Original Article

Prevalence of Orofacial Clefts in Nigeria

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ABSTRACT

Orofacial clefts (OFC) are the most common malformations of the head and neck. In Africa, OFC is under-ascertained with little or no surveillance system in most parts for clefts and other birth defects. A Nigerian craniofacial anomalies study "NigeriaCRAN" was established in 2006 to support cleft research specifically for epidemiological studies, treatment outcomes and; studies into etiology and prevention.

We pooled data from seven of the largest Smile Train treatment centers in the six geopolitical zones in Nigeria. Data from September 2006 to June 2011 were analyzed and clefts compared between sides and gender using the Fisher's exact test.

A total of 2197 cases were identified during the study period with an estimated prevalence rate of 0.5/1000. Of the total number of OFC, 53.3% are males and 47%.7 are females. There was a significant difference (p=0.0001) between unilateral left clefts and unilateral right clefts and; significant difference (p=0.0001) between bilateral clefts and either clefts on the left or right side. A significant gender difference (p=0.03) with more females than males was also

observed for CP. A total of 103 (4.7 %) associated anomalies were identified, nine syndromic cleft cases and 10.4 % of the total number of clefts individuals have an affected relative.

The significant difference between unilateral clefts and gender differences in the proportion of cleft palate only are consistent with the literature. The present study emphasizes the need for birth defects registries in developing countries in order to estimate the exact prevalence of birth defects including OFC.

Key words: Prevalence, OFC , Nigeria

Nigeria is the most populous country in Africa and the most populous black nation in the world with a population of over 160 million people that live in 776 Local Government Areas (LGA) spread across 36 states in 6 geo-political zones (Federal Ministry of Health, 2011). The average growth rate is about 3.2% with 51.22% males and 48.7% females. Over 50% of Nigerians live below the poverty line (less than $1/day) and this may contribute to the low life expectancy age of 46.5years, in spite of a high adult literacy level of about 69.1% (African Peer Review Mechanism, 2008). Infant mortality is high in Nigeria as a result of malnutrition, infections such as malaria, HIV and tuberculosis and congenital birth defects and the country is currently ranked as the 13th in the world with the highest infant mortality rate- 96/1000 births (United Nations, 2011).

Birth defects are reported to contribute significantly to infant morbidity and mortality in developed countries where access to medical care is better (WHO, 2005). These changes in trends are well documented in these countries where birth defect registries exist (Bermejo-Sánchez *et al*., 2011). In most developing countries especially in Africa, the proportions of birth defects are unknown and contribution to mortality rates are yet to be established. Therefore, in order to design studies into the etiology and prevention of birth defects in Africa, efforts should be made to improve ascertainment.

Orofacial clefts (OFC) are complex traits seen in 1/1000 live births and this can be up to1/700 live births in the order of magnitude (WHO, 2004). Rates vary in different geographical regions and ethnic groups across the world (Mossey *et al*., 2009). The differences in rate could be as a result of genetic influences leading to increased risks and outcomes, differences in environmental exposures that contribute to increased risk or the interaction between genetic risk factors and environmental exposure factors. It could also be due to a lack of surveillance and ascertainment leading to estimates that do not represent the exact epidemiology of OFC (Butali and Mossey, 2009).

Recent reports of prevalence and distribution of OFC in Africa suggest that the rates vary from country to country. In Ethiopia, a rate of 1.4/1000 live births was reported in a hospital based study (Eshete et *al.*, 2011). A retrospective study in Tanzania reported individuals with higher proportions of cleft lip only (Manyama *et al.*, 2011) and this is similar to reports from another study in Kenya (Spritz *et.al*, 2007). A significant side difference (more unilateral left sided clefts than unilateral right sided clefts) was reported in studies in Ghana, Nigeria and Tanzania (Carneiro and Massawe, 2009; Agbenorku *et al.*, 2011; Butali *et al.*, 2011).

The present study reported the prevalence rate of OFC, proportions of overt cleft sub-phenotypes and associated anomalies in Nigeria using data from cleft

registries established since 2006 under the Nigerian Craniofacial Anomalies Network "NigeriaCRAN". The objective of the NigeriaCRAN is to establish cleft research infrastructure for epidemiological studies and studies into etiology and prevention of orofacial clefts in Nigeria.

