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ORIGINAL ARTICLE

Relationship between dental calcification of mandibular teeth and cervical vertebrae maturity in patients with unilateral complete cleft lip and palate

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Abstract

Objective The purpose of this study was to investigate the relationship between the dental calcification stage (DCS) of the mandibular teeth and the cervical vertebral maturation stage (CVMS) in patients with unilateral complete cleft lip and palate (UCLP).

Methods One hundred sixty-two UCLP patients (100 males and 62 females) between 8–16 years old were included in this study. The DCS was estimated by the Demirjian method and was converted to the dental age (DA). The CVMS was evaluated by the Baccetti method. The DA of mandibular teeth on two sides of the cleft were analyzed using a *t*-test. Spearman correlation was used to study the association between CVMS and DCS. The correlation coefficient between the two sides of the cleft was then compared.

Results The total DA was significantly smaller on the cleft side than on the noncleft side in males ($p=0.022$). The Spearman rank correlation coefficient revealed a significant correlation between the DCS of each examined tooth and the CVMS ($r=0.627$–0.793 in males and $r=0.806$–0.899 in females). Additionally, the correlation of the two sides was not significantly different ($p>0.05$). The DCS of the first premolar showed the strongest correlation with the CVMS.

Conclusion The results confirm the utility of the DCS on both sides of the mandible in male UCLP patients as a simple first-level diagnostic test to evaluate growth and development. The findings also indicate that both the DCS and the CVMS should be assessed if the maturity stage of a growing UCLP patient is relevant to clinical practice.

Keywords Unilateral complete cleft lip and palate · Dental calcification stages · Cervical vertebral maturation stages · Mandibular teeth · Demirjian method · Baccetti method

Introduction

Cleft lip and palate (CLP) is the most common malformation in the head and neck region [1]. According to an epidemiological survey, the average prevalence of cleft lip with or without cleft palate was 7.94 per 10,000 live births in the world and 10.07 per 10,000 live births in China. The prevalence rate has declined compared with that of more than 30 years ago, but CLP is still a common congenital malformation [2]. Unilateral complete cleft lip and palate (UCLP) is the most common

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congenital malformation. Most Cleft patients usually have skeletal problems, especially maxillary hypoplasia [3, 4]. Some cleft patients require growth modification or orthognathic surgery to improve this skeletal problem. In addition, CLP patients suffer from hypodontia and may require implant placement as part of the treatment [5, 6]. Appropriate timing of the treatment is key for optimal treatment outcomes. Age determination is of has great importance when treating growing orthodontic patients [7]. Therefore, it is important to know the stage of maturation of these individuals [8]

In orthodontic clinical work, the stages of growth and development of children and adolescents are often assessed by dental calcification stages (DCS), cervical vertebral maturation stages (CVMS), hand-wrist assessment, and chronological age [9]. Recently, the CVMS and the DCS have been widely used [10–12]. In clinical work, panoramic radiographs are more commonly used during routine oral examinations. In addition, some researchers have pointed out that tooth development, which is slightly affected by systemic factors such as endocrine and nutritional status, corresponds well with chronological age [13, 14]. Due to the simplicity of the assessment of tooth development and the wide availability of panoramic radiographs, the method of tooth maturity was determined to be a preliminary assessment of the level of skeletal maturity in children [15–17]. One of the most well-known and commonly used methods for ascertaining the DCS is Demirjian's eight-stage method, which was originally applied to a large sample of Canadian children in 1973 [15]. As early as the twentieth century, some scholars proposed that the formation of mandibular permanent teeth in CLP children was delayed [18, 19]. However, there have been few studies on the DCS symmetry of mandibular teeth in UCLP patients. In addition, many previous studies found that there is a correlation between CVMS and DCS in noncleft patients [12, 20, 21]. However, no previous study has correlated the relationships between CVMS and DCS in UCLP patients.

The purpose of this study was to investigate the characteristics of mandibular dental formation by evaluating the DCS in patients with UCLP and to study the correlated relationship between DCS and CVMS. The expected benefit was that this study would provide a simple clinical evaluation method, to quickly determine the growth and development stage of patients when they first present as UCLP patients, as well as to develop timely diagnosis and treatment plans.

