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Third molar agenesis as a potential marker for craniofacial deformities

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ABSTRACT

The identification of clinical patterns of tooth agenesis in individuals born with craniofacial deformities may be a useful tool for risk determination of these defects. We hypothesize that specific craniofacial deformities are associated with third molar agenesis.

Objective: The aim of this study was to identify if third molar agenesis could have a relation with other craniofacial structure alterations, such as cleft lip and palate, skeletal malocclusion, or specific growth patterns in humans.

Design: Data were obtained from 550 individuals ascertained as part of studies aiming to identify genetic contributions to oral clefts. 831 dental records of patients aged over eight years seeking orthodontic treatment were also included. SN-GoGn angle were used to classify the growth pattern (hypo-divergent, normal and hyper-divergent), and the ANB angle was used to verify the skeletal malocclusion pattern (Class I, II and III). Panoramic radiographs were used to determine third molar agenesis.

Results: A high frequency of third molar agenesis among individuals born with cleft lip with or without cleft palate (55%), as well as among their relatives (93.5%) was found. Third molar agenesis was not associated to skeletal malocclusion or growth pattern.

Conclusion: It appears that third molar agenesis is associated with the disturbances that lead to cleft lip and palate.

1. Introduction

Evidence-based practice in dentistry has been suggested to discourage treatment that is of questionable value. The American Public Health Association in a policy statement from 2008 called the attention for the indiscriminate removal of third molars, suggesting that the argument that retaining third molars, whether or not impacted, will likely lead to sufficient harm has no support from the current scientific evidence. The common reasons given for prophylactic removal of third molars are: eruption is unpredictable, adjacent teeth could be damaged, the teeth may be source of periodontal pathogens, eruption may lead to tooth misalignment, and they are easier to extract when patient is an adolescent. These reasons are not supported by any scientific evidence (American Public Health Association, 2008). On the contrary, the sparse literature that can be found suggests that there is no increased harm when third molars are present (Stanley, Alattar, Colett, Stringfellow, Spiegel, 1988; Ahlqwist & Gröndahl, 1991; Valmaseda-Castellon, Berini-Aytes, Gay-Escoda, 2001; Friedman, 2007).

Third molar agenesis is quite common, reported to range from 12.6% to 51.1% (García-Hernández, Toro, Veja, Verdejo, 2008; Celikoglu & Kamak, 2012). This prevalence is substantially higher than agenesis reported for the rest of the dentition, which can range from 0.3% to 11.2% (Celikoglu, Bayram, Nur, 2011).

Due to the fact that third molars are more commonly missing than other teeth, either congenitally or due to prophylactically or clinically indicated extractions, these teeth are not considered in epidemiological

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surveys for dental caries or periodontal diseases. Third molar agenesis has been associated with other dental anomalies (number and/or structure variations) (Celikoglu et al., 2011) and malformations (García-Hernández et al., 2008), and was even associated with mandibular prognathism (Celikoglu & Kamak, 2012). Studies that looked if third molar agenesis is associated with crowding in the lower arch are inconclusive (Antanas & Giedrè, 2006; Karasawa, Rossi, Groppo, Prado, Caria, 2013).

Third molars are considered to have little functional value for the masticatory system and their importance for modern people is questioned (Silvestri Jr. and Singh, 2003; Pitekova & Satko, 2009). Furthermore, third molar agenesis has been considered a sign of evolution of the human species (García-Hernández et al., 2008). Since alterations in the dentition typically occur along with other modifications in craniofacial structures, we have been interested in identifying if dental alterations, particularly third molar agenesis, could indicate potential risk for other craniofacial structure alterations, such as cleft lip and palate, skeletal malocclusion, or specific growth patterns in humans.

2. Materials and methods

2.1. Sample selection

2.1.1. Cleft lip and palate

Data were obtained from a sample of 550 individuals ascertained as part of studies aiming to identify genetic contributions to oral clefts in the Patagonian region of Argentina (Fonseca et al., 2015). The sample consisted of cleft lip with or without cleft palate patients. 159 individuals were born with oral clefts, 341 were their unaffected relatives, and 50 were unrelated unaffected individuals. Three calibrated dentists (A.R.V., F.M.C., I.F.M.J.) performed dental clinical evaluations and data on dental anomalies were recorded. Additional physical evaluations were performed and biological samples for future DNA extractions were obtained. The study protocol and informed consent form were approved by the Comité de Ética en Investigación del Centro de Educación Médica e Investigaciones Clínicas (Dr. Norberto Quirno), in Buenos Aires, Argentina (IRB-1745, IORG-0001315; approval number: #238) and by the Institutional Review Board of the University of Pittsburgh, Pittsburgh, PA, USA (approval number: 0405013). Prospective study patients and their families were informed about the nature of the study and all subjects provided written informed consent before enrollment.

