Original Article

Risk of Congenital Cardiovascular Anomalies in Patients with Non-Syndromic Orofacial Cleft: A Preliminary Case-Control Study

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ABSTRACT

Background: Orofacial clefts (OCs) are one of the most common craniofacial anomalies and are reported to be associated with congenital cardiovascular anomalies (CCAs). However, there is paucity of data in African populations on the risk of CCAs in OC patients compared to the general population. **Aims:** This study aims to determine the odds of congenital cardiovascular anomalies in patients with OC compared to the general population. **Subjects and Methods:** A case-control study design was used. Case subjects were non-syndromic OC subjects, while controls were non-syndromic subjects without OC. All subjects were thoroughly assessed by a pediatric cardiologist for CCAs; and grouped by OC phenotypic type (cleft lip and/or alveolus, cleft lip and palate, cleft palate only and Tessier cleft). Statistical analysis was done using STATA version 14 (College Station, Texas), and significance was placed at P value ≤0.05. **Results:** A total of 120 subjects (60 cases and 60 controls) were enrolled in the study. In total, 23.3% of the subjects had CCAs. Among the case group, 40% had CCAs compared to 6.7% in the control group. Patent foramen ovale (18.3%) and atrial septal defects (10.0%) were the most common type of CCAs in cases, respectively. Further, cases had significantly higher odds of CCAs compared to controls (OR: 9.3; CI: 2.8, 39.4). **Conclusions:** Our finding reveals that the odds of CCAs are significantly higher in patients with OC than the general population. Future studies could assess the effect of CCAs on surgical outcome.

KEYWORDS: *Congenital cardiovascular anomalies, orofacial cleft*

INTRODUCTION

Orofacial clefts (OCs) are one of the most common congenital craniofacial anomalies seen globally.[1] The incidence of OCs globally is estimated at 7–10/10,000 live births, with variations depending on population group and geographic region.[1,2] These variations may be due to differences in genetic and environmental exposures. The prevalence of OC is highest among Asians and Native-Americans, followed by Caucasians and least in African populations. In Nigeria, a prevalence of 0.5 per 1,000 live births has been reported.[3]

Identification and knowledge of risk factors and co-existing associations with OCs are important for multidisciplinary management.

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Thirty percent of patients with OCs have been reported to have coexisting syndromes and/or anomalies.[4] These anomalies include cardiovascular, neurological, renal, and musculoskeletal structures.[4,5] The presence of coexisting congenital cardiovascular anomalies is common in patients with OC.[6,7] Congenital cardiovascular anomalies are defects in the structure of the heart which could result in cardiac morbidities and complications. A systematic review of the literature between 1980 and 2015 detailed congenital heart defects in 7.42% of patients with

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non-syndromic OC, with the risk highest in cases of cleft palate and least in cases of cleft lip only, compared with the general population.[8] In Nigeria, the prevalence of congenital heart defects in patients with OC ranges between 3.8% and 15%.[9,10] However, there exists a dearth of literature on the risk congenital cardiovascular anomalies in OC patients compared to the non-cleft population, particularly in African populations.

The aim of this study is to investigate the odds of congenital cardiovascular anomalies (CCAs) in patients with non-syndromic OC compared to the general population. Findings from this study may support the development of pre-operative screening protocols to rule out cardiovascular risk in OC patients in resource-limited settings. These screening protocols may reduce anesthetic risk and help identify previously undiagnosed cardiovascular anomalies.

Subjects and Methods

Study design and location: This study was an unmatched case-control study conducted at the cleft and community health outpatient clinics of a tertiary hospital in Lagos State, Nigeria between January 2017 and January 2019.

Ethics: Ethical approval was obtained from the Health Research and Ethics Committee of the Lagos University Teaching Hospital Health Research Ethics Committee with number: HREC/APP.1678. The parents and legal guardians of the enrolled participants were informed about the study and written consent was obtained before Paediatric cardiovascular evaluation.

Research participants

Cases: We enrolled children under the age of 5 years with non-syndromic OC undergoing management at the cleft clinic of the tertiary hospital. Sixty parents/guardians and their children were informed about the study and enrolled after consent was obtained.

Controls: Sixty healthy children without OC and syndromic defects below 5 years were enrolled from the community health clinic of the hospital. The community health clinic where controls were enrolled provides primary health vaccination services to children of diverse socioeconomic backgrounds within the state.

Eligibility criteria: The inclusion criterion was all subjects born with CL/P aged between 0 and 5 years for cases (non-syndromic), and subjects born without CL/P aged between 0 and 5 years for controls (without other congenital anomalies). The exclusion criteria were syndromic children 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 OC in a child patient. In this study, the term OC is subsequently defined as cleft lip with or without palate (CL/P). Cases of OC were grouped into as cleft lip (isolated cleft lip with or without alveolus- CL), cleft lip and palate (CLP), cleft palate (isolated cleft of palate- CP), and Tessier cleft (facial clefts).

