Cleft Lip and Palate: Association with Other Congenital Malformations

Soraya Beriaghi* / Sandra L Myers** / Scott A Jensen*** / Shanti Kaimal**** / Cynthia M Chan***** / G Bradley Schaefer******

Orofacial clefts are frequently associated with other congenital malformations. Studies vary in incidence and types of anomalies. ***Objective:*** *To evaluate associated malformations in orofacial cleft patients at a major research hospital.* ***Study Design:*** *Medical records of 1127 patients, in the Cleft Palate / Craniofacial Clinic, Boys Town National Research Hospital, from January 1980 through February 2000 were reviewed. Patients were divided into two categories: 1) cleft palate only (CP), and 2) cleft lip, with or without cleft palate (CL±P). Further categorization included location and type, if any, of other congenital malformations.* ***Results:*** *47.2% of patients had CP and 52.8% had CL±P. 32.2% of all cleft patients had associated congenital malformations. The orofacial region was the most common site, followed by cardiovascular, central nervous, and skeletal systems. Congenital malformations were more common in CP (38.7%), than CL±P (26.4%). Of malformations diagnosed, 63.1% were chromosomal/syndromic anomalies while 36.9% were non-chromosomal/syndromic.* ***Conclusions:*** *Recognition of the spectrum of congenital malformations, associated with orofacial clefting, is essential for further diagnostic testing and in some cases genetic counseling.*

Keywords: *congenital malformations, anomalies, orofacial clefts, syndromes*
J Clin Pediatr Dent 33(3): 207–210, 2009

INTRODUCTION

Congenital malformations are present in 3-7% of all births, and 75% of these anomalies involve craniofacial and neck structures. Among craniofacial anomalies, orofacial clefts are among the most common congenital malformations observed in humans.[1-3] According to their embryologic and genetic differences "typical" orofacial clefts are classified as: 1) isolated cleft palate (CP), and 2) cleft lip with or without cleft palate (CL±P).[1,4] CL±P affects unilaterally or bilaterally the upper lip, and the alveolar ridge.

CP and CL±P may be present as an isolated anomaly or associated with other findings as part of a syndrome.[5] More than 350 syndromes, either chromosomal or Mendelian, have been reported in association with orofacial clefts.[2] Furthermore, non-syndromic CP and CL±P may present as sporadic cases or may present with familial aggregation as well as follow a dominant or recessive pattern.

Rates of occurrence for clefting vary considerably among studies, depending on the source of information, region, and ethnic group studied. Clefts have a prevalence of approximately 1/700 births[6] (range 2.2-11.7 per 10000).[3] The prevalence of CL±P is higher than CP alone.[1,7] The reported prevalence of congenital malformations associated with clefts, syndromic or non-syndromic, varies considerably, from 3% to 71.1%.[8-14] This heterogeneity of rates shows some inconsistency and probably reflects ascertainment bias, as well as differences in the diagnostic evaluation, method of data collection and population studied.[2,3,13,15,16]

Variations between older and newer studies are most likely related to refined guidelines and utilization of new technologies in the diagnostic process. Therefore, the relationship between non-syndromic clefts and other major congenital malformations has not been clearly delineated and

* Soraya Beiraghi, DDS, MSD, MS, Cleft Palate and Craniofacial Clinic, Division of Pediatric Dentistry School of Dentistry, University of Minnesota, Minneapolis, MN
** Sandra L Myers, DMD, NIDCR's TMJ Implant Registry and Repository, School of Dentistry University of Minnesota, Minneapolis, MN
*** Scott A Jensen, DDS, Private Practice, American Fork, UT, USA.
**** Shanti Kaimal, BDS, MDS, NIDCR's TMJ Implant Registry and Repository, School of Dentistry University of Minnesota, Minneapolis, MN
***** Cynthia M Chan, DDS, Department of Hospital Dentistry, University of Nebraska Medical Center, Omaha, NE, USA
****** G Bradley Schaefer, MD, University of Arkansas for Medical Sciences, Division of Medical Genetics and Department of Pediatrics, Little Rock, AR USA

