Congenital Anomalies Associated with Cleft Lip and Palate Defects in a High Volume Indian Centre

Srinivas Gosla Reddy, *MDS, MBBS*
Rajgopal R. Reddy*, BDS, MBBS*
Karunakar Konte, *MD*
Rajendra Prasad, *BDS, MDS*
Anke M. Ettema, *MD, PhD*
Stefaan J. Berge, *MD, DDS, PhD*
Wilfred A. Borstlap*, MD, DDS, PhD*

Abstract

Objective: *The objective of this study was to find the prevalence of associated anomalies in patients with cleft lip and palate defects. A number of associated anomalies were noticed by the authors while routinely examining patients with cleft and craniofacial defects at their center. An accurate study to identify the prevalence of associated anomalies in cleft lip and palate patients was needed, to emphasize the need for a thorough investigation of children with cleft lip and palate and the need for a multidisciplinary team to diagnose cleft lip and palate. There was also a need to study the impact of associated anomalies on the burden of cleft care in a developing country like India.*

Design and Setting: *This is a retrospective study of 800 consecutive patients with cleft lip and palate CL=184, CLP=532, CP=84 seen in the year 2006. The data was collected retrospectively by processing the case history of the patients. The patient's cleft defect, age and sex was noted along with the religious background, level of income and consanguinity. The anomalies were classified under 10 headings depending on the organ system affected.*

Results: *Associated anomalies were present in 330 cases (41.3%). The highest prevalence of 46.4% was found in patients with cleft lip and palate. The lowest prevalence of 27.7 % was found in isolated cleft lip patients. There was no significant difference of prevalence found between unilateral or bilateral clefts and complete or incomplete clefts. The skeletal system was affected the most. Anomalies of the skeletal system count for 42% of all anomalies. Logistic Regression was used to calculate if any of the other background data increased the chance of having an associated anomaly showed that having an isolated cleft palate decreased the chance of having an associated anomaly as was being a Muslim or from another religion as compared to being a Hindu. Other background data did not have a statistically significant chance to have an associated anomaly with clefts.*

Conclusion: *There was a high prevalence of associated anomalies in the study done at this center. There was, however a need to study the reasons for such anomalies further. There is also a need to study the impact of such anomalies on the burden of cleft care in developing countries.*

Key words: *cleft lip, cleft palate, congenital anomalies, associated anomalies, high volume centre.*

Authors:

Srinivas Gosla Reddy, MDS, MBBS
Director, GSR Institute of Craniofacial Surgery, Hyderabad A.P., India

Rajgopal R. Reddy, BDS, MBBS
GSR Institute of Craniofacial Surgery, Hyderabad A.P., India

Karunakar Konte, MD
Division of Pediatrics, GSR Institute of Craniofacial Surgery, Hyderabad A.P., India

Rajendra Prasad, BDS, MDS
Dean, A.B. Shetty Memorial Dental College and Hospital, Mangalore, Karnataka, India.

Anke M. Ettema, MD, PhD
Department of Oral and Maxillofacial Surgery, Radboud University Medical Center, Nijmegen, The Netherlands.

Stefaan J. Berge, MD, DDS, PhD
Head of Oral and Maxillofacial Surgery, Radboud University Medical Center, Nijmegen, The Netherlands.

Wilfred A. Borstlap, MD, DDS, PhD
Department of Oral and Maxillofacial Surgery, Radboud University Medical Center, Nijmegen, The Netherlands.

