MORPHOLOGY OF C1 - C3 VERTEBRAE IN PATIENTS WITH UNOPERATED NONSYNDROMIC CLEFT PALATE - A RETROSPECTIVE CBCT STUDY

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ABSTRACT

Introduction*: Palate cleft is one of the most frequent craniofacial abnormalities, also reported in association with other anomalies or malformations, with possible involvement of cervical vertebrae. Cervical vertebrae anomalies are important to know in trauma and in the case of surgical treatment - screw procedures. The aim of this study is to investigate the C1-C3 morphology and possible anomalies in patients with unoperated nonsyndromic palate cleft compared to a control group of patients without palate. We used a newer 3D imaging technique, rarely used for vertebral diagnosis.*

Materials and methods*: The overjet group with palate cleft consisted of 20 patients (4-22 years): 5 females and 15 males. The control group consisted of 20 patients (6-29 years): 8 females and 12 males. We retrospectively reviewed the CBCT images of the patients and examined the C1-C3 vertebrae.*

Results*: Anomalies or anatomical variants were found in 80% of the palate cleft group, compared to 35% of the control group. Atlantoaxial rotatory fixation was found in 65% of the cleft group and in 10% of the control group. Other anomalies encountered were incomplete transverse foramen, unfused vertebral arches, ossiculum terminal, dens bicornis, and deviated spinous process.*

Conclusion*: Our study confirmes a higher occurrence of cervical vertebrae anomalies among patients with palate cleft. Our findings support the results reported by the other authors but also report other anomalies less discussed and occult to 2D imaging. Although the etiology of atlantoaxial rotatory fixation is still unknown, our study showed a high incidence among patients with unoperated palate cleft.*

Keywords: *Orofacial cleft, Cervical vertebrae, Cervical vertebral anomalies, CBCT; Skeletal morphology,Atlantoaxial rotatory fixation.*

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Introduction

Palate cleft is one of the most frequent of craniofacial abnormalities, affecting ~1 in 700 live births[(1)]. Although in the majority of cases, palate cleft is not associated with other defects[(2)], being referred to as non-syndromic, there are also cases that report palate cleft associated with other anomalies or malformations or as part of syndromes[(3,4)], such as Van der Woude syndrome, median facial dysplasia syndrome and Pierre Robin Sequence[(5)].

The primary palate originates from the first pharyngeal arch and develops from the intermaxillary segment, formed after the fusion of two symmetrical maxillary prominences[(6)]. Any perturbation during embryonic development can lead to a defect of fusion between the two halves of the lip and/or palate, called a cleft[(7-9)].

On the other hand, in the development of the vertebral column, after segmentation, the somites develop into sclerotomes, and each sclerotome will help to form more than one anatomical piece.

For example, the axial segment of the proatlas sclerotome will help develop the basion of the basiocciput (the clivus) and the apical segment of the dens, while the lateral segments of the proatlas will form the occipital condyle, lateral rim, and opisthion of the foramen magnum. Also, the C1 sclerotome will help develop both parts of the C1 vertebra (the posterior atlantal arch) and part of the C2 vertebra (the basal segment of the dens)[10]. While observing a common embryological pathway for part of the skull base and the first cervical vertebrae, we can accept at least theoretically that a minor vertebral abnormality might associate at least another occult one at the skull base. The pathophysiology of facial clefting is essential and appears to be multifactorial, containing both a genetic and environmental component[1,11].

Patients with orofacial clefts will require special medical attention, most of the time surgical[9], as orofacial clefts may affect the quality of life[12]. In some cases, orofacial clefts are associated with different systemic anomalies and pathological changes in the paranasal sinuses[8], but also at the limbs, different organs (cardiovascular, skull, eye, brain, skeleton, genital, renal, ENT, teeth, spine[3,8,9,12,13]. Some studies have also indicated a higher incidence of cervical vertebral anomalies (fused vertebrae, an unusual atlas shape or posterior arch deficiency - spina bifida, dehiscence) associated with orofacial clefts[3,14-18], sometimes diagnosed as incidentally and sometimes investigated as part of a multiple anomaly syndrome[3]. This considered some of the solitary cases reported might also associate some undiagnosed malformations[19]. Still, a clear correspondence between orofacial clefts and specific spine anomalies is not yet proved .

