Congenital Heart Defects in Orofacial Cleft: A Prospective Cohort Study

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Abstract

Background: Congenital heart defects (CHDs) are one of the most common associated anomalies in patients with an orofacial cleft (OFC). However, few studies have shown the association between cleft type and CHDs in our population. This study aimed to assess the prevalence of CHDs in a cohort of OFC patients at a tertiary health facility in Nigeria, as well as assess the risk of CHD by OFC type. **Materials and Methods:** This was a prospective study design. Patients with an OFC were consecutively enrolled at a single OFC treatment facility. All subjects were assessed by a paediatric cardiologist and had echocardiography done. They were categorised based on the presence of CHDs, as well as the OFC phenotypic type (cleft lip and/or alveolus, cleft lip and palate and cleft palate only). Statistical analysis was done using STATA version 14 (College Station, Texas), and significance was set at $P < 0.05$. **Results:** A total of 150 subjects enrolled in the study over a period of 2 years (2018–2020). The median age of subjects was 6 months (interquartile range: 2–24), and 54.7% were female. The prevalence of CHDs in the subjects reviewed was 30.7%. Based on the severity of CHDs, the majority presented with simple defects (95.6%). Overall, the most common presentation was patent foramen ovale (12.7%), followed by septal defects (8.0%). There was no significant association between cleft type and the odds of a CHD. **Conclusion:** The study reports a relatively high prevalence of CHDs in patients with OFC; however, there was no association between the risk of CHD by cleft type. Although a majority of CHDs may pose a low operative risk, cardiac evaluation is recommended for all cases of OFC to aid the identification of potentially high-risk cases.

Keywords: Cleft lip and palate, cleft lip, cleft palate, congenital heart defects, non-syndromic clefts, syndromic clefts

Introduction

Orofacial clefts (OFCs) are birth defects that affect approximately 1 in every 600 newborn babies worldwide.[1] OFC is often associated with other congenital abnormalities or organ defects, and cardiovascular anomalies are one of the most common congenital anomalies in patients with OFCs.[2] Globally, the incidence of congenital heart diseases (CHDs) and anomalies ranges from 1 to 11.3 per 1000 live births.[3] The presence of these congenital anomalies tends to complicate the surgical management of cleft lip and/or palate (CLP). Harry *et al*.[4] reported a delay of 2 months in the timing of surgical repair of cleft palate in patients with associated CHDs.

Otaigbe *et al*.[5] in a preliminary investigation of the association of OFC with CHDs, done in Nigeria, reported a prevalence of 15% in a sample of 20 cases. Similarly, in a relatively small sample of 30 OFC cases, CHDs were recorded in 20% of the cases, with two-thirds associated with cleft lip and palate.[6] In addition, a retrospective study in Nigeria reported a prevalence of CHDs of 3.8% among a larger OFC population of 133.[7] Studies from other population groups outside Nigeria have reported an incidence ranging between 5.4% and 25.8% for CHDs in patients with OFCs.[4,8-11] Among CHDs, septal defects and patent ductus arteriosus (PDA) defects are the most common defects.[3,4]

While three studies have investigated this relationship in our population,[5-7] additional data from our cleft treatment facility

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will serve to validate these findings and add to the existing body of knowledge. This study aimed to assess the prevalence of CHDs in children with OFCs at a tertiary health facility in Nigeria, as well as assess the risk of CHD by OFC type. Findings from this study will guide the preoperative planning and risk stratification of patients with an OFC.

Materials and Methods

Study design

We conducted a prospective study in a cohort of patients with OFCs. The study forms part of the project on cardiovascular anomalies in OFC funded by the University of Lagos Central Research Committee grant.

Study population and settings

Participants in this study were patients from the OFC clinic at the Lagos University Teaching Hospital Lagos, Nigeria. Approval was obtained from the Health Research Ethics Committee of the Hospital (HREC/APP/1678). The period of the study was between August 2018 and August 2020.