Corresponding address:

Dr. Gosla Srinivas Reddy
Director, GSR Institute of Craniofacial and Facial Plastic Surgery
No. 17-14-1, Vinaynagar Colony,
I.S Sadan, Saidabad
Hyderabad, A.P, INDIA
Phone: 040-6576 4884,
Fax: 040-24530000,
Email: goslareddy@gmail.com

INTRODUCTION

Cleft lip with or without cleft palate (CLP, CL), and isolated cleft palate (CP), collectively termed as oral clefts (OC), are major human birth defects that represent a significant public health burden with a worldwide prevalence of 1 in every 500 to 1000 births (Derijcke, 1996, Murray, 2002,). Orofacial clefts occur in all races, in both sexes, and in all socioeconomic groups. Nevertheless, the reported rates of clefts, as well as the types of associated anomalies, vary considerably (Shprintzen et al., 1985; Lilius, 1992; Milerad et al., 1997; Croen et al., 1998; Stoll et al., 2000), and this variation is highly dependent on the methods of ascertainment (Rittler et al. 2008). In India the birth rate of clefts according to a study done in 1994 showed an prevalence of CLP to be 0.93 per 1000 and CP alone to be 0.17 per 1000Mossey et al.2009) .

Preferential associations are nonrandom associations between two or more anomalies, and their detection is the first step to identify new patterns of birth defects (Rittler et al. 2007). In the past, several studies on the prevalence of associated anomalies were performed, but they had different results (Shprintzen et al., 1985; Lilius, 1992; Milerad et al., 1997; Croen et al., 1998; Stoll et al., 2000). Not only were the results on prevalence different, but there was also no consensus about which organ system was affected the most. Results on whether isolated cleft palate or cleft lip and palate patients have more anomalies are also inconsistent (Shprintzen et al., 1985, Milerad et al. 1997). The different outcomes of previous studies resulted in this study to determine the prevalence of associated anomalies in the patient population at this Institute.

Based upon this, a retrospective study was performed in a high-volume centre for craniofacial surgery in India. The aims were (1) to identify preferential associations between three types of oral clefts (CL, CLP, and CP) and other anomalies in a large case series of cases, (2) based on their association patterns, to emphasize the need for thorough investigation before the treatment, and (3) to know the common and different anomalies associated with these oral clefts.

MATERIALS AND METHODS

The data for this retrospective study were obtained medical records from a high-volume centre for cleft and craniofacial surgery located in Hyderabad, India. 800 consecutive patients with CL, CP and CLP, admitted for treatment in 2006, were included in this study (n=800). Atypical facial clefts were excluded from the study.

The patient's cleft defect, age and sex was noted along with the religious background, level of income and consanguinity. The anomalies were classified under 10 headings depending on the organ system affected.

A pediatrician or a surgeon performed general physical examination to ascertain associated anomalies. A standardized assessment form was used to record the data, which contained information on the type of cleft and information on associated anomalies on organ system. The anomalies were classified under ten groups according to the organ system affected. In case of any superficial anomalies, the primarily affected organ system was recorded. If there was any suspicion for an anomaly, which could not be defined by physical examination, these patients were sent to specific departments for further evaluation. If this further examination showed that there was an anomaly, the primarily affected organ system was also noted in the patient record. Anomalies of the central nervous system were only recorded if they were obviously apparent during physical examination.

SPSS 14.0 for Windows was used for statistical analysis. Comparisons between groups were made using independent samples-t-tests.

RESULTS

Of the 800 patients studied, the number of patients with isolated cleft lips (CL) was 184 (23.0%), the number of patients with isolated cleft palates (CP) was 84 (10.5%) and those with cleft lip and palates (CLP) were 532 (66.5%). Of the CL, 164 (89.1%) were unilateral and 20 (10.9%) were bilateral. Of the CLP 406 (76.3%) were unilateral and 126 (23.7%) were bilateral. 448 (56%) of the patients were male and 352 (44%) were female. 656 (82%) practiced the Hindu religion, 112 (14%) practised Islam, 28 (3.5%) practised Christianity and 4 (0.5%) practised Sikhism. 228 (28.5%) patients were children of a consanguineous marriage.

