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Article

Timing of Spheno-Occipital Synchondrosis ossification in children and adolescents with cleft lip and palate

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Abstract: Background: Cleft lip and palate can affect the development of the maxilla, which may create a midfacial deficiency as well as an interference of the facial growth pattern and dentofacial esthetics. Objective: Estimate the chronological age of complete fusion of the spheno-occipital synchondrosis in cleft lip and/or palate patient´s and a control group, using cone beam computed tomography images. **Methods**: In this retrospective study, 125 patients were enrolled (cleft lip and/or palate group (n=91); control group (n=34)). Age comparison was made with Chi-square test and a Kaplan-Meyer analysis determined the median time to reach complete fusion of the spheno-occipital synchondrosis ($p<0.05$). **Results**: The experimental group showed statistically significant differences in the median time for complete ossification between males and females ($p=0.019$). No statistically significant differences were found in the control group between males and females ($p=0.104$). The median time for complete ossification of the spheno-occipital synchondrosis was, for males, 15.0 years in both groups; for females, it was 14.0 years in the experimental group and 13.0 years in the control group. **Conclusions**: The present study showed no differences in the ossification of the spheno-occipital synchondrosis between individuals with and without cleft lip and/or palate.

Keywords: Cleft lip; Cleft palate; Cone-beam computed tomography.

1. Introduction

Patients with isolated cleft lip and palate (CLP) have an anatomical defect that may occur during the 4th and 12th week of pregnancy [1-2]. CLP prevalence is 1 in 500 – 2,500 live births and has a multifactorial etiology such as geographic location, ancestry, prenatal exposures, maternal age and socioeconomic status [1-3].

CLP is known to affect the development of the maxilla by a combination of functional, intrinsic and iatrogenic factors, which may lead to a retruded position of the maxilla and create a midfacial deficiency, negatively influencing the facial growth pattern and dentofacial esthetics [4-5].

Some studies demonstrate that CLP is not a localized phenomenon and that a deviant morphology could be observed in different structures of the craniofacial complex, such as the basicraniu [6-8]. There are three important endochondral growth centers in the craniofacial skeleton: the spheno-ethmoidal synchondrosis, the intersphenoid synchondrosis and the spheno-occipital synchondrosis (SOS) [9]. The SOS is a cartilaginous union between the body of the sphenoid and the basilar part of the occipital bone and it is the last of the synchondroses of the cranial base to fuse [10-11]. Its’ growth will influence the anteroposterior dimension of the cranial vault (contributing to 25% of the growth of the skull base) as well as the height and depth of the upper face by moving the anterior cranial base upward and forward, and its attached maxillary complex, away from the foramen magnum [7,9,10,12-14].

The SOS fusion is affected by individual growth and maturation, following acceleration and deceleration stages, reaching a plateau at the end of the pubertal cycle [14]. The literature suggests that the average fusion of the SOS normally starts around the age of 7, with a complete ossification for females between 11 to 14 years and 13 to 16 years for males, which may be related to female early growth [9,13,15-17]. Premature fusion of the SOS has been associated with midface hypoplasia in humans with syndromic craniosynostoses, such as Apert and Crouzon syndromes [11-12,15,18-19].

1.1. Objective

The purpose of this study was to estimate the chronological age of complete ossification of the Spheno-Occipital Synchondrosis in cleft lip and/or palate patient´s and a control group, using cone beam computed tomography (CBCT) images. The null hypothesis was that there were no significant differences regarding the chronological age of complete ossification of the spheno-occipital synchondrosis, between subjects with and without cleft lip and palate.

2. Materials and Methods

2.1. Trial design and registration

This study was approved by the ethical committee (process number CE-050/2019) of the Faculty of Medicine, University of Coimbra in accordance with the Declaration of Helsinki. All participants signed an informed consent agreement. Records were obtained from the patients' database that sought treatment at the Department of Dentistry, between January 2014 to January 2019.

