The Characteristics and Distribution of Dental Anomalies in Patients with Cleft

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Background: Dental anomalies associated with different severities of cleft lip and palate have been rarely reported. This retrospective study investigates the characteristics of dental anomalies associated with different types of cleft, and compares the dental anomaly traits based on sex and severity of cleft.

Methods: Cleft patients born in 1995 with qualified diagnostic records from 7 to 11 years were included for evaluation. Records were retrieved from database of Chang Gung Craniofacial Center, including panoramic radiographs and intraoral photographs. In total, 196 patients with complete records were included in the evaluation. This study compares the dental anomalies associated with each type of cleft.

Results: The frequency of dental anomalies in the maxillary incisor area in the cleft palate (CP) group (20%) was significantly lower than that in other groups. The frequency of missing maxillary lateral incisors (MLIs) increased as the cleft severity increased. Supernumerary teeth and missing lower incisors exhibited the opposite trend. No sexual dimorphism appeared in terms of the frequencies of peg laterals and missing MLIs. The distribution patterns of missing MLIs and peg laterals in males, but not in females, were consistent for the three types of unilateral clefts.

Conclusion: Regarding the characteristics of dental anomalies among the three unilateral clefts, missing MLIs, supernumerary teeth, and missing lower incisors were found to be related to cleft severity. The maxillary lateral incisor was the most affected tooth in the cleft area. The frequency of missing MLIs and peg laterals was not sexual dimorphic, but the distribution pattern was different between the sexes.

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Key words: dental anomaly, cleft lip and palate, congenital tooth missing, peg lateral, supernumerary teeth

Dental anomalies occur more frequently in cleft patients than in the general population.[1,2] Dental anomalies differ in patients with different types of cleft, and even in those with microforms of cleft lip. Common dental anomalies in clefts include tooth agenesis, microdontia, ectopic eruption, trans-

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position of the maxillary canines and premolars, delayed tooth development, and crown and root malformation. The maxillary lateral incisors are the most susceptible tooth to be affected in the vicinity of the cleft. Functional, periodontal, and restorative problems may be concerns during the treatment of different types of dental anomalies.[3]

In the 6th week of intrauterine life, the bilateral medial nasal processes merge to form the center of the upper lip and primary palate, which comprises the alveolar process and four upper incisors. The maxillary processes and medial nasal processes fuse together in the middle of the 6th week. Failure of the maxillary process to fuse with the medial nasal process results in a cleft lip. At almost the same time, the oral epithelium proliferates and forms the dental lamina in the region of the future alveolar processes.[4,5] The dental lamina develops into tooth buds, which then proceed from the bud to the cap and bell stages of tooth formation. The association between the dental anomalies and cleft lip and palate may come from their proximate anatomy, the timing of cleft formation and the timing of dental development.

Research in the last decade has shown that genetic factors play an important role in dental anomalies. Genes, environmental factors, and their interaction play a significant role in causing craniofacial cleft.[6,7] Some genes may contribute to both orofacial clefting and congenital dental anomalies.[8] Msx1 and PAX9 are the signaling molecules that affect the position and shape of teeth.[9] Animal models using mice show that a lack of Msx1 function causes cleft palate, deficient alveolar bones, and a failure of tooth development.[10] A heterozygous Msx1 nonsense mutation was identified in a Dutch family exhibiting various types of orofacial clefting and missing teeth.[11] Mutations in Msx1 and PAX9 have been associated with non-syndromic tooth agenesis in humans,[12] and both genes are essential for tooth and secondary palate development in mice.[10] The IRF6 gene is associated with Van der Woude syndrome, lip pit, and tooth agenesis, and the PVRL1 (poliovirus receptor related-1) gene is associated with cleft lip and palate-ectodermal dysplasia syndrome.[13] Dental anomaly information will increase the possibility of finding susceptibility loci for clefts, which may in turn help in the identification of genes that increase cleft susceptibility.[8]

Previous studies have examined the prevalence of dental anomalies in cleft patients, but most of these studies have focused on only one cleft type, or merely compare unilateral and bilateral cleft lip and palate. Few studies have investigated the characteristics of dental anomalies in unilateral clefts with different severities (unilateral cleft lip, unilateral cleft lip and alveolar, and unilateral cleft lip and palate).

