UNIVERSIDADE DE SÃO PAULO
HOSPITAL DE REABILITAÇÃO DE ANOMALIAS CRANIOFACIAIS

RENATA MAYUMI KATO

Comparison of Treacher Collins Syndrome and Pierre Robin Sequence: a CBCT study

Comparação entre Síndrome de Treacher Collins e Sequência de Robin Isolada: um estudo com TCFC

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Dissertação constituída por artigos apresentada ao Hospital de Reabilitação em Anomalias Craniofaciais da Universidade de São Paulo para obtenção do título de Mestre em Ciências da Reabilitação, na área de concentração Fissuras Orofaciais e Anomalias Relacionadas.

Orientador: Prof.ª Dr.ª Daniela Gamba Garib Carreira

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“A tarefa não é tanto ver aquilo que ninguém viu, mas pensar o que ninguém ainda pensou sobre aquilo que todo mundo vê.”

Arthur Schopenhauer

RESUMO

RESUMO

Kato, RM. Comparação entre Síndrome de Treacher Collins e Sequência de Robin Isolada: um estudo com TCFC [dissertação]. Bauru: Hospital de Reabilitação de Anomalias Craniofaciais, Universidade de São Paulo; 2020.

Introdução: A Síndrome de Treacher Collins (STC) e a Sequência de Robin Isolada (SR) compartilham a deficiência mandibular como um achado clínico similar. A proporção ramo-corpo, o grau de assimetria mandibular e a morfologia dos côndilos ainda não foram comparadas entre a SR e a STC.

Objetivos: O objetivo deste estudo foi comparar a morfologia da face e dimensões da mandíbula em indivíduos com STC e SR.

Métodos: A amostra consistiu de tomografias computadorizadas de feixe cônico (TCFC) provenientes do arquivo do HRAC-USP. O Grupo STC foi composto por 17 indivíduos com STC e apresentava idade média de 11,5 anos (7 do sexo masculino, 10 do sexo feminino). O Grupo SR foi pareado por sexo e idade com o grupo STC. Avaliações quantitativas foram realizadas em reconstruções da telerradiografia (2D) e tridimensionais da mandíbula. Os softwares utilizados foram Dolphin (Dolphin Imaging 11.0 & Management Solutions, California, United States) e Mimics Innovation Suite 17.0 (Materialize, Leuven, Belgium). A comparação intergrupos foi realizada por meio do teste t independente/Mann-Whitney e do teste ANOVA e Tukey para a análise bidimensional e tridimensional, respectivamente ($p<0.05$).

Resultados: A base do crânio e a posição sagital da maxila foram similares entre os grupos. A mandíbula na STC demonstrou maior grau de assimetria que a SR. As dimensões transversais do ramo e do côndilo, os comprimentos efetivo da mandíbula e do corpo mandibular e a altura do côndilo mostraram-se reduzidos no grupo STC em relação ao grupo SR. O grupo STC exibiu um ângulo goníaco mais aberto com maior tendência ao crescimento vertical quando comparada à SR.

Conclusão: As diferenças dentoesqueléticas mais marcantes entre as duas síndromes foram encontradas na mandíbula. A síndrome de Treacher Collins apresentou uma mandíbula menor, mais assimétrica e mais vertical que a sequência de Pierre Robin Isolada.

Descritores: Síndrome de Pierre Robin. Disostose mandibulofacial. Tomografia computadorizada de feixe cônico.

ABSTRACT

ABSTRACT

Kato, RM. Comparison of Treacher Collins Syndrome and Pierre Robin Sequence: a CBCT study [dissertation]. Bauru: Hospital de Reabilitação de Anomalias Craniofaciais, Universidade de São Paulo; 2020.

Introduction: Treacher Collins Syndrome (TCS) and non-syndromic Pierre Robin Sequence (PRS) share mandibular deficiency as a similar clinical finding. The ramus-body ratio, the degree of mandibular asymmetry and the condyle morphology were not compared between TCS and PRS.

Objectives: The aim of this study was to compare the facial morphology and mandibular dimensions in individuals with TCS and PRS.

Methods: The sample consisted of cone-beam computed tomography (CBCT) from a single center. Group TCS was composed by 17 individuals with TCS and presented an average age of 11.5 years (7 males, 10 females). Group PRS was paired by sex and age with the Group TCS. Quantitative evaluations were performed using CBCT-derived cephalometric reconstructions (2D) and three-dimensional reconstructions of the mandible. The softwares used was Dolphin (Dolphin Imaging 11.0 & Management Solutions, California, United States) and Mimics Innovation Suite 17.0 (Materialize, Leuven, Belgium). Intergroup comparison was performed using the independent t test/Mann-Whitney and the ANOVA/Tukey test for two-dimensional and three-dimensional analysis, respectively ($p < 0.05$).

