ACTA ODONTOLOGICA SCANDINAVICA
2020, VOL. 78, NO. 5, 384–389
https://doi.org/10.1080/00016357.2020.1731594

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ORIGINAL ARTICLE

An analysis of third molar mineralization in Brazilian patients with cleft lip and palate

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ABSTRACT

Purpose: This study investigated the third molar mineralization in patients with cleft lip and palate.
Materials and methods: From a total of 253 digital panoramic radiographs from patients with cleft lip and palate within the age range of 7–21 years, 97 radiographs were selected (cleft group). A control group was formed from same sex individuals, without malformation and chronological age matched within 30 days. The analysis of third molar mineralization was carried out by three calibrated examiners using Demirjian's and Nolla's methods. McNemar and Wilcoxon test for paired samples were used for pairwise comparisons between the groups. The Likelihood Ratio test was used to check for an association between the type of cleft and tooth calcification.
Results: In both methods, the mineralization means were smaller in the case group than in the control, with significant differences for all third molars ($p < .05$). The type of cleft affected dental mineralization. There was no significant difference when comparing the left or right sides, but maxillary molars showed earlier mineralization.
Conclusions: A significant delay in third molar mineralization was observed in patients with cleft lip and palate according to Demirjian's and Nolla's methods.

ARTICLE HISTORY
Received 8 October 2019
Revised 26 January 2020
Accepted 13 February 2020

KEYWORDS
Cleft palate; radiography; panoramic; molar; third

Introduction

The orthodontic planning and treatment of patients with cleft lip and palate remains challenging. Deficiency of hard tissues (bones and teeth) and unpredictability of the growth course in some patients [1,2] are key factors that may delay the development of the permanent dentition [3–5]. Nevertheless, while it is imperative to reassess and adjust the treatment plan over time, orthodontists should define the optimum timing for treatment in these patients in order to minimize the frequency of procedures to which they are exposed [1,2,6].

The assessment of the optimal timing to start treatment should consider the patient's skeletal maturation to determine whether further growth is expected or the pubertal growth spurt (PGS) has been completed. Due to variations in PGS length, chronological age is not a reliable indicator of skeletal maturation in most cases [6]. Dental maturation detected by panoramic radiography, on the other hand, has been reported in the literature as an accurate predictor of skeletal maturation [2,3,7].

Age estimation through dental development is more accurate if one considers the degree of tooth mineralization in radiographic examinations [2,3,7], since tooth eruption is a transient phenomenon which can be influenced by genetic and/or external factors, such as ethnic group, sex, systemic diseases or nutritional status [8].

Radiographic analysis can be a useful tool for classification into different dental development stages. Demirjian et al. [9] and Nolla [10] proposed methods in which selected teeth are coded according to predetermined degrees of mineralization.

Third molars present the advantage of having a longer and later period of development, being the period in which orthodontic treatments are usually started [11]. The objective of this study was to evaluate the mineralization of third molars in cleft patients, considering that there are no data in the literature about the development of these teeth and these findings may be important for surgical and orthodontic treatments and forensic studies.

Materials and methods

This study was previously approved by the Research Ethics Committee (CAAE 23683913.0.0000.5181). This was a cross-sectional study with 97 pairs of digital panoramic radiographs (total $n = 194$) from same sex individuals with or without cleft lip and palate, with an age difference of up to 30 days, within the age range of 7–21 years. The study

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universe consisted of dental records and digital panoramic radiographs of 253 patients treated at Lauro Wanderley University Hospital of Federal University of Paraiba, Brazil.

Individuals without syndromes and systemically healthy, who did not present tooth agenesis or missing third molars, were included in the sample. Those whose records had incomplete information, absence of panoramic radiographs or poor-quality images were excluded from the analysis.