This study investigates the dental anomalies in each type of cleft and the occurrence of dental anomalies associated with the severity of cleft, with sex, and with cleft sidedness.

METHODS

Subjects who were born in 1995 with oral clefts were retrieved from the database of Chang Gung Craniofacial Center. All the patients were Taiwanese. The inclusion criteria were complete records from the age of 7 to 11 years, including panoramic, occlusal radiographs, intraoral photographs, and clinical dental charts. All the patients received standard cleft treatment, and had no previous orthodontic treatment or history of permanent teeth extraction. The exclusion criteria were patients with incomplete data, patients with fuzzy radiographs that were difficult to evaluate, and patients with incomplete follow up records. Syndromic cleft patients were also excluded to avoid the possible influence on dental anomalies of the syndrome.

The anterior permanent teeth (canine and incisor) were evaluated based on the records from 7 to 9 years old in an attempt to reduce the misinterpretation of counting the extracted peg laterals or supernumerary teeth as missing teeth. This is because many peg laterals or supernumerary teeth are extracted at an early age. The panoramic films from 11-year-old patients were used to evaluate the posterior teeth (premolar and molar), as second premolars may develop after ages of 6 or 7 years old.[14,15] Furthermore, patients with cleft lip and palate often have delayed tooth development compared with the non-cleft population.[16,17] Hence, the evaluation of premolars was based on the panoramic films taken at 11 years old.

The maxillary lateral incisor (MLI) was considered present either on the mesial or distal side of the cleft, regardless of tooth morphology. When more than one lateral incisor was observed, the distal one

(if the tooth size was similar) or the smaller one was regarded as the supernumerary tooth. When a maxillary supernumerary primary lateral incisor and supernumerary permanent lateral incisor simultaneously existed, the judgment was based on the stage of root development and tooth color. The root development of primary maxillary lateral incisor is complete at age two on average, while the root development of the permanent maxillary lateral incisor is complete at 11 years old on average. For this reason, a maxillary supernumerary lateral incisor with a yellowish color and incomplete root development was regarded as a permanent tooth. On the other hand, a maxillary supernumerary lateral incisor with a white color and complete root formation was regarded as a primary tooth. The number and position of teeth with hypodontia or microdontia, supernumerary teeth, and transposition were also recorded. A single examiner analyzed radiographs and photographs. The optimal identification of undistinguishable radiographs was verified by an experienced specialist. The clefts were classified into five main groups for analysis of the frequency of dental anomalies:

Unilateral cleft lip (UCL): the alveolar process and palate were not affected; the lip was involved on one side completely or incompletely.

Unilateral cleft lip and alveolus (UCLA): in addition to the cleft lip, the alveolar process was involved, but the palate was intact.

Unilateral cleft lip and palate (UCLP): in addition to the unilateral involvement of lip and alveolar process, the palate was involved, either unilaterally or bilaterally.

Bilateral cleft lip and palate (BCLP): in addition to bilateral involvement of lip and alveolar process, the palate was involved, either unilaterally or bilaterally.

Cleft palate (CP): only the palate was involved. Cleft palates with different severities from submucous cleft palate to complete cleft palate were included.

This study also compared three types of unilateral clefts, including UCL, UCLA, and UCLP, to evaluate the effect of the severity of cleft on the occurrence of dental anomalies.

Statistical analysis

Fisher's exact test was used to compare the frequencies of dental anomalies among the different cleft types and genders. A *p*-value below 0.05 was considered to be statistically significant. The data were analyzed using the Statistical Package for Social Science Version 12.0 for Windows (SPSS, Inc., Chicago, Illinois, U.S.A.).

