perceptual in nature and perceptual assessment (though an integral aspect of speech assessment) is usually flawed by the listeners' bias and experience[12,26]. Therefore, future studies with more objective means of assessment will be desirable.

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PERIOPERATIVE ANTIBIOTIC THERAPY IN OROFACIAL CLEFT SURGERY. WHAT IS THE CONSENSUS?

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ABSTRACT

Clefts of the primary and secondary palate represent one of the commonest congenital anomaly for which surgical correction is required. The perioperative care of the patients varies widely across centers and among surgeons and range from preoperative swab of palatal clefts for microbiological studies to prophylactic and or therapeutic antibiotic care. These practices have economic implications especially in the Low and Middle Income Countries (LMIC) where the cost of care are borne directly by the parents. The clinical implications of indiscriminate antibiotic use may also include development of resistant strains and hypersensitivity reactions which may be life threatening. Surgical site infections and its possible sequelae of dehiscence and fistulae is another concern for the surgeon and the patient.

This review examines the microbiological pathogens, surgeon's perspectives as well as the current evidences for the use of perioperative antibiotic therapy in orofacial cleft surgery and concludes with a need for a large multicenter randomized clinical trial to answer critical aspects of the subject.

Keywords: Cleft lip and palate, Orofacial clefts, Antibiotic in cleft surgery

INTRODUCTION

The oral cavity and nasopharynx of children with unrepaired cleft lip and palate are recognized to be at an increased risk of colonization by bacterial pathogens. Significant interest has been generated among clinicians about the role of infections in the development of complications following cleft surgery in these patients. A causal relationship has long been established between infection and failure of surgical repair[1-3].

Several publications on children with clefts have identified oral flora of microorganisms pre-operatively and the association of post-operative complications with pathogenic organisms found in the perioperative period[4-7]. These complications can result in systemic infection for the child, secondary heamorrhage, wound dehiscence, palatal fistulae with resultant prolonged hospital stay. Subsequent morbidities may include poor speech, impaired appearance and impaired facial development[8]. Hupkens *et al.*[9] reported a strong association between preoperative cultures especially of Group A Streptococcus and Staphylococcus aureus and postoperative palatal dehiscence. Previous studies have also confirmed that patients with orofacial clefts are at increased risk for the development of caries and periodontal diseases compared to noncleft children[10,11].

Primary closure of cleft lip and palate is classified as a clean contaminated operation, and wound infection is a recognized risk. The risks are associated with the duration of operation especially with primary cleft operations often requiring 1–2 h of operating time.[12] The consequences of surgical wound infection after repair of cleft lip or palate can be devastating in both the short and the long term. A major wound infection after primary repair of a cleft anomaly is likely to require a further admission for a secondary intervention; however, final outcomes such as speech and growth may also be compromised.

Antibiotics are likely to reduce the incidence of wound infection and complications, but this has never been clearly shown in randomized clinical trials in repair of clefts[8]. Despite the beneficial effects of antibiotics, its widespread use may result in increasing rates of antibiotic resistance in addition to increased cost of care especially for families making out of pocket payment for their children's care[13]. This can constitute additional burden on such parents. Unfortunately, there is currently no global, regional or national guidelines for the rational use of antibiotic prophylaxis in repair of orofacial clefts.

This review seeks to evaluate the arguments for or against the use of peri-operative antibiotics therapy for CLP surgeries based on available literature and draw conclusions that could guide rational choice by surgeons and other practitioners.

Bacteremia in Cleft and Oral Surgeries

Several studies have documented significant bacteremia following cleft lip and palate and intraoral surgeries[14-19]. These procedures were diverse and ranged from cleft lip and palate (CLP) surgeries, tooth extraction and removal of osteosynthesis plates, third molar surgeries and some maxillofacial procedures. Previous assertions have been that bacteremia associated with oral surgeries in healthy individuals is transient without significant sequel[20,21]. However, a recent study has documented bacteremia following cleft lip and palate surgeries persisting for up to 15 minutes in 53% of the patients[19]. The bacteremia in this group of patients was also higher than those for oral procedures such as orthodontic procedures and root scaling. The implication of the finding is that cleft-related surgery could be harmful in patients at risk, especially those with associated cardiac anomalies. Factors that were associated with development of bacteremia in patients with CLP anomaly included age less than 62.3 months and the male gender (59.4%), although these factors were not statistically significant. On the relationship between bacteremia and the specific type of surgery, the authors found that the prevalence of bacteremia in cleft lip surgery was 40.9%, whereas the incidence in cleft palate surgery was 33.3%. A prevalence of 50% was recorded for alveoloplasty. No reason was proposed for these differences. It was also found that bacteremia associated with CLP surgeries in the study was polymicrobial, similar to findings from several other studies that reported polymicrobial bacteraemia following other dental procedures[14,16,18,22]. These organisms in the oral cavity can gain access into the blood stream during these procedures[23-25].