The aim of this study is to establish the C1-C3 morphology in patients with unoperated palate cleft compared to a control group, with a newer but less used 3D imaging technique.

Materials and methods

Cone Beam Computerized Tomography (CBCT) images of 441 patients, performed between April 2013 and January 2015, were retrospectively examined, selecting only patients presenting orofacial cleft. All CBCT examinations were in a private imaging clinic in Iași, Romania. Twenty-two patients with unoperated nonsyndromic palate cleft were identified, and only twenty were included in our study. The imaging investigation had been recommended by a plastic surgeon or an oral maxillofacial surgeon after a physical exam. Our primary inclusion criteria consisted of the presence of complete C1-C3 vertebrae, good quality of CBCT images, and absence of artifacts. The selected patients had an age range of 4-22 years (mean 10.25 years, SD 5.00 years). The randomly chosen control group consisted of 20 patients, with a similar sex distribution as the study group, with an age range of 6-29 years (mean 20.80 years, SD 6.47 years), with the absence of palate cleft or other orofacial anomalies. The scans were obtained with a Promax® 3D Mid (Planmeca Oy, Helsinki, Finland) dental CBCT (90 kV, 8 mA, 18 s). The CBCT effective dose was determined based on our clinically used exposure protocols, with a FOV of 7/17 or 20/20 mm. All the CBCT images were MPR reconstructed in the axial, sagittal, and coronal planes and viewed with 1 mm thickness. To examine the CBCT images and create 3D volume rendering reconstructions, we used the Radiant Dicom Viewer 5.0.1 software, 64-bit (Medixant Maciej Frankiewicz, Poznan).

Two experienced radiologists examined the CBCT images and their 3D volume rendering reconstructions. The study was double-blinded. We calculated the interobserver reliability (the percent agreement for two raters was 87.5%).

We divided the possible C1-C3 anomalies according to their anatomical location, to the vertebral component affected and, respectively, changes of the normal curvature and alignment of the vertebrae. Data was analyzed for the distribution of each abnormality/anatomical variant found and its association with palate cleft. T-test and Fisher's exact tests were used for the comparison of cervical vertebrae anomalies , and anatomical variants identified associated with palate cleft. For calculating the homogeneity of variance, we used Levene's test. We chose a significance level of 0.05, and we used Microsoft Office Excel. The study has been carried out according to the instructions of the author's institutional Human Investigations or Ethics Committee.

Results

In our study, we encountered the following cervical vertebral anomalies: transverse foramen anomalies, arch anomalies, spinous process anomalies, dens anomalies, vertebral alignment anomalies, and cervical curvature anomalies. Five of the patients with palate cleft presented bilateral cleft (type III cleft lip and palate) and 15 of the patients

presented unilateral cleft (type II cleft lip and palate) - 6 presented right cleft, and 9 presented left cleft. The cervical anomalies mentioned were found in 16 patients with palate cleft (80%) and in 7 patients from the control group (35%) (Table 1).

found was bilateral in three patients from the CPG (15%) - one at C1 and two at C2 (Fig.1) and in one patient (5%) from the NCG (at C2). There was no correspondence between the side of the incomplete transverse foramen and the side of the palate cleft.