The study subjects of the case group were grouped into five categories according to the classification proposed by the American Cleft Palate-Craniofacial Association (ACPA), as follows: (1) unilateral cleft lip (UCL): when only the lip is affected, with or without the involvement of the alveolar ridge on one side; (2) bilateral cleft lip (BCL): when only the lip is affected, with or without the involvement of the alveolar ridge on both sides; (3) unilateral cleft lip and palate (UCLP): when there is involvement of the lip, alveolar ridge and palate on one side; (4) bilateral cleft lip and palate (BCLP): when there is involvement of the lip, alveolar ridge and palate on both sides; (5) cleft palate (CP): when only the palate is affected, without the involvement of the lip or the alveolar bone.

Panoramic radiographs were obtained with the Panoramic Digital X-ray apparatus Instrumentarium Orthopantomograph OP100 D (Instrumentarium Corp., Imaging Division, Tuusula, Finland), which was previously set at 13 s exposure time, 10 mA and kilovoltage according to patient characteristics (age, weight and density).

All radiographic images were exported to a folder, masked and number coded to prevent the occurrence of information bias during the analysis. The radiographs were analyzed by three previously calibrated examiners in a darkened environment using a 23″ monitor and Windows Image and Fax Viewer Program (Windows XP).

The degrees of third molar mineralization were evaluated according to the classification proposed by Demirjian et al. [9] and Nolla [10]. A 2-week interval was considered for calibration purposes. To assess the intra-examiner concordance, the examiners scored 20 randomly selected digital panoramic radiographs (which were not part of the final sample), and after 4 weeks rescored the same 20 exams. Differences in the diagnostic performance of evaluating dental mineralization between the first and second observations of the radiographs were compared by paired *t*-tests. For comparisons, all the *p*-values were greater than .05. The inter-examiner concordance was evaluated by the weighted kappa statistic and a satisfactory concordance was obtained (weighted κ value$>$ .87). The three examiners evaluated simultaneously the radiographic images for each method, and the mineralization stages of the third molars were determined by consensus. Thus, all three examiners evaluated the whole sample of radiographic images sequentially in anticlockwise direction from tooth #18 (maxillary right third molar) to tooth #48 (mandibular right third molar).

Data distributions and statistical measures were obtained. The mineralization stages proposed by Demirjian's and Nolla's methods were similarly coded as follows: 1 for stage A, 2 for B, 3 for C, and so forth.

McNemar test was used to compare the mineralization stages between groups, whereas Wilcoxon test for paired samples was used where the sum of the numerical coding was considered. The Likelihood Ratio test was used to check for an association between the type of cleft and the third molar mineralization stage.

The data were tabulated into Microsoft Office Excel spreadsheets and analyzed in SPSS (Statistical Package for the Social Sciences), version 21.0. A 5% margin of error was considered.

Results

The study sample consisted of 97 pairs of digital panoramic radiographs (cleft and control group), with a total sample size of 388 third molars for analysis. The distribution of samples' age in both groups are shown in Table 1.

Table 2 shows the degrees of third molar mineralization in cleft and non-cleft patients according to the criteria proposed by Demirjian and Nolla. Demirjian's method indicated that each third molars in each quadrant in cleft patients were most frequently found in calcification stage 'A' as opposed to 'B' in non-cleft patients. Nolla's method indicated that the third molars of cleft patients were more frequently found in the mineralization stage '2' as compared to '3' in non-cleft patients.

The largest percentage differences between the groups corresponded to stages '2' and '3' for the four third molars. There were significant differences suggesting that cleft patients have a delay in the mineralization of third molars as compared to non-cleft patients ($p < .001$).

Table 3 shows the distribution of third molar mineralization by the type of cleft according to Demirjian's and Nolla's methods. The types of cleft identified in participating subjects were UCLP, BCLP, UCL and CP. There were no patients with BCL in the study sample. The Likelihood Ratio test indicated that the type of cleft significantly influenced third molar mineralization ($p < .001$).

The codes of each mineralization stage and their respective means are shown in Tables 4 and 5. The mean mineralization values were lower among cleft patients than non-cleft ones, with significant differences for all third molars ($p < .05$) (Table 4). These findings suggest that cleft patients have a delay in third molar mineralization as compared to those in the control group. The mean differences in tooth mineralization between cleft and non-cleft patients ranged from 0.94 to 1.18.

