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Clinical Characteristics of the Cleft Lip and/or Palate: Association with Congenital Anomalies, Syndromes, and Chromosomal Anomalies

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ABSTRACT

Background Cleft lip and/or palate (CL/P) can be accompanied by other congenital anomalies. We conducted a long-term evaluation of the associations between cleft patterns, sex distribution, and accompanying congenital anomalies of patients with CL/P.

Methods The medical records of 739 patients with CL/P, seen between January 1967 and December 2020, were retrospectively reviewed. Fisher's exact test was used for statistical analysis.

Results Among the 739 patients with CL/P, the male-to-female ratio was 1.1. Regarding the cleft pattern, 121 (16.4%), 104 (14.1%), 280 (37.9%), 198 (26.8%), and 36 (4.9%) patients had cleft lip (CL), cleft lip and alveolus (CLA), cleft lip and palate (CLP), cleft palate (CP), and submucous cleft palate (SMCP), respectively. Congenital anomalies were identified in 107 (14.5%) cases, of which 53 (49.5%) had congenital heart disease. The frequencies of congenital anomalies patients with in CL/P were 14/225 (6.2%), 36/280 (12.9%), 43/198 (21.7%), and 14/36 (38.9%) for a combination of CL and CLA, CLP, CP, and SMCP, respectively. Accompanying syndromes and chromosomal anomalies were identified in 40 (5.4%) cases, in which Pierre Robin sequence (16 cases of CP and 4 cases of SMCP) was the most frequent.

Conclusion No sex differences were observed in CL/P, and CLP and CP were the most common cleft patterns. Congenital anomalies associated with CL/P were dominated by congenital heart disease and were most frequently identified in CP and SMCP cases. Notably, the Pierre Robin sequence, a complex syndrome characterized by micrognathia, glossoptosis, respiratory obstruction, and a U- or V-shaped CP, was found in cases of both CP and SMCP, and accounted for the symptoms in most cases.

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Abbreviations: ASD, atrial septal defect; CHD, congenital heart disease; CL, cleft lip; CLA, cleft lip and alveolus; CLP, cleft lip and palate; CL/P, Cleft lip and/or palate; CP, cleft palate; PDA, patent ductus arteriosus; SMCP, submucous cleft palate; VSD, ventricular septal defect

Key words chromosomal anomalies; cleft lip; cleft palate; congenital anomalies; congenital heart disease

Cleft lip and/or palate (CL/P) is the most common craniofacial anomaly with an incidence of approximately 1 per 700 live births.[1–3] The prevalence of CL/P varies among ethnic groups and geographical regions, and is higher in Asia and lower in Africa.[2] Dixon et al. reported that the prevalence of CL/P is 1 per 500, 1 per 1,000, and 1 per 2,500 live births in Asia, Western countries, and Africa, respectively.[1] CL/P can cause various disorders related to esthetics, feeding, speech, and hearing. To resolve these issues, cheiloplasty is generally performed at 4–6 months of age, and palatoplasty at 1.5–2 years of age.

CL/P can occur as an isolated anomaly, be accompanied by congenital anomalies, or be associated with symptoms as part of syndromes or chromosomal anomalies.[4, 5] Several studies have reported that congenital heart disease (CHD) is the anomaly most associated with CL/P.[4, 6, 7] However, the prevalence of congenital anomalies in CL/P may vary depending on the study design. Congenital anomalies accompanied by CL/P may influence the treatment strategy for CL/P. For instance, severe CHD could be a high-risk factor for general anesthesia, which may result in the delay or discontinuation of surgical treatment for CL/P.[8] Additionally, the identification of accompanying chromosomal anomalies may be less frequently described in clinical studies of CL/P.

Understanding the type and frequency of congenital anomalies associated with CL/P is crucial for the multidisciplinary treatment of CL/P. This study aimed to evaluate the accompanying congenital anomalies associated with CL/P and provide insights for the multidisciplinary approach to CL/P.

In previous clinical studies, CL/P was almost always classified into cleft lip (CL), cleft lip and palate (CLP), and cleft palate (CP).[4, 5] Cleft lip and alveolus (CLA), in which CL accompanies an alveolar cleft, may be included within CL. However, only a few studies have included submucous cleft palate (SMCP) with the other cleft patterns of CL/P.[9, 10] This may be because SMCP is often discovered and diagnosed at a