Anomalies			Found in our study		
Classification				CPG n (%)	NCG n (%)
C1 and the basiocciput	Occipital vertebra	Pre Basioccipital arch/ Third occipital condyle/ Paracondylar process/ Basilar processes			
	Unfused clivus				
	Platybasia				
	C1 occipitalization				
	Basilar invagination				
C1	Aplasia/hypoplasia of C1 hypochordal bow				
	Arch anomalies	Unfused anterior arch/ Unfused posterior arch	Unfused anterior and posterior C1 arches	1 (5%)	0
		Ponticulus posticus			
		Other congenital anomalies of the posterior arch			
	Transverse foramen anomalies	Incomplete/double/triple/asymmetrical transverse foramen (citare)	Incomplete transverse foramen	2 (10%) - from which 1 bilateral	0
	Accessory ossicle of C1				
C2	Aplasia/hypoplasia				
	Arch anomalies	High riding vertebral artery/ other anomalies			
	Dens anomalies	Persistent ossiculum terminale/Os odontoideum/Hypoplasia/Aplasia/Bicornuate odontoid/Os avis	Persistent ossiculum terminale	3 (15%)	1 (5%)
			Bicornuate odontoid	7 (35%)	0
	Spinous process anomalies	Unfused/deviated/bifid spinous process			
	Transverse foramen anomalies	Incomplete/double/triple/asymmetrical transverse foramen (citare)	Incomplete transverse foramen	3 (15%) - from which 2 bilateral	4 (20%) - from which 1 bilateral
C3	Vertebral body anomalies	Hemivertebra/Block vertebra/Butterfly vertebra			
	Spinous process anomalies	Unfused/deviated/bifid spinous process	Deviated spinous process	1 (5%)	1 (5%)
	Transverse foramen anomalies	Incomplete/double/triple/asymmetrical transverse foramen (citare)			
	Other arch anomalies				
C1-C3	Curvature anomalies	Cervical lordosis		1 (5%)	0
		Cervical scoliosis		1 (5%)	0
	Alignment anomalies	Rotatory subluxation/ atlantoaxial rotatory fixation	Type I- rotatory fixation without anterior displacement of the atlas	13 (65%)	2 (10%)

Table 1: Possible C1-C3 anomalies according to their location.

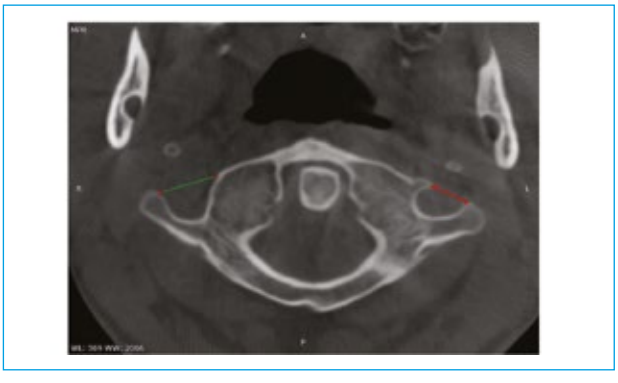

Fig. 1: Bilateral Incomplete transverse foramen of the atlas in a 22-year old patient from the CPG - axial view.

Incomplete transverse foramen of the atlas or axis was found in 5 patients (3 cases at C2 and 2 cases at C1) with cleft palate (25%), respectively in 4 of the patients from the control group (20%), all of them at C2. The incomplete transverse foramen

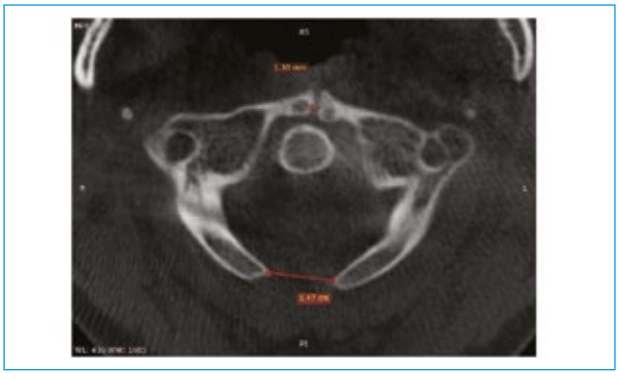

Fig. 2: Unfused anterior and posterior C1 arches in a 12-year old patient from the CPG - axial view (**anterior defect of 1.3 mm and posterior defect of 14.7 mm*)

One patient (12-year old) with palate cleft presented unfused anterior and posterior C1 arches (5%) (Fig. 2). The C3 spinal process was deviated

(Fig. 3) in one patient with palate cleft (5%) and in one patient from the control group (5%).