Materials and methods

Subjects

A total of 162 patients aged 8–16 years old (100 males, 12.33 ± 1.91 years; 62 females, 12.07 ± 1.33 years) with UCLP were selected. All patients routinely took panoramic and cephalometric radiographs routinely before orthodontic treatment. This study was approved by the institutional review board.

Inclusion criteria:

1) Having lived in Qingdao or other cities near Shandong Province, China since birth with Han nationality.
2) Without craniofacial syndrome.
3) With UCLP.
4) Having undergone CLP repair during infancy.
5) Without other facial traumas or surgical history. No history of orthodontic treatment or systemic diseases.
6) With clear and complete images on panoramic and cephalometric radiographs.
7) No congenitally missing mandibular teeth, fused teeth, impacted teeth in the mandible or obvious root resorption in the mandibular teeth except in the third molars.

DCS assessment method

To analyze the asymmetry of the mandibular teeth, we performed a DCS evaluation of the canine, first premolar, second premolar and second molar on two sides of the mandible in the panoramic radiographs using the Demirjian method [15, 16]. The total number of mandibular teeth was 1296 (162*2*4).

Then, we converted the DCS to the dental age (DA) by the Demirjian method. The specific method is shown below:

1. Stage A: Cusp tips begin to calcify, but no fusion of these calcified points are presented.
2. Stage B: Fusion of the calcified points and the outline of the occlusal surface can be identified.
3. Stage C: Enamel formation is completed at the occlusal surface. Dentine begins to form. The pulp chamber has a curved shape at the occlusal border.
4. Stage D: Crown formation is completed at the cementoenamel junction level. Root begins to form. In uniradicular teeth, the pulp chamber has curved at the superior border and is concave towards the cervical region. In molars, the pulp chamber has a trapezoidal form.
5. Stage E: In uniradicular teeth, root length is less than the crown height. The walls of the pulp chamber form a straight line. In molars, the initial formation of bifurcation is seen.
6. Stage F: Root length is equal to or greater than the crown height. The apex ends in a funnel shape. In uniradicular teeth, the walls of the pulp chamber form an isosceles triangle shape. In molars, the development of bifurcation is adequate to identify the roots.

7. Stage G: The walls of the root canal are now parallel and its apical end is still partially opened (distal root in molars).
8. Stage H: The apical end is completely closed (distal root in molars); the periodontal membrane has a uniform width around the root and the apex.

Total maturity scores were converted to the DA for all the selected teeth based on the percentile curves of a table of standards for boys or girls. The total DA of the mandibular teeth on the cleft side was then compared with that of the noncleft side to determine the DA asymmetry between the two sides of the mandibular teeth. A second comparison utilized the DA of individual mandibular teeth in all CVMS and in each CVMS to compare the tooth maturation on the two sides.

CVMS assessment method

Referring to the cephalometric radiographs, we determined the CVMS according to the Baccetti method [22, 23]. The CVMS was determined in 6 stages according to the morphological changes in the C2, C3 and C4 cervical vertebrae in the cephalometric radiographs. The specific instructions are as follows:

1.Cervical stage 1(CS1): The lower borders of C2–C4 are flat. The bodies of both C3 and C4 are trapezoid in shape.
2.Cervical stage 2(CS2): The lower border of C2 is concave. The bodies of C3 and C4 are still trapezoid in shape.
3.Cervical stage 3(CS3): Concavities at the lower borders of both C2 and C3 are presented. The bodies of C3 and C4 may be either trapezoid or rectangular horizontal in shape.
4.Cervical stage 4(CS4): Concavities at the lower borders of C2, C3 and C4 are now are presented. The bodies of both C3 and C4 are rectangular horizontal in shape.
5.Cervical stage 5(CS5): The lower borders of C2, C3 and C4 are still concave. At least one of the bodies of C3 and C4 is square in shape. If not, the body of the other cervical vertebra is still rectangular horizontal.
6.Cervical stage 6(CS6): The concavities at the lower borders of C2, C3 and C4 are still evident. At least one of the bodies of C3 and C4 is rectangular vertical in shape. If not, the body of the other cervical vertebra is square.