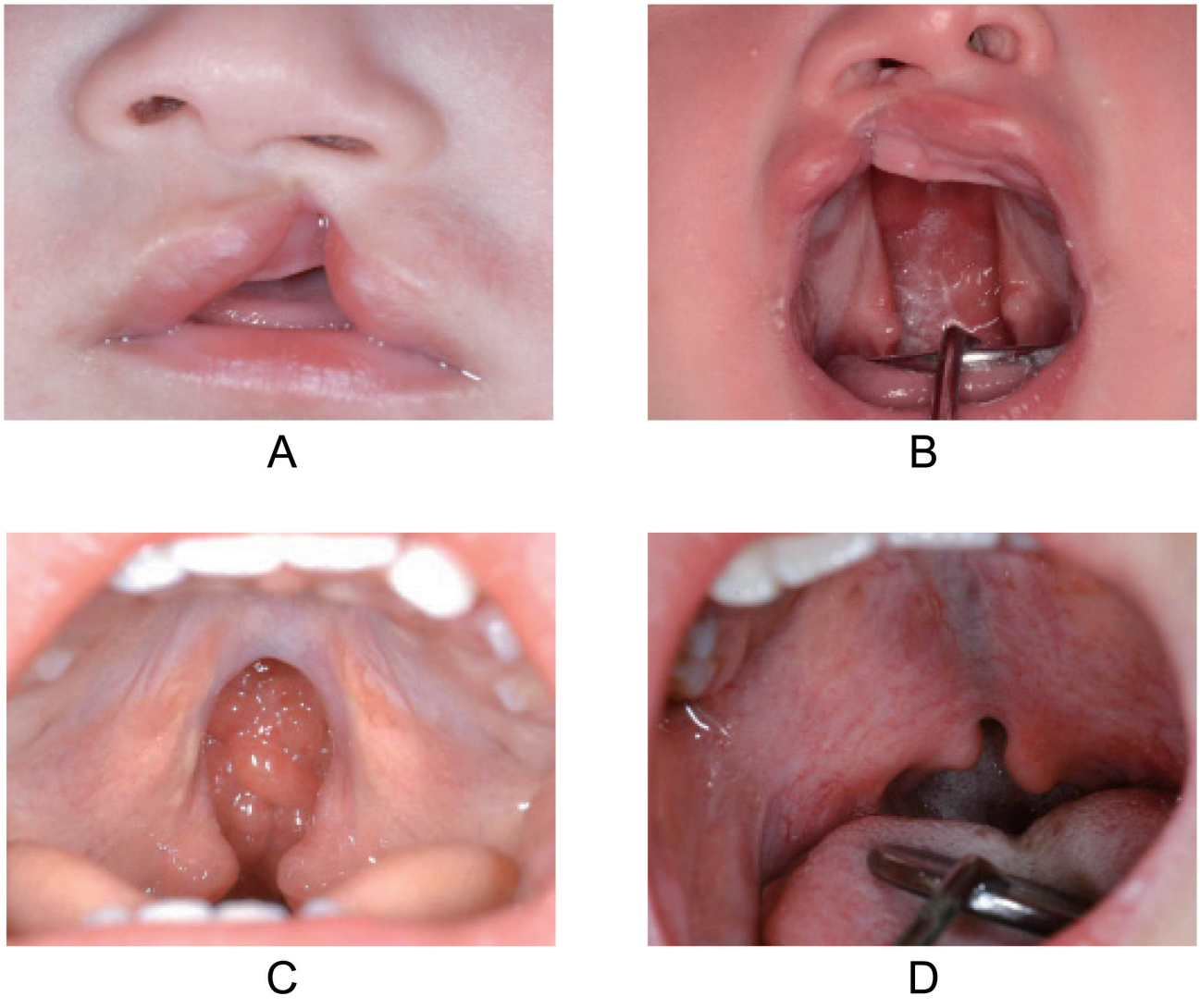

Fig. 1. Photographs of different types of CL/P. **A**: unilateral cleft lip; **B**: unilateral cleft lip and palate; **C**: cleft palate; **D**: submucous cleft lip. CL/P, cleft lip and/or palate.

late stage. The clinical aspects of SMCP, especially the exact prevalence of congenital anomalies, syndromes, and chromosomal anomalies associated with SMCP, and their difference from other cleft patterns, remain unclear. Thus, in this study we focused on describing SMCP as a primary cleft pattern.