Power analysis

The findings of a previous study conducted by Otaigbe *et al*.[5] were used to estimate the prevalence of CHDs in patients with OFCs[5] and by Ferencz *et al*.[3] used to estimate a 1.1% prevalence of CHDs in the normal population. With a two-sided significance level (1-alpha) at 95% and power (1-beta, % chance of detecting) of 80%, a sample size of 146 was estimated. The sample size was subsequently increased to 150 to account for non-response.

Eligibility criteria

The inclusion criterion was all subjects born with an OFC (syndromic and non-syndromic). Diagnoses of the OFC were coded according to the International Classification of Diseases (ICD), and the 10th ICD revision was used for this study (ICD 10. Q35–37 code).[12] The exclusion criteria were subjects with Tessier clefts and subjects from whom we were unable to obtain parental/guardian consent to participate in the study.

Study variables

The primary outcome was the presence or absence of congenital cardiovascular anomalies. The exposure we investigated was the type of OFC. In this study, the term OFC is subsequently defined as cleft lip with or without palate (CL/P). OFCs were grouped into three types: cleft lip (CL) (CL with or without alveolus-CL), cleft lip and palate (CLP) and cleft palate (isolated cleft of palate-[CP]) alone.

For congenital heart diseases, detailed medical history, physical examination and transthoracic echocardiography were performed on all subjects by a paediatric cardiologist at the time of presentation and diagnosis in the OFC clinic. The SonoScape SS1 ± 8000 Series Digital, Color Doppler Ultrasound System (SonoScape Medical Corp., Shenzhen, China) with a 2.0–5.0 MHz, phased array transducer and CX50 Philips portable ultrasound machine with S8-3 and S5-1 transducer probes were used for echocardiography. Standard two-dimensional, M mode and Doppler studies were done following the American Society of Echocardiography guidelines for paediatric echocardiogram.[13] Classification of the severity of CHDs was based on the studies by Bosi *et al*. and Hoffman *et al*.[14,15] with the study population grouped into no defect, simple and complex defects.

Statistical analysis

Frequencies, percentages (approximated to the nearest decimal unit) and Chi-square were used to compare groups as appropriate. Univariate and multivariate logistic regressions were conducted to assess the odds of CHDs by the three cleft types, adjusting for sex and the presence of a congenital syndrome. Statistical significance was defined as $P < 0.05$. The analysis was carried out using the STATA 15.0 software (StataCorp LLC Lakeway Drive, College Station, Texas, USA).

Results

A total of 150 subjects were enrolled in this study over 2 years (2018–2020). The median age of subjects with an OFC was 6 months (interquartile range: 2–24) within a range of 1–204 months. There were more females (54.7%; $n = 82$) with OFC anomalies than the males (45.3%; $n = 68$) with a ratio of 1.2:1 [Table 1].

The prevalence of CHDs in the subjects reviewed was 30.7% ($n = 46$) [Table 1]. The most common congenital cardiovascular anomaly was patent foramen ovale (PFO) in 12.7% ($n = 19$), followed by septal defects in 8.0% ($n = 12$) and PDA in 7.3% ($n = 11$) of the subjects. Among subjects with septal defects, atrial septal defects (ASDs) accounted for 4.7% ($n = 7$), whereas ventricular septal defects (VSDs) were 3.3% ($n = 5$). Other defects observed were tetralogy of Fallot (0.7%, $n = 1$) and truncus arteriosus (0.7%, $n = 1$). Based on the severity of the anomalies, a majority (95.5%) presented with simple defects compared to 4.5% ($n = 2$) who presented with complex defects. Almost half (49.3%) of the subjects investigated had cleft lip and palate, and a majority (89.3%) were non-syndromic [Table 1].

Of the 16 subjects that presented with a syndromic OFC, seven had CHDs (7/16, 44%) [Table 2]. Further, Table 3 demonstrates a bivariate and multivariate logistic regression model assessing the odds of a child presenting with a CHD based on sex, the presence or absence of a congenital syndrome and the type of OFC. The bivariate model showed no significant association between sex (odds ratio [OR]: 0.67; 95% confidence interval [CI]: 0.33, 1.35; *P*: 0.26), presence or absence of syndromes (OR: 1.89; 95% CI: 0.66, 5.44; *P*: 0.24) and type of cleft, with the presence of a congenital cardiovascular anomaly. Further, after adjusting for sex and the presence or absence of a congenital syndrome, the type of cleft did not demonstrate a significant relationship with the presence of a congenital cardiovascular anomaly.