The presence or absence of concavity at the lower border of C2–C4, as well as the shape of the vertebral bodies of C3 and C4 (trapezoidal, horizontal, square, and vertical), were examined. Six developmental stages were described from cervical stages 1–6 (CS1–CS6).

Bias prevention

The CVMS and DCS of the mandibular canine, first premolar, second premolar, and second molar on the two sides of the cleft were evaluated continuously in each patient using the above-described method. In view of the recommendations of the studies of Levesque and Demirjian [24], this study was completed by four researchers to reduce discrepancies among the evaluators, who were two professionally trained postgraduates in orthodontics, a physician with a doctorate degree, and an associate chief physician with many years of experience in reading X-ray. To calculate the intra-examiner reproducibility of the ratings for each of the two methods, the Spearman-Brown formula was used. The panoramic radiographs and cephalometric records of 15 randomly selected patients were examined and evaluated by the same experienced operators five weeks after the initial rating. There were no significant differences among the results ($p > 0.05$). After the initial evaluation, discrepancies between these examiners were found in approximately 30% of the cases of DCS and 24% of the cases of CVMS. The final DCS and CVMS were determined after discussion and analysis.

Statistical analysis

All statistical analyses were performed with the Statistical Package for Social Science version 17.0 (SPSS 17.0) for Windows. Descriptive statistics (mean values and standard deviations) for all DA on both sides of the patients were determined. Then, a t test was used to compare the DA on the two sides of the cleft. A Spearman rank correlation analysis was performed to assess the correlation of CVMS and DCS for the mandibular canine, the first premolar, the second premolar, and the second molar on the cleft and noncleft sides. The correlation of DCS and CVMS between the two sides of the cleft was then compared.

Results

The number of UCLP patients at each CVMS, in terms of gender, is presented in Table 1.

In this research, the DA for the four teeth we used represented the total maturity scores of mandibular teeth, and the DA for each tooth represented the maturity scores for individual mandibular teeth. Table 2 shows the *t*-test results for the total maturity scores on the two sides of the cleft in the lower jaw of males and females. The descriptive statistics (mean + standard deviation) for the DA of mandibular teeth showed that the total maturity scores on the cleft side were smaller than those on the noncleft side. However, there was a statistically significant difference in the DA of the first premolar on the two sides only in males ($p = 0.022$).

Table 1 The number of UCLP patients at each CVMS

CVMS	Male	Female	Total
CS1	11	13	24
CS2	24	11	35
CS3	24	7	31
CS4	19	9	28
CS5	13	14	27
CS6	9	8	17
Total	100	62	162

Table 2 *T*-test for the mandibular DA on the two sides of the cleft (year)

	Number of teeth	Cleft side (M + SD)	Non-cleft side (M + SD)	*p*
Male	400	11.6 + 2.7	12.0 + 2.4	0.022*
Female	248	11.9 + 2.4	12.0 + 2.3	0.647

M mean, *SD* standard deviation

*$p < 0.05$ statistically significant

In addition, although there were no statistically significant differences in DA on either side of the cleft in each CVMS, the DA was smaller for the cleft side than for the noncleft side in males (Fig. 1a).

To create an assignment for each of the four mandibular teeth, rather than an overall mandibular dental age, we compared the DA of each mandibular tooth. The B graph in Fig. 1 shows a significantly smaller DA of the mandibular first premolar on the cleft side compared with the noncleft side in males. Additionally in males, the DA of the mandibular canine, second premolar and second molar was smaller on the cleft side than on the noncleft side, but this difference was not statistically significant. In females, although there was no statistically significant difference, the DA of the mandibular first premolar and second molar was smaller on the cleft side than on the noncleft side.

