Cleft lip and palate in southwestern Iran: an epidemiologic study of live births

Mohammad Hossain Rajabian,* Shahin Aghaei†

BACKGROUND: Cleft lip with or without cleft palate (CL/P), is the most common congenital anomaly in the head and neck worldwide. We studied the prevalence of cleft lip (CL) and palate (CP) in Shiraz, which is located in southwestern Iran.

METHODS: Data was collected from the teaching hospitals of the Shiraz University of Medical Sciences. Records of 147 608 consecutive live births delivered in three hospitals during the 10 years from November 1993 to November 2003 were reviewed.

RESULTS: One hundred nineteen cases of CL/P or CP alone were registered for a prevalence of 0.80 per thousand live births. The overall male/ female ratio was 1.25. The male/female ratio was 1.22 in the CL patients and 1.58 in the CL/P patients. A male predominance was obvious in both groups.

CONCLUSION: This study shows that the prevalence rate of CL and CP in southwestern Iran is closer to the low prevalence reported in African countries and is lower than the prevalence reported in previous reports in Caucasians.

*From the *Shiraz University of Medical Sciences, Department of Plastic Surgery, Shiraz, Iran, and the †Jabrom Medical School, Department of Dermatology, Jabrom, Iran*

Correspondence:
Shahin Aghaei, MD
Jabrom Medical School,
Department of Dermatology
Jabrom, Iran
Fax: 98-0711-229-6439
shahinaghaei@yahoo.com

Accepted for publication
May 2005

Ann Saudi Med 2005;25(5):385-388

Cleft lip with or without cleft palate (CL/P), is the most common congenital anomaly in the head and neck worldwide.^{1,2} A multifactorial mode of inheritance is suggested by almost all authors.³⁻¹¹ Epidemiological studies for prevention of cleft lip (CL) and palate (CP) are lacking while surgical techniques for proper treatment are growing rapidly. There have been few published epidemiologic investigations in Iran.¹²⁻¹⁴ The objective of this study was to assess data from three maternity university hospitals in Shiraz, which is located in the center of a large province in southwest Iran.

Methods

In a cross-sectional study, we determined the prevalence of CL and CP in 147 608 live births that occurred from 1993 to 2003. The birth records were from three university maternity hospitals in Shiraz, located in the center of Fars province in southwest Iran. The births from these hospitals accounted for the majority of births during this time period. The data elements abstracted were the cleft type, date of birth, sex, and presence of other anomalies. Syndromic clefts were excluded and sub-mucous clefts were not usually diagnosed. The cleft types were classified as CL (right, left, or bilateral), CL and CP (right, left, bilateral), or CP (complete, incomplete). Statistical analysis was carried out with the chi-square test using a frequency table. Probability values of 0.05 or less were taken to be statistically significant.

Results

The overall prevalence of cleft live births over this 10-year period was 0.80 per 1000, or 1 in 1240 live births. The prevalence of cleft births varied from year to year, ranging from 1 in 1487 in 1993, to a high of 1 in 992 in 1999 (Table 1). Among 119 cleft cases, there were 35 cases of CL, 54 cases of CL and palate, and 30 cases of CP (Table 2). The overall male/female ratio was 1.25. The male/female ratio was 1.22 in the CL patients, and 1.58 in the CL and palate patients (Table 3). A male predominance was obvious in both groups. This ratio was 0.88 in the CP babies with a female preponderance. There was no statistically significant correlation with sex and the type of cleft ($P=0.44$).

Unilateral cleft cases (47.05%) occurred more frequently on the left side than on the right side in both CL only and CL and palate patients, but there was no significant correlation between laterality and the type of cleft (Table 4) ($P=0.87$). Bilateral cleft cases (20.16%) were more frequent in the CL and palate group (31%) than in the only CL group (20%). There was nothing significant in the laterality pattern of deformities in 9 patients (9.24%).

Eight of 119 cases (6.72%) of CL (P) were associated with other malformations (Table 5). All these anomalies were single. There were 2 cases of congenital heart diseases and 2 cases of neural tube anomalies, followed by one each ear, gastrointestinal, male genitalia and extremity malformations. Cases with syndromes and chromosomal malformations were not included in this study.