Results: The cranial base and the sagittal position of the maxilla were similar in both groups. The mandible in group TCS showed a higher degree of asymmetry than group PRS. The transversal dimensions of the mandibular ramus and condyle, the effective mandibular and mandibular body length and the condyle height were reduced in TCS compared PRS. Group TCS exhibited a greater gonial angle with a more severe vertical growth pattern when compared to PRS.

Conclusion: The most important dentoskeletal differences between the craniofacial anomalies were observed in the mandible. Treacher Collins Syndrome had a smaller, more asymmetrical and more vertical mandible than the non-syndromic Pierre Robin Sequence.

Keywords: Pierre Robin Syndrome. Mandibulofacial dysostosis. Cone-beam computed tomography.

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SUMMARY

1 INTRODUCTION

1 INTRODUCTION

Treacher Collins Syndrome (TCS) was first described in 1900 by Edward Treacher Collins (McKenzie and Craig, 1955) and include a group of defects closely related to the head and neck, arising from abnormalities in the development of craniofacial structures derived from the first and second branchial arches (Magalhães et al, 2007). Its estimated incidence is 1:50,000 births (Fazen et al, 1967; Rovin et al., 1964). It is a condition resulting from mutations in the TCOF1 gene, with more than 130 mutations identified throughout the gene and linking to chromosome 5q32 locus (Treacher Collins Syndrome Collaborative Group, 1996). Although it is an autosomal dominant disorder of craniofacial morphogenesis (Fazen et al., 1967; Rovin et al., 1964), about 60% of the cases do not have a family history and are caused probably by new mutations (Jones et al, 1975).

The main characteristic is malar and mandibular hypoplasia, frequently with limited formation of the zygomatic complex (Zhang et al, 2009). The posteriorly positioned maxilla and the arising mandibular plane in the TCS can lead to mandibular deficiency and glossoptosis with airway obstruction (Steinbacher and Bartlett, 2011). Hypoplasia of the facial bones may result in dental malocclusion. The teeth may be widely spaced, malpositioned or reduced in number. Anterior open bite is a common finding in TCS. In many cases, the palate is high, arched and occasionally cleft (28%) and in severe cases, the zygomatic arches may be completely absent (Poswillo, 1975). Presents a variable expressiveness and milder cases may go unnoticed due to lack of diagnosis (Rovin et al, 1964).

Pierre Robin sequence (PRS) consists of the clinical triad of congenital micrognathia, glossoptosis and airway obstruction frequently associated with U-shape cleft palate (Elliot, 1995). The incidence in the general population ranges from 1:8500 to 1:14000 live births (Bush and Williams, 1983; Printzlau and Andersen, 2004). One of the earliest descriptions is credited to Saint Hilair in the year of 1822 (Altmann, 1992), however who first described the anomaly was the french stomatologist, Pierre Robin, in 1923, presenting glossoptosis as the fall of the base of the tongue over the hypopharynx, resulting in airway obstruction and, consequently, respiratory difficulties (Robin, 1923). In 1934, Robin associated glossoptosis with maxillary atresia and

mandibular hypotrophy and added the cleft palate as an aggravating factor. Therefore, the anomaly was initially called Pierre Robin Syndrome (Robin, 1934). However, after other studies that allowed a better understanding of the pathophysiology and associated conditions, its nomenclature was changed to Pierre Robin Sequence in 1984 by Pasyayan and Lewis (1984), who believed it would be a sequential pathogenesis with micrognathia or mandibular retrognathia as the primary events leading to respiratory obstruction and cleft palate (Pasyayan and Lewis, 1984).

It is a heterogenic pathological entity and it can be found in various situations: 1) isolated, 2) as a component of a syndrome, and 3) associated with other developmental defects that, taken together, do not represent a specific syndrome (Cohen, 1976). According Marques et al (2005), non-syndromic PRS is the most prevalent (53%) (Marques et al, 2005). The most associated syndromes are Fetal Alcohol Syndrome, Velocardiofacial Syndrome and Stickler Syndrome (Shprintzen, 1992, Marques et al, 2001a, Marques et al, 2001b). The Robin sequence is associated with Treacher Collins syndrome in 5% of cases (Richard and Kirschner, 2009, Franklyn Cladis 2009, Frost et al., 2011).

Children with TCS and PRS share mandibular deficiency as a similar clinical finding. However, different areas of the jaw can be affected. Patients with TCS present a short mandibular and a relatively normal mandibular body, whereas patients with PRS present a reduced mandibular body and a relatively normal mandibular ramus (Chung et al, 2012). Nevertheless, ramus/body ratio and condyle morphology have not been compared between TCS and PRS with three-dimensional evaluation. In addition, the degree of mandibular asymmetry in each anomaly is unknown. Considering these aspects, the mandibular comparison of individuals with TCS and PRS through three-dimensional evaluation becomes pertinent.