The Spearman rank correlation coefficient revealed relationships between the DCS of all examined mandibular teeth and the CVMS (Table 3): $r = 0.627–0.793$ in males and $r = 0.806–0.899$ in females ($p < 0.01$). The teeth that showed the strongest relationship with CVMS were the first premolars in males ($r = 0.793$ on the cleft side; $r = 0.779$ on the noncleft side) and in females ($r = 0.899$ on the cleft side; $r = 0.895$ on the noncleft side). The correlation coefficient between CVMS and DCS for the first premolar was larger on the cleft side than on the noncleft side. However, the difference in the correlation coefficient between DCS and CVMS on the two sides of the cleft was not statistically significant ($p > 0.05$). The lowest correlation, independent of gender, was noted for the second molar on both sides (male $r = 0.627$ on the cleft side, $r = 0.693$ on the noncleft side; female $r = 0.824$ on the cleft side, $r = 0.809$ on the noncleft side). However, this difference was not significant.

In the present study, the correlation coefficient between CVMS and the DCS was largest for the mandibular first premolar on the cleft side and noncleft side. Consequently, we performed a further analysis of the distribution of the mandibular first premolar DCS in CVMS. The DCS distribution of the first premolar in CS1–CS6 of males and females is shown in Fig. 2. In CS1–CS2, the distribution percentage was largest at stage E. In CS3–CS4, the distribution percentage was largest at stage F. In stage CS6, the percentage was largest at stage H.

Discussion

The relationship between CVMS and DCS for individual mandibular teeth has been described by different authors [21, 22, 25, 26]. The abovementioned studies were all conducted in subjects without any dento-maxillofacial deformities, and relatively few studies have examined the relationship between DCS and CVMS in CLP patients. The relationship between CVMS and DCS in CLP patients is also affected by many factors. Therefore, we analyzed the mandibular dental formation by evaluating the DCS in patients with UCLP and the association between CVMS and DCS in UCLP patients living in the Qingdao or surrounding areas of Shandong Province, China. Unlike other studies, in this study we performed a DCS evaluation of the canine, first premolar, second premolar and second molar on two sides of the mandible. The reasons are as follows: The DCS of the central and lateral incisors as well as the first molars shows the weakest correlations with CVMS in prior research [26]. The central and lateral incisors and the first molars of subjects aged 6–18 years have completely erupted, which is greatly affected by the oral hygiene environment. In addition, our subjects were UCLP patients, and all the incisors of those patients were located on one side of the cleft. Thus, we did not include the central incisors, lateral incisors or first molars in this study. Because of this asymmetry in distribution, we chose to study the mandibular teeth on both sides of the fissure, which is different from the original method by Demirjian, in which the 7 left lower teeth are taken into consideration.

It is known that the crown-to-root formation of the contralateral teeth is relatively symmetric in noncleft subjects [15, 16]. However, the prevalence of asymmetrically developing contralateral teeth is increased in CLP patients [27–32]. In this study, we found that overall, the mandibular teeth in male patients were asymmetrically distributed on both sides of the cleft, and the difference was statistically significant (Table 2). This finding is similar to the results of Tan and Ranta et al., who found that teeth exhibiting retarded

