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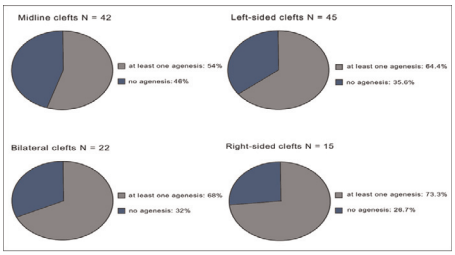
Congenitally missing teeth and labio-palatal clefts: keep to the left



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SUMMARY

Objectives: *dental anomalies are more frequent for individuals with clefts than for the general population. Our objective is to evaluate the prevalence of dental ageneses in a sampling from Alsace made up of 124 children with clefts (81 boys and 43 girls, average age 12.5 years old).*

Method: *clinical and radiographic exams make it possible to specify the dental formula as well as the type of clefts that are divided into 4 groups: simple Labial Clefts (LC – 12.9%), Labio-Alveolar Clefts (LAC – 4%), Labio-Palatal Clefts (LPC – 49.2%) and Palatal Clefts (PC – 33.9%).*

Results: *63% of the patients present one or more ageneses mainly involving the maxillary lateral incisors (54%) and the maxillary or mandibular second premolars (32%). The percentage of children with congenitally missing teeth is, in ascending order, minimal in the case of LC (33%), average in the case of PC (54%) and highest in cases of LPC (79%). The frequency of ageneses increases proportionally with the severity of the cleft. The left side is most affected ($p < 0.01$) regardless of the side of the cleft.*

Conclusions: *dental ageneses are more frequent on the left side, regardless of the side of the cleft. The greater prevalence on the left side could suggest the intervention of overlapping etiopathogenic factors when clefts and dental ageneses are involved.*

KEY WORDS

Dental ageneses,
Labio-palatal clefts,
Clefts in oral cavity,
Prevalence.

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1 – INTRODUCTION

Oro-facial clefts are congenital anomalies that occur with an incidence rate comparable to that of Down's Syndrome, namely 1/700 births and as high as 1/300 in populations of South America or South Asia[17,20].

Their clinical classification makes it possible to distinguish the Palatal Cleft (PC: OMIM* 119540) from the Labio-Alveolar Cleft with or without Palatal lesion (LAC/P: OMIM 119530). LAC/P represents 70 to 80% of non-syndromic cases. Presently, it is generally accepted that these nonsydromic LC/PC/LPC are plurifactorial, linking genetic and exogenous factors, without any one single factor prevailing[5,16,27,28].

The frequency of dental ageneses is higher in patients with LC/PC/LPC than in the general population: 77% out of 278 patients[22], 67.6% out of 179 patients[1], 47.5% out of 120 patients[23]; moreover, this frequency varies from 3.2 to 5.5 in males and from 4.6 to 7.6 in females in control populations[19]. However, this prevalence is variable according to the type of tooth, the placement (upper or lower jaw, the afflicted side or not), the type of cleft and the sex of the patient.

The goal of this study is to evaluate the type and number of ageneses in a sampling of patients with LC/PC/LPC, and to investigate a possible association between these two pathologies.

2 – METHOD

The criteria for inclusion in this study were based on the diagnosis of a non-syndromic orofacial cleft in a population of patients with LC/PC/LPC, drawn on one hand from the orthopedic dento-facial and buccal-dental surgery Medical Center of Strasbourg and on the other hand from the multidisciplinary consultation group of the Center of Excellence for labio-palatal clefts of Strasbourg.

Clinical and radiographic exams allowed us to gather three types of data. The analysis of a panoramic view either directly or indirectly (picture of the view) illustrates the dental formula. In cases of a missing tooth, the therapeutic origin must be rejected. The third molars are excluded. A clinical examination makes it possible to report the type of cleft (classification LC, LAC, LPC, PC) and the existence of a syndromic context or not (S, NS). Finally, the contact information of the treating practitioner, and the age and sex of the patient are documented. The clinical data are compared to the information collected in the medical record of the patient.