RESULTS

A total of 565 newborn patients with cleft were enrolled at Chang Gung Craniofacial Center in 1995. The most frequent type among these 565 cleft patients was CP (29%), followed by UCLP (27%), UCL (14%), BCLP (12%), and UCLA (9%). Male and left side predominance appeared for the three unilateral cleft types. When gender and cleft side were examined, the difference in percentages was greatest for UCLP (with 43% and 44.4% for sex and cleft side, respectively), followed by UCL (25% and 34%) and UCLA (4.4% for both sex and cleft side). Among the 565 patients, 38 patients had syndromic clefts, and 331 patients had incomplete records or unidentifiable radiographs. Therefore, 196 patients were included for subsequent investigation. The 196 patients consisted of 83 with UCLP, 31 with UCLA, 20 with UCL, 38 with BCLP, and 20 with CP. Table 1 presents the occurrence percentage of the dental anomalies for each type of cleft patients.

Dental anomalies in the maxillary incisor area

The frequency of missing MLIs was highest in the BCLP group (65.8%), followed by the UCLP group (56.7%), the UCLA group (35.5%), the UCL group (20%), and the CP group (10%). The frequency of missing MLIs in the CP group was significantly lower than that in the BCLP and UCLP groups ($p = 0.02$), and the UCL group was significantly lower than the BCLP group ($p = 0.046$). The frequency of missing maxillary lateral incisors increased as the severity of the cleft increased.

The frequency of peg laterals was highest in the UCLA group (61.3%), followed by the BCLP group (58%), the UCLP group (48.2%), the UCL group (45%), and the CP group (10%). The frequency of peg laterals in the CP group was significantly lower than that in the UCLA, BCLP, and UCLP groups ($p = 0.038$).

The UCL group exhibited the highest frequency of supernumerary teeth (15%), followed by the

UCLA group (9.7%) and the UCLP group (4.8%). The ratio of total frequency of supernumerary teeth was approximately 3:2:1 in the UCL, UCLA, and UCLP groups, respectively. The frequency increased with the severity of cleft decreased, but exhibited no significant differences. The frequency of dental anomalies in the maxillary incisor area was smallest in the CP group (20%), and was significantly lower than that in other groups ($p = 0.029$).

Dental anomalies outside the maxillary incisor area

Missing maxillary second premolar occurred in approximately one fifth of UCLP subjects (19.2%), and in 10% and 7.6% of the CP and BCLP subjects. The most frequent missing premolars were the maxillary second premolar (9.2% in all patients), followed by mandibular second premolar (1.5%), and maxillary first premolar (0.5%).

Transposition only occurred in the BCLP (10.6%) and UCLP (3.6%) groups, and the transposed teeth were all maxillary canine and 1st premolars. Table 1 shows that the distribution pattern was unrelated to cleft sidedness. The frequency of missing lower incisors increased as the severity of cleft decreased (UCL: 10%, UCLA: 3.2%, UCL: 2.4%) although there were no significant differences. For the total frequency of dental anomalies outside the

