

PREVALENCE AND PATTERN OF TOOTH AGENESIS AMONG PATIENTS WITH ISOLATED CLEFT LIP AND PALATE IN THE TAWANCHAI CLEFT CENTER

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ABSTRACT

The aims of this study were to evaluate the prevalence of tooth agenesis in a group of patients with isolated cleft lip and palate (CLP). Secondly, we aimed to investigate the relationship of maxillary lateral incisor missing with laterality and cleft type in non-syndromic cleft lip and palate patients. 194 patients with non-syndromic isolated CLP who had been treated at Tawanchai cleft center, Khon Kaen University, Thailand from 2012 to 2022, were enrolled in this study. Medical records, dental records, and radiographic examination (either orthopantomogram (OPG) or cone beam computed tomography CBCT) were evaluated to diagnose tooth agenesis. Prevalence and frequency of tooth agenesis, average number of missing teeth per patient, maxillary lateral incisor agenesis occurrence and location were analyzed by cleft type. 77.32% of the patients experienced with missing teeth. Bilateral CLP (BCLP) patients had a higher number of missing teeth (88.14%), and unilateral left CLP patients (ULCLP) (73.63%) had a higher one compared to unilateral right CLP patients (URCLP) (70.45%). Distribution of maxillary lateral incisor agenesis tended to be higher missing at the left side (45.9%) than right side (18.8%) and both sides (35.3%). In this study, more than three quarters of patients diagnosed with non-syndromic cleft lip and palate exhibited tooth agenesis. The maxillary lateral incisor emerged as the tooth most affected, with a notable tendency for agenesis on the left side, regardless of the specific type of cleft.

Keywords: Isolated Cleft Lip and Palate, Tooth Agenesis, Lateral Incisor

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INTRODUCTION

Cleft lip with or without cleft palate is one of the most frequent craniofacial congenital malformations, with a listed prevalence of 0.3-0.45 cleft patients per 1,000 live births globally (Salari et al., 2022). The prevalence is high, with 2.14 per 1,000 live-birth cleft patients in Thailand, according to the nation-wide registry-based study in Thailand (Fuangtharnthip et al., 2021). The cleft formation is frequently related to dental abnormalities in number, size, shape, structure, and time of eruption (Cakan et al., 2018; Howe et al., 2015). Since tooth development is affected by clefting, the cleft population has experienced tooth agenesis, which is found at a much higher frequency than in its healthy Asian non-cleft population (Marzouk et al., 2021). Upper permanent incisors could be mostly influenced by incomplete fusion of the maxilla. Consequently, the division of tooth buds or a proliferation of the dental lamina can lead to supernumerary teeth at the cleft site, mostly at the maxillary lateral incisor region. Moreover, dysfunctional, or incapable growth of a tooth can result in micro-form or even loss of the tooth (Howe et al., 2015). Besides these environmental impacts, many experts believed that there are different genetic factors, such as *MSXI*, *PAX9*, and *BMP7*, that caused the combined development of orofacial clefts and dental anomalies in number. According to their genetic etiology, tooth agenesis could also be seen in some syndromic clefts (Matalova et al., 2008).

Although there are several studies on the prevalence of dental anomalies and tooth agenesis at the cleft side, fewer studies have focused on the relationship between tooth agenesis ipsilateral and contralateral sides of the cleft patients. Dental anomalies often affect the maxillary lateral incisors in the cleft population. The analysis of dental anomalies in “tooth number” according to the region of cleft would provide some clues for the early and systematic treatment protocol. Therefore, in cleft patients, the radiographic evaluation should be performed to detect anomalies, not only at the cleft side but also outside the cleft region.

Consequently, missing teeth have severe implications for speech, swallowing, tooth alignment, and psychological well-being, seriously affecting the quality of life of these individuals. Cleft patients need an interdisciplinary approach involving oral and maxillofacial surgery, speech therapy, orthodontics, and pediatric dentists, for example. Therefore, localization of tooth buds and stage of tooth must be closely monitored to set the time and allocate the space for facilitating orthodontic treatment planning.

The aims of this study were to evaluate the prevalence of tooth agenesis in patients with cleft lip and palate from the Tawanchai cleft center and, secondly, to investigate the relationship between maxillary lateral incisor missing with laterality and cleft type in non-syndromic cleft lip and palate patients.

