Prevalence and Characteristics of Non-Syndromic Orofacial Clefts and the Influence of Consanguinity

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*The **Objective** of this study was to identify the prevalence and describe the characteristics of non-syndromic orofacial cleft (NSOFC) in Jeddah, Saudi Arabia and examine the influence of consanguinity. **Study Design**: Six hospitals were selected to represent Jeddah's five municipal districts. New born infants with NSOFC born between 1st of January 2010 to 31st of December 2011 were clinically examined and their number compared to the total number of infants born in these hospitals to calculate the prevalence of NSOFC types and sub-phenotypes. Referred Infants were included for the purpose of studying NSOFC characteristics and their relationship to consanguinity. Information on NSOFC infants was gathered through parents' interviews, infants' files and patient examinations. **Results**: Prospective surveillance of births resulted in identifying 37 NSOFC infants born between 1st of January 2010 to 31st of December 2011 giving a birth prevalence of 0.80/1000 living births. The total infants seen, including referred cases, were 79 children. Consanguinity among parents of cleft palate (CP) cases was statistically higher than that among cleft lip with or without cleft palate (CL/P) patients (P=0.039). Although there appears to be a trend in the relationship between consanguinity and severity of CL/P sub-phenotype, it was not statistically significant (P= 0.248). **Conclusions**: Birth prevalence of NSOFC in Jeddah City was 0.8/1000 live births with CL/P: 0.68/1000 and CP: 0.13/1000. Both figures were low compared to the global birth prevalence (NSOFC: 1.25/1000, CL/P: 0.94/1000 and CP: 0.31/1000 live births). Consanguineous parents were statistically higher among CP cases than among other NSOFC phenotypes.*

***Keywords**: Prevalence, Saudi Arabia, cleft lip, Cleft palate, orofacial cleft, consanguinity*

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INTRODUCTION

Non-syndromic orofacial clefting (NSOFC) is defined as partial or complete fissuring of the upper lip with or without fissuring of the palate (isolated cleft lip (CL) or cleft lip and palate (CLP)) or fissuring of the palate alone (isolated cleft palate (CP).[1] NSOFC with or without associated anomalies is the most common craniofacial defect throughout the world.[2,3] The estimated overall global prevalence of NSOFC is 1.25 in every 1000 live births.[4] The prevalence of NSOFC varies considerably across geographic areas and ethnic groupings, for example occurring more commonly among Asian than African populations.[5] In addition, the presence of consanguineous marriages in a community has been suggested to increase the prevalence of congenital anomalies recessive gene disorders.[6] Therefore, it is important to know the prevalence of craniofacial anomalies in every community and understand the possible predisposing factors, to determine the magnitude of the problem and health care challenges including the possibility of prevention.

Table 1. Birth prevalence of NSOFC from Jan 2010 to Jan 2011 according to place of birth and OFC phenotype

Hospitals	Total births	CL	CLP	CP	Total NSOFC	Birth prevalence NSOFC/1000 births
Al-Messadia Maternity	13,004	3	3	2	8	0.62
King Abdulaziz University	8,725	3	7	3	13	1.5
National Guard	9,690	5	4	0	9	0.93
King Fahad Armed	10,969	3	1	1	5	0.46
Al-Azizia Maternity	3,508	2	0	0	2	0.57
Total	45,896	16	15	6	37	
Birth prevalence /1000 births	1000	0.35	0.33	0.13		0.80

Saudi Arabia, a population with high consanguinity, does not have national epidemiological data on NSOFC. Few of the main hospitals have statistical or medical records for the frequency of NSOFC cases attending their hospitals. However, the only accurate detailed registry is in King Faisal Specialized Hospital and Research Centre in Riyadh.[7] Studies that have been carried out investigating the prevalence of NSOFC in Saudi Arabia and Middle East countries have reported highly variable birth prevalence and incidences ranging from 0.3 to 2.19 per 1000 births.[8-12] In addition, the studies carried out in Saudi Arabia were all single hospital based and none were carried out in Jeddah city. Therefore, the aim of this study was to identify the prevalence and describe the characteristics of non-syndromic orofacial cleft (NSOFC in Jeddah, Saudi Arabia and examine the influence of consanguinity

MATERIALS AND METHOD

This is a descriptive study, where NSOFC cases were prospectively identified through surveillance of births in governmental hospitals of Jeddah area for a period of two years. Referred Infants with NSOFC were also included in the study.

