Prevalence of Hypodontia in Unilateral and Bilateral Cleft Lip and Palate Patients Inside and Outside Cleft Area: A Case-Control Study

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Objectives: *The aim of this study is to evaluate the prevalence and distribution of hypodontia, inside and outside the cleft area, in an Italian population with a non-syndromic unilateral (UCLP) and bilateral (BCLP) cleft lip and palate on panoramic radiographs and comparing it with a control sample.* ***Study design:*** *Case group was ethnically uniform and consisted in 233 patients. The control group was composed of 1000 subjects. Patients included were between seven and fifteen years old. Descriptive analysis, using absolute and relative frequencies, was performed to check out the prevalence of gender distribution, hypodontia and cleft formation. Statistical analysis was conducted with Chi-squared test, Yate's correction and the Fisher's exact test. The power was set higher than 0.8 for each test.* ***Results:*** *160 cleft patients (68.68%) presented at least one missing tooth, while 88 patients in the control groups presented agenesis (8.80%). A statistically significant difference was found in case and control groups for upper lateral incisors (37.34% and 48.07% in the case group against 2.50% and 2.60% in the control group), upper and lower second premolars (8.58%, 6.44%, 5.58% and 6.01% in the cleft group and 0.60%, 0.60%, 2.50% and 2.70% in the control group).* ***Conclusion:*** *Higher prevalence of dental agenesis in the maxillary dental arch is explained by the cleft defect. Higher prevalence of mandibular second premolars agenesis cannot be explained by the anatomical defect and suggests a multifactorial aetiology, including environmental and genetic factors, of the cleft condition.*

Key words: *Cleft, Hypodontia,*

INTRODUCTION

Clefts are the most frequent anomalies in the craniofacial region showing a prevalence of 1-2:1000 in the European and American population. Cleft can present as an isolated condition or in association with other syndromic patterns [1–4]. Prevalence of clefts was investigated in several studies and it is correlated with genetic, environmental and nutritional factors [4–6] as well as racial origin and geographical location[7–12]. Clefts are caused by a modified and altered embryological development of the orofacial structures[1] and can present in different forms: from the cleft lip and alveolus with or without cleft palates, to isolated cleft palates[2]. Previous studies reported a higher prevalence of dental anomalies in cleft lip and palate patients than the general population[13,14].

Some authors observed that biological factors causing cleft occur in the same fetal period of odontogenesis and can affect the physiological development of dentition[15]. Hypodontia is the most frequent dental anomaly in cleft patients with a prevalence between 29.5% and 77% [16], significantly higher than in the general population, in which it ranges between 2.7 and 11.3% [17]. Dental anomalies and agenesis were initially observed inside the cleft region in association to the cleft type and by comparing unilateral and bilateral cleft [18,19]. The prevalence of hypodontia in cleft patients was evaluated in different populations focusing especially on the upper lateral incisors: A Japanese study reported a prevalence of 56.9% [20], a US study of 74%[16] and a Hungarian study of 69% [12]

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Hypodontia was extensively investigated inside the cleft region but significantly less attention was given to dental anomalies outside the cleft area. These anomalies should be considered for their functional and aesthetic implications, as well as a part of a comprehensive multidisciplinary treatments [21]. Increasing evidence of higher prevalence of dental anomalies and hypodontia in the lower arch suggests the predominance of genetic factors on environmental factors[21,22] Research on dental anomalies and hypodontia can increase the knowledge on the genetic basis of clefts and they may be used as a genetic risk factor for orofacial cleft.

The aim of this study is to evaluate the prevalence and the distribution of tooth agenesis, inside and outside the cleft area, in an Italian population affected by non-syndromic unilateral (UCLP) and bilateral (BCLP) cleft lip and palate on digital panoramic radiographs and comparing them with a control sample of healthy orthodontic patients.

MATERIALS AND METHOD

This is a retrospective study on digital panoramic radiographs. Data were obtained from the Maxillo-Facial surgery clinic of San Bortolo Hospital (Vicenza, Italy).

The group of cleft patients was racially uniform, and consisted in 233 Italian patients (151 males, 82 females). The control group consisted in 1000 subjects (529 females, 471 males). The case group was recruited in the study according to the following inclusion criteria: unilateral or bilateral cleft lip and palate diagnosis, no other syndromes, no previous orthodontic treatment, no previous teeth extractions and a good quality of digital panoramic radiographs. Controls were selected randomly from the University of Padua Dental Clinic database setting the same age limitations of the case study group. Gender was not considered as a confounding factor for hypodontia, in line with previous literature[12].

Authors decided to consider approximately four controls per case to improve the precision of the results. Investigations examining rare outcomes can have a limited number of cases to select from, whereas, the source population from which controls can be selected is much larger. In such scenario, the study may be able to provide more information if multiple controls per case are selected. This method increases the "statistical power" of the investigation by increasing the sample's size.