MATERIALS AND METHODS

We pooled data from seven of the largest Smile Train treatment centers (Table 1) in the six geopolitical zones in Nigeria (Figure 1). These seven centers (in six states) are amongst the 65 treatment centers in Nigeria (spread across the 36 states) that offer free cleft surgeries. A total of 6,500 free cleft surgeries have been recorded as of September 2012 and the seven centers included in this study account for over 50% of all treated cases. A description of the type of data entered into the NigeriaCRAN registry has been previously reported (Butali *et al.,* 2011). Data from September 2006 to June 2011 were analyzed and clefts compared between sides and gender using the Fisher's exact test. For a broad comparison between cleft types, all unilateral cleft types (cleft lip only and cleft lip without or without palate) were pooled together and designated as either unilateral left clefts or unilateral right clefts. In Table 1, data for cleft lip are cleft lip with cleft palate and cleft lip without cleft palate. Similarly, all bilateral cleft types (cleft lip with or without cleft palate) were designated bilateral clefts for analysis. A sub-analysis comparing the cleft sub-phenotypes between males and females was carried out to

131 determine gender differences. During recruitment, we recorded data for all
132 recognizable anomalies in individuals with OFC and obtained information on the
133 OFC status of affected relatives. These data and information are included in the
134 present analysis.
135 The total number of live births during the five year period was estimated from the
136 Federal Ministry of Health in Nigeria report on Newborn Health as 4.6 million live
137 births for the six states (Federal Ministry of Health, 2011).

138 The prevalence rate was estimated by dividing the total number of OFC
139 (numerator data) by the total number of live births during the study period
140 (denominator data) and the value multiplied by 1000.Comparison between sides
141 and gender differences was carried out using the Fisher's exact test.

142 **RESULTS**

143 A total of 2,197 cases including nine syndromic clefts (5 with van der
144 woudes syndrome and 4 with Apert syndrome) and 4.6 million births were
145 estimated for the six states (seven centers) which includes Lagos (1.9 million live
146 births) and Kano (2 million live births) – two states with the highest population and
147 number of live births (Figure 1). A prevalence rate of 0.5/1000 for OFC was
148 estimated from the total number of cases and live births during the study period.

Figure 1: Map of Nigeria showing the seven treatment centers located in six states across the six geopolitical zones.

A total of 2,197 OFC were recorded during the period. However, gender information was only available for 2,182 (53.3% males and 47%.7 females) (Table 1). The difference in the number of clefts per center is due to the area of coverage and access to care. For instance, the center in Kano is the largest center in the North West and this center has a mobile cleft treatment unit that provides care to satellite villages in and around Kano. Therefore, there is better access to care and this may account for the number of OFC recorded in Kano during the study period.

Table 2 shows the types of cleft and there were more unilateral left clefts (ULC) which is statistically significant compared to unilateral right clefts (URC) (p=0.0001) and between bilateral clefts (BC) and clefts on either side (p=0.0001). Significant gender differences were also observed for cleft palate (CP) (p=0.03).

Table 3 shows the number of associated anomalies recorded during the study period and a total of 103 (4.7%) associated anomalies were identified.

Table 4 shows the number of affected relatives that were reported by individuals and families examined during the period. In total, 10.4% of the total number of clefts individuals provided a history of having one or more affected relatives. In

Lagos, three related individuals with clefts are among those included in this study and we do not have information on other related individuals.

DISCUSSION

The opportunity to provide free surgical care for OFC has opened a new vista for research and treatment outcomes in Nigeria and most parts of Africa. These opportunities have also created avenues for public awareness in order to address some cultural issues that may contribute to infanticide as a result of clefts.

The present study estimated the prevalence rate as 0.5/1000 for OFC comparable to previous rates reported for Nigeria, South Africa and Zaire (Iregbulem 1982, Kromberg and Jenkin, 1982; Ogle, 1993). Although the rates reported for Nigeria are similar, the present study provides robust data that truly represents the rates and proportions considering that data was obtained from large cleft centers across the country. However, the prevalence rate reported in this study is in contrast to rates reported for other parts of Africa and Europe (Gundlach and Maus, 2006; Eshete *et al.*, 2011). Proportions of cleft types and gender differences from this study validate reports from a previously reported prospective study by Butali *et al.* (2011). The difference between unilateral right and left, bilateral and unilateral clefts and gender differences are also consistent with previous reports in the literature (Mossey and Little, 2002).