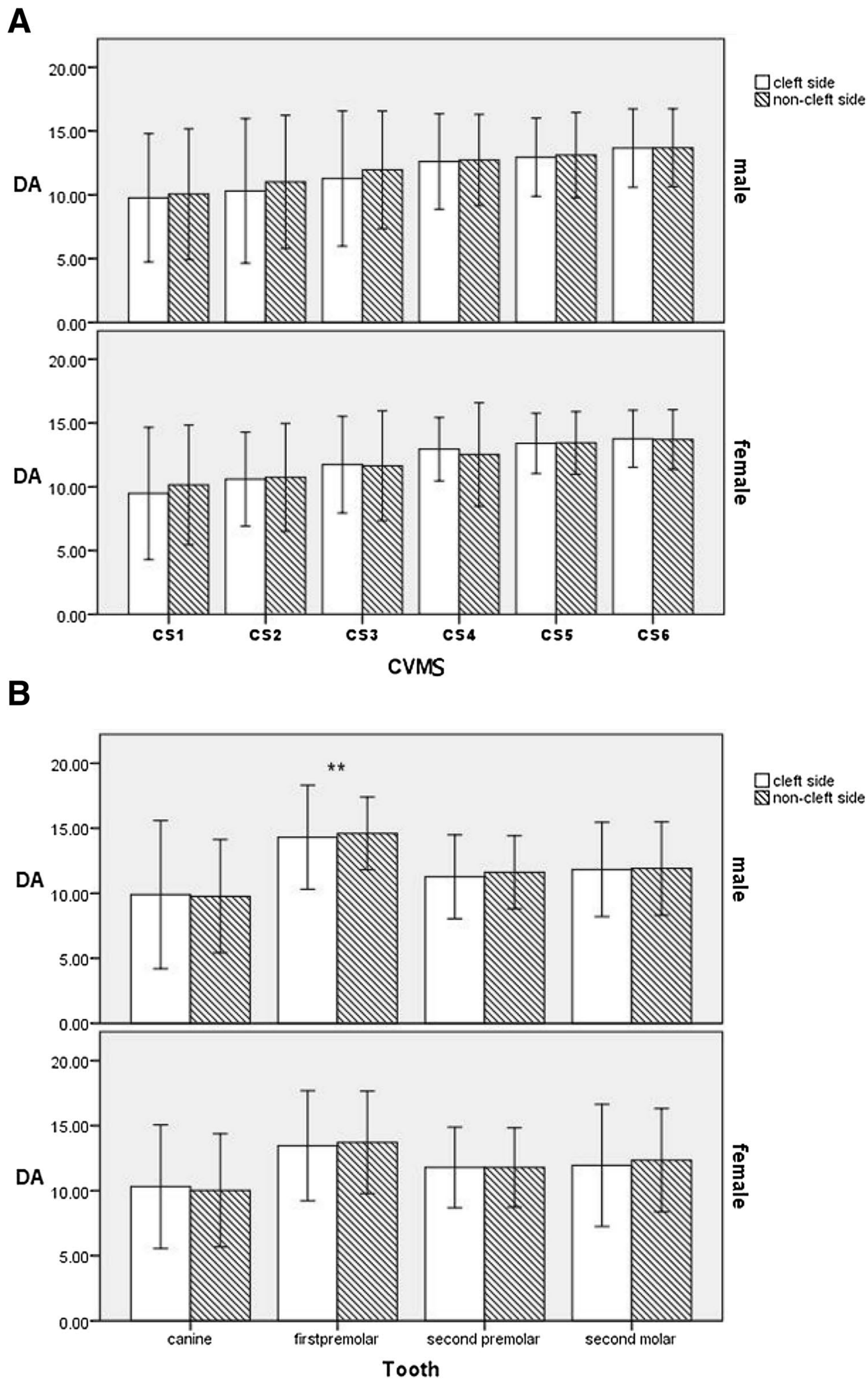

Fig. 1 Graph showing a comparison of DA on the two sides of the cleft. **a** The difference in DA on two sides of the cleft in different CVMS. In males, the DA for the cleft side was smaller than for the noncleft side in CS1-CS4, but this difference was not statistically different. **b** The DA for different teeth on the two sides of the cleft. In males, the DA of first premolar was larger for the noncleft than the cleft side, and this difference was statistically significant. Although the DA for remaining teeth was greater on the noncleft side than the cleft side, but no significant difference was observed. There was no obvious difference in the DA for the two sides of cleft in females. **$p < 0.01$ = extremely statistically significant

formation in the asymmetrically developing tooth-pairs had a significantly higher risk of occurring on the cleft side in both the maxilla and mandible [17, 33]. Ranta observed that asymmetric growth occurred most frequently in both jaws with equal frequency in patients with cleft palate [28, 34]. According to published reports, the main reason for the asymmetry of tooth development in the upper jaw is the influence of the cleft itself [17, 35]. Ranta and Lai found that the cleft itself is the cause of hypodontia and asymmetric formation on both sides. In addition, genetic factors can also