Discussion

Birth defects arise from the interplay of multiple genetic and environmental factors. Although such complex traits are characterized by familial aggregation, recurrence rates within families are relatively low; the risk that an affected child will have a sibling who is also affected is typically less than 5 percent.¹⁵ Zuccherro et al. identified the gene that encodes interferon regulatory factor 6 (IRF6) as a candidate gene on the basis of its involvement in an autosomal dominant form of CL and CP, known as Van der Woude's syndrome. DNA-sequence variants associated with IRF6 are major contributors to CL/P.¹⁶ The most important implication of Zuccherro's study is that it provides a promising lead for identifying other genes linked to CL or CP and for elucidating the mechanisms of environmental exposure, which are substantial steps forward.

CL, CP, or the combination of the two is a common birth defect that varies in prevalence according to ethnicity and geographic origin, with populations of Asian and Amerindian ancestry having the highest rates and groups of African ancestry the lowest.¹⁸⁻³¹ The prevalence in Caucasian populations varies from 0.6 to 1.89 per 1000, the mean prevalence being approximately 1 per 1000.^{7,32-48} The reported prevalence in Japanese and Korean populations tends to be higher than in Caucasians,^{3,49-55} as do rates from Native American populations,^{52,56-58} being approximately 0.5 per 1000. Several reports from different countries show figures between these two extremes.^{8,52,59-64}

There have been few reports of the birth prevalence of CL/P from Iran¹²⁻¹⁴ and other countries of

Table 1. Cleft births in 147 608 live births, 1993-2003.

Year	Male	Female	Total	Total births	Per 1000 births	Ratio per live births
1993	7	4	11	16361	.672	1:1487
1994	6	6	12	15521	.77	1:1293
1995	5	6	11	15020	.73	1:1365
1996	8	4	12	14343	.83	1:1195
1997	6	4	10	14264	.70	1:1426
1998	11	2	13	14065	.92	1:1081
1999	6	8	14	13893	1.007	1:992
2000	4	6	10	14516	.68	1:1451
2001	6	8	14	14877	.94	1:1062
2003	7	5	12	14748	.81	1:1229
Total	66	53	119	147608	0.80	1:1240

Table 2. Distribution of cleft types

Type	Frequency	Percent (95% confidence interval)
Cleft lip	35	29.41 (21-38)
Cleft lip and palate	54	45.38 (36-54)
Cleft palate	30	25.21 (17-33)
Total	119	100

Table 3. Cleft types by sex.

Type of cleft	Male		Female	
	Frequency	%	Frequency	%
Cleft lip	22	55	18	45
Cleft lip and palate	30	61.2	19	38.8
Cleft palate	14	46.7	16	53.3

Table 4. Laterality of clefts.

Type of clefts	Unilateral		Bilateral	Uncertain	Total
	Right	Left			
Cleft lip	11 (31%)	14 (40%)	7 (20%)	3 (9%)	35 (29.4%)
Cleft lip and palate	13 (24%)	18 (33%)	17 (31%)	6 (11%)	54 (45.4%)
Cleft palate					30 (25.2%)
Total	24 (20.2%)	32 (26.9%)	24 (20.2%)	9 (9.2%)	119 (100%)

Table 5. Associated malformations in the 119 cases.

Malformation	Frequency	Percent (%)
Neural tube	2	1.68
Cardiac	2	1.68
Ear	1	0.84
Gastrointestinal	1	0.84
Male genitalia	1	0.84
Extremity	1	0.84
Total	8	6.72

Western Asia.^{22-25,65,66} The recording and documentation of CL and CP in Iran is limited to registration in maternity hospitals. There is no national registration system for congenital anomalies, hence no nationwide epidemiologic study.

In this investigation, the overall prevalence of cleft births over a 10-year period was 0.80 per 1000, which is remarkably lower than previous Iranian reports. The prevalence of CL or CP or both was 1.03 per 1000 births in 1991 ($P < 0.05$).¹⁴ We are not sure whether this data resulted from a real reduction in prevalence or a reduction in the number of children delivered. Some have also speculated that a woman who delivers a baby with a cleft as a first child tends not to have another child.

The population in our study was fairly homogeneous genetically and has almost the same culture and environment. Thus, we could find no convincing reason for the dramatic variation in cleft prevalence from

year to year (Table 1). The distribution of type of cleft (Table 2) and sex ratios (Table 3) in this study were comparable to those observed in a previous Iranian report,¹⁴ and in other Caucasian reports.^{7,32,60,66-68} Both Iranian studies showed a significant predominance of males with CL/P and of females with CP. A higher prevalence of CL in males than in females in this study is compatible with other Caucasian reports, but contrasts with the previous Iranian report, which showed a female preponderance. There was a left-sided predominance of clefts, with a higher frequency of bilaterality (20.16%) compared with the range of 9.6% to 16% in other reports.⁶⁹⁻⁷¹ The ratio of unilateral left to unilateral right to bilateral clefts was about 4:3:3. Although neural tube and cardiac anomalies had a higher range of occurrence, the result should be interpreted with caution because of the small total number and the absence of adequate control data.

