ORIGINAL REPORT

Epidemiological Aspects of Cleft Lip and Palate in Iran

Alireza Karimee Yazdee[1], Babak Saedi[1], Amir Arvin Sazegar[1], and Parvin Mehdipour[2]

[1] *Department of Otolaryngology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran*

[2] *Department of Medical Genetics, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran*

Received: 12 May 2008; Received in revised form: 2 Sep. 2009; Accepted: 7 Nov. 2009

Abstract- Orofacial clefts, including cleft lip with or without cleft palate (CL (P)), are common congenital malformations, second only to clubfoot in frequency of occurrence. The epidemiology and genetics of this disorder have been studied extensively in various countries by several investigators. The objective of this study is to assess the epidemiology and some genetic aspects of orofacial clefting at Imam Khomeini Hospital in Tehran. This study was a 7-year case series (retrospective) study from 1999 to 2006. The setting for the study was Imam Khomeini Hospital in Tehran, and the participants were all consecutive surgical cases with orofacial clefts referred to this hospital. One hundred and 77 cases of cleft lip and/or cleft palate were recorded during these 7 years. Seventy four of them (41.8%) were female and 103(58.2%) were male (M/F Ratio=1.39). Of all patients, 40 persons (22.6%) had isolated CP, 45 (25.4%) had cleft lip without cleft palate, and 92 (52%) had cleft lip with cleft palate (CL+P). Their M/F ratios were 1.66, 0.6 and 1.96 respectively. Of all CL (P) probands, 41 patients (29.9%) were bilaterally affected. In unilateral cases, the left side was affected nearly twice as frequently as the right side. Among the patients, 23 cases (13%) had other malformations; most commonly head and face abnormalities and then congenital heart disease. Fifty-four patients (30.5%) had consanguine parents; 33 (18.6%) were first cousins, 7 (4%) were second cousins, and 14 (7.9%) were distant relatives. There was a positive family history for cleft syndrome in 23 cases; most commonly CL-P. Our study reveals that the epidemiologic aspects of oral clefts in Iran are very similar to other Caucasian populations. It also suggests that a routine screening such as echocardiography and ruling out skeletal, hearing and visual problems may be necessary in cleft patients especially in children. It seems that genetic counseling and karyotyping can be very useful in patients with multiple malformations.

Acta Medica Iranica, 2011; 49(1): 54-58.

Keywords: Cleft lip; Cleft palate; Abnormalities; Congenital abnormalities; Epidemiology; Iran

Introduction

Orofacial clefts including cleft lip (CL), cleft palate (CP) and cleft lip and palate (CL+P)) are common congenital malformations, second only to clubfoot in frequency of occurrence. Every day some 700 children with cleft lip and/or cleft palate are born in the world, which means that a baby with cleft is born every 2 minutes or 240,000 children per year (1, 2).

Cleft lip and/or cleft palate account for 65% of all head and neck anomalies(3). In the United States, 20 infants are born with an orofacial cleft on an average day, or 7500 every year. Children who have an orofacial cleft require several surgical procedures and complex medical treatments; the estimated lifetime medical cost for each child with an orofacial cleft is $100,000, amounting to $750 million for all children with orofacial cleft born each year in the United States(4). The location makes these anomalies readily recognizable at birth. Clefts can occur as isolated malformations (nonsyndromic clefts) or associated with other malformations. Sometimes they are a feature of a specific malformation syndrome(3, 5, 6).

The epidemiology and genetics of cleft lip and palate have been studied extensively in various countries by several investigators(7, 8). The etiology of cleft of lip, alveolus and palate is very complex and includes environmental effects in addition to the interaction of genetic predisposition(9). This holds also true for isolated clefts of the palate(10) . In Caucasian populations, the incidence of clefts ranges from 1.0 to 2.21 per 1000 live births.

Only few comprehensive epidemiological studies have yet been conducted on the epidemiological and

Corresponding Author: Babak Saedi
Department of Otolaryngology, Imam Khomeini Hospital, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran
Tel: +98 9123872469, Fax: +98 21 66932288, E-mail: saedi@tums.ac.ir

genetic aspects of clefts in Iran. Therefore we undertook a survey to assess the epidemiology and some genetic aspects of facial clefting in Iran.

Patients and Methods

In this nonrandomized retrospective case series study, records of all cases of oral cleft reconstruction admitted to the 2 ENT and Plastic Surgery wards at Imam Khomeini Hospital in Tehran (a tertiary referral center) during the 7-year period between April 1999 and March 2006 were reviewed. The studied variables included sex, age at referral time, age at first CL and/or CP operation(s), type and side of cleft, presence of other malformations such as congenital heart disease, skeletal anomalies, parents' consanguinity, and family history of orofacial clefts. Most patients were referred by other physicians or centers in different age groups, mostly for secondary repair of clefts or other stages of cleft reconstruction. Therefore, we recorded only the age at first operation for CL or CP.