All government hospitals were surveyed for birth prevalence via the Ministry of Health statistical records.[13] Accordingly, six hospitals that represent all districts and covered most of the cities births were selected. These hospitals included three from the Ministry of Health; Al-Messadia Maternity Hospital and Al-Azizia Maternity Hospital covering 67.3% of the total births in the Ministry of Health hospitals in Jeddah;[13] and King Fahad Hospital which is a referral centre for maxillofacial surgery. In addition, three other referral centres; King Abdulaziz University Hospital, King Abdulaziz Medical city, and King Fahad armed Hospital were also included. Cases from King Fahad Hospital and Al Mesadia Maternity Hospital were combined and the two hospitals were considered as one centre as they are located in the same district. All infants born in the designated hospitals were included in this study to calculate the prevalence. Also, infants referred to these hospitals during the period of the study that were 18 months or less, were included for the purpose of studying the characteristics of NSOFC and their relationship to consanguinity.

Ethical approval was obtained from the Ministry of Health, from the National Guard Hospital and from King Fahad Armed Hospital. Information on patients born, and referred, with NSOFC was obtained by the research coordinator. Identification of patients was carried out prospectively by actively inquiring about patients every two weeks through nurses working in neonatal unit, neonatal intensive care (NICU), plastic surgery and orthodontic clinics.

Data collection was carried out through (a) clinical examination by one person (the research coordinator), (b) parental interview. In addition, OFC diagnosis was confirmed by (c) reviewing the medical records and (d) contacting the infants' paediatrician.

NSOFC phenotype was classified according to LASHAL classification which subdivided cleft lip and alveolus according to side

Table 2. Distribution of NSOFC sub-phenotypes born in 2010 and 2011 in the included hospitals according to gender

Phenotype	Sub-Phenotype	Frequency of NSOFC			
		Frequency of NSOFC in 2011			Frequency of NSOFC in 2010 & 2011 (%)
		Male	Female	In 2011 (%)	
CL	Right incomplete CL	3	0	3 (14.3)	3 (8.1)
	Left incomplete CL	1	1	2 (9.5)	4 (10.8)
	Left complete CL	1	0	1 (4.8)	2 (5.4)
	Bilateral incomplete CL	3	1	4 (19)	6 (16.2)
	Bilateral complete CL	1	0	1 (4.8)	1 (2.7)
CLP	Right incomplete CLP	1	0	1 (4.8)	2 (5.4)
	Right complete CLP	2	1	3 (14.3)	4 (10.8)
	Left complete CLP	0	1	1 (4.8)	1 (2.7)
	Left incomplete bilateral CLP	1	0	1(4.8)	3 (8.1)
	Bilateral complete CLP	0	1	1 (4.8)	5 (13.5)
CP	CP	1	2	3 (14.3)	6 (16.2)
Total		14	7	21 (100)	37 (100)

Table 3. Distribution of the NSOFC cases according to gender and sub-phenotype in born and referred cases

Phenotype	Sub-phenotype	Male	Female	Frequency	Percentage
CL N=30	Right incomplete CL	3	2	5	6.3
	Left incomplete CL	2	7	9	11.4
	Left complete CL	4	3	7	8.9
	Left incomplete right complete bilateral CL	1	0	1	1.2
	Bilateral incomplete CL	4	2	6	7.6
	Bilateral complete CL	1	1	2	2.5
CLP N=34	Right incomplete CLP	4	1	5	6.3
	Right complete CLP	2	4	6	7.6
	Left complete CLP	4	4	8	10.1
	Left incomplete right complete bilateral CLP	4	2	6	7.6
	Bilateral complete CLP	7	2	9	11.4
CP N=15	CP	6	9	15	19
	Total	43	36	79	100.0

(right or left), and palate to hard and soft (14). In this study, CP was not further divided to soft and hard as this information was not always available because some referred patients were seen after the surgery which made it difficult to accurately record CP sub-phenotype.