A single anomaly was found in 239 patients (29.9%), two anomalies were found in 63 patients (7.9%), three anomalies were found in 23 patients (2.9%), four anomalies in 4 patients (0.5%), and there was one patient with five anomalies. Anomalies of the skeletal system accounted for 42% of all anomalies, which was the highest organ system involved. (Table 2).

Logistic regression was applied to analyze the relation of background factors and clinical presentations on the chance of having associated anomalies

Table 1. Distributions of associated anomalies classified under each heading

1. Skeletal system n = 189			
Anomaly of the skull	38	Syndactly	11
Anomaly of the mandible	35	Retarded Growth	11
Anomaly of the limbs	23	Frontal Bossing	10
Polydactly	15	Microcephaly	3
Anomaly of the fingers or toes	14	Acrocephaly	2
Anomaly of the foot	14	Anomaly of the Zygomatic Complex	4
Anomaly of the hand	13		
2. Facial anomalies n = 73			
Facial asymmetry	34	Exophylic growth of lower lip	1
Facial Cleft	31	Torus of palate	5
Lower Lip Pits	3		
3. Central nervous system n = 44			
Mental Retardation	32	Myelomeningocele	2
Encephalocele	3	Spina Bifida	3
Hydrocephaly	3		
4. Ear n = 37			
Eartags	21	Hearing Loss	1
Microtia	15	Unspecified	17
5. Eye n = 37			
Strabismus	9	Exopthalmus	5
Coloboma	10	Microphtalmia	3
Corneal aberrations	10		
6. Cardiovascular system n = 33			
Pulmonary stenosis	9	Ventricular septal defect	11
Tetralogy of Fallot	5	Atrial septal defect	3
Coarctation of aorta	4		
7. Skin n = 14			
Skin Discoloration	8	Unspecified	6
8. Urogenital system n = 11			
Unilateral renal agenesia	5	Hypospediasis	6
9. Respiratory system n = 10			
Choanal atresia	5	Laryngeal anomaly	2
Pulmonary agenesia	2	Nose anomaly	1
10. Digestive system n = 7			
Common mesentery	2	Duodenal atresia	2
Esophageal atresia	2	Umblical Hernia	1

with clefts. In this logistic regression, model independent variables that were studied were: sex, income, presence of cleft lip, presence of cleft palate, being child of consanguineous marriage and religion. The results of this analysis are to be found in table 3.

A statistical significant relation was found both between CP and associated anomalies and Religion and associated anomalies. Children with a CP have 27.8% (1-0.722) less chance of having associated anomalies (p=0.001). With regard Religion it was seen that being a Muslim as compared to Hindu gives a 52% lower chance on associated anomalies (p=0.002), while this reduction for "Other Religion" as compared to Hindu was found to be 64.9% (p=0.043). It should be noted that due to the multivariate analysis, these effects are to be seen as the "pure effects" and are corrected for the influence of other variables in the model.

DISCUSSION

The main objective of this article was to present prevalence and baseline characteristics of cases with OCs and associated anomalies. At least 50 publications have reported prevalence rates of associated malformations ranging from 4.3% to 63.4% (Wyszynski et al., 2006).

This study was done in a center that exclusively treats children with cleft and craniofacial defects. It is a tertiary referral center that gets its patients from a radius of 1000 kilometers around it. This study does not show the prevalence of clefts and associated anomalies in a given population but attempts to calculate the presence of associated anomalies in a given population of patients with cleft defects.

Table 2 - Prevalence of associated anomalies according to type of cleft

	Total	Isolated Cleft Lip	Isolated Cleft palate	Cleft Lip and Palate
Number of patients	800	184	84	532
% with associated anomaly	41.3	27.7	38.1	46.4
95% Confidence Interval	37.8-44.7	21.2-34.3	27.5-48.7	42.2-50.7

Table 3. Analysis of relation between patients characteristics and the prevalence of associated anomalies.