Statistical analyses

The aggregate statistical analyses were done at the Public Department of Health of H.U.S., using R software for statistical computing (*R Development Core Team-2010)*. For the continuous variables, a summary of the shape distribution of values aligned to

show the average, standard deviation and mean. For qualitative variables, the categorical outcome is the percentage of each modality over the aggregate of registered clefts for which the variable is set. An exact binomial test was used to compare the observed percentages. In order to compare the number of respective clefts to one another, a chi-square test[2] was used.

3 – RESULTS

The data from 157 patients, or from their legal guardians, who had signed consent forms, was collected. Among these patients, 33 were excluded from the study either because (their radiographic view was unusable or because they were too young < 5 years old). Therefore, our study dealt with 124 patients with LC/PC/LPC (M = 81 and F = 43; NS 109 and S = 15; average age 12.5 years old.

3 – 1 – Prevalence of LC/PC/LPC

In our sampling, there are significantly more boys (65.3%) than girls ($p < 0.001$) with clefts.

In decreasing order of frequency, LPC appeared most often (49.2% of the cases), then PC (33.1%) and finally LC (12.1%). The left side (36.3%) is afflicted three times more often than the right side (12.1%), and generally speaking, the left side is usually where the affliction is most significant ($p < 0.001$).

3 – 2 – Prevalence of dental ageneses

The overall prevalence (maxillary and mandibular) of dental ageneses found in our sampling is 63%.

As for the upper jaw, 14% of patients have at least one congenitally absent tooth; missing second premolars are most common (51% of ageneses) (Fig. 1). However, on the lower jaw, the absence of the lateral incisors represents 59.9% of ageneses and 13% of the missing teeth are second premolars. Among the participants in our study, we compared the number of ageneses on the upper jaw and lower jaw, and found a 3 to 1 ratio, for every 3 missing maxillary teeth there was one missing tooth on the mandible.

The prevalence of stunted teeth and supernumerary teeth is respectively 12 and 10% in our sampling.

3 – 3 – Dental ageneses and type of cleft

In our cohort, patients with LPC are the most affected by dental ageneses (78.7 of the cases). The frequency of dental ageneses clearly increases with the severity of the cleft and the involvement of the secondary palate.

Ageneses present most often on the lower jaw regardless of the type of cleft. Surprisingly, the ratio between maxillary/mandibular involvement changes from 3/1 to 5/4 when there is a PC. In other words, we find 3 missing teeth from the upper jaw versus one tooth from the lower jaw