Based on their findings, Adeyemo et al[19] advocated for the need for prophylactic antibiotic therapy for CLP because of the patients with associated congenital heart defects and the risks for bacteria endocarditis in this group of patients.

Bacteriology of Oral Flora

The oral cavity, which remains sterile throughout prenatal development, becomes a diverse ecosystem colonized by several microorganisms during the first few hours after delivery. The skin and mucus membranes of neonates are colonized by microbiota as a result of contact with the external environment. A significant part of the oral microbiota in the early neonatal period originates from the mother and is transient population of microorganisms consisting of intestinal bacteria[26]. The spectrum of organisms at this stage depends mainly on factors such as the gestational age of the baby, the mode of delivery, type of feeding and the length of hospital stay[26-32].

The early oral microbiota occurring within several hours following delivery is composed of viridans streptococci and Streptococcus salivarius (S. salivarius), which are commensals permanently colonizing the oral cavity[28]. Along with other bacteria, they participate in the formation of a "colonization cascade" that determines future indigenous microbiota[28,29,33]. Congenital orofacial malformation affects the structure and functions of the oral cavity, thereby significantly modifying its characteristics[9]. Both abnormal morphology and improper function of the oral cavity in newborns with cleft palate create a different environment from that of healthy neonates. Therefore, these abnormalities may affect oral microbiota[34].

The oral cavity is replete with diverse strains of microorganisms. Organisms that are commonly found include Staphylococcus aureus (SA) and b-hemolytic streptococci (bHS), when compared with the normal population[19,34,35]. More than 500 different bacteria strains have been identified in the oral cavity[36]. The oral microbial community is normally in equilibrium, but a compromise of the ecological balance can occur and result in surgical site infection. A list of the most important bacteria commonly isolated from the oral cavity is presented in Table 1[37].

Antibiotic Therapy in Cleft Surgery

Operations in the aero digestive tract are frequently considered as clean contaminated and the incidence of surgical site infections (SSI) is about 10 to 15% which represents a significant health burden[38]. By definition, a SSI is an infection that develops within 30 days after an operation or within 1 year of an implant being placed, where the infection appears to be related to the surgery[39]. Perioperative antibiotics are generally used in surgery to prevent SSI. In contrast to therapeutically used antibiotics, the perioperative treatment aims to reduce contamination of the bacterial flora in the specific surgical area. The basic purpose of antibiotic prophylaxis is, therefore, to provide an adequate drug level in the tissues before, during, and for the shortest possible time after the procedure[38]. Prophylactic antibiotic treatment is defined as the use of antibiotics before, during, or after a diagnostic, therapeutic, or surgical procedure to prevent infectious complications. It has been estimated that approximately half of SSIs are preventable by application of evidence-based strategies[40].

Table 1: Bacteria commonly isolated from the oral cavity

Genus	Species
Strict anaerobic bacteria	
Gram-negative rods	
Porphyromonas	P. gingivalis, P. endodontalis, P. catoniae
Prevotella	P. oralis, P. oris, P. buccae, P. corporis, P. denticola, P. loescheii, P. intermedia, P. nigrescens, P. melaninogenica,
Fusobacterium	F. nucleatum spp. nucleatum, spp. vincentii, spp. polymorphum
Mitsuokella	M. dentalis
Selenomonas	S. sputigena, S. noxia
Campylobacter	C. sputorum, C. rectus, C. curvus
Treponema	T. denticola, T. vincentii, T. socranski
Bacteroides	B. forsythus
Gram-positive rods	
Eubacterium	E. alactolyticum, E. lentum, E. yurii
Propionibacterium	P. acnes, P. propionicus, P. jensenii, P. granulosum, P. avidum
Lactobacillus	L. catenaforme, L. crispatus, L. oris, L. uli, L. grasseri
Actinomyces	A. israelii, A. odontolyticus, A. meyeri
Arachnia	A. propionica
Gram-negative cocci	
Veillonella	V. parvula, V. alcalescens
Gram-positive cocci	
Peptostreptococcus	P. asaccharolyticus, P. magnus, P. micros, P. anaerobius P. prevotii
Facultative anaerobic bacteria	
Gram-negative rods	
Eikenella	E. corrodens
Capnocytophaga	C. ochracea, C. sputigena, C. gingivalis, C. haemolytica, C. granulosa
Actinobacillus	A. actinomycetemcomitans
Actinobacillus	A. actinomycetemcomitans
Haemophilus	H. aphrophilus H. influenzae, H. parainfluenzae, H. paraphrophilus, H. segnis
Gram-positive rods	
Corynebacteriu	C. xerosis, C. matruchotii
Actinomyces	A. naeslundii, A. viscosus
Rothia	R. dentocariosa
Lactobacillus	L. acidophilus, L. brevis, L. buchneri, L. casei, L. salivarius, L. fermentum
Gram-negative cocci	
Neisseria	N. flavescens, N. mucosa, N. sicca, N. subflava
Branhamella	B. catarrhalis
Gram-positive cocci	
Streptococcus	S. mutans, S. sanguis, S. salivarius, S. sobrinus, S. rattus, S. downei, S. mitis, S. milleri, S. oralis, S. intermedius, S. constellatus
Staphylococcus	S. aureus, S. epidermidis
Enterococcus	E. faecalis, E. faecium