2.2. Selection and Description of Participants

The experimental group consisted of 91 patients with cleft lip and palate, 53 males and 38 females, with a mean age of 11.6 years for males and 12.1 years for females. The patients were classified into 4 subgroups: unilateral CLP (60%), bilateral CLP (23%), isolated labial cleft (9%) and secondary palate cleft (8%).

The control group comprised 34 patients without cleft lip and palate, 17 males and 17 females, with a mean age of 12.3 years for males and 12.7 years for females.

The inclusion criteria for both groups were: (1) age from 7 to 17 years, (2) Caucasian and (3) CBCT scan with a big field of view. The exclusion criteria were (1) syndromes and (2) endocrine and/or metabolic disorders, all according to medical history.

The European Academy of Dental and Maxillofacial Radiology basic principles on the use of CBCT were followed in both groups.

2.3. Methods

CBCT scan images were obtained with an iCAT scanner machine (Imaging Sciences International, Hatfield PA, USA) set at 0.3mm voxel size, 120 kV tube voltage, 5mA current, 100 FOV, 4s of scanning time and a slice thickness interval of 1mm. The CBCT images were then exported in a format of Digital Imaging and Communications in Medicine and imported into Invivo5 Advanced 3D Imaging Software (Anatomage, San Jose, CA, USA) for image analysis (these images were not manipulated in any way).

All CBCT images were standardized as follows:

- In the axial view, by positioning the vertical plane in the middle of the anterior border of the foramen magnum (Figure 1a);
- In the frontal view, by leveling the horizontal plane with the palatal plane (Figure 1b).

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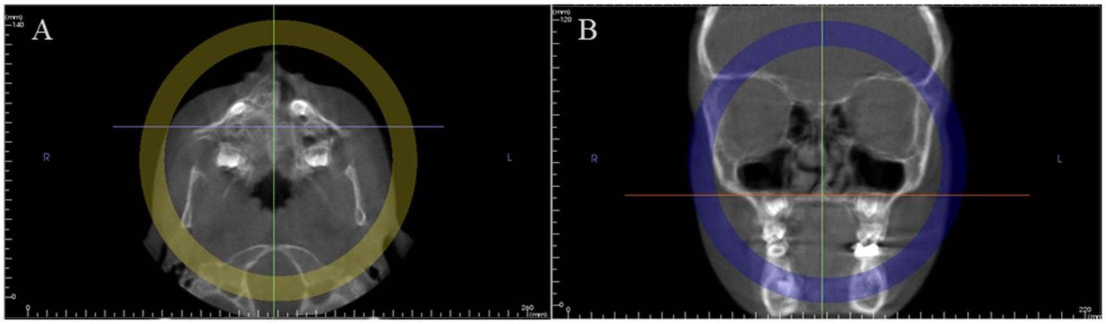

Figure 1. Example of a CBCT record: A, axial view; B, frontal view.

- A mid-sagittal section of the skull base, passing through the middle of the sella turcica (Figure 2a and 2b) and the anterior border of the foramen magnum (Figure 2c and 2d), was considered to assess the SOS. Then the full extent of the synchondral cartilage was observed in search of bone bridges. This method increased the total amount of information collected by the 3D exam.