*OMIM: Online Mendelian Inheritance in Man

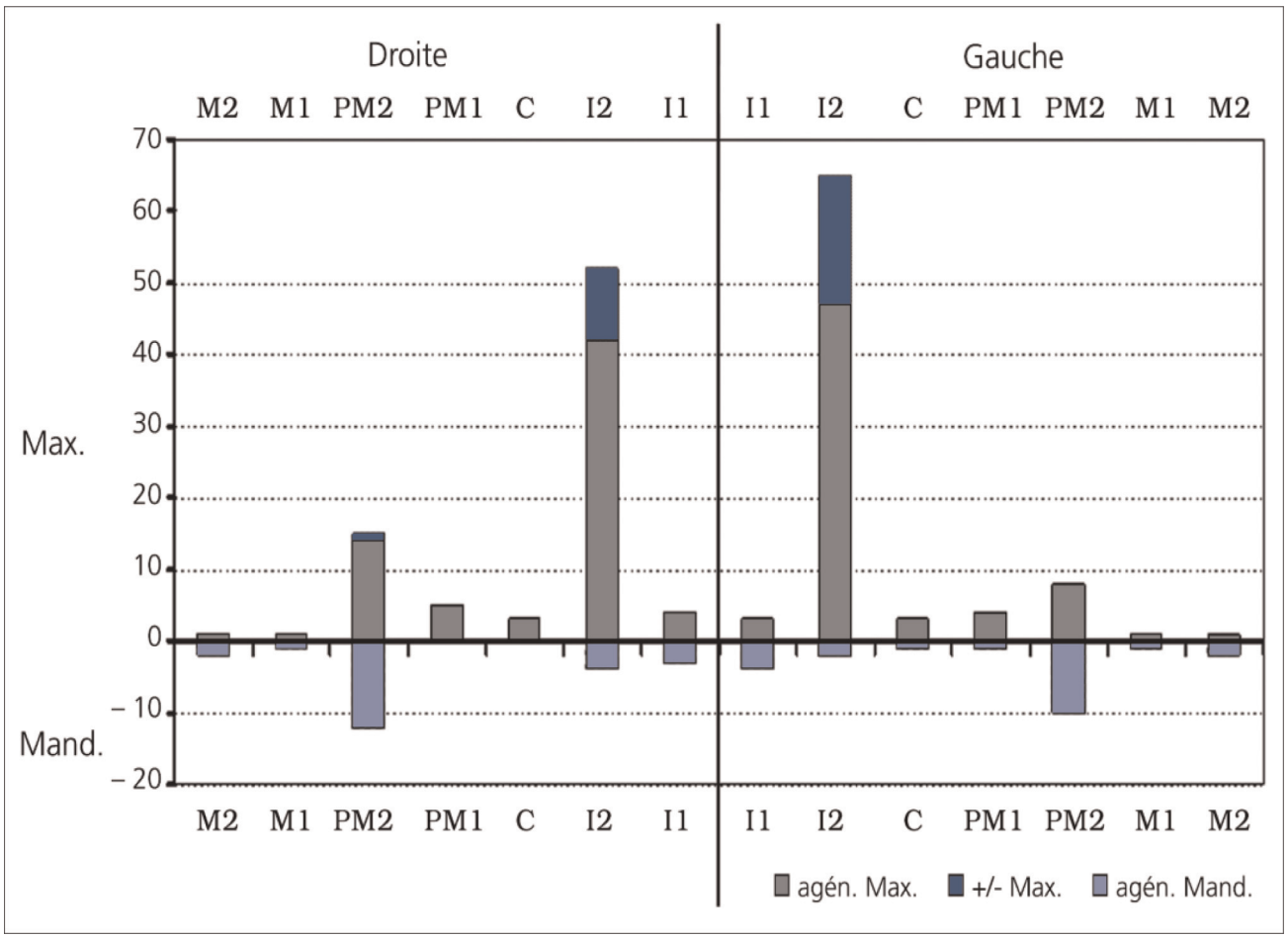

Figure 1

Schematic representation of the number and location of the ageneses / dental anomalies presented by the participants in our study group as a whole.

For each type of tooth, the number of ageneses and anomalies (supplemental, supernumerary or abnormally shaped teeth) on the upper jaw is represented by the dark gray and dark blue columns rising respectively above the 0 (zero) line.

For the mandible, the descending light blue columns represent the number of missing teeth: there are no other dental anomalies on the mandible.

M1-M2: first and second molars;
PM1-PM2: first and second premolars;
C: canine;
I1 – I2: central and lateral incisors, respectively;
Agen. Max.: number of ageneses on the maxillary jaw;
+/- Max.: other dental anomalies on the maxillary jaw;
Agen. Mand.: number of ageneses on the mandible.

in cases of LC, LAC and LPC; 5 missing maxillary teeth for every 4 missing mandibular teeth in the case of CP.

3 – 4 – Dental ageneses and side of the cleft

Among the 124 patients, a distinction must be made between lateralized clefts (*N* = 60) and midline facial clefts (PC) along with bilateral clefts (LC/LPC) (*N* = 64).

Among the 64 cases of midline or bilateral clefts, 30 are combined with ageneses on the right and 28 on the left (certain cases present ageneses on both sides).

However, among the 60 patients who have right-sided clefts (*N* = 15) or left-sided clefts (*N* = 45), 20 have no agenesis, 24 have at least one unilateral or contralateral agenesis with their cleft and 16 have bilateral ageneses (Fig. 2).