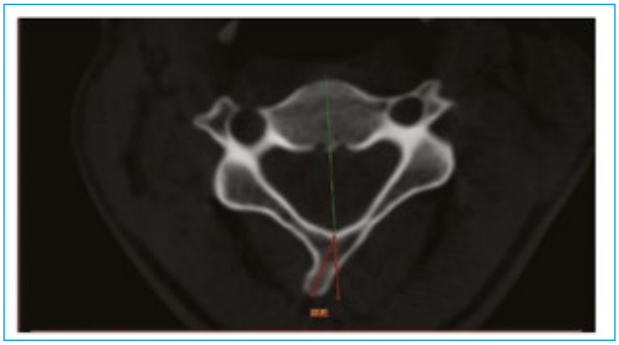

Fig. 3: C3 Spinal process-oriented to right in an 18-year old patient from the CPG - axial view (**the spinal process and the anterior-posterior axe of C3 make an angle of 25.3*)

We found an ossiculum terminal aspect in 3 patients (15%) from the CPG (aged 6, 9 and 10 years) and in 1 patient (5%) from the NCG (aged 18 years). A bicornuate odontoid aspect was found only in 7 patients (35%) from the CPG (aged 4-8 years) (Table 1). The most encountered anomaly we found was type I- rotatory fixation without anterior displacement of the atlas. This cervical vertebral alignment was found in 13 patients with palate cleft (65%) and in only 2 patients from the control group (10%). Cervical curvature anomalies were found only in 2 patients from the GPG - respectively, one patient with cervical scoliosis (5%) and one patient with accentuated cervical lordosis (5%) (Fig.4).

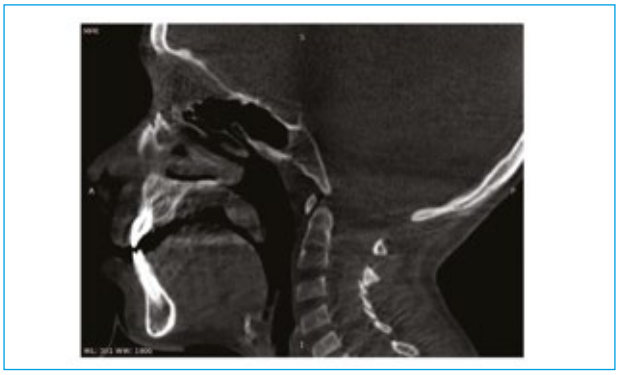

Fig. 4: C3 Spinal process-oriented to right in an 18-year old patient from the CPG - axial view (**the spinal process and the anterior-posterior axe of C3 make an angle of 25.3*)

Discussions

In this study, we analyzed the morphology of the C1-C3 vertebrae in patients with palate cleft as well as in patients with the absence of palate cleft or other orofacial anomalies and found anomalies or anatomical variants of the spine (Table 1).

Cervical vertebrae anomalies were found in 80% of the patients with palate cleft ,while in only 35% of the patients from the control group. Previous studies reported cervical vertebrae anomalies of 13.3%[20], 10%[15], 23.3%, respectively 38.7%[17], all of them with an incidence higher in the palate cleft group than the control group. The most recent related study found an increased percent of cervical anomalies but mostly based on the increased cases with submental cartilaginous remnants (81.45%) and without comparison to a control group[18].

The most encountered cervical vertebral anomalies encountered in our study were changes affecting the normal alignment and curvature of the cervical spine, changes far more frequent for the CPG (65%) than for the NCG (10%). Atlantoaxial rotatory fixation is an acquired C1-C2 anomaly in which C1 is rotated transversely compared to C2. This anomaly is encountered mostly in children and less in adults, with yet unknown cause[21,22]. The atlantoaxial rotatory fixation in adults is most of the time posttraumatic[23,24].

Atlantoaxial rotatory fixation or rotatory subluxation is a rare anomaly, which is why data, including etiology, have been based predominantly on case reports and case series. The associated pathologies that may cause atlantoaxial rotatory fixation are head and neck trauma, inflammatory pathologies, and also surgery[25]. Atlantoaxial rotatory fixation is classified into four types: type I - C1-C2 rotation with no anterior displacement; type II - C1 is rotated on one articular process with 3-5 mm displacement; type III - C1 is rotated on both articular processes with more than 5 mm displacement; type IV - rotation and posterior displacement of the atlas[25]. In our study, the patients with this anomaly were 4 to 22 years old (CPG), respectively 9 and 16 years old (NCG). We only found one study associating atlantoaxial rotatory fixation to palate cleft[26], but the two cases of atlantoaxial rotatory fixation presented were diagnosed/manifested ulteriorly to surgery (pharyngoplasty). Atlantoaxial rotatory fixation is difficult to diagnose with 2D imaging techniques[27]. Considering the fact that most of the previous studies that concentrated on the cervical vertebral anomalies associated with orofacial cleft used 2D imaging methods, the limited data about atlantoaxial rotatory fixation and palate cleft is understandable.