The total number of NSOFC infants born in these hospitals from 1st of January 2010 to 31st of December 2011 was compared to the total number of births in these hospitals taken from the statistical records of each of these hospitals in the same period to calculate NSOFC birth prevalence. The additional referred NSOFC patients were not included in the estimated birth prevalence.

In order to assess the severity of CL and its relationship to consanguinity, cleft lip with or without palate (CL/P) which included CL and CLP cases, were grouped according to the extent of cleft lip as complete CL (with absence of Simonart's Band) and incomplete CL (and presence of Simonart's Band). In this grouping bilateral CL with incomplete CL in one side and complete CL of the other side could not be classified as either complete or incomplete CL/P and were omitted from sub-phenotype analysis. Also, to assess the severity, CL/P was grouped according to site to unilateral CL/P and bilateral CL/P.[4]

Statistical analysis

The data were analyzed using statistical Package for Social Studies (SPSS) version 16. The descriptive epidemiology of NSOFC was displayed in frequency and percentage. Chi square was used to test for significance in the relationship between consanguinity and severity of CL/P. Also it was used to assess the relationship between consanguinity and NSOFC. Significance level was set as $P<0.05$.

Table 4. The relationship between NSOFC phenotype and consanguinity

Cleft type	Consanguinity (%)		Total (100%)	P value
	Yes	No		
CL	14 (56)	11 (44)	25	0.039*
CLP	14 (45.2)	17 (54.8)	31	
CP	12 (85.7)	2 (14.3)	14	
Total	40 (57.1)	30 (42.9)	70	

*Statistically significant

RESULTS

Data collection throughout the period of the study revealed 79 NSOFC cases. There were 37 cases born and 42 cases referred (18 months of age or less) in the six designated hospitals. Of these, ten cases (12.6%) had missing information because the research coordinator was not able to reach the parents of the infant. However, available information for these cases gathered through examination and file records were included in this study.

Birth prevalence of NSOFC

Table 1 demonstrates the birth prevalence of NSOFC according to place of birth and OFC phenotype. Of 45,896 births between 1st of January 2010 and 31st of December 2011in the included governmental hospitals, 37 of the infants were classified as having NSOFC, giving a prevalence of 0.8 NSOFC per 1000 births. The birth prevalence for CL was 0.35/1000 births, for CLP was 0.33/1000 births, and 0.13 for CP (Table 1).

Table 2 shows the distribution of NSOFC sub-phenotypes born in 2010 and 2011. The frequency of bilateral CL/P was 15 cases (40.5%) including; seven bilateral CL (43.7%) compared to the total CL (16 cases) and eight bilateral CLP (53.3%) compared to the total CLP (15 cases). In unilateral CL, most clefts were left sided (6 cases) compared to the right side (3 cases). On the other hand, unilateral CLP occurred more in the right side (6 cases) compared to the left side (1 case).

Out of the 79 cases, 43 (54.4%) were males and 36 (45.6%) were females. The most common NSOFC phenotype was CLP; 34 cases (43%), then CL; 30 cases (38%), and the least common was CP; 15 cases (19%). The most common site of unilateral CL was the left site for CL; 16 (76.2%) compared to the right side; 5 cases (23.8%) and the right side for CLP; 11 cases (58%) compared to left side; 8 cases (42%) see Table 3. Complete unilateral or bilateral CL/P was seen in 32 cases (56%). There were 14 cases associated with other anomalies (17.7%).

Consanguinity and NSOFC phenotype

There were 40 cases (57.1%) NSOFC children born from consanguineous parents, with 23 cases (33%) being 1st cousins. Table 4 shows that Consanguinity among parents of cleft palate (CP) cases

Table 5. The relationship between consanguinity and the severity of CL/P sub-phenotype.