2.1.2. Orthodontic patients

The sample consisted in 1047 dental records including initial radiographs (panoramic and lateral cephalometric), photos, and study models of all patients treated from 2000 to 2013 at the Departments of Orthodontics, School of Dentistry, Federal University of Rio de Janeiro (UFRJ) and Brazilian Dental Association Rio de Janeiro section (ABORJ). One calibrated examiner (C.C.A.F.) extracted all the data. This study was approved by the local Ethics Committee for Research (Hospital Universitário Clementino Fraga Filho – HUCFF/UFRJ – Number: 619 096).

2.2. Inclusion and exclusion criteria

Patients eight years of age (Barka, Marathiotis, Protogerakis, Zafeiriadis, 2013) and older and whose dental records contained both initial radiographs, with good technical quality, enabling the visualization of all teeth and surrounding structures, were included. Patients presenting syndromes and/or endocrine imbalances and metabolic disorders, being those genetic/hereditary, were excluded.

2.3. Characterization of growth pattern and skeletal classification

At this stage, all measurements were obtained from the lateral cephalometric radiographs. To characterize the growth pattern, the values of the mandibular plane angle (SN-GoGn) were used according to the standard recommended by Steiner (Steiner, 1953):

- SN-GoGn Angle $< 32^{\circ}$ = Hypo-divergent;
- SN-GoGn Angle $= 32^{\circ}$ = Normal;
- SN-GoGn Angle $> 32^{\circ}$ = Hyper-divergent.

The skeletal classification was determined by the values of sagittal intermaxillary angle (SNA – SNB = ANB), according to the cephalometric standard for skeletal type recommended by Steiner (Steiner, 1953):

- ANB Angle with values between 0° and 4° = Class I;
- ANB Angle with values $> 4^{\circ}$ = Class II;
- ANB Angle with values $< 0^{\circ}$ = Class III.

2.4. Diagnosis of third molar agenesis

In the cleft lip and palate cohort, third molars were considered absent when that was a confirmation that these teeth were not extracted and they were radiographically absent. We used a portable X-ray (MinXray P200D MarkIII; Toshiba, Japan) to confirm the diagnosis of tooth agenesis. In addition, missing teeth by caries was an important distinction to be made. We conducted careful exams and collected comprehensive caries data (data not shown) to aid in the differential diagnosis.

In the orthodontic patient cohort, third molars were considered absent when there was a confirmation that the teeth were not extracted (in the dental records) and also no evidence of mineralization of the third molar crown in the panoramic radiograph. When it was not possible to observe the mineralization of the crown in the initial panoramic radiograph, a posterior radiograph was evaluated when avaiable. In addition, when the confirmation of the third molar extraction was not possible, patients were excluded from further analysis, similar to previously published protocols (García-Hernández et al., 2008; Celikoglu et al., 2011; Celikoglu & Kamak, 2012; Barka et al., 2013).

Data of third molar agenesis were collected by tooth, laterality (unilateral or bilateral), side (right, left, or both), and arch (maxillary or mandibular). Using the clinical assessment in the cleft lip and palate cohort, and the initial panoramic radiography, photos, and study models in the orthodontic patients, the presence of other dental anomalies of number, size, position, and shape (such as agenesis of other elements, supernumerary teeth, microdontia, macrodontia, impaction, transposition, giroversion, crown and root dilaceration, odontoma, taurodontia, among others) were also determined. Information about age, sex, and ethnicity were also collected using a survey (cleft lip and palate cohort) or from the dental records (orthodontic patient cohort).

2.5. Calibration for the cleft lip and palate sample

An experienced examiner (A.R.V.) performed the evaluation of more than half of the sample and trained two additional examiners (F.M.C. and I.F.M.J.) in the details of the examination protocol and diagnostic decisions for the completion of the remaining data collection. These exams are done in the field in one single visit for each study participant and there is no opportunity to redo any of those exams and calculate intra- or inter-examiner reliability scores.