Send all correspondence to: Soraya Beiraghi, Division of Pediatric Dentistry, University of Minnesota, 6-150 Moos Tower, 515 Delaware St, S.E., Minneapolis Min. 55455

Phone: (612) 624-5997
Fax: (612) 625-2902

E-mail: beira001@umn.edu

there is no consensus as to which organ system is most often affected. This has been documented in numerous studies reported in the literature.[8-10,13,14,17-19] This type of information has importance to clinicians as they evaluate these patients for additional associated anomalies. The objective of this retrospective study was to evaluate, the relationship between orofacial clefts and associated congenital malformations using the large craniofacial center database, obtained by a multidisciplinary team, at Boys Town National Research Hospital in Omaha, Nebraska.

MATERIALS AND METHODS

This study utilized medical records of 1127 unique patients with CL±P or CP who were seen in the Craniofacial Clinic, Boys Town National Research Hospital from January 1980 through February 2000. The subjects consisted of both genders, varied ethnicity, and ranged in age from one month to 18 years. Most of the patients were from Nebraska and referred by health care providers in this state. The research was conducted in accordance with the principles of the World Medical Association Declaration of Helsinki. Written informed consent, in compliance with Institutional Review Board Regulations, was obtained from all patients, their parents or guardians. Patients were examined by a craniofacial team consisting of a pediatrician, clinical geneticist, oral surgeon, plastic surgeon, orthodontist, pediatric dentist, and an otolaryngologist. The patients also received a formal genetic evaluation including a dysmorphology exam, genetic testing, and other laboratory/imaging studies as needed, in order to identify any associated congenital malformation. Data was recorded in the patient's chart and entered in the Craniofacial Clinic database.

Patients were divided into two groups according to the type of orofacial cleft present: Group I: CP, and Group II: CL±P. These two groups were each further subdivided into 3 categories for analysis of associated congenital malformations: 1) patients with chromosomal/syndromic anomalies, 2) patients with non-chromosomal /syndromic anomalies, and 3) patients with no other detected associated anomalies. The clefts were not further categorized as to locations or types (right versus left or unilateral versus bilateral), and associated congenital malformations were not designated as major or minor. Slight variations of normal including tooth anomalies (due to close proximity of the dentition to clefting), neurological and behavioral abnormalities were not included in this study. Statistical comparisons were made using the chi-square test and the Fischer's exact test.

RESULTS

Out of 1127 patients with orofacial clefts, CP was present in 532 (47.2%) patients while 595 (52.8%) had CL±P. This follows the rate in the general population where prevalence of CL±P is higher than CP alone.[1,7] In the 532 patients with CP, 206 (38.7%) patients had one or more associated congenital malformations. Of the 206 patients, 138 (25.9%) had chromosomal/syndromic malformations while 68 (12.8%) had malformations that were non-chromosomal/syndromic. In the 595 patients with CL±P, 157 (26.4%) had one or more associated congenital malformations. Of these 157 patients, 91 (15.3%) had chromosomal/syndromic malformations while 66 (11.1%) had malformations that were non-chromosomal/syndromic. Figure 1 shows the most common identifiable chromosomal/syndromic malformations observed in patients with CP. Pierre Robin sequence, Stickler syndrome, and oculo-auriculo-vertebral (OAV) spectrum accounted for 66.7% of malformations. Figure 2 shows the most common identifiable chromosomal/syndromic malformations observed in patients with CL±P. Pierre Robin sequence and OAV accounted for 45.1% of cases.

The most common malformations classified by anatomical site for patients with CP only are shown in Figure 3 and for CL±P, in Figure 4. Some patients had more than one site affected. For both cleft groups, 20-25% of malformations were in the facial region. Examples included bifid nose, frontonasal dysplasia, hypoplasia of malar eminence, median cleft nose, and choanal atresia. Ear malformations included bifid ear lobe, ear pits, Mondini malformation, preauricular sinus or fistula, preauricular skin tags, and preauricular cysts. Eye malformations included anterior segment dysgenesis, coloboma, congenital cataract, congenital fistula of the eyelid, hypertelorism, micropthalmos, and atresia of the lacrimal duct.