Description of NSOFC		Consanguinity		Total (100)	P value	OR (CI)
		Yes	No			
CL extension in CL/P N=50*	Complete	17 (56.7)	13 (43.3)	30	0.248	OR=1.96 CI=0.54 – 7.30
	Incomplete	8 (40.0)	12 (60)	20		
Site of CL in CL/P N=56**	Bilateral	13 (56.5%)	10 (43.5)	23	0.415	OR=1.56 CI=0.47 -5.25
	Unilateral	15(45.5)	18 (54.5)	33		

* Total less than 79 after excluding Bilateral CL/P with incomplete CL in one side (7 cases), CP and cases with missing information

** Total less than 79 after excluding CP cases and cases with missing information.

(85.7%) was statistically higher than that among CL (56%) and CLP (45.2%) cases (P=0.039). Out of the CL/P cases, isolated CL was more frequent in infants with consanguineous parents than CLP.

Table 5 shows the relationship between consanguinity and CL/P sub-phenotype severity. Cases with severe CL/P were more frequent in infants with consanguineous parents than those with non-consanguineous parents (complete CL in CL/P were 17 cases (56.7%) compared to 8 cases (40%) with incomplete CL, and 13 (56%) bilateral CL/P cases compared to 15 (45.5%) unilateral CL/P cases) but the relationship was not significant (P= 0.248).

DISCUSSION

This study is the first multicentre based study describing the birth prevalence of NSOFC in Jeddah city. In addition, it describes NSOFC sub-phenotype and consanguinity.

The birth prevalence of NSOFC over two year period was 0.8/1000 live births with CL/P 0.68/1000 and CP 0.13/1000 live births. Both of these figures were low compared to the global birth prevalence which was 1.25/1000 for NSOFC, 0.94/1000 for CL/P and 0.31/1000 for CP.[14] In 2012, a systematic review that was carried out to assess the prevalence of NSOFC in Saudi Arabia and Middle East countries found a wide range of results, from 0.3 to 2.19/ 1000 births.[15] The lowest prevalence of NSOFC was seen in Riyadh (0.23 and 0.3/1000 live births)[7,11] and the highest prevalence was seen in Al-Qaseem (2.19).[10] The differences in the birth prevalence of this paper from previous reports could again be due to the differences in study sample, study design and ascertainment with data collected from six centres through a single examiner. It could also be influenced by the differences in the prevalence of consanguinity in the different studied population. Consanguinity was reported by El-Hazmi *et al* to be 62.8% in Riyadh, 57.1% in Al-Qaseem and 44% in Makkah region which includes Jeddah city.[16] The birth prevalence of CL being similar to CLP differs from the global finding and previous studies in the Middle East which reported higher birth prevalence of CLP than CL.[3,15] This finding is supported by Mossey and Modell (2012) who suggested a decreases in the ratio between CLP and CL in regions with low prevalence of NSOFC.[4] They also suggested a less severe trend of OFC which was different from what we found in this research as the prevalence of bilateral CL/P (43.7% of CL cases and 53.3% of CLP cases) was higher than what was reported in other studies (about 10% in CL cases and 30% in CLP cases).[17-19] In unilateral CL, the left side was more common than the right side. However, in unilateral CLP, a right sided prevalence was more common than a left sided one. This was different from reports in previous studies where the left side was more commonly affected than the right side for both CL and CLP.[17,20,21] In addition, all cases with right complete unilateral CLP occurred in infants with consanguineous parents. This could indicate a specific etiological factor and a rare variant of a homozygous recessive transmitted gene that causes a specific OFC phenotype in the Saudi population. However, further national collaborative research that includes other medical centres from other cities in Saudi Arabia relating consanguinity with CL/P sub-phenotype is needed to clarify this observation.