Concerning the cervical vertebral curvature, the data was again limited. We found studies that associated lordosis to palate cleft, but only mentioned

it generally. We didn't find previous studies that investigated cervical vertebral anomalies in patients with palate cleft referring to cervical scoliosis specifically as one of the changes or anomalies found.

Another anomaly found in our study was the incomplete transverse foramen, but the percentages between the two groups were similar - 25% in the CPG and 20% in the NCG. For the CPG, we did not find a correspondence between the side of the incomplete transverse foramen and the side of the palate cleft. The transverse foramen is a cervical vertebral structure that contains the vertebral artery, the vein, and sympathetic nerve fibers[28]. Incomplete septation is an anatomical variant that may harm the containing structures determining pain and vascular or neural insufficiency, and it can as well be mistaken for a fracture[29]. Our search in the literature did not find studies that reported incomplete transverse foramen to palate cleft. This may be again the low sensibility of the 2D imaging methods used, as well as the acceptance of the incomplete transverse foramen as an anatomical variant and less as an anomaly.

Concerning the deviation of the C3 spinous process, the anomaly was rare, and the percentage was equal for the two groups - 5% for the CPG and 5% for the NCG. Our search in the literature did not find studies concentrating or mentioning the association of the spinous process anomalies (especially deviation) and palate cleft, proving that there might not be an association between the two. Although the deviation of C3 spinous process should not determine symptoms or complications, knowing its presence is essential in the case of cervical surgery.

Congenital anomalies of the posterior arch of the atlas (C1) are relatively common anomalies, that although most of the time asymptomatic and found incidentally, can lead to neurological outcomes. Together with congenital anomalies of the anterior arch of the atlas, they are important to be aware of to exclude possible fractures. Anterior and posterior arches normally fuse until the age of six[30]. The only patient with unfused anterior and posterior C1 arches from our study was 12 years old and was from the CPG (5%). Other studies reported posterior arch deficiency in a higher percent - 10.5% (20), respectively 23% and 43.8% (17), but also in a lower percent - 3.22% (18) of the patients with palate cleft, while anterior arch deficiency was more frequent in one study - 18% [13].

Orthotopic ossiculum terminal was present in our study in 3 patients (15%) of the patients from the CPG and in 1 patient (5%) from the NCG. Orthotopic ossiculum terminal represents a secondary ossification center, and its aspect may change and even disappear until the age of 10. According to other studies, ossiculum terminal may fuse even after the age of twenty (31). In our study, the patients from the CPG with an ossiculum terminale aspect were aged 6, 9 and 10 years, while the one from the NCG was 18 years old. Hoenig and Schoener found the ossiculum terminal aspect in 10% of the patients with palate cleft[17], a percentage close to the one we found, while researchers de Rezende Barbosa et al. found this anomaly in 1.72%[18].

Bicornuate odontoid or dens bicornis represents the bicornuate aspect of the tip of the basal dental segment after bilateral secondary ossification centers. The tip of the odontoid represents a third ossification center, not yet ossified at birth, but ossified usually until the age of 3. In our study, there were 7 patients (35%) from the CPG with a dens bicornis aspect aged 4-8 years. Our search in the literature did not find studies that reported dens bicornis in patients with palate cleft, among the cervical vertebral anomaly found. There was one study that generally reported 5.7% cases of anomalies of the odontoid process in patients with palate cleft[17].