Based on Mouton and Robert (2)

The Scottish Intercollegiate GL Network (SIGN) guideline "Antibiotic prophylaxis in surgery" defines two regimens; the short-term prophylaxis administered any time before or after surgery for up to 24 h after the surgical intervention and long-term antibiotic prophylaxis that is continued for longer than 24 h. In contrast, therapeutic antibiotic treatment is used to reduce the growth or reproduction of bacteria, including eradication therapy. Antimicrobial therapy is then prescribed to clear infection by an organism or to clear an organism that is colonizing a patient but is not causing infection[41].

Despite the obvious benefits of antibiotics, their excessive and indiscriminate use may not only be uneconomical but also result in the risk for developing multiple drug resistance in bacteria which is claimed to be a major cause of the failure of therapy in many human infections[42]. Therefore, appropriate use of antibiotics is seen as a national health priority to prevent the morbidity of infections and the development of resistant organisms[40].

The consequences of surgical wound infection after repair of cleft lip or palate can be devastating in both the short and the long term. A major wound infection after primary repair of a cleft is likely to require a further admission for a secondary intervention; however, final outcomes such as speech and growth may also be compromised. Antibiotics are likely to reduce the incidence of wound infection and complications[8] but there are limited randomized clinical trials on the use of perioperative antibiotics in repair of clefts.

A survey among surgeons doing primary cleft surgery in the UK and Ireland showed a lack of consensus and considerable disparity among cleft centres in the UK about antibiotic prophylaxis for primary cleft surgery. Most of these cleft surgeons use an antibiotic for prophylaxis during repair of a cleft lip, some surgeons continue this for 5 days although there is no supporting evidence of additional benefit. Unusually, a slightly higher proportion of surgeons would not use any form of antibiotic prophylaxis for repair of a cleft palate than for isolated repair of a cleft lip, and although nearly half would not use any antibiotic prophylaxis afterwards, a third would continue to give it for 5 days[8].

A similar survey among members of the American Cleft Palate-Craniofacial Association found out that eighty-five percent of the surgeons administered prophylactic antibiotics, including 26% who used a single preoperative dose. A further 23% gave 24 hours of postoperative therapy; 12% used 25 to 72 hours, 16% used 4 to 5 days, and 12% used 6 to 10 days. Five percent of surgeons administered penicillin, 64% administered a first-generation cephalosporin, 13% administered ampicillin/sulbactam, and 8% gave clindamycin. The authors also retrospectively reviewed 311 patients out of which 173 received antibiotics and 138 did not. They found out that delayed healing and fistula rates did not differ between the groups: 16.8% versus 15.2% ($p = 0.71$) and 2.9% versus 1.4% ($p = 0.47$), respectively[43].

A prospective, double blind randomized placebo controlled clinical trial conducted in India reported a higher incidence of early complications (13.8%) among the patients in the placebo group compared to 8.7% ($p=0.175$) in the antibiotic group which consisted of a five-day course of postoperative oral amoxicillin (50mg/kg/day). The study also found a higher incidence of fistulae (17.1%) in the placebo group compared to the antibiotic group (10.7%) ($p= 0.085$). These differences in the early and late complication rates were however not statistically significant[44]. A large retrospective series comprising 3,108 patients from India found no difference in the wound infection rates between the group which had postoperative antibiotics and the group which did not[45].

CONCLUSION

Although the efficacy of perioperative prophylactic antibiotics in preventing postoperative wound infections after clean-contaminated surgery where the aerodigestive tract is violated has been clearly established in clinical trials[46-48], only scarce evidence exists for its use in cleft lip, alveolus and palate surgery. Primary efficiency endpoint was occurrence of postoperative fistulae. Here, antibiotic prophylaxis as single shot or 5-day regime failed to show reduction of statistical significance[43,44]. In addition, incidence of wound infections was low even without the use of postoperative antibiotics[45]. Up to date, the use of antibiotic prophylaxis in cleft lip and palate surgeries have not been substantiated. A large multicenter randomized clinical trial with specific selection criteria is recommended to further elucidate the benefit or otherwise of prophylactic and therapeutic antibiotic therapy in the surgical management of orofacial cleft.

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