This study shows that the prevalence rate of CL and CP in southwestern Iran is closer to the prevalence reported in African countries and is lower than the prevalence reported in previous reports in Caucasians.

The authors appreciate the cooperation from the maternity hospitals of the Shiraz University of Medical Sciences in allowing access to their records. They also are indebted to the Research Consultation Center of the University for the technical assistance in analyzing the data. For her valuable contribution in collecting the data, the authors thank Mrs. M. Javan.

References

- Murray JC. Face facts: genes, environment, and clefts. *Am J Hum Genet.* 1955;57:227-232 [Pub Med Citation].
- Kim S, Kim WJ, Oh C, Kim JC. Cleft lip and palate prevalence among the live births in the Republic of Korea. *J Korean Med Sci.* 2002;17:49-52.
- Fraser FC. The genetics of cleft lip and cleft palate. *J Med Genet.* 1970;23:236.
- Woolf CM. Congenital cleft lip, a genetic study of 496 porosity. *J Med Genet.* 1971;8:65.
- Chung CS, Ching GHS, Morton ME. A genetic study of cleft lip and palate in Hawaii 2. Complex segregation analysis and genetic risks. *Am J Hum Genet.* 1974;26:177-188.
- Carter CO. Genetics of common single malformations. *Br Med Bull.* 1976;32(1):21-26.
- Bonaiti C, Briard ML, Feingold J, Pavy B, Psaume J, Migne-Tufferaud G, and Kaplan J. An epidemiological and genetic study of facial clefting in France. 1. Epidemiology and frequency in relatives. *J Med Genet.* 1982;19:8-15.
- Dan-Ning Hu, Jing-Hai Li, Hui-Ying Chen, Hua-Song Chang, Bao-Xin Wu, Zheng-Kang Lu, De-Zhao Wang and Xin-Guo Liu. Genetics of cleft lip and cleft palate in China. *Am J Hum Genet.* 1982;34:999-1002.
- Demenais F, Bonaiti-Pelli C, Briard ML and Feingold J. An epidemiological and genetic study of facial clefting in France. 2. Segregation analysis. *J Med Genet.* 1984;21:436-440.
- Wyszynski DF, Beaty TH and Maestri NE. Genetics of nonsyndromic oral clefts revisited. *Cleft Palate Craniofac J.* 1996;33:406-417.
- Tenconi R, Clementi M and Turolla L. Theoretical recurrence risks for cleft lip derived from a population of consecutive newborns. *J Med*