Although there were several previous studies that investigated the incidence of cervical vertebrae anomalies in patients with cleft lip and/or palate, most of them were based on lateral cephalograms[17,32]. A recent meta-analysis that followed the association between the cervical vertebrae anomalies and cleft lip and palate found only 10 eligible articles published before March 2018 (clinical studies that evaluated cervical vertebrae anomalies having both a group of patients with cleft and a control group), and from these, nine used teleradiography and only one used CT as the imaging method[17]. Concerning the fact that lateral cephalograms offer 2D images, with superposition of anatomical elements and that the image quality depends on the compliance of patients and their capability of maintaining a certain position during exposure[33], lateral cephalograms might imply several false positive[34] or false-negative results[35] and have limitations[13]. We found few studies that have used a 3D imaging tool to analyze the cervical vertebrae's anatomy, either computed tomography (CT)[15] or cone-beam computed tomography (CBCT)[13,36]. We found even fewer studies that have investigated the association between the

palate cleft and cervical vertebral anomalies using a 3D imaging method, but most of them via CT. We found only two studies that investigated incidental findings associated with clefts using CBCT[8,18]. In one of them, the cervical vertebral anomalies reported were 3.2% (1.6% with fused vertebrae and 1.6% with an unusual atlas shape), but the study did not focus only on the cervical vertebral anomalies, them being mentioned among other findings (ENT, TMJ, sinuses, skull, maxilla and mandible, soft tissue) and without a control group for comparison[8]. The second one was more recent (2020) but had different results than our study (18). The later study is also retrospective and follows only specific cervical vertebral anomalies - the 12 most encountered in previous studies, without mentioning other possible cervical anomalies and without a control group. Considering the fact that most of the cervical vertebral anomalies in the literature are 2D diagnosed, the fact that some of the anomalies we found, such as curvature and alignment anomalies, are not discussed is explainable. The patients with cleft lip palate enrolled had a wide age range - 5 to 51 years old, including children, young adults, and old adults, while in our study, the oldest patients from the cleft lip palate group were 22 years old. It is again important to mention that all the patients from our CPG had the palatine bony defect unoperated, this canceling the postsurgery possible explanation to atlantoaxial rotatory fixation, while the study mentioned does not specify the surgical history of the patients. With all the details mentioned, our study is important, new and original.

In our study, we found cervical vertebral anomalies such as atlantoaxial rotatory fixation, incomplete transverse foramen, persistent ossiculum terminal, and dens bicornis in patients with palate cleft while in the literature, we couldn't find mentioned these anomalies as associated to palate cleft. Still, most of the studies mentioned used a 2D imaging technique, and most of the anomalies listed can only be diagnosed with a 3D imaging method (CT or CBCT).

Our study concentrates exclusively on the morphology of the cervical vertebrae on patients diagnosed with palate clefts, examined with CBCT. CBCT is an important alternative to CT, which also offers 3D information[37], but with a lower irradiation dose[38], a higher spatial resolution and short scanning time[38], and a sensitivity comparable to CT when analysing the bony structures[39,40].

Our study did provide important information. Most of the cervical anomalies and modifications we found were mild, and some were anatomical variants. Still, we can affirm that the incidence was higher for the cleft group compared to the control group, as in the previous studies.

We should also consider the fact that we can only report to the small number of patients diagnosed or investigated in the private imaging clinic where the study took place, which is not high (22 patients with orofacial cleft during 22 months), but the number of those with soft palate cleft, submucous cleft or mild asymptomatic vertebral anomalies is very likely to be higher[11]. Also, not all cervical vertebrae anomalies can be diagnosed on a lateral cephalogram, not all radiologists are trained to notice the ones that can be [19]. In some situations, patients are investigated exclusively for some indications, and the imaging result specifies exclusively the problem investigated, without mentioning possible existing benign anomalies or anatomical variations outside the target area[8].

Our study had several limitations. Because of the small lots of patients, we could not consider the prevalence according to gender or age category, nor divide the groups according to the palate cleft type (unilateral left/right or bilateral). Concerning the homogeneity of variance, the requirement of homogeneity was met, with the f-ratio value of 1.95488, the p-value of 0.17017, and a significance level of $p<0.05$.

Conclusions

Our study confirmes a higher occurrence of cervical vertebrae anomalies among patients with palate cleft and highlights the importance of 3D imaging. Our findings support some of the results reported by the other authors but also report other anomalies less discussed and occult to 2D imaging. Although the etiology of atlantoaxial rotatory fixation is still unknown, our study showed a high incidence among patients with an unoperated orofacial cleft.

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