The data obtained were statistically analyzed by use of SPSS software version 15.0. Where applicable, chi-square and ANOVA tests were used to determine the statistical significance of the data. $P< 0.05$ was accepted as statistically significant.

Results

Analysis of the data collected showed that 177 patients with congenital orofacial clefts were admitted during the study period; 115 patients (65%) in the Plastic Surgery ward and 62 patients (35%) in the ENT ward. Of these, 103 patients were male (58.2%) and 74 were female (41.8%) (Table 1).

Additionally, Type of cleft and sex ratio among cases were evaluated. Table 2 demonstrates the distribution of cases by sex and by type of cleft among the 177 cases. These data show that cleft lip and cleft palate occur more frequently together (52.0%) than separately (25.4% cleft lip and 22.6% cleft palate).

Table 1. Total and annual frequency and gender of patients in this 7-year study

Year	Female	Male	Total
1999	12(52.2%)	11(47.8%)	23(13%)
2000	11(44.0%)	14(56.0%)	25(14.1%)
2001	10(40.0%)	15(60.0%)	25(14.1%)
2002	13(50%)	13(50%)	26(14.7%)
2003	8(38.1%)	13(61.9%)	21(11.9%)
2004	12(44.4%)	15(55.6%)	27(15.3%)
2005	8(26.7%)	22(73.3%)	30(16.9%)

Table 2. Distribution of cleft type

	Cleft lip (CL-P)	Cleft lip & palate (CL+P)	Cleft palate (CP)	Total
Female	28(62.2%)	31(33.7%)	15(37.5%)	74(41.8%)
Male	17(37.8%)	61(66.3%)	25(62.5%)	103(58.2%
M/F Ratio	0.60	1.96	1.66	1.39
Total	45(25.4%)	92(52.0%)	40(22.6%)	117(100%)

Table 3. Distribution of cleft side

Type of cleft	Unilateral		bilateral	Total
	Left	Right		
Cleft lip	30(69.8%)	10(23.2%)	3(7%)	43(24.29%)
CL+P	22(27.5%)	20(25%)	38(47.5%)	80(45.2%)
CL not Classified	-	-	-	2(1.1%)
CL+P not classified	-	-	-	12(6.8%)
Cleft palate	-	-	-	40(22.6%)
Total	52(29.4%)	30(16.9%)	41(23.2%)	100%

Table 4. Age at first operation.

Age	First CL operation		First CP operation	
	CL-P	CL+P	CP	CL+P
1-18m	22(49%)	57(62%)	7(18%)	14(15%)
18m-5y	7(16%)	8(9%)	20(50%)	23(25%)
5y-18y	8(18%)	13(14%)	5(13%)	25(27%)
>=18y	4(9%)	0(0%)	6(15%)	3(3%)
Missing Data	4(9%)	14(15%)	2(5%)	27(29%)

Clefts of the lip, without associated clefts of the palate, were more common in females than in males (62.2%: 37.8% = 1.64/1), whereas clefts of the lip with associated clefts of the palate were significantly more common in males than in females (66.3%:33.7%=1.96, P<0.00001). CP was more common in males than in females (62.5%:37.5%=1.66/1).

Table 3 shows results concerning the side on which clefts occurred. Of all CL (P) probands, 41 patients (29.9%) were bilaterally affected. In unilateral cases, the left side was affected nearly two times as frequently as the right side. In 92 out of 137 cases of CL (P), (67.15%), cleft palate was associated with CL. In bilateral cases, this association was still more frequent. Laterality of clefts could not be determined in 2 CL (1.1%) and 12 CL+P (6.8%) patient charts.

Age at the first operation was reviewed and Table 4 demonstrates the distribution of first operation age for cleft lip and palate among our 177 patients.

The mean age at first operation for cleft lip in CL-P patients was significantly lower than that in CL+P (6.16 vs. 2.16 years<0.001). Although the mean age at first operation for cleft palate in CL+P was lower than in isolated CP patients (5.1 vs. 6.7 years) the difference was not statistically significant (P>0.2).

Associated malformations were another item that has been studied in this research

Table 5 shows the distribution of malformations associated with clefts in survivors. A great majority of these malformations were single. Among the 177 probands, 23 cases had another malformation that was diagnosed at birth (13% of all cleft patients). These patients include 8 cases of isolated CP (20%), 1 case of CL-P (2.22%), and 14 cases of CL+P (15.2%). The most common anomalies in these patients were head and face malformations followed by congenital heart disease.