- Genet. 1988;25:243-246.
12. Farhud DD, Valizadeh GR and Kamali MS. Congenital malformations and genetic diseases in Iranian infants. *Hum Genet.* 1986;74:382-385.
13. Taher AA. Cleft Lip and palate in Tehran. *Cleft Palate Craniofac J.* 1992;29:15-16.
14. Rajabian MH and Sherkat M. An epidemiologic study of oral clefts in Iran: Analysis of 1669 cases. *Cleft Palate Craniofac J.* 2000;37:191-196.
15. Mossey PA, Little J. Epidemiology of oral clefts: an international perspective. In: Wyszynski DF, ed. *Cleft lip and palate: from origin to treatment.* Oxford, England: Oxford University Press. 2002;127-58.
16. Zuccchero TM, Cooper ME, Maher BS, Daack-Hirsch S, Nepomuceno B, Pibeiro L, et al. Interferon regulatory factor 6 (IRF6) gene variants and the risk of isolated cleft lip or palate. *N Engl J Med.* 2004;351:769-80.
17. Chakravarti A. Finding needles in haystacks—IRF6 gene variants in isolated cleft lip or palate. *N Engl J Med.* 2004; 351:822-24.
18. Vandas AP. Prevalence of cleft lip, cleft palate, and cleft lip and palate among races: a review. *Cleft Palate J.* 1987;24:216-225.
19. Fraser GR, Calnan JS. Cleft lip and palate: Seasonal prevalence, birthweight, birthmark, sex, side, associated malformations and parental age. *Arch Dis Child.* 1961;36:420-423.
20. Althumus LA. The prevalence of cleft lip and palate among North American Negros. *Cleft Palate J.* 1966;3:357-361.
21. Iregbulem LM. The prevalence of cleft lip and palate in Nigeria. *Cleft Palate J.* 1982;19:201-205.
22. Salem G, Holm SA, Fattah R, Basset S, Nasser C. Developmental oral anomalies among school-children in Gizan region, Saudi Arabia. *Community Dent Oral Epidemiol.* 1987;15:150-151.
23. Mir NA, Soni A, Kisham J, Galczek W. Facial clefting in Arab infants. *Ann Saudi Med.* 1988;8:206-208.
24. Srivastava S, and Bang RL. Facial clefting in Kuwait and England: a comparative study. *Br J Plast Surg.* 1990;43:457-462.
25. Kumar P, Tasdiq HM, Cardoso E, Bassam HM, Hassanain J. Facial clefts in Saudi Arabia: an epidemiologic analysis in 179 patients. *Plast Reconstr Surg.* 1991;88:955-958.
26. Zlotogora J. Genetic disorders among Palestinian Arabs: 1. Effects of consanguinity. *Am J Med Genet.* 1997;68:472-475.
27. Leck I. The etiology of human malformations: Insights from epidemiology. *Teratology.* 1972;5:303-314.
28. Khoury MJ, Erickson JD, James LM. Maternal factors in cleft lip with or without palate: Evidence from interracial crosses in the United States. *Teratology.* 1983;27:351-357.
29. Conway H, and Wagner KJ. Prevalence of clefts in New York City. *Cleft Palate Craniofac J.* 1996;3:284-290.
30. Croen LA, Shaw GM, Wasserman CR, Tolarova MM. Racial and ethnic variations in the prevalence of orofacial clefts in California, 1983-1992. *Am J Med Genet.* 1998;79:42-47.
31. Msamati BC, Igbigbi PS, Chisi JE. The prevalence of cleft lip, cleft palate, hydrocephalus and spina bifida at Queen Elizabeth Central Hospital, Blantyre, Malawi. *Cent Afr J Med.* 2000;46(11):292-296.
32. Fogh-Andersen P. *Inheritance of harelip and cleft palate.* Copenhagen: Arnold Busck, 1942.
33. Mac Mahon B, Keown T. The prevalence of harelips and cleft palate related to birth rank and maternal age. *Am J Hum Genet.* 1953;5:176-183.
34. Azaz B, and Koyoumdjisky KE. Prevalence of clefts in Israel. *Cleft Palate J.* 1967;4:227-233.
35. Fraser FC. The genetics of cleft lip and cleft palate. *Am J Hum Genet.* 1970;23:336-352.
36. Melnick M, Bixler D, Fogh-Andersen P, and Conneally PM. Cleft lip+ cleft palate: an overview of the literature and an analysis of Danish cases born between 1941 and 1968. *Am J Med Genet.* 1980;6:83-97.
37. Hagberg C, Larson O, and Milerad J. Prevalence of cleft lip and palate and risks of additional malformations. *Cleft Palate Craniofac J.* 1988;35:40-45.
38. Jensen BL, Kreiborg S, Dahl E, Fogh-Andersen P. Cleft lip and palate in Denmark, 1976-1981: Epidemiology, variability and early somatic development. *Cleft Palate J.* 1988;25:267-269.
39. Stoll C, Alembik Y, Dott B, Roth, MP. Epidemiological and genetic study in 207 cases of oral clefts in Alsace, Northeastern France. *J Med Genet.* 1991;28:325-329.
40. Gregg TB, Richardson A. The prevalence of cleft lip and palate in Northern Ireland from 1980-1990. *Br J Orthod.* 1994;21:387-392.
41. Derijcke A, Eerens A, Carels C. The prevalence of oral clefts: A review. *Br J Oral Maxillofac Surg.* 1996;34:488-494.