The exposure we investigated was the presence of a congenital cardiovascular anomaly in the child.

Case definition for congenital cardiovascular anomalies: The medical history, physical examination, and transthoracic echocardiography were performed on all subjects by a Pediatric cardiologist. The Sonoscape SS1 ± 8,000 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 2D, M mode, and Doppler studies were done following the American Society of Echocardiography guidelines for Pediatric echocardiogram.[11] Subjects with CCAs were identified and stratified to simple or complex defects based on a classification proposed by Bosi *et al*. and Hoffman *et al*.,[12,13] with the exclusion of Tetralogy of Fallot which was grouped as a complex defect. Simple CHD include isolated major entities, while Complex CHD include Tetralogy of Fallot and CCAs that do not fit into defined categories and required a more comprehensive description of each defect.[12]

Sample size: Sample size was calculated using Kelsey's method in observational epidemiology studies on Open Epi (https://www.openepi.com/SampleSize/SSCC.htm) for case-control studies. Findings of a previous study conducted by Otaigbe *et al*.[10] was used to estimate the percentage of CCAs in cases (15%), and a proportion of non-cleft children with CCAs of 1% was based on another study.[8] Based on an OC to control ratio of 1:1, an 80% power and a 95% two-sided confidence interval, 59 children were required in each group. This was increased to 60 in each group to account for non-response, and a total of 120 participants.

Statistical analysis: Frequencies, percentages (approximated to nearest decimal unit), Fischer's exact test, and logistic regressions were used to compare groups as appropriate. Univariate and multivariate logistic regressions were conducted for type of OC defects to assess the odds of CCAs in cases compared to controls. Analysis was conducted with STATA version 14 (College Station, Texas). Statistical significance was defined as ≤0.05.

Results

General characteristics of subjects

A total of 120 subjects, with 60 cases and 60 controls. The mean age of enrolled subjects was 18 months (range of 2–120 months), while the male to female ratio was 1.4:1. In total, 23.3% of the subjects had CCAs. Among the case-subjects, 40% had CCAs compared to 6.7% in the control-subjects. Patent foramen ovale (18.3%) and atrial septal defects (10.0%) respectively were the most common type of CCAs in cases with OC; and Patent ductus arteriosus (3.3%) and ventricular septal defects (3.3%) respectively, were the most common in controls without OC. The most common cleft types seen among case-subjects were cleft lip and palate (38.3%) and cleft lip with or without alveolus (36.7%) respectively [Table 1].

Table 1: Description of variables by case and control population

Variable	Case (%)	Controls (%)
Sex		
Male	33 (55)	36 (60)
Female	27 (45)	24 (40)
Cardiovascular anomaly (CCA)		
Present	24 (40.0)	4 (6.7)
Absent	36 (60.0)	56 (93.3)
Type of CCA		
No defect	36 (60.0)	56 (93.3)
Patent Foramen Ovale	11 (18.3)	0 (0)
Patent Ductus Arteriosus	4 (6.7)	2 (3.3)
Atrial Septal Defect	6 (10.0)	0 (0)
Ventricular Septal Defect	2 (3.3)	2 (3.3)
Tetralogy of Fallot	1 (1.7)	0 (0)
*CCA severity		
No defect	36 (60.0)	56 (93.3)
Simple	23 (38.3)	4 (6.7)
Complex	1 (1.7)	0 (0)
Cleft type		
No cleft defect	0 (0)	60 (100)
Cleft lip +/- alveolus only	22 (36.7)	0 (0)
Cleft lip and Palate	23 (38.3)	0 (0)
Cleft Palate only	13 (21.7)	0 (0)
Tessier cleft only	2 (3.3)	0 (0)

*CCAs: Congenital cardiovascular anomalies

Table 2: Odds of CCAs in Cases and Controls

Study characteristics	Case	Control	OR [95% CI]	*P*
Cardiovascular defect				
Present	24	36	1 [reference]	
Absent	4	56	9.33 [2.83, 39.35]	0.000*

**P*<0.05. CCAs: Congenital cardiovascular anomalies. OR: Odds ratio. CI: Confidence interval

Table 3: Multivariate logistic regression with CCA as binary outcome variable

CCAs	Odds ratio (95% CI)	*P*
No cleft	1	
Cleft lip +/- alveolus only	9.69 (2.58, 36.40)	0.001*
Cleft lip and Palate	8.99 (2.42, 33.53)	0.001*
Cleft Palate only	8.75 (1.93, 39.57)	0.005*

**P*<0.05. CCAs: Congenital cardiovascular anomalies

Distribution of CCAs severity by Cleft defect type

A vast majority of anomalies seen were simple defects (99%), with one case of a complex defect (tetralogy of fallot) recorded. A majority of CCAs were recorded among subjects with cleft lip with or without alveolus (33.3%), followed by subjects with cleft lip and palate (29.6%), cleft palate only (18.5%), and least among subjects with Tessier cleft (3.7%) [Table 1].