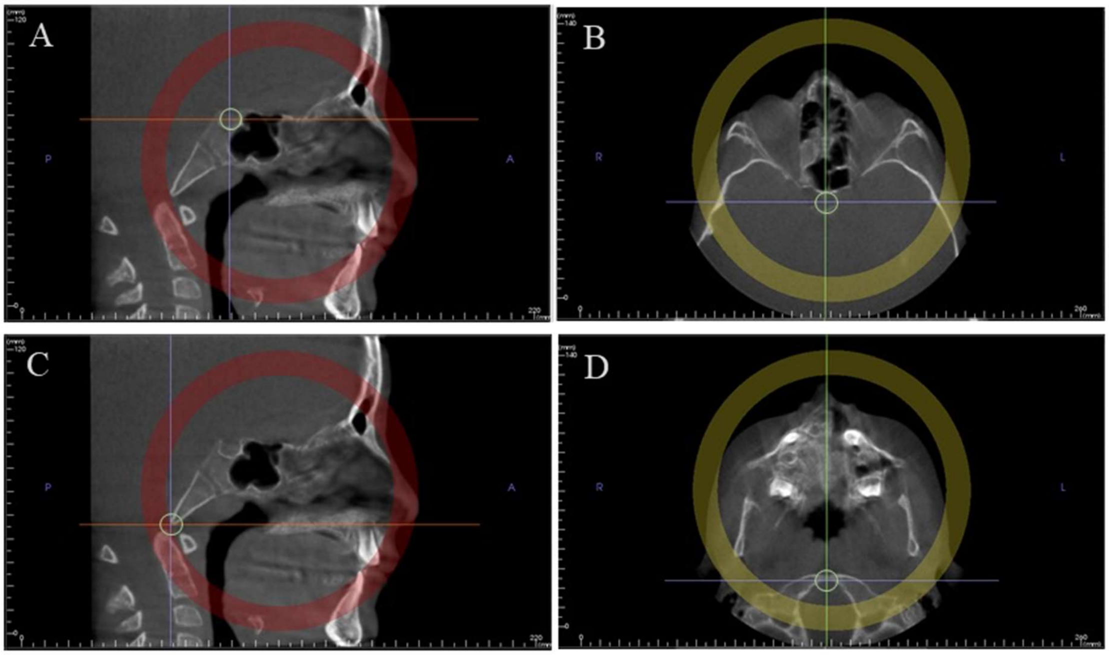

Figure 2. Method used to determine the mid-sagittal plane for evaluation. Middle of sella turcica in the sagittal view (A) and in the axial view (B); anterior border of the foramen magnum in the sagittal view (C) and in the axial view (D).

Each patients´ synchondrosis fusion stage was assessed by using a 5-stage system, proposed by Bassed et al.[20] modified from that developed by Powell & Brodie [9]. The definition of the staging system is shown in Appendice A and B. This system was chosen because it is possible to observe a fusion scar on CBCT images (Stage 4), unlike conventional radiographs [20].

2.4. Statistical Analysis

Twenty-five random images were selected using random.org and rescored by the same examiner with a 1-month interval. An intra-examiner agreement was determined using Cohen's Kappa coefficient.

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Age distribution was described with a histogram in each group, and each group per sex. A Kolmogorov-Smirnov test was used to assess the differences between age distributions between the two independent groups.

A chi-square test was used to assess the association between sex and group. Although data were acquired within a period time resembling a transversal study, it is important to notice that a time-to-event analysis was performed. The first data point corresponds to the birth moment, for which it was assumed that the event (complete SOS ossification) had not occurred. Considering this rationale, the median time to reach the complete ossification of SOS was evaluated resorting to survival analysis, notably Kaplan-Meyer analysis. The definition of the event (complete SOS ossification) was defined as reaching at least stage 4 of the staging system.

All statistical analyses were performed using the IBM© SPSS© version 24 software. A p-value of less than 0.05 was considered statistically significant.

3. Results

The intra-examiner reproducibility value showed a good agreement with a kappa coefficient of $k = 0.920$ ($p < 0.001$).

A total of 125 patients were included in this study and divided into an experimental and a control group. Table 1 and 2 show the sample distribution in these groups respectively. Patients of both groups showed adequate comparability regarding sex (Table 3), and table 4 depicts the age distribution by sex in both groups.

Table 1. Sample distribution: experimental group.

Fusion stage	Sex	Number of individuals	Mean age	Min	Max	CI95%	SD
1	M	29	10	7	14	[9.4; 11.1]	2.2
	F	9	9	7	13	[7.3; 10.5]	2.1
2	M	9	11	8	14	[9.4; 12.9]	2.3
	F	3	11	10	12	[8.5; 14.2]	1.2
3	M	3	14	13	14	[12.2; 15.1]	0.6
	F	5	12	8	14	[9.0; 14.6]	2.3
4	M	7	15	12	17	[13.3; 16.4]	1.7
	F	9	12	10	14	[11.3; 13.4]	1.4
5	M	5	15	14	16	[13.5; 15.7]	0.9
	F	12	15	13	17	[13.7; 15.5]	1.4

Table 2. Sample distribution: control group.