Information regarding consanguinity parents was missing from patient files in 58 cases (32.8%).Of the remaining 119 couples, 54 (45.4%) were consanguineous (Table 6); 33 (18.6%) were first cousins and 7 parents (4 %) were second cousins. Finally, 14 parents (7.9%) were far relatives.

Table 5. Associated malformations in 177 probands

Number of cases				Malformation
Total	CL+P	CL-P	CP	
5(21.7%)	7(50%)	0(0%)	2(25%)	**Head & face**
9(39.1%)	0(0%)	0(0%)	2(25%)	**Ear**
2(8.7%)	4(28.6%)	1(100%)	3(37.5%)	**Skeletal**
8(34.8%)	4(28.6%)	0(0%)	4(50%)	**Cardiac**
5(21.7%)	2(14.3%)	0(0%)	3(37.5%)	**CNS & neural tube**

Table 6. Consanguinity of patients' parents

Cumulative %	%	Number	Relation
	18.6	33	Cousin
22.6	4	7	Second cousin
30.5	7.9	14	Remote relation
67.2	36.7	119	No relation
-	32.8	58	unclassified

Of the 177 patients presented in this study, the recorded family history was complete in 157 cases (88.7%); 23 (13.0%) had a positive family history for clefting. Among the relatives of our 157 cases, apparently nonsyndromic clefts were found in 14 first-degree relatives. In 3 cases (12.5%), one of the parents (never both) had apparently nonsyndromic cleft anomaly. In 9 cases (37.5%), one sibling was affected. In 1 case (4.2%) one parent and one sibling had apparently nonsyndromic clefts. In 11 cases (45.8%) there was a nonsyndromic cleft in a second-degree relative (5 on the paternal and 6 on the maternal side).

The distribution of cleft types in our patients' relatives was 12% CP and 42% CL+P. The most common type was CL (46%).

Discussion

In the total sample of our 177 patients, the distribution the three main types of clefts was 25.4% with CL, 52% with CL+P, and 22.6% with CP, which is compatible with other reports from Caucasian populations (11-14).

This study showed a significant predominance of males with CL+P as well as CP and of females with CL-P. The M/F ratios were 1.96, 1.66, and 0.60, respectively. These results are partially compatible with other reports (12, 15-17), while the higher incidence of CL in females and CP in males shown in our series is contrary to these reports.

When all types of lip and palate clefts are considered together, males were more frequently affected (M/F ratio=1.34). This peculiar sex distribution of the types of clefts was described by Fogh-Andersen in 1942.

In terms of the side of the cleft, compared with other reports(18), we also found left predominancy among unilateral cases.

Several associated malformations, especially head and face anomalies and congenital heart disease, appeared to be more common among our patients with CL (P) than the normal population. A higher rate of other malformations among CL (P) infants was found by other investigators(14, 19). The low incidence of associated malformations in this study, particularly cardiac defects, is most probably due to poor screening programs. Unfortunately only 56 patients (31.6%) of our sample had echocardiography during their cardiology counseling prior to surgery. Another reason may be the young age at the time of referral in the majority of cases, when some signs and symptoms might not have manifested.

Although most congenital anomalies can be ruled out by a systematic physical examination, it seems that a routine screening including echocardiography and ruling out skeletal anomalies, hearing and visual problems may be necessary in CL (P) patients. Genetic counseling and karyotyping in CL (P) patients with multiple congenital anomalies are also suggested.

In the offspring of consanguineous unions, the frequency of multifactorially determined conditions can be expected to be elevated. However, most studies found no significant association(20) between consanguinity and clefts(13, 15, 21, 22) a few investigations did reveal an increased rate of incidence of CL (P) and CP in the offspring of consanguineous marriages(14, 23). In the present study, the parental consanguinity in an Iranian population of 119 valid cases was 45.4% (Table 6). The parental consanguinity in Iran was previously estimated to be 43.1% (Sadeghi, personal communication) or 45.8%(24). Comparing these figures indicates that there are no significant differences between our patients and the general population.

Although we had the frequencies of apparently nonsyndromic clefts in the relatives of patients, available information was not adequate to determine the recurrence risk and heritability, which are necessary and should be used for genetic counseling. We believe that noninvasive investigations should be carried out in subsequent gestations if parents of patients with CL (P) plan to have more children.

Since this study was retrospective and dependent on available patient files, it seems that planning and performing a prospective study with an appropriate control group can provide more precise information.