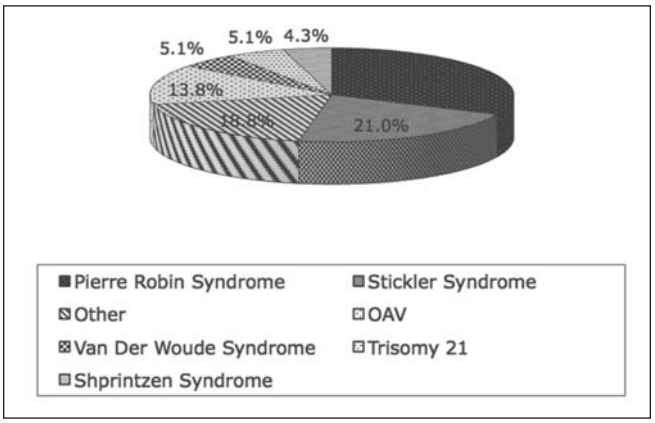

Figure 1.

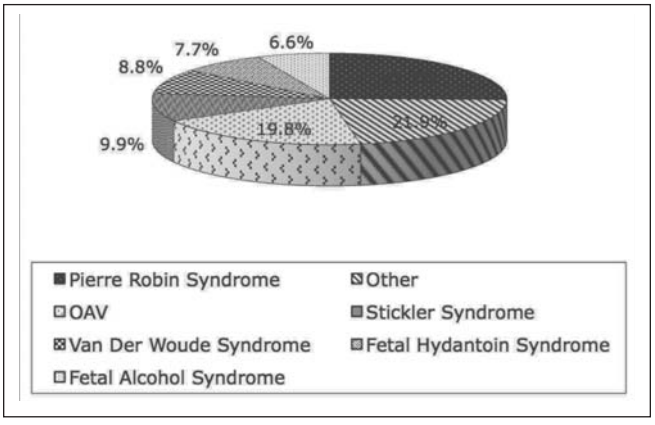

Figure 2.

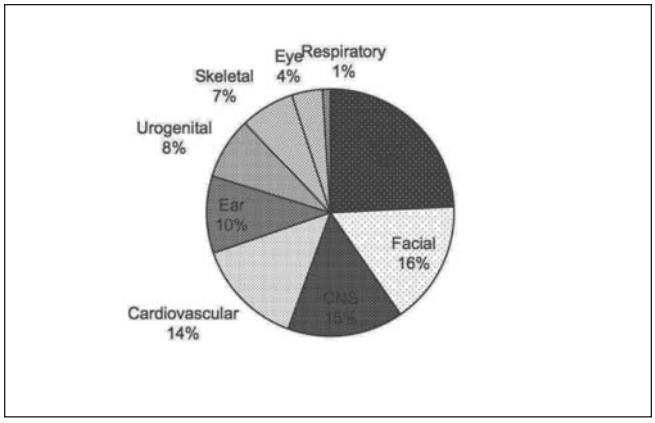

Figure 3.

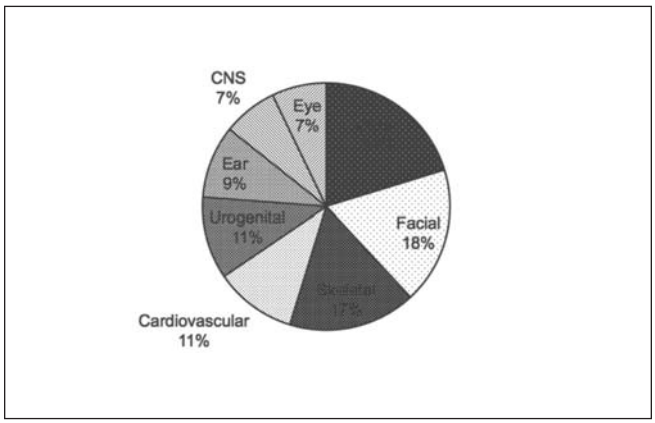

Figure 4.