Table 1. Percentage Occurrence of Dental Anomalies in Cleft Patients

Cleft Type	UCLP N = 83	UCLA N = 31	UCL N = 20	BCLP N = 38	CP N = 20
Dental Anomalies in the Maxillary Incisor Area					
Missing MLI at the ipsilateral side	36.1	32.3	15	26.3	5
Missing MLI at the contralateral side	6	0	0		
Missing MLI at both side	14.6	3.2	5	39.5	5
Total Frequency of Missing MLI	56.7	35.5	20	65.8	10
Peg laterals at the ipsilateral side	42.2	48.3	30	28.9	5
Peg laterals at the contralateral side	2.4	6.5	0		
Peg laterals at both side	3.6	6.5	15	28.9	5
Total Frequency of Peg Laterals	48.2	61.3	45	57.8	10
Supernumerary teeth in the cleft area	3.6	9.7	15	13.2	0
Supernumerary teeth outside the cleft area	1.2	0	0	0	0
Total Frequency of Supernumerary teeth	4.8	9.7	15	13.2	0
Missing upper central incisor	1.2	0	0	5.3	0
Total frequency of dental anomalies in the maxillary incisor area	110.9	106.5	80	142.1	20
Dental Anomalies outside the Maxillary Incisor Area					
Missing U5 at the ipsilateral side	12	0	0	2.6	5
Missing U5 at the contralateral side	6	0	0		
Missing U5 at both side	1.2	0	0	5	5
Total of Missing U5	19.2	0	0	7.6	10
Missing L5 at the ipsilateral side	2.4	0	0	0	5
Missing L5 at the contralateral side	0	0	0		
Missing L5 at both side	0	0	0	0	0
Total of Missing L5	2.4	0	0	0	5
U3&U4 transposition at the ipsilateral side	1.2	0	0	5.3	0
U3&U4 transposition at the contralateral side	1.2	0	0		
U3&U4 transposition at both side	1.2	0	0	5.3	0
Total of U3&U4 transposition	3.6	0	0	10.6	0
Missing lower incisor	2.4	3.2	10	2.6	5
Total frequency of dental anomalies outside the maxillary incisor area	27.6	3.2	10	20.8	20

Abbreviations: MLI: maxillary lateral incisor; U5: maxillary second premolar; L5: mandibular second premolar; U3&U4: maxillary canine and maxillary first premolar.

maxillary incisor area, only the UCLA group was significantly lower than the UCLP group ($p = 0.015$). The BCLP, UCLP, UCL, and CP groups exhibited no significant differences in dental anomalies outside the maxillary incisor area.

The following provides further comparisons of unilateral clefts (UCLP, UCLA and UCL). No sexual dimorphism appeared in the frequencies of peg laterals and missing MLIs for the UCLP, UCLA, and UCL ($p > 0.05$) groups (Fig. 1). The distribution patterns of peg laterals and missing MLIs in males were similar for the three unilateral clefts, with the highest frequency appearing on the ipsilateral side, followed by both sides and then the contralateral side (Fig. 2A, B). The frequencies of missing MLIs decreased as the severity of the cleft decreased (Fig. 2A). However, the distribution patterns of missing MLIs and peg laterals in females were significantly different for the three unilateral cleft types ($p < 0.001$), and was not correlated with the severity of the cleft (Fig. 2C, D).

DISCUSSION

To our knowledge, relatively few papers have compared the dental anomalies of patients in relation to the different severities of cleft defect.[1,18,19] Baek and Kim showed that male and left sidedness predominance in UCLP and were significantly higher than in UCLA,[1] which agrees with the current findings. On the other hand, in our study, male and left sidedness predominance in UCL was higher than in UCLA, which disagrees with Baek et al. The percentage of missing MLIs on cleft side is similar between these studies, with most research reporting results from 48.8% to 51.8%.[20-22] The only exception appears to be the study of Lai et al,[23] in which the frequencies of missing MLIs on cleft side in UCLP (19.2%) and BCLP (20.5%) were much lower than in the current study. However, Lai's study examined subjects aged from 3 to 17 years. This wide range in age may have led to misinterpretation because it is difficult to identify tooth germs when the patient is young, and the possibility of tooth extraction increases the risk of misdiagnosis if the patient is older. Hence, the present study used panoramic films, occlusal films, and photos taken at the ages 7 and 9 years to observe the dental anomalies of the anterior teeth, and at 11 years to evaluate the posterior teeth.

The frequency of missing MLIs and the presence of peg laterals in unilateral clefts were similar for both sexes, which agrees with other studies.[21,24,25] However, the distribution patterns of missing MLIs and peg laterals in males were consistent in the three unilateral clefts, but inconsistent in female patients. The consistency of distribution pattern in males implies that genes may play roles in the cleft defect and associated dental anomalies.