2.6. Calibration for the orthodontic patients sample

For the determination of third molar agenesis, dental anomalies, and values of the SNA, SNB, ANB and SN-GoGn angles, a calibration was performed considering the gold standard evaluator (C.V.C.A.P.), a specialist in Orthodontics with over 15 years of experience. The gold

standard evaluator performed the assessment of 30 individuals through their panoramic radiographs (for third molar agenesis and other dental anomalies) and lateral cephalometric radiographs (for the values of the angles), with the aid of a negatoscope in a dark and quiet room. Soon after, a single examiner (C.C.A.F) performed the same assessments under the same conditions to compare the results. In an interval of 15 days, a repetition of these same assessments was performed by the examiner to obtain an inter examiner reliability (results between the evaluator and examiner) and intra examiner (results between the examiner's initial and final assessments).

2.7. Statistical analysis

Data were analyzed using SPSS version 20.0 (Statistical Package for Social Sciences, SPSS Inc, Chicago, III). The agreement between the investigator and the gold standard evaluator was determined by Kappa index (in the panoramic radiograph) and Index of Intra-Class Correlation (ICC) (cephalometric measurements in the lateral cephalometric radiograph). The frequency of third molar agenesis and other dental anomalies was computed and variables such as age, sex, ethnicity, and cephalometric measurements were taken in consideration when appropriate. Chi-square, Fisher's exact, and Student's *t* tests were used to test for differences with a significance level of 5%. Furthermore, odds ratios and 95% confidence intervals were calculated when appropriate.

3. Results

3.1. Cleft lip and palate

Out of the 159 individuals born with cleft lip and palate, 31 had tooth agenesis outside the cleft area (19.5%). 92 of the 341 unaffected cleft relatives had also tooth agenesis (27%). No unrelated unnaffected individuals had tooth agenesis. A high frequency of third molar agenesis among individuals born with cleft lip and palate (55%), as well as among their relatives (93.5%) was found. Tooth agenesis is more prevalent in the opposite side of clefts (Table 1). Agenesis or anomaly of the maxillary lateral incisor opposite to the unilateral cleft lip side occurred at a high frequency (29%; 7 in 24 cases).

3.2. Orthodontic patients

1047 dental records were analyzed and 216 were excluded due to the impossibility of diagnosis of third molar agenesis (absence of evidence of third molar extraction and impossibility of subsequent radiographic evaluation to confirm the presence of the tooth). The prevalence of third molar agenesis was 11.2% (n = 93), considering the remaining 831 records. Kappa and ICC tests showed excellent reliability with 0.91 and 0.87, respectively. It was found that on average 1.88 (± 1.10) third molars were absent and 75.3% of patients (n = 70) had another dental anomaly besides the third molar agenesis.

Table 2 shows the characteristics of the sample, including the distribution of sex (females = 53.3%; males = 46.7%), ethnicities (Whites = 48.1%; Blacks = 36.7%), age (average 14.11 years ± 7.1 years) and averages of the angles between the individuals with and without third molar agenesis. It was not possible to classify 126 (15.2%) patients as either Black or White these were excluded from this variable. There was no statistical difference between groups ($p > 0.05$).

The frequency of dental anomalies among individuals with or without third molar agenesis is shown in Table 3. The most prevalent dental anomalies in individuals with third molar agenesis were impaction, giroversion and agenesis of other dental elements with frequencies of 40.9% (n = 38), 37.6% (n = 35) and 17.2% (n = 16), respectively. There was an association of agenesis of other dental elements, microdontia, and impaction with third molar agenesis ($p < 0.01$). Impaction showed an inverse association with third molar agenesis.

In Table 4, the individuals with third molar agenesis were divided according to the number of missing teeth (1 to 4 teeth affected). 175 third molars were diagnosed absent and the upper right third molar was

Table 1
Cleft lip and palate sample.

Cleft Lip Side	Tooth Agenesis Side		
Number of Cases	Bilateral	Left	Right
Bilateral	4	1	–
Left Unilateral	10	2	5
Right Unilateral	5	2	–

Note: Fisher's Exact test p = 0.001 if expected values include having tooth agenesis only at the same side of the unilateral cleft lip

Table 2
Population characteristics according to sex, ethnicity, angles average (SNA, SNB, ANB and SN-GoGn) and age – Patients with and without third molar agenesis.