DISCUSSION

Orofacial clefts are frequently associated with other congenital anomalies and their prevalence and location varies widely in the literature.[2,3,11,13,16] Differences in sample size and selection, geographic distribution, and population diversity complicate comparisons between studies.[1] Moreover, variations in clinical and research methodologies are impacted by availability and utilization of new technologies, and differences in the diagnostic approach to evaluating congenital malformations.[2,3,11]

The retrospective nature of this investigation has potential limitations based on the fact that patients were examined by a group of specialists that varied in its membership over 20 years. Types of cases referred to this specific site are additional sources of bias for this study. Variations in age, gender and geographic diversity of the study population are also potential limitations. However, the study is important since the data gathered is from a population similar to that treated daily in major craniofacial centers across the United States. The advantages of a multidisciplinary approach, in evaluating and following orofacial cleft patients, are numerous and include comprehensive and accurate diagnostic evaluation, and enhanced monitoring capabilities over time.

The overall frequency of associated congenital malformations in our study was 32.2% (206 CP + 157 CL±P). Other reports give a range of 3% to 71.1%[8,10,12,13,18] for associated anomalies and report them to be more frequent in patients with CP.[7,9] The lowest frequency reported at 3% may have come from a population-based study. However, our results differ from those in the literature, in that a large percentage of our patients with clefts had no other associated malformations (CP 61.3% versus CL±P 73.6%).

The wide variation in incidences of associated malformations may be due to a number of factors including a non-homogenous study population, and inclusion of associated congenital malformations documented via other sources such as birth or death records. Such non-uniform study criteria may result in either an over or underestimation of the incidence of associated congenital anomalies in a population.[15] Ascertainment bias and accuracy of diagnosis may differ as well between studies. For instance, one researcher may define an anomaly as a minor malformation and not include it in the study, whereas another may include it, considering it a major malformation. Moreover, studies that use a craniofacial team in diagnosing malformations may be more accurate than studies relying on a single clinician or discipline. Current understanding of craniofacial genetics has enabled researchers to more accurately diagnose and classify malformations.

In our study, the most common anomaly associated with CP and CL±P was Pierre Robin sequence, followed by Stickler syndrome and OAV spectrum. Of these, Pierre Robin sequence, Stickler syndrome, Trisomy 21, and Shprintzen syndrome occurred more frequently in patients with CP than with CL±P. Stickler Syndrome is often associated with Pierre Robin sequence, which can be isolated or associated with numerous genetic and teratogenic conditions. Due to the limitations of this study, it was not possible to determine precisely which cases of Stickler were associated with the Pierre Robin sequence or how many cases may have represented isolated findings. Shprintzen[13] found approximately half of the Pierre Robin cases had Stickler syndrome, while Herrmann[5] estimated the number at roughly one-third. The incidence of Shprintzen syndrome may have been impacted by and underestimated due to the lack of widely available diagnostic testing prior to 1990.

Shprintzen[13] and Rustemeyer[17] found craniofacial anomalies to be the most common, whereas Stark and Lilius observed more malformations of the extremities.[19,20] These findings differ from Calzolari, Sárközi, and Stoll who more recently reported increased malformations in the central nervous and skeletal systems.[14,18,21] In our study, the facial region was the most common location for congenital malformations, despite the fact that eye and ear malformations were considered separately from the facial group. This was followed by malformations of the cardiovascular, central nervous, and skeletal systems. Changes in the order of organ systems affected might occur as grouping and inclusion criteria for malformations are further standardized. In addition, the occurrence of associated malformations may change in relation to specific genetic, and/or environmental influences.

CONCLUSIONS

This study heightens the awareness of congenital malformations and syndromes associated with orofacial clefts. The recognition that there is a high association of congenital malformations and syndromes with orofacial clefts is vitally important and indicates the complexity of this patient population. Health care providers should be aware that patients with CP or CL±P frequently present with other associated chromosomal/syndromic or non-chromosomal/syndromic anomalies. A multidisciplinary approach, incorporating the expertise of both medical and dental professionals, will promote ongoing evaluation and comprehensive care.