			95.0% C.I.for OR	
	P value	OR	Lower	Upper
Income (0= "<12000 INR",1= ">12.000INR")	0.327	1.163	0.860	1.572
Consanguineous marriage (1=y, 0=n)	0.464	1.129	0.816	1.564
CL (1=y, 0=n)	0.069	0.806	0.639	1.017
CP (1=y, 0=n)	0.001	0.722	0.598	0.873
Religion	0.001			
Muslim compared to Hindu	0.002	0.480	0.304	0.760
Other (Christian or Sikh) compared to Hindu	0.043	0.351	0.128	0.968
Sex (1=m, 2=f)	0.460	1.120	0.830	1.511

This study found a prevalence of 41.3% of associated anomalies in 800 cleft patients. This is a higher percentage than that found in other recent studies like Calzolari et al. 2007 who showed an prevalence of 29.2%, Sarkozi et al. 2005, 26.5 % Stoll et al. 2000 36.5%, and Rustemeyer, 2000, 33%, but less than studies done by Shprintzen et al. 1985, which showed an prevalence of 63.4% and Berge et al. 2001, 66% . This impressive variety can be explained in several ways. Different definitions of what an anomaly is could be one of the causes. In the Milerad et al. study 1997 for example, anomalies were only included if treatment or follow-up was required. The age of the OC-patient at the moment of investigation may also play a dominant role. This might explain the high prevalence outcome in this study, since the length of time after birth that cases were examined was rather late. Furthermore, it is even more likely that the high age at examination resulted in an underestimation of the actual prevalence. Druschel et al. (1996) pointed out that first-year-of-life mortality is relatively high in cleft patients with associated anomalies and Bergé et al. (2001) described a high mortality rate of prenataly detected OC-fetuses with associated anomalies. Since only the survivors were included in this study, the prevalence of associated anomalies in OCs may be even much higher. Secondly early clinical signs maybe very subtle, so one might reasonably miss them during the first year of life. On the other hand, due to variation in the timing of the development of abnormalities, detection may be restricted until the child is 4 or 5 years of age. For example, the pits in the van der Woude syndrome may not always develop early in life (Wyszynski et al. 2006). A final explanation for the wide variation in estimates of prevalence is the small sample sizes (Wyszynski et al. 2006).

Wyszinski et al. (2006) summarized it very clearly by stating that prevalence of associated anomalies varies considerably because of differences in case definition and inclusion/exclusion criteria, length of time after birth that cases are examined, variability of clinical expression of associated anomalies, knowledge and technology available to produce syndrome delineation, selection of patients, sources of ascertainment and sample size, true population differences and changes in frequency over time.

All the above mentioned reasons make it difficult to compare this study outcome to previous ones. The clinical and technical facilities to detect an anomaly were limited at this center. Patients were only referred to a specialized department for further investigation if there were any suspicions for an anomaly during physical examination. No standardized neurological investigation was performed, so major underestimation of CNS anomalies is probable. There was also no technology available to detect syndromes by genetic investigation due to lack of facilities at the center.

The highest rates of consanguineous marriage have consistently been associated with low socioeconomic status, illiteracy, and rural residence (Bittles et al., 1991; Bittles, 1994; Grant and Bittles, 1997).The poor socioeconomic and environmental situation of most patients can be a plausible cause of the high prevalence of anomalies. But there seems to be a

genetic component as well, because of the significant difference between Hindus and Muslims. Consanguinity has been reported as an important factor in the appearance of autosomal recessive diseases and congenital anomalies, including hydrocephalus, postaxial hand polydactyly, and CL±P (Vogel and Motulsky, 1996; Rittler et al., 2001). This might also have been one of the reasons for the high prevalence of anomalies in our study. The distribution of subjects in this study is 82% and 14% of Hindus and Muslims respectively which corresponds to national distribution of 80.5% and 13.4% respectively (Census of India 2001).