	Total n	Third Molar Agenesis	No Third Molar Agenesis	p-value
	831[a]	93 (11.2%)	738 (88.8%)	
Sex		n (%)		*0.754**
Male	388 (46.7)	42 (45.2)	346 (46.9)	
Female	443 (53.3)	51 (54.8)	392 (53.1)	
Ethnicity[b]				*0.56**
White	400 (48.1)	49 (52.7)	351 (47.6)	
Black	305 (36.7)	29 (31.2)	276 (37.4)	
Angles Average		Mean (DP)		
SNA	82.62 (± 4.4)	83.02 (± 4.35)	82.57 (± 4.42)	*0.35***
SNB	79.38 (± 4.6)	80.08 (± 4.99)	79,29 (± 4.51)	*0.12***
ANB	3.25 (± 3.8)	2,96 (± 4.01)	3.28 (± 3.82)	*0.44***
SN-GoGn	37.07 (± 6.3)	36.9 (± 7.9)	37.09 (± 6.06)	*0.79***
Age	14.11 (± 7.1)	14 (± 6.4)	14.12 (± 7.19)	*0.876***

Notes: *Indicates chi-square test; **Indicates Student's *t* test.
All *p*-values were not significant ($p > 0.05$).
[a] 216 patients were excluded because it was not possible to confirm the status of the third molars.
[b] It was not possible to classified 126 (15.2%) patients as either Black or White and they were excluded.

Table 3
Distribution of dental anomalies among individuals with and without third molar agenesis.

	Third Molar Agenesis (%) 93[b] (11.2)	No Third Molar Agenesis (%) 738[b] (88.8)	p-value	Odds Ratio (95% Confidence Interval)
Dental Anomalies	*n (%)*			
Agenesis	16 (17.2)	41 (5.6)	> 0.01[a]	3.52 (1.89–6.59)
Supernumerary	3 (3.2)	24 (3.3)	0.989	0.99 (0.29–3.36)
Microdontia	11 (11.8)	24 (3.3)	> 0.01[a]	3.99 (1.89–8.44)
Macrodontia	–	2 (0.3)	0.615	1.13 (1.09–1.15)
Impaction	38 (40.9)	478 (64.8)	> 0.01[a]	3.3 (1.72–4.16)
Transposition	2 (2.2)	29 (3.9)	0.394	0.54 (0.13–2.29)
Giroversion	35 (37.6)	327 (44.3)	0.221	0.76 (0.49–1.18)
Root Dilaceration	2 (2.2)	18 (2.4)	0.864	0.88 (0.20–3.85)
Crown Dilaceration	–	1 (0.1)	0.722	1.13 (1.10–1.15)
Odontoma	1 (1.1)	1 (0.1)	0.081	8.01 (0.50–129.16[c])
Taurodontism	–	1 (0.1)	0.722	1.13 (1.10–1.15)

Notes: P-value is based on chi-square test.
[a] Statistically significant ($p < 0.05$).
[b] 216 patients were excluded because it was not possible to diagnose third molar agenesis.
[c] Unstable numbers due to low frequency.

Table 4
Characteristic features of third molar agenesis in the different groups according to the number of teeth absent.

GROUPS (Total number of teeth absent)	1Teeth Agenesis (47)	2 Teeth Agenesis (50)	3 Teeth Agenesis (18)	4 Teeth Agenesis (60)	3M Agenesis[a] (175)
Teeth	n (%)				
UR 3M	19 (40.4)	16 (64)	4 (66.7)	15 (100)	54 (58.1)
UL 3M	8 (17)	15 (60)	3 (50)	15 (100)	41 (44.1)
LL 3M	11 (23.4)	9 (36)	6 (100)	15 (100)	41 (44.1)
LR 3M	9 (19.1)	10 (40)	5 (83.3)	15 (100)	39 (4.1)
Laterality	Patients n (%)				
Unilateral	47 (100)	1 (4)	–	–	48 (51.6)
Bilateral	–	24 (96)	6 (100)	15 (100)	45 (48.4)
Affected Side	Patients n (%)				
Right	28 (59.6)	1 (4)	–	–	29 (31.2)
Left	19 (40.4)	–	–	–	19 (20.4)
Both (bilateral)	–	24 (96)	6 (100)	6 (100)	45 (48.4)
Affected Arch	Patients n (%)				
Maxilla	27 (57.4)	14 (56)	–	–	41 (44.1)
Mandible	20 (42.6)	8 (32)	–	–	28 (30.1)
Both	–	3 (12)	6 (100)	15 (100)	24 (25.8)
Skeletal Classification	Patients n (%)				
Class I*	17 (36.2)	12 (48)	3 (50)	8 (53.3)	40 (43)
Class II*	21 (44.7)	10 (40)	2 (33.3)	2 (13.3)	35 (37.6)
Class III*	9 (19.1)	3 (12)	1 (16.7)	5 (33.3)	18 (19.4)
Growth Pattern	Patients n (%)				
Hypo-divergent*	9 (19.1)	4 (16)	2 (33.3)	5 (33.3)	20 (21.5)
Normal*	1 (2.1)	4 (16)	–	1 (6.7)	6 (6.5)
Hyper-divergent*	37 (78.7)	17 (68)	4 (66.7)	9 (60)	67 (72)