SUBJECTS AND METHODS

Patients

We collected the medical records of 739 patients with CL/P who were seen in Oral and Maxillofacial Surgery at Tottori University Hospital between January 1967 and December 2020, after obtaining approval from the Tottori University Ethical Review Board (reference number: 21A179). Informed consent from all patients was obtained by providing patients with opportunity to opt out of study inclusion. The collected data included cleft patterns, sex, associated congenital anomalies, and accompanying syndromes or chromosomal anomalies. CL/P was classified into five groups according to the cleft pattern: CL, CLA, CLP, CP, and SMCP. Photographs of different types of CL/P are shown in Fig. 1. CP may involve either the soft palate alone or both the hard and soft palate. SMCP was diagnosed based on Calnan's classic triad, which comprises the bifid uvula, translucent zone in the midline of the soft palate, and bony notch in the posterior edge of the hard palate.[11] A definitive diagnosis was provided in all cases with congenital anomalies, syndromes, or chromosomal anomalies. The cleft patterns and their association with congenital anomalies, syndromes, or chromosomal anomalies were retrospectively reviewed. Additionally,

Table 1. Frequency and sex distribution of all patients with CL/P

	CL (n = 121)	CLA (n = 104)	CLP (n = 280)	CP (n = 198)	SMCP (n = 36)	Total (n = 739)
Male	78	57	172	68	15	390
Female	43	47	108	130	21	349
Male:female ratio	1.8:1	1.2:1	1.6:1	1:1.9	1:1.4	1.1:1

CL, cleft lip; CLA, cleft lip and alveolus; CLP, cleft lip and palate; CP, cleft palate; SMCP, submucous cleft palate. CL/P, cleft lip and/or palate.

the types and frequencies of CHD were investigated in detail.

Statistical analyses

We used Fisher's exact test to compare and test categorical variables among more than two groups. Bonferroni's correction was applied for comparisons among more than three groups; then the *P*-value was adjusted. For the statistical analysis, CL and CLA were grouped together as CL/CLA because of the small number of cases. We performed the statistical analysis using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (version 4.1.2, R Foundation for Statistical Computing, Vienna, Austria), which is more precisely a modified version of R commander (version 2.7-2) designed to add statistical functions frequently used in biostatistics.[12] A *P*-value of < 0.05 was considered statistically significant.

RESULTS

Frequency and sex distribution of CL/P

Of the 739 patients with CL/P, 390 (52.8%) were males and 349 (47.2%) were females. Table 1 shows the frequency and sex distribution of all patients with CL/P. Male predominance was observed in CL, CLA, and CLP, whereas female predominance was observed in CP and SMCP. Of the 739 patients with CL/P, 121 (16.4%), 104 (14.1%), 280 (37.9%), 198 (26.8%), and 36 (4.9%) had CL, CLA, CLP, CP, and SMCP, respectively.

Frequency and distribution of major congenital anomalies

Associated congenital anomalies were identified in 107 (14.5%) patients. The frequency of congenital anomalies according to cleft pattern was as follows: 14/225 (6.2%), 36/280 (12.9%), 43/198 (21.7%), and 14/36 (38.9%) in CL/CLA, CLP, CP, and SMCP, respectively (Fig. 2). Statistically significant differences were observed between the following groups: CL/CLA-CP ($P < 0.001$), CL/CLA-SMCP ($P < 0.001$), and CLP-SMCP ($P < 0.01$).

Among the 107 cases with congenital anomalies, CHD was the most frequent (53; 49.5%), followed by limb (23; 21.5%) and ear anomalies (23; 21.5%) (Table 2). The top two diagnoses for each anomaly are shown in Table 2. As 170 congenital anomalies were identified in 107 cases, the average number of additional congenital anomalies in CL/P cases was 1.6. In addition, the maximum number of congenital anomalies was 2 in CL/CLA and 6 in CLP, CP, and SMCP.

Frequency and distribution of CHDs

CHDs included ventricular septal defect (VSD), atrial septal defect (ASD), patent ductus arteriosus (PDA), pulmonary stenosis, double-outlet right ventricle, tetralogy of Fallot, coarctation of the aorta, and hypoplastic left heart syndrome, in order of frequency (Table 3). VSD was the most common CHD (21 cases) and was identified in all cleft patterns, followed by ASD (11 cases) and PDA (8 cases). Those with CLP most frequently had CHDs among those with CL/P; however, statistical significance was not observed ($P = 0.61$).

Frequency and distribution of syndromes and chromosomal anomalies

Accompanying syndromes and chromosomal anomalies were identified in 40 (5.4%) patients. As shown in Fig. 3, the frequency of syndromes and chromosomal anomalies according to the cleft pattern was as follows: 2/121 (0.9%), 8/280 (2.9%), 23/198 (11.6%), and 7/36 (19.4%) in CL/CLA, CLP, CP, and SMCP, respectively. Statistical significance was observed between the following groups: CL/CLA-CP ($P < 0.001$), CL/CLA-SMCP ($P < 0.001$), CLP-CP ($P < 0.01$), and CLP-SMCP ($P < 0.01$). Seven types of non-chromosomal syndromes and ten types of chromosomal anomalies were identified, of which Pierre Robin sequence (16 cases of CP and 4 cases of SMCP) was the most common (Table 4).