The frequency of supernumerary teeth in this study was greatest in the UCL group, and decreased as the severity of the cleft increased. This agrees with the findings of previous studies.[24,26] Tsai et al. hypothesized that the odontogenic region of the lateral incisor comes from the medial nasal and maxillary processes, and that nonfusion of these two processes results in two separated lateral incisors.[20] Another hypothesis is that the supernumerary teeth come from the postfusion rupture of the cleft in the lateral incisor area, and the tooth germ of the lateral incisor is split into two separate teeth.[27] Patients

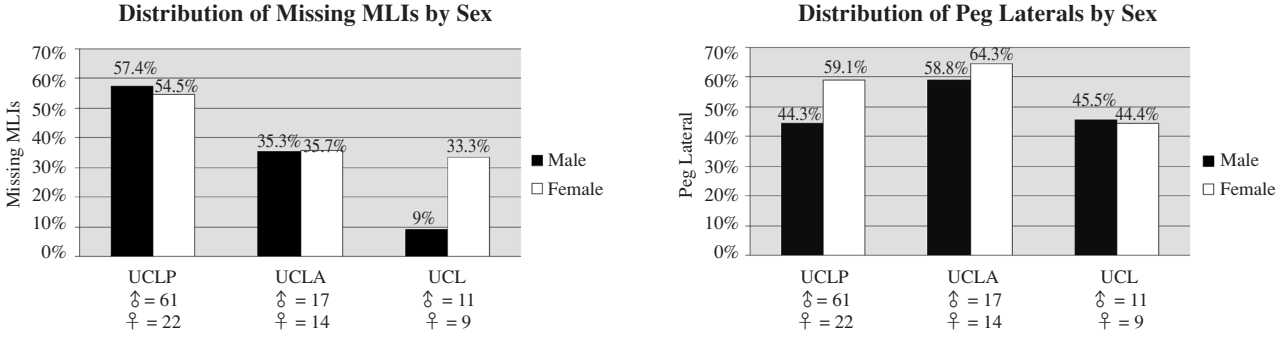

Fig. 1 Distribution of missing MLIs and peg laterals by sex.