Table 1. Distribution by age range in cleft and non-cleft patients.

Age range (years)	Group			
	Cleft patients		Non-cleft patients	
	n	%	*n*	%
7–9	27	27.8	27	27.8
10–12	40	42.3	40	41.2
13–15	21	20.6	21	21.6
16–18	5	5.2	5	5.2
19–21	4	4.1	4	4.1
Total	97	100.0	97	100.0

Table 2. Analysis of third molar mineralization in cleft and non-cleft patients according to Demirjian's and Nolla's methods.

	Mineralization stage				Mineralization stage			
	Demirjian's method	Cleft patients *n* (%)	Noncleft patients *n* (%)			Cleft patients *n* (%)	Noncleft patients *n* (%)	
Tooth	Total	97 (100.0)	97 (100.0)	*p*-Value	Nolla's method	97 (100.0)	97 (100.0)	*p*-Value
#18 (maxillary right third molar)	A	49 (50.5)	16 (16.5)	$p^a < .001$*	1			$p^a < .001$*
	B	17 (17.5)	24 (24.7)		2	49 (50.5)	16 (16.5)	
	C	11 (11.3)	14 (14.4)		3	17 (17.5)	24 (24.7)	
	D	12 (12.4)	22 (22.7)		4	10 (10.3)	14 (14.4)	
	E	2 (2.1)	13 (13.4)		5	7 (7.2)	15 (15.5)	
	F	4 (4.1)	3 (3.1)		6	6 (6.2)	7 (7.2)	
	G	1 (1.0)	3 (3.1)		7	2 (2.1)	13 (13.4)	
	H	1 (1.0)	2 (2.1)		8	4 (4.1)	3 (3.1)	
					9	1 (1.0)	3 (3.1)	
					10	1 (1.0)	2 (2.1)	
#28 (maxillary left third molar)	A	49 (50.5)	16 (16.5)	$p^a < .001$*	1			$p^a < .001$*
	B	16 (16.5)	25 (25.8)		2	49 (50.5)	16 (16.5)	
	C	12 (12.4)	12 (12.4)		3	16 (16.5)	25 (25.8)	
	D	12 (12.4)	23 (23.7)		4	11 (11.3)	12 (12.4)	
	E	2 (2.1)	12 (12.4)		5	7 (7.2)	16 (16.5)	
	F	4 (4.1)	4 (4.1)		6	6 (6.2)	7 (7.2)	
	G	1 (1.0)	3 (3.1)		7	2 (2.1)	12 (12.4)	
	H	1 (1.0)	2 (2.1)		8	4 (4.1)	4 (4.1)	
					9	1 (1.0)	3 (3.1)	
					10	1 (1.0)	2 (2.1)	
#38 (mandibular left third molar)	A	54 (55.7)	21 (21.6)	$p^a < .001$*	1			$p^a < .001$*
	B	16 (16.5)	31 (32.0)		2	54 (55.7)	21 (21.6)	
	C	11 (11.3)	12 (12.4)		3	16 (16.5)	31 (32.0)	
	D	8 (8.2)	8 (8.2)		4	9 (9.3)	12 (12.4)	
	E	2 (2.1)	16 (16.5)		5	3 (3.1)	5 (5.2)	
	F	4 (4.1)	5 (5.2)		6	7 (7.2)	6 (6.2)	
	G	1 (1.0)	2 (2.1)		7	2 (2.1)	13 (13.4)	
	H	1 (1.0)	2 (2.1)		8	4 (4.1)	5 (5.2)	
					9	1 (1.0)	2 (2.1)	
					10	1 (1.0)	2 (2.1)	
#48 (mandibular right third molar)	A	53 (54.6)	19 (19.6)	**	1			**
	B	15 (15.5)	33 (34.0)		2	53 (54.6)	19 (19.6)	
	C	14 (14.4)	11 (11.3)		3	15 (15.5)	33 (34.0)	
	D	7 (7.2)	10 (10.3)		4	12 (12.4)	10 (10.3)	
	E	2 (2.1)	16 (16.5)		5	2 (2.1)	8 (8.2)	
	F	4 (4.1)	4 (4.1)		6	7 (7.2)	5 (5.2)	
	G	2 (2.1)	2 (2.1)		7	2 (2.1)	14 (14.4)	
	H	–	2 (2.1)		8	4 (4.1)	4 (4.1)	
					9	2 (2.1)	2 (2.1)	
					10	–	2 (2.1)	