DISCUSSION

We examined all the cleft patterns of CL/P to evaluate the correlation between other congenital malformations and CL/P. The novelty of this study was the inclusion of SMCP and analysis of the prevalence of chromosomal anomalies in CL/P, since they are less frequently

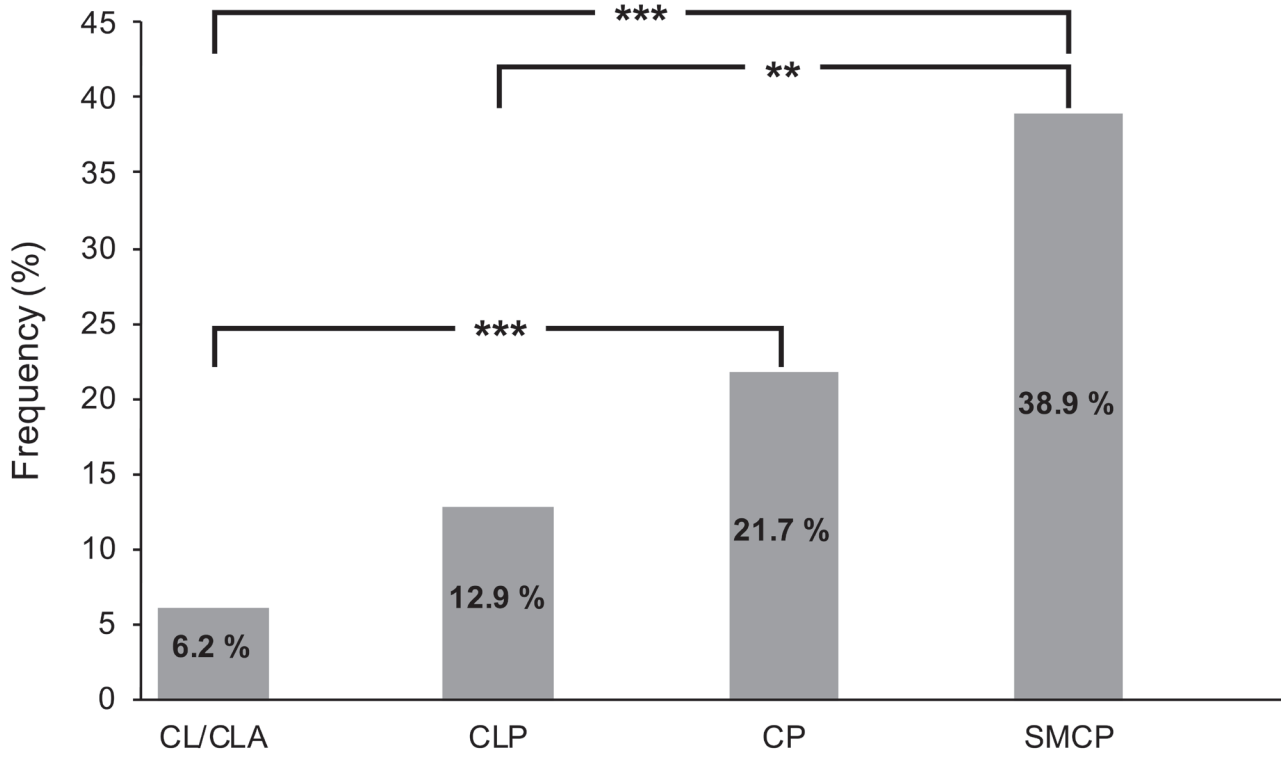

Fig. 2. Frequency of congenital anomalies in different types of CL/P. SMCP presented with congenital anomalies most frequently, followed by CP, CLP, and CL/CLA. $^{**}P < 0.01$. $^{***}P < 0.001$. CL, cleft lip; CLA, cleft lip and alveolus; CLP, cleft lip and palate; CP, cleft palate; SMCP, submucous cleft palate. CL/P, cleft lip and/or palate.

Table 2. Distribution of the major congenital anomalies in CL/P

Organ	*n*	Diagnosis
Cardiac	53	Ventricular septal defect, atrial septal defect, and others
Limbs	23	Polydactyly, syndactyly, and others
Ear	23	Low-set ear, accessory auricle, and others
Urogenital	21	Cryptorchism, hypospadias, and others
Craniofacial	16	Microcephaly, nasolacrimal duct obstruction, and others
Trunk	15	Inguinal hernia, atresia of anus, and others
Eye	13	Epicanthal fold, esotropia, and others
Oral	6	Lower lip pit and ankyloglossia
Total	170	

CL/P, cleft lip and/or palate.

mentioned in most clinical research on CL/P.