Table 3 Comparison of the Spearman correlation between DCS and CVMS for the two sides of the cleft in UCLP patients

	Mandibular tooth	r_C	r_{NC}	Z	p
Male patients	Canine	0.752**	0.731**	0.4597	> 0.05
	First premolar	0.793**	0.779**	0.3609	> 0.05
	Second premolar	0.743**	0.774**	0.7198	> 0.05
	Second molar	0.627**	0.639**	0.1972	> 0.05
Female patients	Canine	0.866**	0.806**	1.5466	> 0.05
	First premolar	0.899**	0.895**	0.1573	> 0.05
	Second premolar	0.888**	0.842**	1.4163	> 0.05
	Second molar	0.824**	0.809**	0.3458	> 0.05

r_C correlation coefficient for CVMS and DCS on the cleft side, r_{NC} correlation coefficient for CVMS and DCS on the noncleft side

*Moderate correlation in the range of confidence of 0.001

**High correlation in the confidence range of 0.01. $p > 0.05$ not statistically significant

lead to asymmetric tooth formation in patients [36, 37]. The effects of surgery, the living environment and nutritional status on this asymmetry are not obvious. These factors are related to the asymmetry of the maxillary teeth on both sides of the cleft. However, at present, the cause of the asymmetry in mandibular tooth formation in patients with UCLP is not clear.

In the present study, the results of the *t*-test revealed a delayed DA of the mandibular teeth on the cleft side compared with the noncleft side in males (Table 2). In each CVMS, although there was no statistical significance, the DA in males was smaller for all teeth on cleft side than the noncleft side (Fig. 1a). However, no significant difference was observed for female patients. Thus, the development of teeth on the cleft side was delayed compared with the noncleft side in male patients, as observed in our previous study [38]. The cleft itself and surgical factors affect tooth formation on both sides of the maxillary cleft. Why is the development of the mandibular teeth asymmetrical WR Li et al. [39, 40] investigated the characteristics of the masticatory muscles of CLP patients, and found that the patients chewed unilaterally due to the dentition and jaw malformations of UCLP patients, resulting in a long-term imbalance of the masticatory muscles on both sides of the patient, which may lead to asymmetric muscle function. Thus, the asymmetry of muscle activity will increase the dysfunction of the stomatognathic system. These studies have shown that maxillary formation defects in CLP patients directly affect occlusion and mastication. They further demonstrated that maxillary developmental defects affect the formation of maxillary and mandibular teeth. In brief, the tissue on the cleft side is usually smaller than that on the noncleft side. Due to the asymmetry of the teeth on both sides of the maxillary fissure, there are even missing teeth, resulting in occlusal asymmetry on both sides. Patients with UCLP have