Sub-clinical cleft phenotypes for OFC have been described in the literature and these include: cleft microforms, velo-pharyngeal insufficiencies, discontinuity in the orbicularis oris and dental anomalies (Letra *et al.*, 2007, Menezes and Vieira, 2008, Neiswanger *et al.*, 2007). Furthermore, unaffected relatives without overt forms of cleft have been identified with microforms suggesting that they carry a milder phenotype compared with the affected. In addition, individuals with cleft microforms have been reported to have mutations in the *BMP4* gene, a known non-syndromic clefts candidate gene (Suzuki *et al.*, 2009). In our database, sub-phenotypic description for OFC was limited to the overt forms (cleft lip only, unilateral cleft lip and palate, bilateral cleft lip and palate and cleft palate only). Information on family members were collected during the interview phase and recorded. However, we did not examine the relatives to rule out the possibilities of sub-phenotypes. Therefore, it is possible that relatives of unaffected individuals in our study may have cleft microforms. Dissecting the presence of these microforms will improve our current understanding of cleft etiology, especially now that we can investigate phenotype-genotype correlations. Our group has identified this limitation and plans are ongoing to carry out preliminary investigations in unaffected relatives. There is also evidence of under-ascertainment of sub-mucous clefts since only one case was reported in the database. Majority of the cases in the database are new born and young children and diagnosis for sub-mucous clefts is

carried out in our centers at age 10 years. Therefore, it is possible that we have many more individuals with sub-mucous clefts that have not been identified.

Associated anomalies are increasingly identified with OFC and the ascertainment of the frequency has improved over time (ICBDSR, 2009; Bower *et al.*, 2010; Rittler *et al.*, 2011). The proportions of associated anomalies vary widely from about 8% to 75% (Lopoo *et al.*,1999; Rajabian and Sherkat, 2000). In the present study, 4.7% of the OFC have associated anomalies in contrast to all the previous studies (Lopoo *et al.*,1999; Rajabian and Sherkat, 2000; Rittler *et al.*, 2011). The frequency of anomalies also vary by affected organs and systems and in contrast with studies that showed the cardiovascular system to have the highest number of associated anomalies (Shafi *et al*, 2003; Genisca et al., 2009), musculo-skeletal system have the highest number of associated anomalies in the present study. Information on associated anomalies is obtained during the initial examination by the surgeons and clinical photographs are available in the database. A recent study shows an increase in the ascertainment of associated anomalies after a year follow-up examination (Rittler *et al.*, 2011). In our database, it is possible that these are under estimated since there is no follow-up examination for newborns with clefts. Only one center in our study included the types of clefts with associated anomalies and so we did not include analyses describing the types of clefts with associated anomalies.

Positive family history with non-syndromic OFC varies in the literature and ranges from 17% to 35% (Peterka *et al.*, 1996; Jaruratanasirikul *et al.*, 2008; Martelli *et al.*, 2010). In our study, 10.4% of individuals have one or more affected relatives which are lower than all the previously reported studies.

Currently, there are no clinical geneticists working with cleft teams in Nigeria, meaning we rely solely on the detailed description of identified individuals by the operating surgeons. Therefore the 9% syndromic cases reported in our study is likely under-representing the proportion of syndromic cases which has been widely reported as 30% in the literature (Calzolari *et al.*, 2007). Phenotyping is an essential pre-requisite for very good human genetics and functional studies. Our group has strong collaboration with established and state of the art international craniofacial genetics research centers. With the support of these centers, we are able to define syndromic cases prior to genetic analysis since the two conditions (syndromic and non-syndromic clefts) have different genetic etiologies (Dixon et al., 2011). Clearly there is a need for clinical geneticists to be included in the cleft teams and counseling for families in Nigeria.

Our cleft teams do not have the full complement of professionals as recommended by the American Cleft palate Association and Eurocleft (Strauss, 1998, 1999; Shaw *at al.*, 2001). For instance, there are no speech pathologist

assigned for cleft individuals and only a few have orthodontics as part of their cleft team. This then limits our ability to estimate functional outcomes and provide evidence based holistic care for the families. This gap in expertise has been reported by previous studies (Akinmoladun and Obimakinde *et al.,* 2009; Butali and Adeyemo, 2011). Furthermore, the sociologists and psychologists are also not included in the management of these families leaving them to cater for their own social and psychological problems, which has direct impacts on the entire outcome and integration into the society.