In this study, CL, CLA, and CLP were found to be predominant in males, whereas CP and SMCP were predominant in females. These differences in sex based on cleft patterns were consistent with that reported in previous literature.[4, 13] Urbanova et al. determined the male sensitivity to environmental factors and different stages of palatal shelf elevation between sexes.[14] However, the sex difference in CL/P remains unclear.

Approximately 70% of CL/P cases occur as isolated anomalies, whereas 30% are associated with other congenital malformations or syndromes, which are particularly common in patients with CP.[4, 5, 15] The correlation between CP and congenital malformations can be explained by the possibility that systemic organogenesis is nearly complete before palatal closure;

Table 3. Frequency and distribution of CHDs in different types of CL/P

Type of CHD	CL/CLA	CLP	CP	SMCP	Total
VSD	4	10	5	2	21 (2.8%)
ASD	1	6	2	2	11 (1.5%)
PDA	1	2	4	1	8 (1.1%)
PS	1	3	–	1	5 (0.7%)
DORV	1	1	1	–	3 (0.4%)
TOF	2	–	–	1	3 (0.1%)
Coarctation of the aorta	–	1	–	–	1 (0.1%)
Hypoplastic left heart syndrome	–	–	1	–	1 (0.1%)
Total	7	18	11	5	53 (7.2%)

ASD, atrial septal defect; CHD, congenital heart disease; CL, cleft lip; CLA, cleft lip and alveolus; CLP, cleft lip and palate; CP, cleft palate; DORV, double-outlet right ventricle; PDA, patent ductus arteriosus; PS, pulmonary stenosis; SMCP, submucous cleft palate; TOF, tetralogy of Fallot; VSD, ventricular septal defect. CL/P, cleft lip and/or palate.