MATERIALS AND METHODS

This retrospective study was conducted in the Dental Hospital, Faculty of Dentistry, Khon Kaen University, Thailand, and approved by the ethical review committee, Center for Ethics in Human Research, Khon Kaen University, Thailand (project number HE661161).

All data were obtained from the dental hospital records of the cleft patients who were registered and treated at Tawanchai Cleft Center, Khon Kaen University, Thailand, from January of 2012 to August of 2022. Either analyzable orthopantomogram (OPG) or cone beam computed tomography (CBCT) performed by radiologists were included.

This study recruited Thai male and female patients whose ages ranged from 3 years to 12 years and 11 months at the time of radiographic diagnosis, without any severe medical conditions that could affect odontogenesis, such as coexisting genetic syndrome, heart disease, or intellectual impairment. We excluded 1) patients with an isolated cleft of the lip, an isolated cleft of the palate, bilateral and unilateral clefts of the lip and alveolus, and unique atypical types of clefts; and 2) patients who had already started orthodontic treatment at the time of radiographic examination. For patients who were younger than 6 years of age, the radiographic

examination was rechecked at the age of 6 years to avoid the possibility of inaccuracy while identifying tooth agenesis, especially in second premolars, in a radiograph at an earlier age. All records were screened using the dental records and investigated using at least one clear OPG or CBCT of each patient by a single investigator. If available, in addition, occlusal tomographs and intraoral radiographs were checked for dental anomalies to eliminate ambiguity and ensure results. All the radiographic examinations were chosen at the first-time examination to prevent missing teeth from being extracted. The included patients were double-checked by SM, comparing the findings of dental records and intraoral photographs concerning the correction of data. Tooth counts and percentages were used to describe congenital missing teeth, excluding the third molars.

All radiographic examinations were observed by one examiner (WPA). In cases of inconsistency, difficulty, or unclear findings, these interpretations were discussed with another researcher (SM). If no agreement could be reached, the patient would be excluded from the study.

The prevalence and frequency of tooth agenesis for each cleft type were calculated. The significance of differences in the proportions of tooth agenesis among different cleft types was tested by the chi-square test. The statistical significance for all tests was set at $p < 0.05$. Statistical analysis was performed using IBM SPSS Statistics version 28 (IBM SPSS, Inc., Chicago, IL).

RESULTS

The cleft patients included in this study consisted of 194 patients, with 108 males and 86 females, corresponding to a gender distribution of 1.26:1 male to female. A hundred and thirty-five patients showed unilateral clefts (UCLP patients), 44 right-sided, and 91 left-sided clefts (see Table 1).

Table 1 Distribution of analyzed cleft patients according to cleft type, cleft side and gender

	URCLP n (%)	ULCLP n (%)	BCLP n (%)	Total n (%)
Male	31 (70.45)	38 (41.76)	39 (66.10)	108 (55.67)
Female	13 (29.55)	53 (58.24)	20 (33.90)	86 (44.33)
Total	44 (100)	91 (100)	59 (100)	194 (100)

URCLP, Unilateral right cleft lip and palate; ULCLP, Unilateral left cleft lip and palate; BCLP, Bilateral cleft lip and palate; n, absolute number; (%), percentage value

In our study, tooth agenesis could be found within the cleft collective analyzed, affecting 150 out of 194 cleft patients (77.32%) (see Table 2). Tooth agenesis was observed in 88.14% of BCLP patients, while patients with URCLP and ULCLP experienced missing teeth in 70.45% and 73.63%, respectively (see Table 2). The prevalence of tooth agenesis was not statistically different among the cleft groups. The frequency of missing teeth was presented in Table 2.

Table 2: Characteristics and frequency of patients with tooth agenesis among different cleft types

Dental anomalies	Cleft type (n=194) n (%)			Total (n=194) n (%)	P value ^a
	URCLP (n=44)	ULCLP (n=91)	BCLP (n=59)		
Congenital missing teeth					
Unaffected	13 (29.55)	24 (26.37)	7 (11.86)	44 (22.68)	0.054
Missing	31 (70.45)	67 (73.63)	52 (88.14)	150 (77.32)	
Number of missing teeth	URCLP (n=31)	ULCLP (n=67)	BCLP (n=52)	Total (n=150)	
1 tooth	16	29	20	65	
2 teeth	7	24	20	51	
3 teeth	2	13	5	20	
4 teeth	5	0	6	11	
5 teeth	1	0	1	2	
>5 teeth	0	1	0	1	