ACKNOWLEDGEMENTS

The authors thank Susan Grennan Director of Medical Records at Boys Town National Research Hospital, and Warren Stork, statistician, for their cooperation in preparing this work. Our thanks also to Vladimir Leon-Salazar and Heidi Burns for preparation of this manuscript.

REFERENCES

1. Croen LA, Shaw GM, Wasserman CR, et al. Racial and ethnic variations in the prevalence of orofacial clefts in California, 1983–1992. Am J Med Genet 79: 42–7, 1998.
2. Gorlin R, Cohen M, Hennekam R. Syndromes of the head and neck. New York, Oxford University Press, 2001.
3. Forrester M, Merz R. Descriptive epidemiology of oral clefts in a multiethnic population, Hawaii, 1986–2000. Cleft Palate Craniofac J, 41: 622–628, 2004.
4. Fogh-Andersen P. Inheritance of hare lip and cleft palate. Copenhagen, Arnold Busck, Nordisk Forlag, 1942.
5. Herrmann J, France T, Spranger J, et al. The Stickler syndrome (hereditary arthroophthalmopathy). Birth Defects Orig Artic Ser, 11: 76–103, 1975.
6. Ghassibe M, Bayet B, Revencu N, et al. Orofacial clefting: update on the role of genetics. B-Ent 2 Suppl. 4: 20–4, 2006.
7. Abyholm FE. Cleft lip and palate in a Norwegian population. II. A numerical study of 1555 CLP-patients admitted for surgical treatment 1954-75. Scand J Plast Reconstr Surg, 12: 35–43, 1978.
8. Milerad J, Larson O, Ph DD, et al. Associated malformations in infants with cleft lip and palate: a prospective, population-based study. Pediatrics, 100: 180–6, 1997.
9. Shaw G, Carmichael SL, Yang W, et al. Congenital malformations in births with orofacial clefts among 3.6 million California births 1983–1997. American Journal of Medical Genetics, 125A: 250–256, 2004.
10. Pashayan HM. What else to look for in a child born with a cleft of the lip and/or palate. Cleft Palate J, 20: 54–82, 1983.
11. Wyszynski DF, Sarkozi A, Czeizel AE. Oral clefts with associated anomalies: methodological issues. Cleft Palate Craniofac J, 43: 1–6, 2006.
12. Fraser FC. The genetics of cleft lip and cleft palate. Am J Hum Genet, 22: 336–52, 1970.
13. Shprintzen RJ, Siegel-Sadewitz VL, Amato J, et al. Anomalies associated with cleft lip, cleft palate, or both. Am J Med Genet, 20: 585–95, 1985.
14. Sarkozi A, Wyszynski DF, Czeizel AE. Oral clefts with associated anomalies: findings in the Hungarian Congenital Abnormality Registry. BMC Oral Health, 5: 4, 2005.
15. van der Veen FJ, van Hagen JM, Berkhof J, et al. Regional underreporting of associated congenital anomalies in cleft patients in the Netherlands. Cleft Palate Craniofac J, 43: 710–4, 2006.
16. Vallino-Napoli LD, Riley MM, Halliday JL. An epidemiologic study of orofacial clefts with other birth defects in Victoria, Australia. Cleft Palate Craniofac J, 43: 571–6, 2006.
17. Rustemeyer J, Gunther L, Krause HR, et al. [Associated anomalies in lip-maxillopalatal clefts]. Mund Kiefer Gesichtschir, 4: 274–7, 2000.
18. Calzolari E, Pierini A, Astolfi G, et al. Associated anomalies in multimalformed infants with cleft lip and palate: An epidemiologic study of nearly 6 million births in 23 EUROCAT registries. Am J Med Genet A, 143: 528–37, 2007.
19. Stark R. Cleft palate: a multidiscipline approach. New York, Harper & Row, 1968.
20. Lilius GP. Clefts with associated anomalies and syndromes in Finland. Scand J Plast Reconstr Surg Hand Surg, 26: 185–96, 1992.
21. Stoll C, Alembik Y, Dott B, et al: Associated malformations in cases with oral clefts. Cleft Palate Craniofac J, 37: 41–7, 2000.