In all, considering that each missing tooth is an independent occurrence

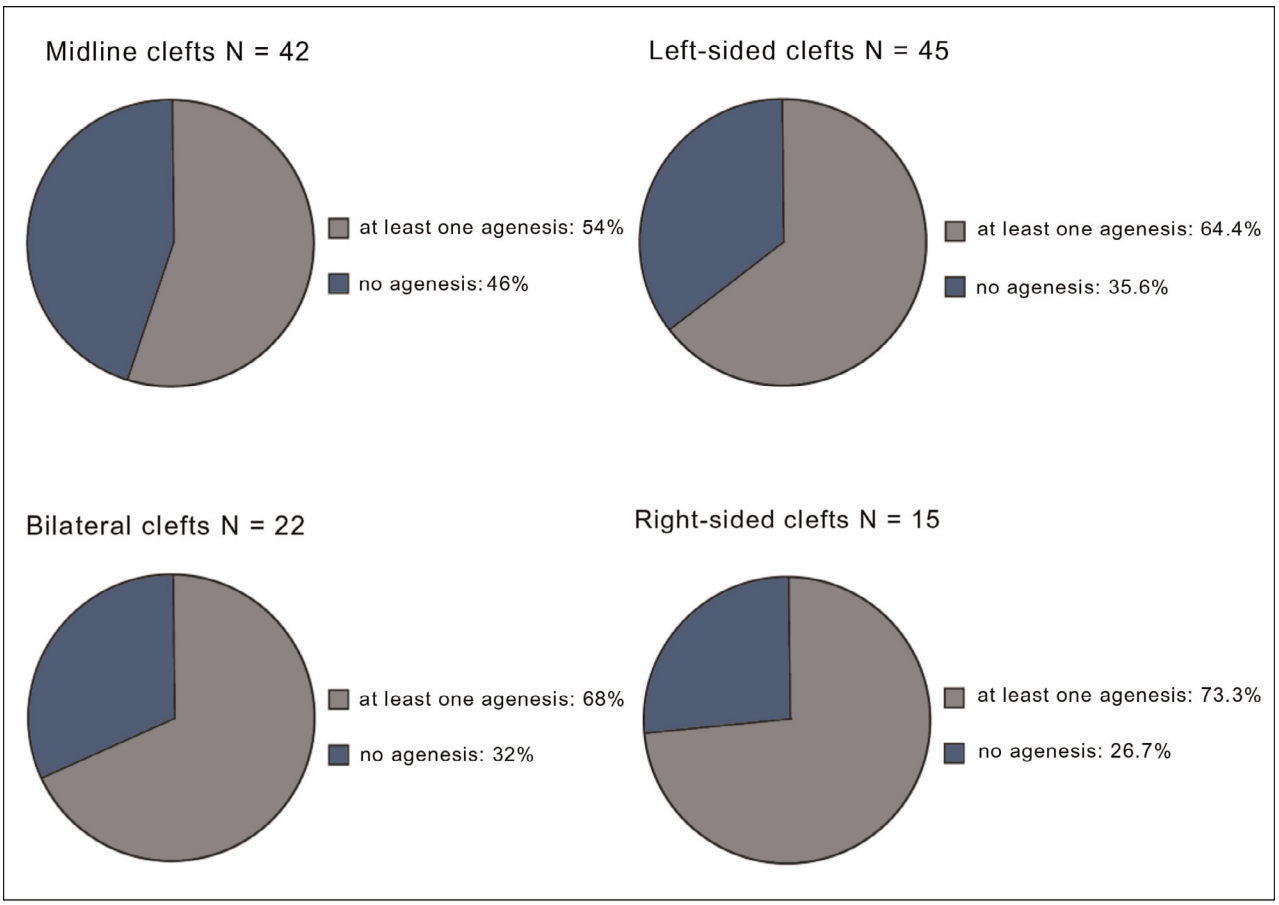

Figure 2
Frequency of dental ageneses based on the type of cleft.
Classification by ascending order, from the top left to the bottom right, of the frequency of dental ageneses in patients presenting respectively a midline, left-sided, bilateral et right-sided cleft.

and not necessarily symmetrical, the figures show 56 cases of ageneses of at least one tooth (24 unilateral + 2 × 16 bilateral). It seems that in 58.5% of the cases, left-sided clefts are correlated to left-sided ageneses, and that 66.7% of right-sided clefts are linked to left-sided ageneses. The chi-square test shows that these numbers significantly differ ($p < 0.01$).

In conclusion, right-sided clefts are more often correlated with contralateral ageneses than left-sided clefts.

3 – 5 – Ageneses are significantly more frequent on the left side

Because:

- there are more left-sided (73%) than right-sided (27%) clefts, if we leave out bilateral and midline clefts ($p < 0.01$);
- significantly, 66.7% of right-sided clefts are linked to contralateral ageneses as opposed to only 41.5% of left-sided clefts ($p < 0.01$);
- but bilateral and midline clefts are not linked to more ageneses on either side.