LIMITATIONS

Although the present study recognizes the limitations in hospital based data and study, it provides for the first time in thirty years a more reliable estimate of the prevalence of OFC in Nigeria and a detailed description of cleft types, associated anomalies and affected relatives. Furthermore, it supports the need for a well established surveillance system for clefts and other birth defects that cause significant mortality and morbidity.

CONCLUSIONS

The prevalence rate of 0.5/1000 reported suggest that prevalence of OFC in Nigeria is low and the significant difference between unilateral clefts and gender

differences in the proportion of cleft palate only are consistent with several reports in the literature. The present study emphasizes the need for birth defects registries in developing countries in order to estimate the exact prevalence of birth defects including CLP. Epidemiology of birth defects provides good rationale and is an essential pre-requisite for studies into treatment outcomes, etiology and prevention of OFC in Nigeria and Africa.

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Table 1: Treatment Centers and hospital registries

Zones	Cleft lip (cleft lip only and unilateral cleft lip without or without palate)[+]		Cleft Palate		Bilateral Cleft lip (bilateral cleft lip with or without cleft palate)Palate[+]	
	Males	Females	Males	Females	Males	Females
A (AKTH)	347	316	7	9	28	5
B(UMTH)	90	62	6	3	8	8
B(NAKOWA)	150	125	5	6	5	14
B (FMC Gombe)	142	107	4	10	4	7
B(FMC Nguru)	119	67	6	4	0	0
D(LUTH)	85	86	28	38	22	13
E (Enugu)	112	81	3	17	17	16
Total*	**1045**	**844**	**59**	**87**	**84**	**63**

A- North West, B- North East, D – South West, E-South East.

[+]Data for cleft lip are cleft lip with cleft palate and cleft lip without cleft palate.

* This does not include 15 cases without gender definition.

Table 2: Distribution of OFC into gender and types

Comparison between clefts on the UCL(R) and UCL(L)			
Cleft types	Males	Females	Total
Unilateral Left clefts (ULC)	613	495	1108
Unilateral Right clefts (URC)	331	282	613
p-values	0.0001[a]		
BCL(P) versus UCL(P)			
Bilateral clefts	185	130	315
ULC	613	495	1108
URC	331	282	613
p-values	0.0001[b]		
Gender Comparison for Cleft lip only (CLO)			
Unilateral left CLO	504	401	905
Unilateral Right CLO	257	228	485
Bilateral CLO	101	67	168
p-values	0.07[c]		
Gender Comparison for Cleft lip with or without cleft palate (CL(P))			
Unilateral Right CL(P)	74	54	128
Unilateral Left CL(P)	109	94	203
Bilateral CL(P)	84	63	147
p-values	0.467[d]		
Gender Comparison for cleft palate only (CPO)			
CPO	26	45	71
Sub-mucous cleft palate	1	0	1
Cleft hard and soft palate Bilateral	5	15	20
Cleft hard and soft palate Right	1	1	2
Cleft hard and soft palate Left	0	1	1
Isolated cleft soft palate Bilateral	18	19	37
(p-values)	0.03[e]		
Oblique facial cleft Right	2	0	2
Oblique facial cleft Left	1	0	1
Oblique facial cleft Bilateral	1	1	2
Maxillary midline cleft lip and palate	4	5	9
Commissural	1	0	1
Multiple Clefts	0	1	1
Unclassified	NA	NA	15
Total	1188	994	2197