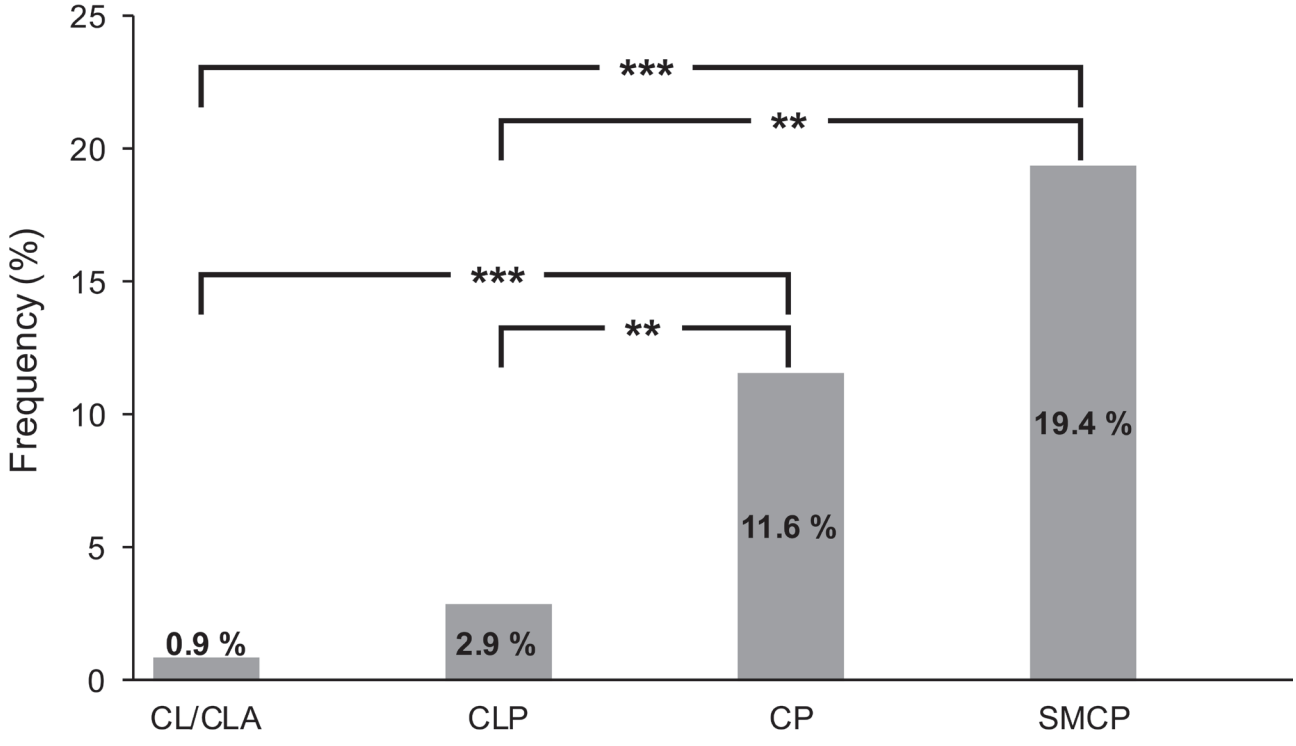

Fig. 3. Frequency of syndromes and chromosomal anomalies in different types of CL/P. SMCP presented with syndromes and chromosomal anomalies most frequently, followed by CP, CLP, and CL/CLA. $^{**}P < 0.01$. $^{***}P < 0.001$. CL, cleft lip; CLA, cleft lip and alveolus; CLP, cleft lip and palate; CP, cleft palate; SMCP, submucous cleft palate. CL/P, cleft lip and/or palate.

thus, the persistence or recurrence of a teratogen for congenital malformations can cause CP and SMCP.[9] In this study, CP and SMCP was more frequently associated with congenital anomalies than CL; however, the total prevalence of accompanying congenital anomalies was 14.5%. In a large survey of Japanese people, the prevalence rates of congenital anomalies associated with CL/P were 11.4%, 16.2%, and 20.7% in CL, CLP, and CP, respectively.[16] Although SMCP was not included, the results of the survey were nearly the same as that of our study, which may also reflect the differences among ethnic groups and geographical regions. In this study, those with SMCP had congenital anomalies more frequently than those with the other cleft patterns,

Table 4. Distribution of syndromes and chromosomal anomalies in different types of CL/P

Type of syndromes and chromosomal anomalies	CL/CLA	CLP	CP	SMCP	Total
Non-chromosomal syndromes					
Pierre Robin sequence	–	–	16	4	20 (2.7%)
First and second branchial arch syndrome	–	–	1	1	2 (0.3%)
Treacher Collins syndrome	–	–	2	–	2 (0.3%)
Apert syndrome	–	–	–	1	1 (0.1%)
Cornelia de Lange syndrome	–	–	–	1	1 (0.1%)
Waadenburg syndrome type I	1	–	–	–	1 (0.1%)
Rubinstein-Taybi syndrome	–	–	1	–	1 (0.1%)
Chromosomal anomalies					
Trisomy 21	–	2	–	–	2 (0.3%)
22q11.2 deletion	1	1	–	–	2 (0.3%)
Pallister-Killian syndrome	–	–	1	–	1 (0.1%)
Trisomy 3q	–	1	–	–	1 (0.1%)
3q duplication	–	1	–	–	1 (0.1%)
4q deletion	–	–	1	–	1 (0.1%)
Trisomy 13	–	1	–	–	1 (0.1%)
Trisomy 18	–	1	–	–	1 (0.1%)
Monosomy 18p	–	1	–	–	1 (0.1%)
18q deletion	–	–	1	–	1 (0.1%)
Total	2	8	23	7	40 (5.4%)

CL, cleft lip; CLA, cleft lip and alveolus; CLP, cleft lip and palate; CP, cleft palate; SMCP, submucous cleft palate. CL/P, cleft lip and/or palate.

which agreed with the results of Sekhon et al.[9] Given these results, accurate general examinations should be performed in patients diagnosed with SMCP given the high possibility of additional congenital anomalies. However, the small number of patients with SMCP may have influenced the results of this study. Therefore, further studies should be conducted to accumulate more cases of SMCP to facilitate better understanding.

CHDs have been reported to be the most common congenital anomalies associated with CL/P,[4, 6, 7] which corresponds with the results of our study. A systematic review of the prevalence rates of CHDs in patients with orofacial clefts showed five prospective studies with prevalence rates of 12.0% and four retrospective studies with prevalence rates of 8.6%.[17] Another systematic review by Munabi et al. reported that 7.43% of non-syndromic patients with CL/P had CHDs, and that the rate of CHDs in the general population was approximately 1%.[18] In this study, the prevalence rate of CHDs in both syndromic and non-syndromic CL/P was 7.2%, which was slightly lower than those in the aforementioned systematic reviews.

In this study, the frequency of syndromes associated with CL/P was significantly higher in patients with CP and SMCP, which was similar to that of syndromes and sequences reported in the study of Galeh et al.[4] Similar to previous literature, Pierre Robin sequence was the most commonly identified syndrome in our study.[4, 5] Pierre Robin sequence is a complex syndrome consisting of micrognathia, glossoptosis, and respiratory obstruction.[19–21] U- or V-shaped CP occurs in up to 90% of cases of Pierre Robin sequence.[20–22] In fact, all previously reported cases of Pierre Robin sequence were accompanied by CP.[23] In this study, Pierre Robin sequence was identified in patients with CP and SMCP, which provides new insights. Thus, when encountering non-cleft congenital anomalies and/or syndromes with speech disorders, it is necessary to consider SMCP and evaluate the presence of Calnan's classic triad.