URCLP, Unilateral right cleft lip and palate; ULCLP, Unilateral left cleft lip and palate; UCLP, Unilateral cleft lip and palate; BCLP, Bilateral cleft lip and palate; n, absolute number; (%), percentage value ^a Chi square test

For characteristics of missing teeth, a total of 287 teeth were reported as missing teeth (see Table 3). The upper lateral incisor was the most commonly missing tooth (46.39%, 180 out of 388 possible teeth), followed by the maxillary second premolar (18.81%). Tooth agenesis frequently occurred in the maxilla at a frequency of 70.62%, in both jaws at a frequency of 4.12%, and exclusively in the mandible at a frequency of 2.58% of the patients (data not shown). The overall average of 1.48 missing teeth per patient was subdivided into 1.76, 1.39, and 1.35 in the BCLP, URCLP, and ULCLP groups, respectively.

Table 3: Distribution of patients with tooth agenesis dependent on cleft type and tooth type

Cleft type	Number of samples n (%)	Type of tooth								Missing teeth per person
		12 n (%)	22 n (%)	14 n (%)	24 n (%)	15 n (%)	25 n (%)	Max n (%)	Mand n (%)	
URCLP	44 (100)	20 (45.45)	17 (38.64)	3 (6.82)	0 (0.00)	8 (18.18)	10 (22.73)	2 (4.55)	1 (2.27)	1.39
ULCLP	91 (100)	23 (25.27)	55 (60.44)	1 (1.10)	6 (6.59)	17 (18.68)	13 (14.29)	3 (3.30)	5 (5.49)	1.35
BCLP	59 (100)	29 (49.15)	36 (61.02)	1 (1.69)	2 (3.39)	14 (23.73)	13 (22.03)	1 (1.69)	7 (11.86)	1.76
Total	194 (100)	72 (37.11)	108 (55.67)	5 (2.58)	8 (5.93)	39 (20.10)	36 (18.56)	6 (3.09)	13 (6.70)	1.48

URCLP, Unilateral right cleft lip and palate; ULCLP, Unilateral left cleft lip and palate; BCLP, Bilateral cleft lip and palate; n, absolute number of patients with tooth missing; (%), percentage value of the patients with tooth missing; Max, other maxillary teeth; Mand, Mandibular teeth

We further analyzed the prevalence and the laterality of the most missing tooth, the maxillary lateral incisor. The prevalence of the missing this incisor was observed without significant differences among cleft groups. However, the laterality of missing maxillary lateral incisor was statistically significant on the left side of the maxilla ($p < 0.001$). Notably, the upper lateral incisor at the cleft side tended to be at higher risk of missing than its counterpart (see Table 4).

Table 4: Laterality of patients with congenital missing of lateral incisor among different cleft types

Lateral Incisor	URCLP (n=44) n (%)	ULCLP (n=91) n (%)	BCLP (n=59) n (%)	Total (n=194) n (%)	P value^a
Unaffected	15 (34.1)	31 (34.1)	15 (25.4)	61 (31.4)	0.490
Missing	29 (65.9)	60 (65.9)	44 (74.6)	133 (68.6)	
	URCLP (n=29)	ULCLP (n=60)	BCLP (n=44)	Total (n=133)	
Right	12 (41.4)	5 (8.3)	8 (13.6)	25 (18.8)	<0.001*
Left	9 (31.0)	37 (61.7)	15 (25.4)	61 (45.9)	
Both	8 (27.6)	18 (30.0)	21 (35.6)	47 (35.3)	

Unilateral right cleft lip and palate; ULCLP, Unilateral left cleft lip and palate; BCLP, Bilateral cleft lip and palate; n, absolute number; (%), percentage value; ^a Chi square test; * Statistically significant at <0.05

DISCUSSION

All patients involved in this retrospective study were derived from the non-syndromic homogeneous ethnicity of the Northeastern Thai population, whose treatments had been performed under the Khon Kaen University Cleft Protocol (Pradubwong et al., 2020). The majority of malformations were unilateral clefts, where the left side was predominant. The gender ratio of the patients was almost equal in the unilateral cleft groups, and male cleft patients were observed a higher in the bilateral cleft groups. There were more proportion of patients with UCLP than those with BCLP, which agreed with the other reports (Cakan et al., 2018; Mangione et al., 2018).