[a]McNemar test. *Significant difference at 5.0%.

Table 3. Distribution of third molar mineralization by the type of cleft according to Demirjian's and Nolla's methods.

	Type of cleft										
	UCLP		UCL		BCLP		CP		Total group		
Mineralization stage	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*p*-Value
Demirjian's method											
A	112	46.7	20	62.5	65	60.2	8	100	205	52.8	$p^a < .001$*
B	37	15.4	5	15.6	22	20.4			64	16.5	
C	34	14.2	1	3.1	13	12			48	12.4	
D	33	13.8	2	6.3	4	3.7			39	10.1	
E	4	1.7	4	12.5					8	2.1	
F	12	5			4	3.7			16	4.1	
G	5	2.1							5	1.3	
H	3	1.3							3	0.8	
Nolla's method											
B	112	46.7	20	62.5	65	60.2	8	100	205	52.8	$p^a < .001$*
C	37	15.4	5	15.6	22	20.4			64	16.5	
D	28	11.7	1	3.1	13	12			42	10.8	
E	15	6.3	2	6.3	2	1.9			19	4.9	
F	24	10			2	1.9			26	6.7	
G	4	1.7	4	12.5					8	2.1	
H	12	5			4	3.7			16	4.1	
I	5	2.1							5	1.3	
J	3	1.3							3	0.8	
Total	240	100	32	100.0	108	100.0	8	100.0	388	100	

[a]Likelihood ratio test. *Significant difference at 5.0%.

Table 4. Quantitative analysis of third molar mineralization according to Demirjian's and Nolla's methods.

Tooth	Method	Group: Cleft patient, mean ± SD (median)	Group: Non-cleft patient, mean ± SD (median)	*p*-Value	Mean of differences (Cleft − non-cleft patients)
#18 (Maxillary right third molar)	Demirjian	2.20 ± 1.60 (1.00)	3.24 ± 1.71 (3.00)	$p^a < .001^*$	1.04
	Nolla	3.35 ± 1.90 (2.00)	4.53 ± 2.08 (4.00)	$p^a < .001^*$	1.18
#28 (Maxillary left third molar)	Demirjian	2.21 ± 1.61 (1.00)	3.25 ± 1.73 (3.00)	$p^a < .001^*$	1.04
	Nolla	3.36 ± 1.90 (2.00)	4.54 ± 2.10 (4.00)	$p^a < .001^*$	1.18
#38 (Mandibular left third molar)	Demirjian	2.06 ± 1.58 (1.00)	3.00 ± 1.81 (2.00)	$p^a < .001^*$	0.94
	Nolla	3.24 ± 1.91 (2.00)	4.26 ± 2.18 (3.00)	$p^a < .001^*$	1.02
#48 (Mandibular right third molar)	Demirjian	2.07 ± 1.54 (1.00)	3.01 ± 1.77 (2.00)	$p^a < .001^*$	0.94
	Nolla	3.25 ± 1.87 (2.00)	4.28 ± 2.14 (3.00)	$p^a < .001^*$	1.03
Total group	Demirjian	2.13 ± 1.58 (1.00)	3.12 ± 1.75 (3.00)	$p^a < .001^*$	0.99
	Nolla	3.30 ± 1.89 (2.00)	4.40 ± 2.12 (4.00)	$p^a < .001^*$	1.10

[a]Wilcoxon test for paired samples.

Table 5. Mean third molar mineralization in cleft and non-cleft patients by dental arch according to Demirjian's and Nolla's methods.