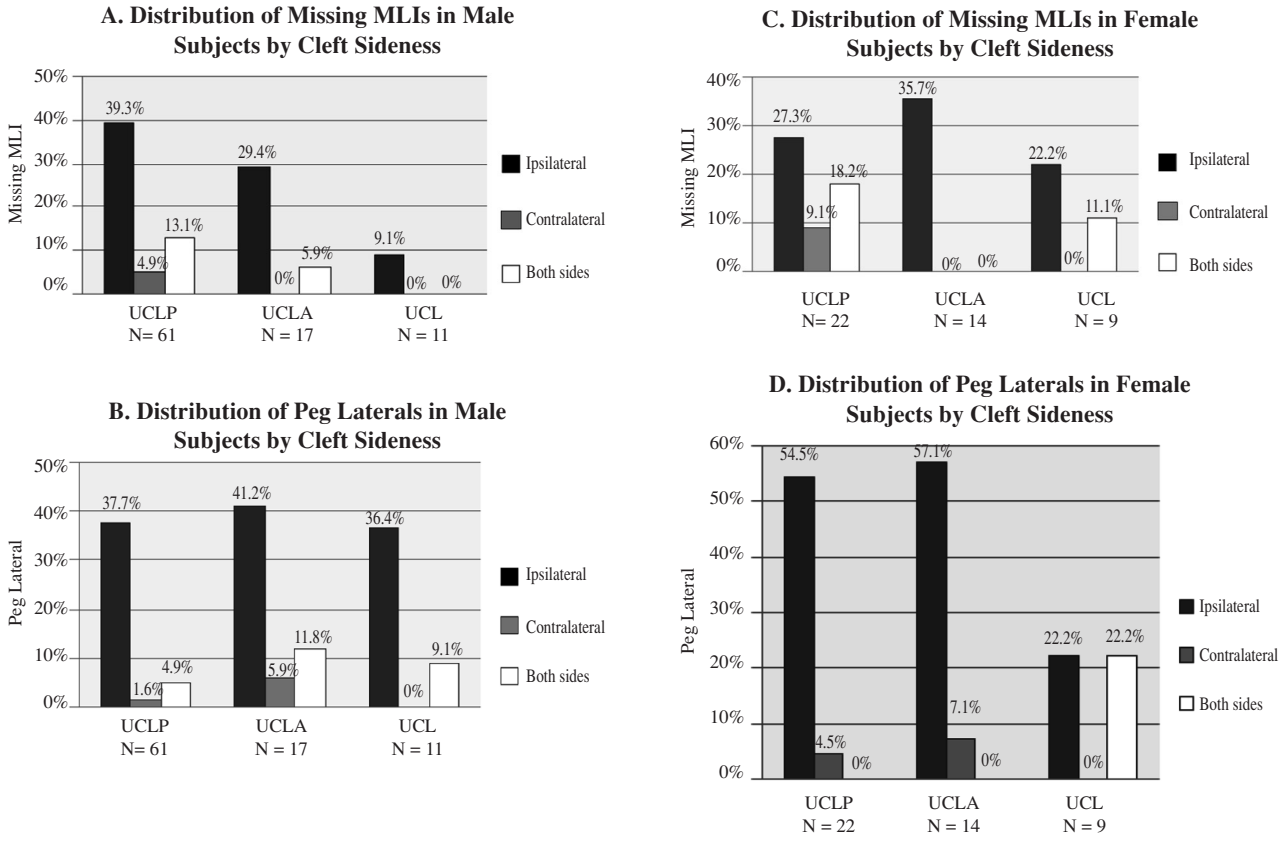

Fig. 2 Distribution of missing MLIs and peg laterals for both sexes by cleft sidedness.

with severe alveolar cleft exhibit greater deficiency in the mesenchymal mass and this resulted in the absence of teeth. In cleft patients with an alveolar process relatively unaffected by the cleft, the tooth germ can develop in spite of cleft formation. These reasons may explain why supernumerary teeth occurred most frequently in cleft lip patients.

The prevalence of missing maxillary second premolars in this study was 19.2% in the UCLP group and 7.6% in the BCLP group. In other studies, the prevalence was not similar, ranging from 10% in the UCLP group[21] to 25% in the BCLP group.[22] The reasons for this wide range of prevalence in missing maxillary second premolar in these studies may due to the variation in patient ages, differences in ethnicity, and the varied nature of maxillary second premolar development.[14] The prevalence of missing mandibular second premolar in the UCLP group in this study was 2.4%, which is similar to the noncleft population (2.9% to 3.2%).[28]

The frequency of missing lower incisor increased as the severity of cleft decreased, resulting in the highest frequency being associated with cleft lip. However, the cause of this trend remains unclear. A recent animal study shows that Msx 1 and PAX9 interact synergistically during lower incisor and upper lip development.[29] Mutations of Msx 1 and PAX9 induce unilateral or bilateral cleft lip and a lack of lower incisors in mice. However, Msx 1 is able to explain only a few cases of tooth agenesis. Therefore further studies are needed to validate the higher frequency of missing lower incisors in the UCL group.

In clinical practice, dental anomalies can be managed in several ways. After considering the severity of dental crowding, the facial profile, and the interocclusal relationship, peg laterals can be restored to mimic the normal size of maxillary lateral incisors, or extracted and substituted with canines. When the lateral incisors in cleft area are missing or

extracted, replacement is not required in most cases. The space in the cleft area can be closed by orthodontic treatment, or by a two-piece Le Fort I osteotomy with asymmetric posterior segment advancement.[3] When the dental space of upper lateral incisor in the cleft area remains open, a removable prosthesis, fixed bridge or single implant can be provided depending on the periodontal condition and integrity of the alveolar ridge. Autotransplantation into the bone-grafted alveolar cleft is another approach,[30] but the long-term prognosis of a tooth transplant to the cleft area remains to be determined. For the transposed maxillary canines and first premolars, complete or incomplete transposition and the complexity of treatment mechanics need to be considered. In cases of complete transposition, possible root dehiscence and jeopardized of periodontal support might occur after full correction of transposition. Leaving the teeth in the transposition position can achieve acceptable esthetics although with less than ideal function. Enamel reduction may be required at the palatal cusp of a transposed first premolar to prevent functional interference.[31] For congenital missing second premolars, prolonged retention of the deciduous molar as a natural space maintainer may be an option during childhood and adolescence. These deciduous molars also preserve the alveolar bone volume for permanent restoration until the patient becomes an adult, or as long as they can be preserved.