Odds of CCAs in subjects with orofacial cleft

Cases with OC had significantly higher odds of CCAs by a factor of 9.3 compared to controls without OC (95% CI: 2.8, 39.4; *P* value: 0.00) [Table 2]. The odds of CCAs among cases was highest among subjects with cleft lip with or without alveolus (OR: 9.7; 95% CI: 2.6, 36.4; *P* value: 0.001), cleft lip and palate (OR: 8.9; 95% CI: 2.4, 33.5; *P* value: 0.001), and cleft palate only (OR: 8.8; CI: 1.9, 39.6; *P* value: 0.005), respectively, compared to controls- subjects without OC [Table 3].

Discussion

This study presents the first data in our region on the risk of cardiovascular anomalies in a population with OC compared to the general (non-cleft) population. Our findings reveal that the odds of CCAs are significantly higher in non-syndromic OC populations compared with the general population. Further investigation by cleft type reveals the odds of CCAs are highest in cases with cleft lip with or without alveolus compared with the general population; while significantly high odds are also recorded in cases with cleft lip and palate, cleft palate only compared with the general population. These findings are supported by several studies in the United States,[14] Brazil,[15] Europe,[16] and Asia[5,7,17,18] and a systematic review of studies from nine countries.[8]

The association between cardiovascular and craniofacial defects, such as OC, may be based on the cardio-craniofacial development module described by Keyte and Hutson.[19] The module is based on the principle that craniofacial tissues are associated with the action of neural crest cells. Cardiac neural crest cells communicate during their caudal migration with different cell types: pharyngeal endoderm, ectoderm, mesoderm, and endothelial cells, thereby providing a connection between neural folds (which form the face),

and the cardiovascular system. Therefore, coexisting cardiovascular and OC anomalies may develop when there is a damage to the cardio-craniofacial development module during embryogenesis.[19]

Further, the presentation of CCAs in patients with OC may differ based on the type of cleft. Munabi *et al*.[8] in a systematic review with data from over 7,000 patients across nine countries, reported the prevalence of CCAs to be highest in cases with cleft palate only (13.0%). After comparing patients of different cleft types, both cleft lip and palate (CLP) and cleft palate only (CP) had significantly increased odds of congenital heart disease (CHD) compared with cleft lip only.[8] On the other hand, our study reveals a higher prevalence of CCAs in patients with CL and CLP than CP. In addition, from our study, the odds of CCAs were highest in CL patients compared with CLP and CP patients. Our findings also differ from Akhiwu *et al*.[9] who reported an equal frequency of CHD in both CL and CLP, and Barbosa *et al*.[20] who reported no correlation between the presence of CCAs and the type of OC.

The most common CCAs in patients with OC from this study were Patent foramen ovale (PFO) and Atrial septal defects (ASD), respectively. Similarly, Akhiwu *et al*.[9] and Asani *et al*.[21] who investigated CCAs in a similar population as this study reported that ASD was the most common CCA in OC patients. However, our findings differ from Otaigbe *et al*.[10] who reported PDA and VSD as the most common CCAs in patients with OC. Further, Patent foramen ovale has been reported as a common finding in OC patients.[14] Nonetheless, a vast body of literature has reported ASD and VSD defects as the most common CCAs in patients with OC.[5,8,9,15-18,22,23]

While this study presents the first evidence of higher odds of CCAs compared to the general population in our region, we acknowledge certain limitations. First, the subjects were drawn from a hospital-based population, which may not be representative of the entire country or region. Second, we used a relatively small sample size, which limited the level of sub-analysis which could be done by cleft type (unilateral and bilateral clefts). Third, we did not adjust for risk factors such as birth weight, parental age, and folic acid use during ante-natal period by mother. However, based on the rigorous methodology used in this study, our findings provide data supporting preoperative screening for CCAs in patients with cleft defects.

Future studies could assess the effect of congenital cardiovascular anomalies on surgical outcome. In addition, the effect of environmental risk factors on the incidence of congenital cardiovascular anomalies in patients with OC could be investigated. We recommend that thorough pediatric clinical assessment with echocardiography be performed on all patients with OC (regardless of type); and proper management of complex congenital cardiovascular anomalies be done before surgical repair of the coexisting cleft defect.

Conclusion

Understanding the risk and potential CCAs in patients with OC is important in pre-operative screening and surgical planning for patients with OC. Our finding reveals that the odds of CCAs is significantly higher in patients with OC than the general population; and more so in patients with cleft lip with or without alveolus. Based on the common types of CCAs seen, PFO, PDA, and ASD may pose low preoperative risk, and should not deter early surgical management.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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