Method/arch	Group: Cleft patients, mean ± SD (median)	Group: Non-cleft patients, mean ± SD (median)	*p*-Value
Demirjian			
Maxilla	2.20 ± 1.60 (1.00)	3.24 ± 1.72 (3.00)	$p^a < .001^*$
Mandible	2.07 ± 1.55 (1.00)	3.01 ± 1.79 (2.00)	$p^a < .001^*$
p-value	$p^b = .001^*$	$p^b < .001^*$	
Nolla			
Maxilla	3.36 ± 1.89 (2.00)	4.53 ± 2.09 (4.00)	$p^b < .001^*$
Mandible	3.24 ± 1.88 (2.00)	4.27 ± 2.16 (3.00)	$p^a < .001^*$
p-value	$p^b = .004^*$	$p^b < .001^*$	

*Significant difference at 5.0%.
[a]Wilcoxon test for paired samples—pairwise comparison between groups for each arch.
[b]Wilcoxon test for paired samples—pairwise comparisons between arches in each group.

Table 6. Mean third molar mineralization in cleft and non-cleft patients by mouth side (right or left) according to Demirjian's and Nolla's methods.

Method/mouth side	Group: Cleft patients, mean ± SD (median)	Group: Non-cleft patients, mean ± SD (median)	*p*-Value
Demirjian			
Right	2.13 ± 1.57 (1.00)	3.12 ± 1.74 (3.00)	$p^a < .001^*$
Left	2.13 ± 1.59 (1.00)	3.12 ± 1.77 (3.00)	$p^a < .001^*$
p-value	$p^b = 1.000$	$p^b = .676$	
Nolla			
Right	3.30 ± 1.88 (2.00)	4.40 ± 2.11 (4.00)	$p^a < .001^*$
Left	3.30 ± 1.90 (2.00)	4.40 ± 2.14 (4.00)	$p^a < .001^*$
p-value	$p^b = 1.000$	$p^b = 1.000$	

*Significant difference at 5.0%.
[a]Wilcoxon test for paired samples—pairwise comparison between groups for each side.
[b]Wilcoxon test for paired samples—pairwise comparisons between sides in each group.

The mean third molar mineralization in cleft and non-cleft patients by dental arch (maxillary or mandibular) and side (right or left) is presented in Tables 5 and 6. Overall, cleft patients showed a delay in the mineralization of third molars. In addition, greater means were observed in the maxillary arch in both cleft and non-cleft patients, which indicates the occurrence of earlier mineralization of maxillary third molars ($p < .05$). In contrast, there were no significant differences in third molar mineralization between the right and left sides in cleft and non-cleft patients ($p > .05$).

Discussion

Cleft lip and palate are relatively common craniofacial malformations with multifactorial etiology consisting of complex interactions of polygenic factors associated with environmental contributors [12].

These malformations may present morphologically distinct and include cleft lip, cleft lip and alveolus, cleft palate, unilateral/bilateral cleft lip and palate and facial cleft [13]. Such conditions are often associated with dental anomalies such as agenesis, enamel hypoplasia, abnormal tooth formation, and irregularities in tooth size and eruption. The extension of the dental anomaly is generally related to the severity of the cleft, being more common on the cleft side [3,5,14].

The study of dental development is critical for diagnosis and orthodontic treatment planning and to indicate the ideal timing to start treatment [1,2,15]. No studies were found that evaluated specifically third molar mineralization. Cassi et al. [12] observed that early orthodontic treatment in patients with cleft lip and palate strongly improved the dental arch

relationship. Patients who started therapy before 6 years of age showed better anterior maxillary expansion.