The control group of patients was recruited in the study according to the following inclusion criteria: no previous orthodontic treatment, no previous teeth extractions and good quality of digital panoramic radiographs. Moreover, authors decided to set an age limit between seven and fifteen years old. Patients younger than seven years old were excluded in order to assure the completion of the crown calcification according with Moorrees *et al* [23]. Patients older than fifteen years old were excluded to avoid previous extraction or other treatments.

The mean age and standard deviation of patients affected by cleft were respectively equal to 10.7 and 2.8 years old, while for the control group they were 10.3 and 2.3 years old.

The total sample size was checked by appropriate statistical calculation using R version 3.2.1. (R Core Team 2015), setting the power of the chi-squared and Fisher test higher than 0.8.

Digital panoramic radiographs were analysed for permanent teeth agenesis in and outside the cleft area, in the upper and lower dental arches. Third molars were excluded from the analysis for their unclear prognosis in early examinations [22].

Statistical analysis

Descriptive analysis, using absolute and relative frequencies, was performed to check out the prevalence of gender distribution, hypodontia and cleft formation. The relative frequencies in each table were calculated as a percentage of the total sample.

All data was entered into Excel 2010 (Microsoft, Remond, WA, USA). The tables were created using Excel 2010. Statistical analyses were carried with the computing environment R version 3.2.1 to verify the association between presence of hypodontia and cleft type. In particular R was used for estimating the p-value of Chi-squared test with Yate's correction, while the Fisher's exact test was used when in 2x2 tables the expected cell frequencies was lower than 5. The test was considered significant if the p-value was lower or equal to 0.05. We also estimated the power of the chi-squared tests and Fisher's tests. The results showed that the power was higher than 0.8 in each test.

RESULTS

The study group consisted of 233 Italian patients with bilateral and unilateral cleft while the control group was composed by 1000 subjects. 160 subjects with cleft (68.68%) presented at least one missing tooth, while 88 patients in the control groups presented at least one tooth agenesis (8.80%). P-value lower than 0.05 (p-value<0.001) indicated a significant dependence between the presence of agenesis and the presence of cleft, as well as significant higher prevalence of agenesis in cleft patients than in the control group (Tab. 1).

In Table 2 authors estimated the number and percentage of agenesis per tooth in the control and the cleft group.

Regarding the maxillary dental arch, the cleft group presented a higher prevalence of agenesis for the right and left lateral incisors in comparison with the control group. The percentage of tooth agenesis was, respectively, 37.34% and 48.07% in the case group and 2.50% and 2.60% in the control group. The right and left premolars in the upper and lower dental arches presented more agenesis in the cleft group than in the control group, with p-values lower than 0.05. Respectively, the prevalence of these teeth was 8.58%, 6.44%, 5.58% and 6.01% in the cleft group and 0.60%, 0.60%, 2.50% and 2.70% in the control group. Another tooth that presented a significant higher prevalence in the cleft group was the first premolar in the upper right side with a p-value lower than 0.05 and a prevalence of 2.58% in the cleft group and only 0.80% in the control group. The upper central incisors presented a percentage of agenesis of 3.00% on the right side and 3.43% on the left side in the cleft group, while no agenesis was detected in the control group. Teeth 13, 16, 23, 26, 33, 36, 37, 43 and 46 presented no agenesis in the case group. No statistical test was performed for these elements as no observations were made.

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Table 1: Number of agenesis per group and statistical comparison description.

Cleft patients (n=233)		Control group (n=1000)		Statistical comparison	
Number of agenesis	Percentage of agenesis	Number of agenesis	Percentage of agenesis	P-value	Method
160	68.68%	88	8.80%	<0.001	Chi-squared test

Table 2: Number and percentage of agenesis per element in the control and the cleft group. P-value and statistical tests were evidenced in the last two columns.

	Cleft patients		Control group		Statistical comparison	
Tooth	Number of agenesis	Percentage of agenesis	Number of agenesis	Percentage of agenesis	P-value	Method
11	7	3.00%	0	0.00%	-	-
12*	87	37.34%	25	2.50%	<0.001	Chi-squared test
13	0	0.00%	0	0.00%	-	-
14	6	2.58%	8	0.80%	0.05	Chi-squared test
15*	20	8.58%	6	0.60%	0	Chi-squared test
16	0	0.00%	2	0.20%	-	-
17	1	0.43%	1	0.10%	0.3424	Fisher test
21	8	3.43%	0	0.00%	-	-
22*	112	48.07%	26	2.60%	<0.001	Chi-squared test
23	0	0.00%	4	0.40%	-	-
24	4	1.72%	6	0.60%	0.1014	Fisher test
25*	15	6.44%	6	0.60%	0	Chi-squared test
26	0	0.00%	0	0.00%	-	-
27	1	0.43%	3	0.30%	0.5678	Fisher test
31	2	0.86%	6	0.60%	0.6505	Fisher test
32	1	0.43%	4	0.40%	1	Fisher test
33	0	0.00%	2	0.20%	-	-
34	1	0.43%	1	0.10%	0.3424	Fisher test
35*	13	5.58%	25	2.50%	0.0252	Chi-squared test
36	0	0.00%	1	0.10%	-	-
37	0	0.00%	2	0.20%	-	-
41	2	0.86%	4	0.40%	0.3175	Fisher test
42	2	0.86%	7	0.70%	0.6813	Fisher test
43	0	0.00%	1	0.10%	-	-
44	1	0.43%	2	0.20%	0.4668	Fisher test
45*	14	6.01%	27	2.70%	0.0196	Chi-squared test
46	0	0.00%	1	0.10%	-	-
47	1	0.43%	2	0.20%	0.4668	Fisher test