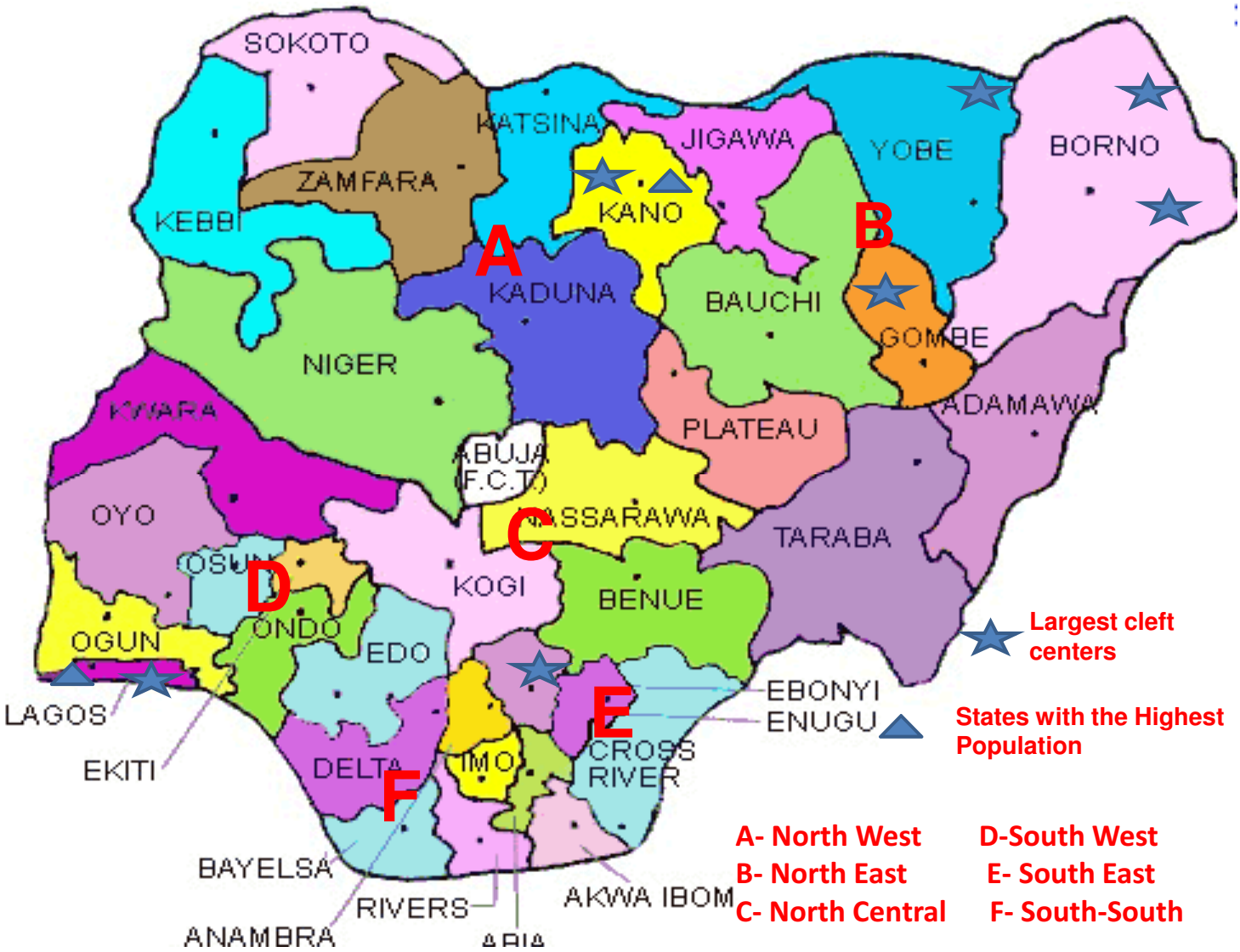
[a] difference between ULC and URC, [b] difference between BC and either ULC or URC, [c] difference between males and females with CL, [d] difference between males and females with CL(P), [e] difference between males and females with CP only.NA- no data.

Table 3: Co-morbidity identified during clinical examination

Patients with Associated Anomalies	Male	Female	Total
Heart	5	3	8
Urinary System	4	1	5
Eyes	11	10	21
Ears	7	6	13
Limbs	6	4	10
Fingers and toes	4	7	11
Skin	2	1	3
Tongue	4	6	10
Skull	6	4	10
Mandible	4	1	5
Retarded Growth	1	2	3
Mental Retardation	2	2	4
Total	56	47	103

Table 4: Family History and affected relatives

Affected Relatives	Male	Female	Total	Percentages
Immediate Relative	56	65	121	5.5%
Distant Relative	55	53	108	4.9%
Total	111	118	229	10.4%


SOKOTO
KATSINA
JIGAWA
YOBE
BORNO
ZAMFARA
KEBBI
KANO
A
B
KADUNA
BAUCHI
GOMBE
NIGER
ADAMAWA
KWARA
PLATEAU
ABUJA (F.C.T)
OYO
NASSARAWA
TARABA
C
OSUN
KOGI
D
BENUE
ONDO
OGUN
EDO
EBONYI
ENUGU
LAGOS
EKITI
E
DELTA
IMO
CROSS RIVER
F
BAYELSA
AKWA IBOM
RIVERS
ANAMBRA
ABIA
Largest cleft centers
States with the Highest Population
A- North West
B- North East
C- North Central
D-South West
E- South East
F- South-South