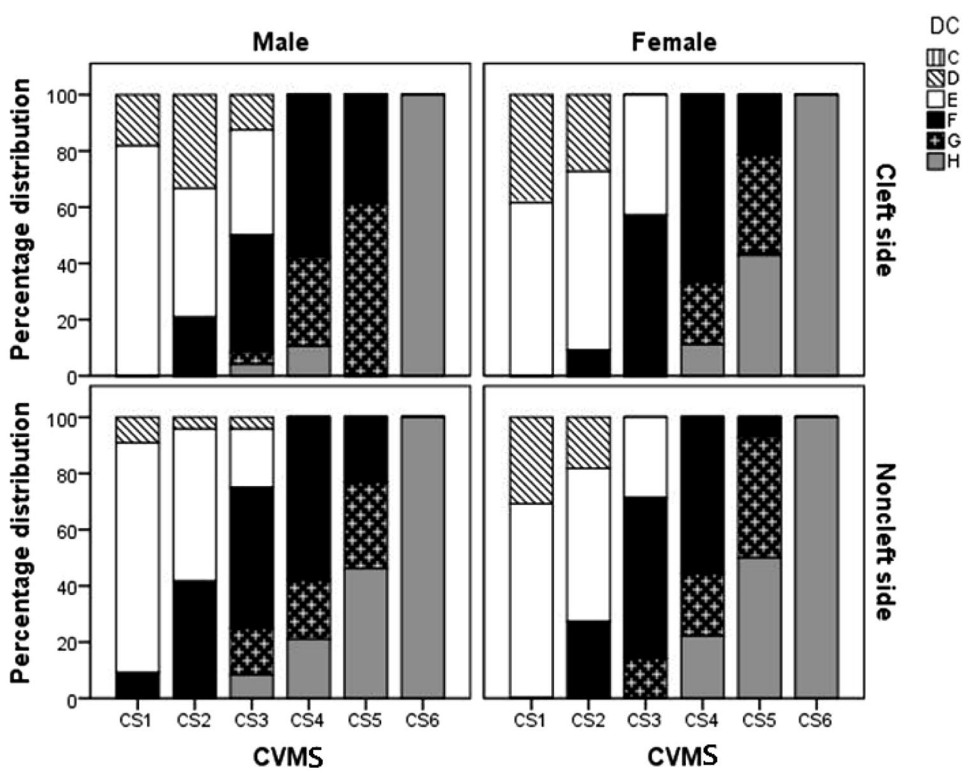

Fig. 2 Number distribution for the mandibular first premolar DCS in CS1–CS6

severe unilateral chewing habits. One side of the mandible of the UCLP patient lacks bite stimulation of the maxilla, making it inoperable and resulting in delayed development of the mandible and tooth formation on the same side. Finally, the changes lead to asymmetric development of the mandible and teeth on both sides.

Moreover, in the present study, the formation of the first premolar showed asymmetry on both sides of the cleft in male patients. The formation of the first premolar was delayed on the cleft side compared with the noncleft side. In addition to the above reasons, this result may be related to the longest period of calcification of the first premolar [41]. Therefore, the tooth formation process of the mandibular first premolar is more susceptible to various factors than to other teeth. In this study, there were no statistically significant differences in the results obtained for female patients. In the past, some researchers have proposed that male subjects with cleft lip (palate) show a statistically significant delay, while female cleft subjects do not [42, 43]. The authors inferred that females are known to develop dentally at a slightly faster rate than males overall, which could help female cleft subjects "catch up" before a significant delay is noted. According to the findings of the above researchers, we speculate that a possible reason for the results observed in female patients is that while the formation of the mandibular teeth of UCLP patients is delayed, the mandibular teeth develop faster in females than the males, thus obscuring the delay in the formation the teeth of the female patients. Additionally, we believe that the number of patients could have affected the results: the number of female patients in this study was smaller than the number of male patients. Therefore, the sample number must be increased in future analyses.

Although the DCS of mandibular teeth on the two sides of the cleft was asymmetrical, a significant correlation was found in this study between UCLP patients' CVMS and DCS of the mandibular canine, the first premolar, the second premolar and the second molar (Table 3, r_C, r_{NC}). The correlation coefficient was largest between the patients' CVMS and DCS of the first premolar, and the correlation coefficient of the second molar was smallest. However, Chongcharueyskul [44] found that the mandibular tooth with the highest correlation was the second molar, while the central incisor had the lowest correlation. This result is different from ours, which may be because their subjects included all types of cleft lip (palate) patients and because they studied the correlation between CVMS and DCS of the left lower tooth. In the present study, the subjects were UCLP patients. We excluded patients with bilateral CLP as well as those with simple cleft lip and with only cleft palate and an alveolar cleft, making the study more targeted. Furthermore, because the DA on the two sides of the cleft were different, another reason may be that our study included lower teeth on both sides.