This study is somewhat limited in that it is retrospective, and the missing data therefore affects the results due to the decreased sample size. Combining the information sources of medical chart, intraoral photos, longitudinal panoramic, and occlusal X-ray films was able to reduce errors and helped to obtain more accurate data.

Conclusion

Regarding the distribution in terms of sex and cleft side, male and left side predominance appeared for the three unilateral cleft types. The predominance was greatest in the UCLP group (43% and 44.4% for sex and cleft side, respectively), followed by the UCL group (25% and 34%) then the UCLA group (4.4% for both of sex and cleft side).

Dental anomalies in the maxillary incisor area

1. The frequency of missing MLIs increased as the severity of cleft increased (UCL: 20%, UCLA: 35.5%, UCLP: 56.7%). The peg lateral frequency was highest in the UCLA group (61.3%). The maxillary lateral incisor was the most affected tooth in the cleft area.
2. The ratio of total frequency of supernumerary teeth was approximately 3:2:1 in the UCL (15%), UCLA (9.7%) and UCLP (4.8%) groups, respectively.
3. In the maxillary incisor area, the CP group had the lowest frequency of dental anomalies (20%, $p = 0.029$).

Dental anomalies outside the maxillary incisor area

1. The most frequently missing premolars in cleft patients were the maxillary second premolars (9.2%), followed by mandibular second premolars (1.5%) and maxillary first premolars (0.5%).
2. The maxillary second premolars were the most affected tooth outside the cleft area (9.2%), followed by the lower incisors (3.6%) and transposition of maxillary canines and first premolars (3.6%).

Sexual dimorphism in terms of peg laterals and missing MLIs

Although there was no sexual dimorphism in the frequency of missing MLIs and peg laterals, the distribution patterns of missing MLIs and peg laterals were different for males and females ($p < 0.001$).

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唇腭裂患者齒性異常之特性及分布

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背 景： 有關不同嚴重程度的單側唇腭裂患者其齒性異常之比較，其文獻有限。本篇回溯性地探討各種唇腭裂類型之齒性異常，並且比較不同嚴重程度單側唇腭裂其齒性異常的特性。

方 法： 觀察的對象包括出生於西元 1995 年並有完整七歲至十一歲牙科記錄之唇腭裂患者。資料擷取自長庚顱顏中心資料庫，包括環口放射片及口內照片等。196 位唇腭裂患者具有完整資料，觀察其齒性異常並記錄之。

結 果： 在上腭門牙區，腭裂發生齒性異常的頻率 (20%) 明顯小於其他組別。上腭側門牙缺失的頻率隨著唇腭裂的嚴重程度增加而提高，但發生多生牙及下腭門牙缺失的情形卻隨嚴重程度增加而減少。兩性在三種單側唇腭裂發生上腭側門牙缺失或錐形側門齒的頻率相等。而男性在三種單側唇腭裂中，此兩種齒性異常在患側及非患側分布的型態相似，但在女性則有顯著不同。

結 論： 上腭側門牙缺失，多生牙及下腭門牙缺失的頻率和唇腭裂嚴重程度有關。上腭側門牙是最容易發生齒性異常的牙齒。男女發生多生牙及上顎側門牙缺失的頻率相同，但是發生時牙齒在患側及非患側的分布情形則不同。

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關鍵詞： 齒性異常，唇腭裂，先天性缺牙，錐形側門齒，贅生牙

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