Associated anomalies were found in 17.7% of cases. Although this is considered low, it is similar to previous studies in the Middle East which reported a range of 13 to 18 % associated anomalies.[10,11,18,22,23] However, other studies reported various ranges of associated anomalies prevalence ranging from 21% to 63%. This could be related to methodological differences, variable diagnosis of associated anomalies and ascertainment.[9, 24-26] Also, in this study, cleft palate had a higher prevalence of associated anomalies than other type of clefts (46.7%) which was consistent with other reports in the world.[3,12,27]

The severity of CL/P was grouped according to the degree of cleft lip extension into complete or incomplete CL/P. This grouping was suggested to investigate the biological rationale behind the prevalence of both groups. In the first group, which is complete clefting of the lip, a mesenchymal defect or failure of the two palatal shelves to meet was suggested. On the other hand, incomplete CL might indicate an alteration of the epithelial component of the palatal shelves and failure of epithelial breakdown. Thus, both groupings might indicate different genetic and environmental etiology.[4,28] The prevalence of complete cleft lip CL/P found in this study (60%) were less than what was reported in previous studies carried out by Silva Filho *et al* in 2006 and 1994 in Brazil with two samples in different years. They reported 70% prevalence of complete cleft lip in 2006 and 80% in 1994.[29,30] This difference could be related to different design of case grouping. As in the first study (2006), bilateral CL/P with complete CL on one side and incomplete CL in the other side was included in the classification groups. On the other hand, the 1994 study excluded all types of bilateral CL/P.

More than half of the patients examined during the time of the study were referred cases born in other hospitals. These referred cases showed more severe phenotypes of NSOFC than those born in the included hospitals. This could indicate a higher demand of health care and management might need to be met by the governmental hospitals provision of facilities and personal.

Consanguinity prevalence in Saudi Arabia is considered one of the highest in the world (56%) and are mainly first degree cousins (41%).[16] According to Leite *et al* [31] and Elahi *et al* [32] consanguinity could be a predisposing factor for orofacial cleft. In this study the prevalence of NSOFC in consanguineous marriages was 57% with

33% being 1st degree cousins which is higher than the prevalence of consanguinity in Makkah region which includes Jeddah city (44%) and 1st degree cousins are (20%).[31] Also, the prevalence of CP was significantly higher in infants with consanguineous parents (85.7%). Although Ravichanran *et al* 2012 reported higher prevalence of CP associated with consanguinity (59%) than CL/P (55.5%), the difference in their findings were less than what was reported in this study.[33] In addition, when considering the extension of CL in infants with non-consanguineous parents, the number of complete CL were almost the same as incomplete CL. However, in consanguineous parents, complete cleft lip was higher than incomplete cleft (56.7% compared to 40%) but the relationship was not statistically significant.

There were some limitations that should be considered in future research. In this study, no cases were reported with sub-mucosal cleft or with bifid uvula. However, bifid uvula is not easily detected, and could have been overlooked by the health providers examining the patients. In addition, sub-mucosal cleft is difficult to identify clinically, usually not detected until children are older and was reported to have a low prevalence.[34] A retrospective data collection with careful examination and registration is needed to detect such cases.[35] Also, stillbirths were not included in this study which might cause some bias.[12,23] However, stillbirth prevalence is expected to be low. It accounts for 15.7 in every 1000 live births recorded by the Ministry of Health, Saudi Arabia.[13]

Larger scale national research that includes other centres in other Saudi cities should be considered in the future in order to adequately and nationally describe NSOFC sub-phenotype in relation to different variables. Private hospitals should be considered in future research as it carries part of the NSOFC cases load.

CONCLUSION

The birth prevalence of NSOFC in Jeddah City was 0.8/1000 live births with CL/P 0.68/1000 and CP 0.13/1000 live births. Both of these figures were low compared to the global birth prevalence which was 1.25/1000 for NSOFC, 0.94/1000 for CL/P and 0.31/1000 for CP. Consanguineous parents were statistically higher among CP cases than among other NSOFC phenotypes. A trend of increased severity of NSOFC sub-phenotype was noticed in infants with consanguineous parents but there was no significant relationship.

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