Table 1: Description of variables in the study population

Variable	*n* (%)
Sex	
Male	68 (45.3)
Female	82 (54.7)
CHDs	
Present	46 (30.7)
Absent	104 (69.3)
Type of CHDs	
No defect	104 (69.3)
Patent foramen ovale	19 (12.7)
Patent ductus arteriosus	11 (7.3)
Atrial septal defect	7 (4.7)
Ventricular septal defect	5 (3.3)
Peripheral pulmonary artery stenosis	2 (1.3)
Tetralogy of Fallot	1 (0.7)
Truncus arteriosus	1 (0.7)
Severity of CHDs	
No defect	104 (70.0)
Simple	44 (28.7)
Complex*	2 (1.3)
Cleft type	
Cleft lip +/− alveolus only	41 (27.3)
Cleft lip and palate	74 (49.3)
Cleft palate only	35 (23.3)
Congenital syndrome	
Non-syndromic	134 (89.3)
Syndromic	16 (10.7)

*Complex defects: Tetralogy of Fallot, Truncus Arteriosus.
CHDs: Congenital heart defects

Table 2: Distribution of congenital heart defects by characteristics of study participants

Variable	No CHD, *n* (%)	CHDs, *n* (%)	*P*
Sex			
Male	60 (57.7)	22 (47.8)	0.26
Female	44 (42.3)	24 (52.2)	
Syndrome			
Syndromic	9 (8.6)	7 (15.2)	0.23
Non-syndromic	95 (91.4)	39 (84.8)	
Cleft type			
Cleft lip +/− alveolus only	28 (26.9)	13 (28.3)	0.27
Cleft lip and palate	48 (46.2)	26 (56.5)	
Cleft palate only	28 (26.9)	7 (15.2)	

CHDs: Congenital heart defects

Table 3 shows that participants with cleft lip and palate had increased odds of presenting with congenital cardiovascular anomalies compared to subjects with a CL (with or without alveolus) only; nonetheless, the relationship was not significant on either the bivariate or multivariate regression models ($P > 0.05$) [Table 3]. On the other hand, subjects with an isolated cleft of the palate had lower odds of presenting with a congenital cardiovascular anomaly compared to subjects with a CL (with or without alveolus) only (OR: 0.53; 95% CI: 0.18, 1.58; *P*: 0.26) [Table 3]. However, this relationship was also not statistically significant.

Discussion

The present study detailed a 30.7% prevalence of congenital cardiovascular anomalies in a cohort of subjects with OFCs. The findings show a higher prevalence compared to prior studies in the country who have reported a prevalence of between 3.8% and 20%.[5-7] However, the estimates from this study are lower than those found in studies outside the country with the prevalence of CHDs as high as 46.7%.[16,17] The relatively wide variation in the reported prevalence across the studies within and outside Nigeria may be based on the difference in the study population characteristics (age), patient selection methods and the diagnostic criteria for CHDs and defects. For example, in a study population with a larger sample of older aged patients with OFC, lesions such as small muscular VSDs may have closed in infancy, and this may produce an artefactual low prevalence.[18] Nonetheless, based on the relatively high prevalence of CHDs in the subjects compared to the general population globally (75 for every 1000 live births),[15,18] findings from this study underline the importance of cardiac screening for patients with an OFC.