The literature presents evidence of the formation of the third molar in early mixed dentition. The crypt formation was observed by Mancini et al. [1] as early as 5.4 years (maxillary and mandibular) and as late as 13.2 years (mandibular) and 13.8 years (maxillary). In females, the same was observed as early as 5.6 years (mandibular) and 6.9 years (maxillary) and as late as 13 years (mandibular) and 14.4 years (maxillary). Much of the literature that evaluates the mineralization of third molars uses age as a parameter in the age range of this study: 5–26 years [2]; 5–16 years [1]; 4–26 years [3]; 3–23 years [4]; 5–21 years [5]. As cleft patients may have variations in dental development [6,7] we sought to cover an age group in agreement with the studied literature.

As cleft patients often present differences and changes in growth, the analysis of their skeletal maturity is critical to drive the orthopedic treatment plan [13,15]. In this study, the development of third molars was chosen as an analytical object because they are individualized and have late mineralization stages, which allows for an accurate age estimation in young individuals [16,17].

Demirjian et al. [9] and Nolla [10] methods were used in this study to estimate the dental age of participating subjects. In their studies, Demirjian et al. [9] analyzed seven mandibular left-sided teeth in French-Canadian children aged 3–17 years and coded tooth development into eight stages (A through H). Nolla's method [10] classified tooth mineralization into 11 stages based on a sample of 50 female and male patients in Michigan, United States. The advantage of using international standardized methods is the comparability of outcomes between different populations and ethnicities. Because different classification systems are used, a direct analytical comparison between the methods is impracticable. Hence, only a descriptive interpretation of the methods was presented herein.

There was a significant difference in third molar mineralization between the case and control groups by both methods, which may indicate the occurrence of late dental development in cleft children. These findings are consistent with the study by Almotairy and Pegelow [3], who analyzed the dental development of Caucasian cleft children aged 9–11 years. The authors examined eight mandibular left teeth using Demirjian and Willems' method and observed a delay in the dental age of cleft children as compared to those of the control group.

Tan et al. [4] studied the development of all permanent teeth in cleft children born and raised in Singapore using Demirjian's method. The authors observed no statistically significant difference between the case and control groups in children aged 9–13 years. However, dental mineralization was late in cleft children aged 5–9 years. The data inconsistency may be a result of different dental maturation patterns between population groups or even between individuals from different cities or regions within the same country [18].

In both methods, there was a statistically significant difference between the type of cleft or the degree of complexity and a possible late third molar development in cleft patients. One study investigated the occurrence of dental anomalies in Iranian cleft patients. The authors found a higher rate of dental anomalies in patients with bilateral clefts as compared to those with unilateral clefts, reinforcing the hypothesis that cleft complexity may affect tooth development [19]. Another study with 40 Chinese patients with cleft lip and palate showed a significantly late dental development of some permanent teeth on the cleft side as compared to the contralateral teeth, especially in the anterior maxillary area [5].

In our study, the type of cleft impacted third molar development in cleft patients, but no significant differences were observed between the right and left sides, regardless of the presence or absence of cleft. On the other hand, maxillary third molars showed early development in relation to the mandible. In contrast, the study by Tan et al. [4] showed late mineralization of maxillary permanent teeth as compared to the mandible in Singaporean cleft children by Demirjian's method, but only on the cleft side, with no differences between the arches for the non-cleft side. Here, the teeth most frequently showing developmental delays were the lateral incisors, followed by the central incisors near the cleft. Thus, it is suggested that the presence of cleft lip and palate may result in late mineralization of maxillary teeth that are close to the cleft when compared to the other teeth of the same individual. This may justify the lack of differences observed in our study in mineralization of third molars between the right and left sides, which were far from the cleft site.

Conclusions

To conclude, cleft patients showed a significantly late third molar mineralization as compared to non-cleft patients according to Dermirjian's and Nolla's methods. While there was no difference in tooth mineralization in terms of the arch side (right or left), maxillary third molars had an earlier development than the mandibular ones.

Collectively, our findings may provide further evidence on the ideal timing to start orthodontic interventions in this group of patients, considering that the treatment of cleft patients is multidisciplinary and extensive. A customized orthodontic treatment plan should be designed to consider individual variations and chronological age. Lastly, there should be a special effort to minimize the number of procedures to which cleft patients are exposed to provide a more humanized care.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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