Fusion stage	Sex	Number of individuals	Mean age	Min	Max	CI95%	SD
1	M	8	10	8	14	[8.5; 12.0]	2.1
	F	3	10	8	11	[5.7; 14.3]	1.7
2	M	4	13	12	14	[11.7; 14.8]	1.0
	F	2	11	11	11	[11.0; 11.0]	0.0
3	M	0	0	0	0	[0.0; 0.0]	0.0
	F	0	0	0	0	[0.0; 0.0]	0.0
4	M	2	14	14	14	[14.0; 14.0]	0.0
	F	8	13	11	16	[11.5; 14.0]	1.5
5	M	3	15	15	16	[13.9; 16.8]	0.6
	F	4	15	14	16	[13.7; 16.8]	1.0

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Table 3. Intergroup comparisons for sex ratio (Chi-square test).

	Experimental group (n=91)	Control group (n=34)	
Sex			0.409*
Male	53 (58.2%)	17 (50%)	
Female	38 (41.8%)	17 (50%)	

*Chi-square.

Table 4. Age distribution histogram for the control and experimental groups.

	Both sexes		Male		Female	
age (years)	Control (%)	Experimental (%)	Control (%)	Experimental (%)	Control (%)	Experimental (%)
7	8.8	18.7	11.8	20.8	5.9	15.8
8	2.9	4.4	5.9	5.7	0.0	2.6
9	5.9	9.9	11.8	11.3	0.0	7.9
10	17.6	7.7	5.9	7.5	29.4	7.9
11	14.7	13.2	11.8	13.2	17.6	13.2
12	11.8	15.4	5.9	9.4	17.6	23.7
13	17.6	16.5	29.4	20.8	5.9	10.5
14	8.8	7.7	11.8	3.8	5.9	13.2
15	11.8	3.3	5.9	5.7	17.6	0.0
16	0.0	3.3	0.0	1.9	0.0	5.3
17	0.0	0.0	0.0	0.0	0.0	0.0
KS	p=0.607		p=0.935		p=0.711	

In this study the median time for complete ossification of the SOS was: for males, 15.0 years for both the experimental (CI95% [14.0, 16.0]) and control groups (CI95% [14.2; 15.8]). There were no statistically significant differences between both groups (p = 0.806); for females, 14.0 years for the experimental group (CI95% [12.7, 15.3]) and 13.0 years for the control group (CI95% [11.9; 14.1]). There were no statistically significant differences between both groups (p = 0.565) (Figure 3).

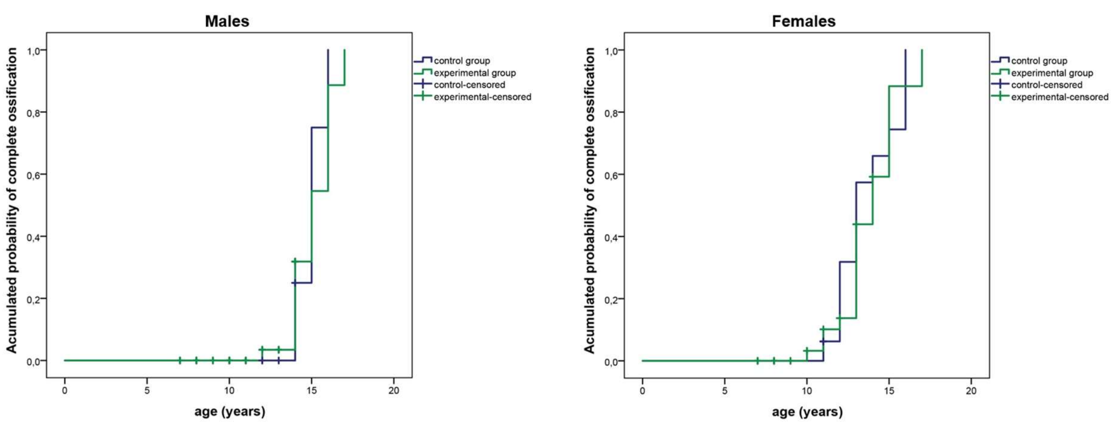

Figure 3. Kaplan-Meyer Graphic. Median age for complete ossification of the SOS: experimental group (green) vs. control group (blue) in males and females.