References

1. Tolarová MM, Cervenka J. Classification and birth prevalence of orofacial clefts. Am J Med Genet 1998;75(2):126-37.
2. Cooper ME, Ratay JS, Marazita ML. Asian oral-facial cleft birth prevalence. Cleft Palate Craniofac J 2006;43(5):580-9.
3. Gorlin RJ CeJ, Pruzansky S. Facial cleft and its syndromes. Birth Defects Res a Clin Mol Teratol. 2001; 7 1-49.
4. Waitzman NJ, Romano PS, Scheffler RM. Estimates of the economic costs of birth defects. Inquiry 1994;31(2):188-205.
5. Cohen MM Jr. Syndromes with cleft lip and cleft palate. Cleft Palate J 1978;15(4):306-28.

6. Duarte R, Leal MJ. The range of congenital malformations associated with cleft lip and palate. Acta Med Port 1999;12(4-6):147-54.
7. Zhou QJ, Shi B, Shi ZD, Zheng Q, Wang Y. Survey of the patients with cleft lip and palate in China who were funded for surgery by the Smile Train Program from 2000 to 2002. Chin Med J (Engl) 2006;119(20):1695-700.
8. Gundlach KK, Maus C. Epidemiological studies on the frequency of clefts in Europe and world-wide. J Craniomaxillofac Surg 2006;34 Suppl 2:1-2.
9. Vujkovic M, Ocke MC, van der Spek PJ, Yazdanpanah N, Steegers EA, Steegers-Theunissen RP. Maternal Western dietary patterns and the risk of developing a cleft lip with or without a cleft palate. Obstet Gynecol 2007;110(2 Pt 1):378-84.
10. Christensen K, Holm NV, Olsen J, Kock K, Fogh-Andersen P. Selection bias in genetic-epidemiological studies of cleft lip and palate. Am J Hum Genet 1992;51(3):654-9.
11. Fogh-Andersen P. Inheritance of Harelip and Cleft Palate. Copenhagen: Nyt Nordisk Forlag- Arnold Busck; 1942.
12. Ingalls TH, Taube IE, Klingberg MA. Cleft lip and cleft palate: epidemiologic considerations. Plast Reconstr Surg 1964;34:1-10.
13. Habib Z. Factors determining occurrence of cleft lip and cleft palate. Surg Gynecol Obstet 1978;146(1):105-10.
14. Stoll C, Alembik Y, Dott B, Roth MP. Epidemiological and genetic study in 207 cases of oral clefts in Alsace, north-eastern France. J Med Genet 1991;28(5):325-9.
15. Czeizel A, Tusnady G. A familial study on cleft lip with or without cleft palate and posterior cleft palate in Hungary 1972;22:405-16.
16. Calzolari E, Milan M, Cavazzuti GB, Cocchi G, Gandini E, Magnani C,Moretti M, Garani GP, Salvioli GP, Volpato S. Epidemiological and genetic study of 200 cases of oral cleft in the Emilia Romagna region of northern Italy. Teratology 1988;38(6):559-64.
17. Sayetta RB, Weinrich MC, Coston GN. Incidence and prevalence of cleft lip and palate: what we think we know. Cleft Palate J 1989;26(3):242-7; discussion 247-8.
18. Meng T, Shi B, Zheng Q, Wang Y, Li S. Clinical and epidemiologic studies of nonsyndromic cleft lip and palate in china: analysis of 4268 cases. Ann Plast Surg 2006;57(3):264-9.
19. Milerad J, Larson O, PhD D, Hagberg C, Ideberg M. Associated malformations in infants with cleft lip and palate: a prospective, population-based study. Pediatrics 1997;100(2 Pt 1):180-6.
20. Harville EW, Wilcox AJ, Lie RT, Vindenes H, Abyholm F. Cleft lip and palate versus cleft lip only: are they distinct defects? Am J Epidemiol 2005;162(5):448-53.
21. Fraser FC. The Genetics of Cleft Lip and Cleft Palate. American Society of Human Genetics All. Am J Hum Genet 1970;22:336-52.
22. Welch J, Hunter AG. An epidemiological study of facial clefting in Manitoba. J Med Genet 1980;17(2):127-32.
23. Al Omari F, Al-Omari IK. Cleft lip and palate in Jordan: birth prevalence rate. Cleft Palate Craniofac J 2004;41(6):609-12.
24. Rajabian MH, Sherkat M. An epidemiologic study of oral clefts in Iran: analysis of 1,669 cases. Cleft Palate Craniofac J 2000;37(2):191-6.