42. Kozelj V. Epidemiology of orofacial clefts in Slovenia, 1973-1993: Comparison of the prevalence in six European countries. *J Craniomaxillofac Surg.* 1996;24:378-382.
43. Czeizel AE, Hirschberg J. Orofacial clefts in Hungary: Epidemiological and genetic data, primary prevention. *Folia Phoniatr Logop.* 1997;49(3-4):111-116.
44. Tolarova MM, Cervenka J. Classification and birth prevalence of orofacial clefts. *Am J Med Genet.* 1998;17:127-132.
45. Croen LA, Shaw GM, Wasserman CR, Tolarova MM. Racial and Ethnic variations in the prevalence of orofacial clefts in California, 1983-1992. *Am J Med Genet.* 1998;79:42-47.
46. Christensen K. The 20th Century Danish facial cleft population—epidemiological and genetic-epidemiological studies. *Cleft Palate Craniofac J.* 1999;36(2):96-104.
47. Jakobson LP, Molsted K, Christensen K. Occurrence of cleft lip and palate in the Faroe Islands and Greenland from 1950 to 1999. *Cleft Palate Craniofac J.* 2003;40(4):426-430.
48. Neel J. A study of major congenital defects in Japanese infants. *Am J Hum Genet.* 1958;10:398-445.
49. Ching GHS, Chung CS. A genetic study of cleft lip and palate in Hawaii. 1. Interracial crosses. *Am J Hum Genet.* 1974;26:162-176.
50. Lowry RB, Trimble BK. Prevalence rates for cleft lip and palate in British Columbia 1952-1971 for North American Indian, Japanese, Chinese, and total populations: Secular trend over 20 years. *Teratology.* 1977;16:277-284.
51. Koguchi H. Population data on cleft lip and cleft palate in the Japanese. *Prog Clin Biol Res.* 1980;46:297-323.
52. Chung CS, Mi MP, Beechert AM. Genetic epidemiology of cleft lip with or without palate in the population of Hawaii. *Genet. Epidemiol.* 1987;4:415-423.
53. Natsume N, Suzuki T, Kawai T. The prevalence of cleft lip and palate in the Japanese. *Br J Oral Maxillofac Surg.* 1988;26:232-236.
54. Sukwha Kim, Woo Jung Kim, Changhyum CH, Jae-Chan Kim. Cleft lip and palate prevalence among the live births in the Republic of Korea. *J Korean Med Sci.* 2002;17:49-52.
55. Trettsven VE. Prevalence of cleft lip and palate in Montana Indians. *Speech Hearing Disord.* 1963;28:52-57.
56. Niswander JD, Adams MS. Oral clefts in the American Indian. *Public Health Rep.* 1967;82:807-812.
57. Niswander JD, Barrow MV, Bingle GJ. Congenital malformations in the American Indian. *Soc Biol.* 1975;22:203-215.
58. Lowry RB, Renwick DHG. Prevalence of cleft lip and palate in British Columbia Indians. *J Med Genet.* 1969;6:67-69.
59. Czeizel A, Tusnady G. A familial study on cleft lip with or without cleft palate and posterior cleft palate in Hungary. *Hum Hered.* 1972;22:405-416.
60. Welch J, Hunter AGW. An epidemiological study of facial clefting in Manitoba. *J Med Genet.* 1980;17:127-132.
61. Burman NTC. Epidemiological aspects of orofacial clefts in Western Australia. *Austral Dent J.* 1983;28:227-232.
62. Chapman CJ. Ethnic differences in the prevalence of cleft lip and/or cleft palate in Auckland, 1960-1976. *NZ Med J.* 1983;96(731):327-329.
63. Fong PH, Yeap CL, Lee ST. Congenital cleft lip and palate in Singapore. *Ann Acad Med Singapore.* 1983;12:363-365.
64. Al-Bustan SA, El-Zawahri MM, Al-Adsani AM, Bang RL, Maher BS, Weinberg S, Marazita ML. Epidemiological and genetic study of 121 cases of oral clefts in Kuwait. *Orthod Craniofac Res.* 2002;5(3):154-160.
65. Al-Talabani J, Shubbar AI, Mustafa KE. Major congenital malformations in United Arab Emirates (UAE): Need for genetic counseling. *Am Hum Genet.* 1998;62:411-418.
66. Tal Y, Dar H, Winter ST, Bar JG. Frequency of cleft lip and palate in Northern Israel. *Isr J Med Sci.* 1974;10:515-518.
67. Calzolari E, Milan M, Cavazzuti GB, Cocchi G, Gandini E, Magnani C, Moretti M, Garani GP, Salvio GP, Volpato S. Epidemiological and genetic study of 200 cases of oral cleft in the Emilia Romagna region of Northern Italy. *Teratology.* 1988;38:559-564.
68. Sayetta RB, Weinrich MC, Coston GN. Prevalence and prevalence of cleft lip and palate: What we think we know. *Cleft Palate J.* 1989;26:242-247.
69. Wilson MEA. A ten-year survey of cleft lip and cleft palate in the South West region. *Br J Plast Surg.* 1972;25:224.
70. Veau V. *Divisione palatine, Anatomie, Ponetique.* Paris: Masson et Cie, 1931.
71. Ladd WE. Harelip and cleft palate. *Boston Med Surg J.* 1926;194:1016.