In the current study, the most common CHDs were PFO and septal defects. In most cases, PFOs close spontaneously in early infancy.[18] Hence, the inclusion of PFOs as simple defects may account for the large prevalence reported in this study. Our findings are similar to reports by Shafi *et al*.[8] who reported septal defects as the most common malformations. Likewise, the relatively common prevalence of A-V septal defects in this study population is supported by Munabi *et al*.[19] who conducted a systematic review of studies on CHDs in non-syndromic OFCs. The systematic review[19] detailed atrial or VSDs as the most common forms of CHDs in cleft lip and/ or palate cases in all the studies reviewed with a prevalence of between 34.8% and 73.7% compared to the 26.1% reported in this study. In addition, within non-cleft populations, septal defects account for the most common form of CHDs seen.[18] However, the clinical implication of septal defects may not be far-reaching as most cases of ASDs are asymptomatic.[15,18] Majority of CHDs-small VSDs or ASDs and small PDAs close spontaneously before adolescence and may not need specialised cardiologic care.[18] Hence, the limited impact of these common findings on the timing of surgery and overall management of OFCs.

Further, the present study assessed the relationship between the type of cleft and the odds of a CHD. While no significant association was demonstrated in the current study, the systematic review by Munabi *et al*.,[19] earlier mentioned, showed that the odds of a CHD was significantly increased by as high as three times, in CP only and CLP, compared to CL only. Several authors confirm similar findings.[16,20,21] Sun *et al*.[2] in a study of 2180 cases of OFC in Eastern China reported a positive relationship between the incidence of

Table 3: Bivariate and multivariate logistic regression analysis of the association between sex, congenital syndromes and the presence or absence of congenital heart defects

Independent variables	CHD		CHD	
	OR (95% CI)	*P*	aOR (95% CI)	*P*
Sex				
Male	1		1	
Female	0.67 (0.33-1.35)	0.26	0.66 (0.32-1.37)	0.27
Congenital syndromes				
Non-syndromic	1		1	
Syndromic	1.89 (0.66-5.44)	0.24	2.21 (0.73-6.69)	0.16
Cleft type				
Cleft lip +/− alveolus only	1		1	
Cleft lip and Palate	1.17 (0.52-2.63)	0.71	1.11 (0.48-2.55)	0.81
Cleft palate only	0.54 (0.19-1.55)	0.25	0.53 (0.18-1.58)	0.26

OR: Odds ratio, aOR: Adjusted OR, CHDs: Congenital heart defects, CI: Confidence interval

CHDs and the severity of cleft type. This relationship may be explained by the action of teratogens such as retinoic acid which contribute to craniofacial abnormalities as well as foetal heart development by downregulation of platelet-derived growth factor C.[22]

Limitations of this study include the use of a single health facility and hospital-based subjects, which limits the pool and diversity of cases seen. Furthermore, the identification of syndromic clefts was based on only clinical evaluation and excluded any form of genetic testing. This is because the study centre does not routinely provide genetic testing for patients with OFCs. Finally, the high rate of PFOs may be attributed to the time of echo testing, as this was not standardised to a particular age, but differed by subjects, depending on the time of presentation at the OFC clinic for diagnosis. Nonetheless, the current study reports the prevalence of CHDs, as well as the severity of CHDs in a cohort of OFC subjects seen at a single OFC treatment facility. An understanding of this relationship is crucial to the surgical planning and safety of OFC patients.

The clinical implication of the findings from this study is that, although a majority of cases are simple defects, cases of OFC will benefit from a cardiac evaluation as part of their pre-operative workup. In limited-resource settings, performing echocardiography on every child that presents with OFC as part of the pre-operative workup may not be practical. Hence, centres may want to consider Kemper *et al*.[23] recommendation of pulse oximetry screening coupled with clinical evaluation by a paediatric cardiologist for cases of OFC, to identify severe forms of CHDs.

Conclusion

The current study reports a relatively high prevalence of CHD in a cohort of subjects with OFCs. A vast majority of CHDs seen were simple defects. Further, while subjects with cleft lip and palate had higher odds of CHDs compared to subjects with CL (with or without alveolus) only, this association was not statistically significant, as seen in literature from populations outside Nigeria. Future studies can use a multi-centre design, as well as a larger and more representative study population that would permit a more definitive inference.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Conflicts of interest

There are no conflicts of interest.

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