DISCUSSION

Hypodontia is a critical aspect for the management of an accurate treatment plan in patients affected by complete unilateral and bilateral cleft lip and palate. Dental anomalies should be considered as the number of missing teeth is associated with the severity of the condition, both in the cleft area and in the mandible, an anatomical district that is not influenced by cleft. Only a few studies analyzed the prevalence and distribution pattern of hypodontia in cleft patients inside and outside the cleft area and compared it with a control group of healthy patients.

Authors decided to include in the case group only non-syndromic complete unilateral and bilateral cleft patients. Syndromic patients, in fact, present a higher association with dental anomalies and other congenital defects that can affect the accuracy of the radiographic evaluation. Furthermore, an age limit between seven and fifteen years old was set to exclude a delayed germ calcification of second premolars that can occur before seven years of age. On the other side, patients older than fifteen years old have an increased prevalence of missing teeth due to previous treatment or premature tooth loss [23,24] Many authors investigated the influence of gender on dental anomalies concluding that it is not a confounding factor

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for this condition in both the healthy general population and cleft lip and palate patients [25,26] For this reason, authors proceeded with a random selection of the control group from a database of healthy patients, setting only the adequate age limit.

This study revealed that 160 out of 233 (68.67%) patients affected by cleft lip and palate presented at least one missing tooth while only 88 out of 1000 (8.8%) presented this condition in the control group. Statistical analysis showed a significant increase in prevalence of hypodontia in the cleft group, confirming what emerged from previous investigations [10,12] .

Our research showed that the most frequently absent teeth were the upper lateral incisors and the upper and lower second premolars in both the cleft and the control group. Moreover, it emerged that the cleft group presented a significant difference from the control group regarding these teeth. This condition was particularly evident for the upper lateral incisors that missed, respectively, in the 37.34% on the right side and 48.07% on the left side in cleft patients, while only in the 2.50% and 2.60% in the control group. Higher prevalence of hypodontia and dental anomalies in the upper arch was explained by different authors as a consequence of the anatomical influence of the cleft defect in the development of the maxilla [19,27,28] However, in this evaluation we show that the upper lateral incisor was frequently missing also in the side not affected by cleft, confirming a common multifactorial etiology of the two conditions.

This hypothesis was also confirmed by the most interesting finding of this research: the prevalence of the mandibular second premolars agenesis is more than double in the case group (5.58% on the right side and 6.01% on the left side) in comparison with the control group (2.50% on the right side and 2.70% on the left side).

In different studies, authors investigated the association between hypodontia and cleft, finding a strong correlation in the maxillary arch, but only weak in the mandibular one [16,27,29,30]both inside and outside the cleft region, and the possible association between the side of the cleft and the side of the missing teeth were studied using radiographs of 278 patients with cleft lip, cleft palate, or both (158 boys and 120 girls. These studies focused on cleft patients without comparing them with a healthy control group. Since the multifactorial etiology of cleft lip and palate, both genetic and environmental factors can affect dental development inside and outside the cleft area, justifying this result. The mandibular arch can be influenced by cleft not for the anatomical proximity to the defect, but for a common multifactorial etiology, in which both genetic and environmental factors can affect the physiological dental development.

Cleft lip and palate was demonstrated to be a significant factor for dental agenesis. Orthodontists should pay particular attention to hypodontia in cleft lip and palate patients to set an appropriate treatment plan and for a proper management of therapy before bone grafting of the defect, to obtain a good function and aesthetics. Finally, dental agenesis in the mandibular arch should be considered since this condition is a complication to a correct management of the occlusion.

CONCLUSION

Cleft lip and palate patients show a higher prevalence of hypodontia than the general healthy population. Hypodontia is a frequent finding in upper and lower dental arches. The most frequent missing teeth were the upper lateral incisors and the upper and lower second premolars. Results regarding lower premolars suggest a multifactorial etiology of the cleft condition, including anatomical, environmental and genetic factors.

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