In the experimental group, there were statistically significant differences in the complete ossification of the SOS between males and females (p = 0.019) (Figure 4).

In the control group, there were no statistically significant differences in the complete ossification of the SOS between males and females (p = 0.104) (Figure 4).

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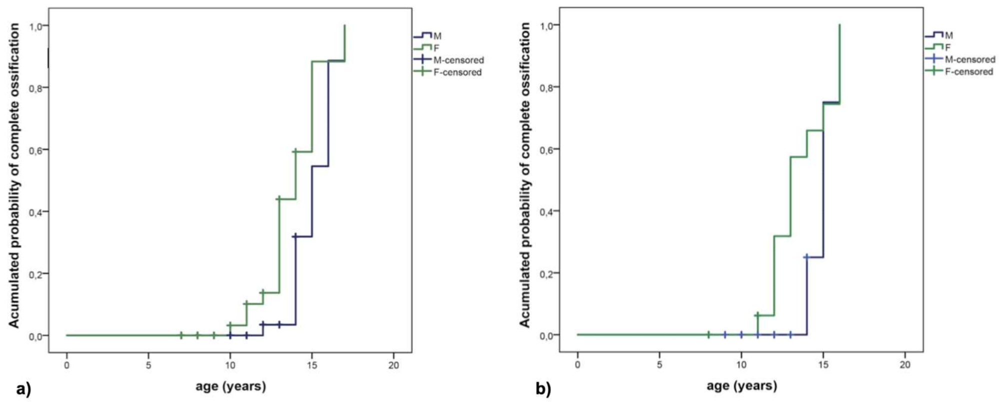

Figure 4. Kaplan-Meyer Graphic. Median age for complete ossification of the SOS: a) experimental group – males (blue) vs. females (green); b) control group – males (blue) vs. females (green).

4. Discussion

The endochondral growth centers in the midline of the cranial base have a close structural interrelationship with the nasomaxillary regions during development, influencing the future position of the maxilla [3,5,9,12]. Hence, when this relationship follows a "normal" development, a good growth of the midface is expected [3]. In patients with craniofacial abnormalities, a deviant morphology could be observed in basic structures of the craniofacial complex, and the development of the midface may be undesirably affected [3,7-8]. Although this aspect is not well studied on CLP patients, some authors believe that it does not only affect oral and peri-oral structures alone [1-2].

Molsted et al. [21], examined the SOS in lateral cephalograms in newborns with major complete and minor incomplete clefts. They concluded that children with major complete clefts had a broader SOS, which could indicate a delayed maturation or deviant growth in the early development of the cartilaginous cranial base. The same authors, in a different study, also found an increase in the cranial base width and the distance between the left and right ala major of the sphenoid bone, in patients with CLP [8]. A lateral skull radiograph can be used to determine the closure of this synchondrosis since it is an inexpensive and conventional exam. While this may be true, it has some disadvantages such as superimposition of structures and low resolution. In recent years, CBCT has become a diagnostic imaging tool in dentistry since it is a three-dimension imaging modality with lower radiation exposure and with a higher definition, allowing a clearer view of anatomical areas without superimposition of structures [22-23]. There are a limited number of studies with CBCT, regarding cranial base morphology in CLP patients.

Previous studies reported that the fusion of the SOS occurred 2 or 3 years earlier in females than in males [7,9,10–12]. The timing of complete ossification of the synchondrosis, however, is still controversial in the literature that is probably due to differences in population, criteria and diagnostic methods [24].