In addition, this research differed in terms of the correlation between CVMS and DCS in UCLP patients compared with that identified in other studies of normal subjects without dento-maxillofacial deformities. Some authors have found that the teeth showing the highest correlation are the mandibular second molars of Chinese men and the mandibular canines of Chinese women [21]. Furthermore, in Asia, Valizadeh, S [12] found that the teeth showing the highest correlation were the mandibular lateral incisors in Iranian women. In Europe, however, different results from ours were obtained for the correlation of DCS and CVMS [9]. As early as the 1960s and 1980s, scholars proposed that the formation of permanent teeth in children with cleft lip, cleft palate, or both, was delayed by approximately 6 months [30, 45]. This delay may occur because children with cleft lip/palate are substantially more likely to experience feeding difficulties, contract upper respiratory infections and undergo repeated hospitalizations for lip and palate repairs; thus, their delayed development may be a consequence of a debilitating postnatal environment [18]. This delay occurs not only in upper but also in lower teeth [19, 30, 46–48]. The overall delay in tooth formation has been quantified in various studies as ranging from 0.3 to 1.1 years [42]. It has also been shown that tooth formation is more susceptible during alterations in early life, and this has been supported by other scholars [49]. This delay may provide an explanation for the different results obtained for UCLP patients and normal subjects in the present study.

In this study, we did not find any differences in the correlation coefficient of DCS and CVMS between the two sides of the cleft (Table 3, $p > 0.05$). Since a significant correlation was observed for DCS and CVMS between the two sides of the cleft of UCLP patients and the correlation between the two sides of the cleft was the same, we can conclude that the DCS of both mandibular sides of the cleft can be used as biological indicators to evaluate the growth and development of UCLP patients. However, in clinical work, it is complicated to evaluate the DCS of all teeth in a patient. Thus, it is necessary to identify the tooth with the greatest correlation between DCS and CVMS to judge the stages of growth and the development of patients. In this study, we found the greatest correlation between the DCS and CVMS of the mandibular first premolar.

Since the correlation coefficient was largest between CVMS and DCS of the mandibular first premolar in this study, the distribution characteristics of DC for the first premolar in CS1–CS6 were further analyzed (Fig. 2). Based on the Baccetti method [22, 23] and according to the chart of the first premolar's DC stages at different CVMS in male and female patients, we can preliminarily conclude that when the mandibular first premolar is in the E phase, the peak mandibular growth of UCLP patients will occur on average 1–2 years after this stage during the early stage of growth and development. Similarly, regardless of whether the patients are male or female, when the mandibular first premolar is in the F stage, the peak mandibular growth of UCLP patients will occur during the year after this stage, or it will occur within 1 or 2 years prior to this stage. When all patients (men and women) are in the H stage, the peak mandibular growth of UCLP patients has ended at least 1–2 years prior. However, the DCS cannot completely replace the CVMS for assessing trends in the growth and development of the whole body.

Due to the simplicity of the assessment of tooth development and the wide availability of intraoral and extraoral X-ray images, the method used to determine tooth maturity was performed as a preliminary assessment of the level of skeletal maturity in children. It must be considered that this tool cannot be used as the sole measure of growth and development, especially for specific patients such as those with UCLP and other symptoms of developmental disability. In these subjects, all information about developmental age was ascertained only when several indices were simultaneously estimated. For patients with CLP, the asymmetry of the DA on both sides of cleft in the mandible cannot be ignored. The results suggest that when using DCS to initially assess the growth and development of UCLP patients, it is necessary to evaluate the mandibular DCS on both sides of the cleft, rather than the unilateral DCS. If the unilateral DCS is assessed, it can easily lead to a judgment of the patient's growth and development as being earlier or later than the actual stage, and there is a risk of affecting the patient's treatment.

Conclusion

1. There was a significant correlation between DCS and CVMS. The correlation level differed for individual teeth: the tooth showing the highest correlation coefficient of the DA with the CVMS classification was the first premolar.
2. The DCS can be used as a simple first-level diagnostic test to evaluate the growth and development of UCLP male patients.
3. The mandibular DA of male UCLP patients is asymmetric on both sides of the cleft.

Overall, all mandibular tooth formation is delayed on the cleft side compared to the noncleft side in male patients.

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Compliance with ethical standards

Conflict of interest The authors declare that there are no relationships/conditions/circumstances that present a potential conflict of interest.

Statement of human and animal rights All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. This article does not contain any animal studies performed by any of the authors.

Informed consent Informed consent was obtained from all patients for inclusion in the study. Additional informed consent was obtained from all patients for which identifying information is included in this article.

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