The prevalence of chromosomal anomalies among CL/P has rarely been described in previous literature; however, Milerad et al. noted a 2.8% prevalence.[24]

Meanwhile, our study demonstrated a prevalence of 1.6% in CL/P cases. The population sizes of these two studies were almost equivalent. Therefore, this inconsistent prevalence may also be attributed to differences in ethnic groups. In general population-based studies, the prevalence of chromosomal anomalies was 3.6 per 1,000 births according to the European Surveillance of Congenital Anomalies and 11.0 per 10,000 perinatal infants according to a cross-sectional analysis from China.[25, 26] These data suggest that the prevalence of chromosomal anomalies is higher in those with CL/P than in the general population.

This study has certain limitations. First, laterality, which refers to the cleft's location (left, right, or bilateral) and extent (incomplete or complete), were not considered. If the laterality of CL/P is extensively discussed, the correlation between the location or extent of the cleft and congenital malformations may become clear. Second, a family history of CL/P and referral to our department were not included. These factors must be also analyzed to expand the research on CL/P. Moreover, the correlation among congenital anomalies, syndromes, and chromosomal anomalies was not analyzed. Future investigations must consider these, since they would be valuable and beneficial to all medical personnel engaged in CL/P treatment.

In conclusion, CP and SMCP have a high prevalence of associations with other congenital anomalies. Patients with congenital anomalies, especially CHDs, should be screened before initiating treatment for CL/P. Pierre Robin sequence accounts for approximately half of the accompanying syndromes and chromosomal anomalies in patients with CL/P. A noteworthy finding is that Pierre Robin sequence can be accompanied not only by CP, but also by SMCP. Under the same condition of accompanying syndromes or chromosomal anomalies, future research must determine how speech outcome and velopharyngeal function differ between CP and SMCP.

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The authors declare no conflict of interest.

REFERENCES

1 Dixon MJ, Marazita ML, Beaty TH, Murray JC. Cleft lip and palate: understanding genetic and environmental influences. Nat Rev Genet. 2011;12:167-78. DOI: 10.1038/nrg2933, PMID: 21331089
2 Setó-Salvia N, Stanier P. Genetics of cleft lip and/or cleft palate: association with other common anomalies. Eur J Med Genet. 2014;57:381-93. DOI: 10.1016/j.ejmg.2014.04.003, PMID: 24768816
3 Vyas T, Gupta P, Kumar S, Gupta R, Gupta T, Singh HP. Cleft of lip and palate: a review. J Family Med Prim Care. 2020;9:2621-5. DOI: 10.4103/jfmpc.jfmpc_472_20, PMID: 32984097
4 Galeh SD, Nouri-Vaskeh M, Alipour M, Fakhim SA. Clinical and demographical characteristics of cleft lip and/or palate in the northwest of Iran: an analysis of 1500 patients. Cleft Palate Craniofac J. 2021;58:1281-6. DOI: 10.1177/1055665620980633, PMID: 33380223
5 Beriaghi S, Myers SL, Jensen SA, Kaimal S, Chan CM, Schaefer GB. Cleft lip and palate: association with other congenital malformations. J Clin Pediatr Dent. 2009;33:207-10. DOI: 10.17796/jcpd.33.3.c244761467507721, PMID: 19476092
6 Sun T, Tian H, Wang C, Yin P, Zhu Y, Chen X, et al. A survey of congenital heart disease and other organic malformations associated with different types of orofacial clefts in Eastern China. PLoS One. 2013;8:e54726. DOI: 10.1371/journal.pone.0054726, PMID: 23349958
7 Abdollahi Fakhim S, Shahidi N, Lotfi A. Prevalence of associated anomalies in cleft lip and/or palate patients. Iran J Otorhinolaryngol. 2016;28:135-9. PMID: 27280100
8 Rao G, Desai A, Kumar N. Congenital heart diseases associated with cleft lip and palate and its impact on surgical treatment planning of patients with cleft lip and palate-a cross-sectional study. Cleft Palate Craniofac J. 2021;58:163-9. DOI: 10.1177/1055665620943082, PMID: 32700576
9 Sekhon PS, Ethunandan M, Markus AF, Krishnan G, Rao CB. Congenital anomalies associated with cleft lip and palate-an analysis of 1623 consecutive patients. Cleft Palate Craniofac J. 2011;48:371-8. DOI: 10.1597/09-264, PMID: 20815715
10 Azadgoli B, Munabi NCO, Fahradyan A, Auslander A, McCullough M, Aflatooni N, et al. Congenital heart disease in patients with cleft lip/palate and its impact on cleft management. Cleft Palate Craniofac J. 2020;57:957-66. DOI: 10.1177/1055665620924915, PMID: 32462926
11 Porterfield HW, Traube JC. Submucous cleft palate. Plast Reconstr Surg. 1965;35:45-50. DOI: 10.1097/00006534-196501000-00006, PMID: 14231379
12 Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant. 2013;48:452-8. DOI: 10.1038/bmt.2012.244, PMID: 23208313
13 Nahas LD, Alzamel O, Dali MY, Alsawah R, Hamsho A, Sulman R, et al. Distribution and risk factors of cleft lip and palate on patients from a sample of Damascus hospitals - a case-control study. Heliyon. 2021;7:e07957. DOI: 10.1016/j.heliyon.2021.e07957, PMID: 34541358
14 Urbanova W, Kotova M, Vankova Z. The incidence of cleft lip and palate in the Czech Republic in 1994–2008. Bratisl Lek Listy. 2013;114:474-9. DOI: 10.4149/BLL_2013_099, PMID: 23944624
15 Wójcicki P, Koźlik MJ, Wójcicka K. Genetic factors in selected complex congenital malformations with cleft defect. Adv Clin Exp Med. 2016;25:977-87. DOI: 10.17219/acem/61911, PMID: 28028964
16 Natsume N, Niimi T, Furukawa H, Kawai T, Ogi N, Suzuki Y, et al. Survey of congenital anomalies associated with cleft lip and/or palate in 701,181 Japanese people. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2001;91:157-61. DOI: 10.1067/moe.2001.112948, PMID: 11174591