UR means Upper Right.
UL means Upper Left.
LR means Lower Right.
LL means Lower Left.
[a] 3M indicates Third Molar.
* Not statistically significant ($p > 0.05$).

the most affected (n = 54). This table shows that unilateral third molar agenesis was the most common with 51.6% (n = 48) frequency and the most affected side was the right side, with a frequency of 31.2% (n = 29). Third molar agenesis is more common in the maxilla (44.1%). Despite the fact that 43% (n = 40) of patients with third molar agenesis were Class I and 72% (n = 67) were hyper-divergent, these frequencies were not statistically difference then the ones in individuals without third molar agenesis.

4. Discussion

It has been proposed that clefting is part of a complex malformation associated with other dental anomalies resulting from disturbed development of the dentition (Stahl, Grabowski, Wigger, 2006; Menezes & Vieira, 2008). The etiology of dental anomalies is still not quite clear, however, it has been demonstrated in the last decade that genetic factors play a major role in dental anomalies (Eerens et al., 2001; Vieira, 2003; Modesto, Moreno, Krahn, King, Lidral, 2006; Letra, Menezes, Granjeiro, Vieira, 2007). Our data show that third molar agenesis is common in individuals born with cleft lip with or without cleft palate and their relatives and may have important predictive value for clefts risk.

According to Barka et al. (2013), the age of third molar first detection in the panoramic radiograph is seven years for females and 08 years for males. In another study it was observed the appearance of third molars already at six years old (Jung & Cho, 2014). To avoid possible variations in this chronology, the sample was standardized from eight years old, regardless of gender. Although some studies showed males were more affected by third molar agenesis (Liu, Chen, Liu, Xu, Fan, 2004; Celikoglu et al., 2011; Alam et al., 2014), females were most noted to have higher prevalence of this dental anomaly in this study, corroborating with others authors (all of them was not statistically significant) (Chung, Han, Kim, 2008; García-Hernández et al., 2008; Celikoglu & Kamak, 2012; Barka et al., 2013).

The ANB angle indicates the maxillary-mandibular relationship in the anteroposterior direction. Variations of angle ANB are commonly used to determine relative jaw relationships in most of the cephalometric evaluations. Cephalometric analyses based on angular and linear measurements have obvious fallacies and clinical application of such an analysis by the orthodontic profession in treatment planning is widely accepted. However, other cephalometric measures should be used because ANB could be affected by growth pattern.

In our study, third molar agenesis was seen more frequently in Class I and hyper-divergent growth pattern: 43% and 72%, respectively. Other studies have observed a higher frequency of third molar agenesis in Classes II (Pitekova & Satko, 2009) and III (Liu et al., 2004; Chung et al., 2008; Celikoglu & Kamak, 2012; Alam et al., 2014) but no difference between the growth patterns (Chung et al., 2008; Celikoglu & Kamak, 2012; Alam et al., 2014).

One emerging pattern appears to be the presence of agenesis in the upper lateral incisor opposite the side of a cleft. According to Letra et al. (2007) and Vieira (2012), agenesis of the maxillary lateral incisor opposite of the cleft lip side may indicate that these specific unilateral clefts could be “unsuccessful” bilateral clefts and should be considered carefully regarding the genetic etiology of different cleft types.

To the best of our knowledge this is the first study that combines the prevalence and pattern of third molar agenesis associated with other dental anomalies, cleft lip with or without cleft palate, skeletal malocclusions and growth patterns.

5. Conclusions

We conclude that third molar agenesis is associated with cleft lip and palate and may be a biological marker for increased familial risks for the defect. Furthermore, overall prevalence of tooth agenesis as a sign of disturbances in dental development was several times higher in individuals with clefts than in unrelated unaffected individuals and further indicates that tooth agenesis can be considered an additional phenotype for clefts, which may indicate that truly isolated forms of clefts may exist but in a frequency that is smaller than 70% of the total individuals born with this defect.

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