4 – DISCUSSION

One of the objectives of this study is to compare the results obtained from a sampling of French patients with studies of the same type for other nationality groups.

For the same genetic mutation responsible for a syndrome, there is a significant variability of the phenotype due to complex systems of proteic regulation.

In line with the study of Kim and Baek[6], we see that boys are significantly more afflicted with clefts than girls.

Similarly, LPC are the most frequent forms and this is also the finding of other authors[1,22]. On the other hand, we note that the distribution of clinical forms of clefts is similar in boys and in girls.

Our study confirms that the left is the side most afflicted with clefts, and this prevalence for clefts on the left side is even greater for girls.

We note that a prevalence of 63% for dental ageneses in our sampling of patients with clefts. These results, clearly greater than the prevalence of dental ageneses in the normal population, correspond to higher proportions found in the literature (77%[22] and 67.6%[1]).

When we cross the variables ''dental anomalies'' and ''type of cleft'', we see an increase in the frequency of dental ageneses with the involvement of the secondary palate that agrees with the findings of other studies[2,4,9,10,12,25]. Surprisingly, we see a marked increase in the number of ageneses on the mandible in cases of isolated cleft palate.

By crossing the variables ''cleft side'' and ''ageneses side'', we logically

expect that the ageneses would be more frequent on the side of cleft. That is the case for left-sided clefts. Given that left-sided clefts are more frequent, the findings of most studies indicate that dental ageneses are more frequent on the left side[1,22]. We confirm these findings in our study and support them in an original way with data showing that in cases of right-sided clefts, left-sided contralateral ageneses are significantly more frequent.

Determining the right-left symmetry in the course of development is a complex subject, given that the molecular data are still incomplete: the laterality of the cephalic region appears to be established independently from that of the body[14]. In addition, the experimental results that establish that signaling by FGF8 and Shh respectively determines the right and left sides of the chicken embryo leads to the opposite conclusion in mice[15]. Nonetheless, it is clear that in all chordates, whatever the initial signaling during early development, the left side is actively determined by the specific expression of a series of three pivotal genes (Nodal → Lefty 1 and 2 → Pitx2) whose expression is repressed on the right side[3].

Therefore, we suggest that right-sided clefts might be the rudimentary form of bilateral clefts: the prevalence of left-sided clefts reflects the dominant influence of the left side in determining lateralization and it might be that the left-sided clefts are linked to dysfunctions that reduce left signaling. Bilateral clefts originate perhaps from gene disorders not linked to laterality and right-sided clefts might be linked to defective genes insufficiently repressed from the right side. Therefore, mice embryos with homozygous mutants of lefty-1 have an abnormal bilateral expression with molecular markers normally expressed uniquely on the left, such as nodal[13].

Given the greater prevalence of dental ageneses in our sampling of patients with clefts (63%), the existence of a common etiopathogeny seems obvious to us. Since a portion of the number of dental ageneses increases with the severity of the affliction (i.e. when the secondary palate is involved), and in addition there is an increase in the number of ageneses on the mandible in cases of isolated cleft palate, we can perhaps incriminate pathway signaling specifically implicated in the formation of the secondary palate, that intervenes at a later moment in embryological time (the primary palate forms between the 4th and 6th week *in utero*, the secondary palate between the 6th and 9th week). Moreover, Mxs1 and Pax9 deficient mice exhibit anomalies that affect simultaneously the palate and the teeth[7,11,16,18,21,26].

5 – CONCLUSION

This study which was conducted in France and which associates dental anomalies with LC/LPC/PC makes it possible to confirm our hypotheses: dental anomalies of number and form are more frequent in patients with clefts.

This frequency, which is greater than in the general population, firmly links these two pathologies and can only lead us to conclude that there is an overlapping etiopathogeny.

We can perhaps even consider the isolated presence of dental agenesis or of supplemental/supernumerary teeth to be a rudimentary form of cleft, and consequently consider these dental anomalies to be destabilizing factors putting these patients at risk[8].

In this context, it might be important to study panoramic views of the ascendants and descendants of patients with a cleft in order to confirm the role of heredity, of genetic versus environmental factors in the appearance of these malformations.

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