In the present study, the skeletal system was affected most frequently which supports information from previous studies (Calzolari et al. 2007; Sarkozi et al. 2005; Stoll et al. 2000; Lilius, 1992). Shprintzen et al. (1985) stated that the face and neck area was affected most frequently. The data from this study support this as well. Stark (1968) and Lilius (1992) agreed that most anomalies occur on the extremities which was not the case in our study. Stoll et al. (2000) and Rustemeyer et al. (2000) reported that central nervous system anomalies were very common. Although central nervous system anomalies were also commonly present in our study, the number is probably an underestimation. Many CNS anomalies require MRI or CT scans in order to be able to detect them, but unfortunately, this tool was not available.

This study found a lower prevalence of anomalies in CP patients (without cleft lip), but the results were not significant and the low prevalence can be caused by the low number of CP patients (n = 84). This study found a significantly lower prevalence for CL patients. This supports previous studies (Calzolari et al. 2007; Stoll et al. 2000; Milerad et al. 1997). Harville et al. (2005) concluded that although CL±P cases might represent the same condition, simply differing in severity, they showed some qualitative differences, such as male predominance for CL±P, and higher twinning and consanguinity rates for CL. They should therefore be analyzed separately. Similarly, CL and CLP cannot easily be considered as distinct entities (Rittler et al. (2007). The fact that CLP shows more positive associations with other defects than CL could be indicating that infants with CLP are more severely affected during prenatal development than infants with only CL, as was noted in our study where 46.4% of patients with CLP were associated with more anomalies than isolated CL or CP patients. Croen et al. (1998), Stoll et al. (2000) and Rustemeyer et al. (2000) stated that patients with isolated cleft palate were more frequently affected than patients with cleft lip and palate. But Milerad et al. (1997) reported the opposite.

Although the cardiovascular system was frequently affected, the number of missed anomalies due to the lack of echocardiography investigations is probably high in our study. The actual number of anomalies in the digestive and urogenital systems is also probably higher than the number we found, due to limited means of investigation and limited sample size.

The center that performed this study was is located in India, which is a developing country with limited resources to treat cleft patients. To study the prevalence of associated anomalies, due to budgetary restraints, only those patients that were found to have an associated anomaly after thorough physical examination were referred to the specialized department to deal with that anomaly. Though a diagnosis could be made for 330 patients with other anomalies, only 119 (36%) could be treated for the associated anomaly either simultaneously with the cleft surgery or were treated separately. The center had to defer cleft surgery for 28 patients (8.5%) since there was no funding to treat the other anomalies before treating the cleft. To diagnose an associated anomaly for cleft patients the center had to absorb the increased expenses for each patient's diagnostic and specialized referral costs, as the patients visiting this center come from a low socio-economic background.

The burden of care, just to diagnose patients with associated anomalies, increased exponentially. Therefore some associated anomalies, though present during physical examination, were not thoroughly examined to reach a logical diagnosis and conclusion. The treatment of associated anomalies would increase the burden of care significantly.

The presence of associated anomalies with cleft defects in a patient raises the demand for additional care and will give rise to additional expectations from the patients themselves. The system of healthcare solutions for these patients has to focus on the entire patient in each case and not just the cleft defect alone.

This area of discussion should be investigated further to propose a plan to treat the patient instead of the cleft defect alone.

CONCLUSION

There is a high prevalence of associated anomalies (41.3%) in this study group of cleft patients.

A routine screening for other malformations, especially skeletal, central nervous system, and cardiac defects, may need to be considered in infants with clefts. Close cooperation between several specialists and pediatrician is of importance to comprehensively cover all aspects of these often complicated cases, before any surgery is undertaken. With such a high prevalence of associated anomalies in the cleft lip and palate patients, the need for a team to include a cardiologist, geneticist, neurologist and orthopedic surgeon increases.

There is also a need to treat each child with an associated anomaly and the cleft defect. In a developing country like India this increases the burden to treat children with cleft defects exponentially. There is therefore an urgent need to implement new protocols and treatment goals for children born with clefts.

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