17 Panamonta V, Pradubwong S, Panamonta M, Chowchuen B. Prevalence of congenital heart diseases in patients with orofacial clefts: a systematic review. J Med Assoc Thai. 2015;98(suppl 7):S22-7. PMID: 26742365
18 Munabi NCO, Swanson J, Auslander A, Sanchez-Lara PA, Davidson Ward SL, Magee WP 3rd. The prevalence of congenital heart disease in nonsyndromic cleft lip and/or palate: a systematic review of the literature. Ann Plast Surg. 2017;79:214-20. DOI: 10.1097/SAP.0000000000001069, PMID: 28570447
19 Robin P. A fall of the base of the tongue considered as a new cause of nasopharyngeal respiratory impairment: Pierre Robin sequence, a translation. 1923. Plast Reconstr Surg. 1994;93:1301-3. DOI: 10.1097/00006534-199405000-00032, PMID: 8171154
20 Evans KN, Sie KC, Hopper RA, Glass RP, Hing AV, Cunningham ML. Robin sequence: from diagnosis to development of an effective management plan. Pediatrics. 2011;127:936-48. DOI: 10.1542/peds.2010-2615, PMID: 21464188
21 Gómez OJ, Barón OI, Peñarredonda ML. Pierre Robin sequence: an evidence-based treatment proposal. J Craniofac Surg. 2018;29:332-8. DOI: 10.1097/SCS.0000000000004178, PMID: 29215441
22 Caouette-Laberge L, Bayet B, Larocque Y. The Pierre Robin sequence: review of 125 cases and evolution of treatment modalities. Plast Reconstr Surg. 1994;93:934-42. DOI: 10.1097/00006534-199404001-00006, PMID: 8134485
23 Vallino-Napoli LD, Riley MM, Halliday JL. An epidemiologic study of orofacial clefts with other birth defects in Victoria, Australia. Cleft Palate Craniofac J. 2006;43:571-6. DOI: 10.1597/05-123, PMID: 16986995
24 Milerad J, Larson O, Hagberg C, Ideberg M. Associated malformations in infants with cleft lip and palate: a prospective, population-based study. Pediatrics. 1997;100:180-6. DOI: 10.1542/peds.100.2.180, PMID: 9240796
25 Dolk H, Loane M, Garne E. The prevalence of congenital anomalies in Europe. Adv Exp Med Biol. 2010;686:349-64. DOI: 10.1007/978-90-481-9485-8_20, PMID: 20824455
26 Xie D, Yang W, Fang J, Li H, Xiong L, Kong F, et al. Chromosomal abnormality: prevalence, prenatal diagnosis and associated anomalies based on a provincial-wide birth defects monitoring system. J Obstet Gynaecol Res. 2021;47:865-72. DOI: 10.1111/jog.14569, PMID: 33372274