The cleft population has more impaired dental anomalies than that in the unaffected population, especially tooth agenesis, which was the most common observed dental anomaly in patients with orofacial clefts (Marzouk et al., 2021). Among various dental anomalies, tooth agenesis is regarded as the most frequently seen dental anomaly in the cleft population (Fonseca-Souza et al., 2022; Marzouk et al., 2021). In our investigation, 77.32% of the cleft patients analyzed had congenital missing teeth. This is a little bit larger than the 52.7-71.25% reported in comparable studies of the Asian population (Ajami et al., 2017; Suzuki et al., 2017; Tan et al., 2018; Wangsrimongkol et al., 2013). Generally, the percentage of tooth agenesis in our study is comparable to the other studies, but higher than that of the European and Australian populations (Fonseca-Souza et al., 2022; Marzouk et al., 2021; Möller et al., 2021). However, the French population still has the highest prevalence of tooth agenesis (Mangione et al., 2018). Nevertheless, the prevalence found in our examination was still 13 times the prevalence of hypodontia calculated for the permanent dentition of a healthy Asian population, excluding third molars (6%) (Khalaf et al., 2014). Local factors, such as the cleft defect itself or surgical trauma, can cause deficiencies in the mesenchymal tissue and blood supply necessary for adequate tooth formation (Cakan et al., 2018). Genetic factors also seem to be involved in the association between tooth agenesis and cleft lip and palate, such as genetic disturbances of the *MSX1* and *PAX9* genes, which contribute to tooth and craniofacial development, which have been associated with tooth agenesis within and outside the cleft area (Seo et al., 2013).

Moreover, the highest rate of missing tooth is maxillary lateral incisor, followed by the maxillary second premolar, which is equivalent to those finding in other studies (Ajami et al., 2017; Mangione et al., 2018; Möller et al., 2021; Suzuki et al., 2017; Tan et al., 2018; Wangsrimongkol et al., 2013). In our studies, the upper lateral incisor was found to be the most commonly missing tooth in cleft patients, with a prevalence of 37.11% and 55.67% on the right and left sides, respectively. These are higher than in others that reported percentages ranging

from 21.9% to 24.1% on the right side and 32.5% to 33.2% on the left side (Ajami et al., 2017; Suzuki et al., 2017). In our study, the missing upper second premolar was higher (19.59% on the right second premolar, 18.04% on the left) than data found in other studies, ranging from 7.8% to 14.4% in the Asian and European populations (Ajami et al., 2017; Möller et al., 2021; Suzuki et al., 2017). Although congenital absence of canine is the most infrequent dental agenesis in CLP individuals, there were two patients with missing canine from UCLP groups in our investigation. This is coherent with other studies that reported the congenital missing of canines (Cakan et al., 2018; Huda et al., 2021; Suzuki et al., 2017).

By considering the cleft type, UCLP patients in our collection were affected by tooth agenesis in 71.11% and BCLP patients in 88.14%. In the UCLP group, tooth agenesis was mainly caused by missing upper lateral incisors (31.85% at the right side and 53.33% at the left side). While comparing these groups, the upper left lateral incisor of the BCLP group was almost affected by tooth agenesis (61.02%). In both unilateral and bilateral CLP, tooth agenesis is significantly higher on the left side. This might explain why tooth missing outside the cleft is correlated with the genetic factor in the experiments with the non-cleft control group (Konstantonis et al., 2017; López-Giménez et al., 2018).

With regard to laterality, tooth agenesis was more observed on the left side in our retrospective study, in agreement with the results of several previous studies (Cakan et al., 2018; Suzuki et al., 2017). In our study, the missing maxillary lateral incisor at non-cleft side was less frequent than that on the cleft side in unilateral cleft groups. However, missing this tooth at the left side in URCLP was more frequent than on the right side in ULCLP. We found that URCLP was more frequently observed with a missing contralateral upper lateral incisor than ULCLP.

In our study, there were some limitations: the number of included patients with complete information according to selection criteria and the unequal distribution of the patients among cleft groups. Further studies are required to provide additional elucidation of the roles played by the implicated genes. The regional prevalence of tooth agenesis in Southeast Asia CL/P require a multi-centered approach involving the centers in the region. These data could be benefit for differentiate the variability of ethnicities that take part in tooth development and cleft formation.

CONCLUSION

We concluded that cleft lip and palate are most commonly found in the orofacial cleft, with a high risk on the left side. Tooth agenesis is experienced the most in BCLP groups. The maxillary lateral incisor is the most frequent missing tooth, which occurs more at the cleft side. Based on all patients from cleft lip and palate groups, the maxillary lateral incisor has a higher percentage at the left side.

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