Jahanbin et al. [4], found no significant difference between patients with unilateral CLP, bilateral cleft lip and palate and patients without cleft regarding the middle cranial base length (Ba-S). Liu et al. [7] in a different study concluded that unilateral CLP patients have smaller Ba-S length comparing to a normal control group after the end of the pubertal growth peak.

Our study was the first to date to evaluate the chronological age of complete ossification of the SOS in patients with and without CLP. The present study suggests that the median time for complete ossification of the SOS occurs earlier in females (13.0 years for the control group - 14.0 years for the experimental group) than in males (15.0 years for both groups), although the statistical significance was not reached in the control group. This finding may be explained by the fact that this group had fewer individuals and consequently a reduced statistical power, which is a limitation of this study. Nonetheless, these results are in line with the age range described in the literature. The reduced sample in the control group can be justified by following the European Academy of Dental

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and Maxillofacial Radiology basic principles on the use of CBCT, which contributes to the limited number of 3D scans available, according to our inclusion criteria [25].

Another point of concern, also a limitation of this study, is the uncertainty associated with the occurrence of the event. Since the event is defined from the staging process one can state that the event has occurred but not knowing exactly its time. The time of the event has an uncertainty that tends to overestimate the mean and the median time of ossification. The alternative to overcome this aspect would be to design a pure longitudinal study, which would imply to submit the subjects to periodic CBCT scans increasing the accumulated radiation dose.

Further studies should be conducted to determine the time of complete SOS ossification in patients with CLP, since there is a lack of research in the literature for comparison, probably because CBCT technology has only become more common recently. Additionally, studies with higher sample sizes would be beneficial.

5. Conclusions

There are no differences regarding the complete ossification of the spheno-occipital synchondrosis, between individuals with and without cleft lip and palate. The complete ossification of this synchondrosis occurs later in males than in females. The use of CBCT scans to evaluate the fusion stage of the SOS could be useful as an additional tool to determine the timing of craniofacial growth and development.

Author Contributions: F.V: Conceptualization, Methodology and Supervision; I.F.: Writing - Review & Editing and Visualization; A.L.: Data Curation; A.R.: Writing - Review & Editing; F.C.: Methodology and Formal analysis; A.S: Software , investigation and Writing - Original Draft. All authors have read and agreed to the published version of the manuscript.

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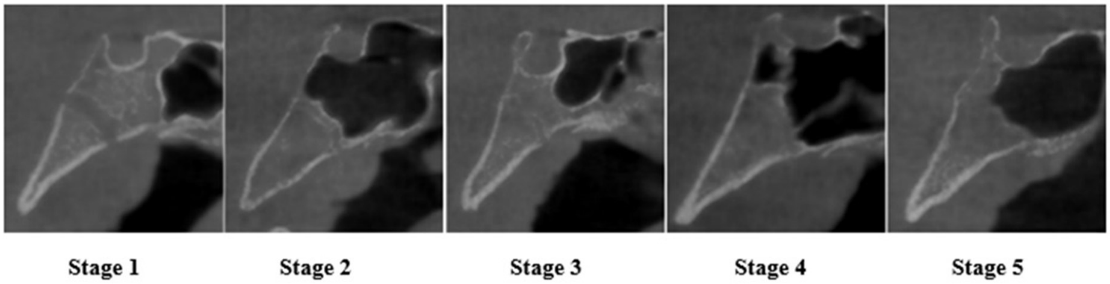
Conflicts of Interest: The authors declare no conflict of interest.

Appendix A

Appendice A – CBCT images of the fusion stages of the spheno-occipital synchondrosis.



Appendix B

Appendice 2. Spheno-occipital synchondrosis fusion based on a five-stage system proposed by Bassed et al. 2010

Stage	Definition
1	Synchondrosis is completely open and unfused.
2	Superior border has fused while the remaining fusion site is open.
3	Superior half of the synchondrosis is fused.
4	Complete fusion with a fusion scar in site still visible.
5	Synchondrosis has been completely obliterated with the appearance of normal bone in site.

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