2 OBJECTIVES

2 OBJECTIVES

This study aimed to compare the mandibular dimensions and morphology in subjects with Treacher Collis Syndrome (TCS) and non-syndromic Pierre Robin Sequence (PRS). The null hypothesis was that TCS and PRS present similar mandibular shape and dimensions.

3 ARTICLES

3 ARTICLES

3.1 ARTICLE 1

Article 1 presented in this Dissertation was written according to American Journal of Orthodontics & Dentofacial Orthopedics instructions and guidelines for article submission.

Manuscript title: Three-dimensional comparison of mandibular morphology between Treacher Collins Syndrome and Pierre Robin Sequence

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ABSTRACT

Objectives: The purpose of this study was to compare the mandibular size and morphology of subjects with Treacher Collins Syndrome (TCS) and non-syndromic Pierre Robin Sequence (PRS).

Methods: Group TCS was composed by 17 subjects (7 male, 10 female) with a mean age of 11.5 years (SD=4.4) from a single center. Group PRS was composed by 17 subjects paired by age and sex with Group TCS. Pre-orthodontic cone-beam computed tomography (CBCT) exams of all individuals were evaluated using Mimics Innovation Suite 17.0 (Materialize, Leuven, Belgium). Eight three-dimensional measurements were performed in segmented 3D images of the mandible. Intragroup comparisons were performed using paired t-tests. Intergroup comparisons were performed using ANOVA and Tukey tests. The significance level considered was 5%.

Results: TCS showed a significant dimensional difference between less and more affected sides for ramus, condyles and mandibular body. The mandibular dimensions in PRS was more symmetrical. Group TCS presented a smaller mandibular effective length and mandibular body length compared to PRS. The condyle width and height and the ramus width were also decreased in TCS. The gonial angle was greater in TCS compared to PRS group.

Conclusion: Treacher Collins Syndrome presented a smaller, vertical and more asymmetrical mandible compared to non-syndromic Pierre Robin Sequence.

Keywords: Pierre Robin Syndrome. Mandibulofacial dysostosis. Mandible. Cone-beam computed tomography.

INTRODUCTION

Severe micrognathia induces both esthetic and functional clinical implications. Treacher Collins Syndrome (TCS) and Pierre Robin Sequence (PRS) show a small and retrognatic mandible[1,2]. In both situations, the micrognathia may cause airway reduction or obstruction[3-5]. Inability to feed, failure to thrive, malnutrition, dehydration, exhaustion, electrolyte imbalance, cor pulmonale, potential of delayed neurocognitive development and death were also related to the small mandible in TCS and PRS[5-8]. Infant interventions include mandibular distraction, endotracheal intubation, continuous positive airway pressure or use of prone position[8-12]. At the end of growth, surgical procedures for mandibular advancement are frequently required both in TCS and PRS[13].

Treacher Collins Syndrome (TCS) was first described in 1900 by Edward Treacher Collins[14]. Its estimated incidence is 1:50,000 births[15,16]. As a result of mutations in the TCOF1 gene[17], STC originates from abnormalities in the development of craniofacial structures derived from the first and second branchial arches[18]. TCS includes a group of head and neck defects with variable expressiveness[18] and the most characteristic find is malar and mandibular hypoplasia, frequently with limited formation of the zygomatic complex[19].

Pierre Robin Sequence (PRS) is a congenital anomaly characterized of a triad of clinical signs: micrognathia, glossoptosis and obstruction of the upper airways, frequently associated with cleft palate[20, 21]. The incidence ranges from 1:8,500 to 1:14,000 in the general population[22,23]. It is a heterogenic pathological entity and it can be found as isolated disease or in association with other syndromes[24]. The most associated syndromes are Fetal Alcohol Syndrome, Velocardiofacial Syndrome and Stickler Syndrome. PRS is associated with Treacher Collins Syndrome in 5% of cases[25-29].

Children with TCS and PRS present the mandibular deficiency as a similar clinical finding. TCS presents a short mandibular and a relatively normal mandibular body, whereas PRS presents a reduced mandibular body and a relatively normal mandibular ramus [30]. Mandibular size and shape have not been compared between TCS and PRS through three-dimensional evaluation. Phenotypic refinement between TCS and PRS is important for the differential diagnosis between these craniofacial anomalies. Additionally, morphological data contribute for surgical planning and

esthetical-functional outcomes. Therefore, the aim of this study was to compare the mandibular size and morphology of subjects with Treacher Collins Syndrome (TCS) and non-syndromic Pierre Robin Sequence (PRS). The hypothesis was that both craniofacial anomalies present similar mandibular size and shape.

METHODS

This retrospective study was approved by the Institutional Research Ethics Committee of the Hospital for Rehabilitation of Craniofacial Anomalies, University of São Paulo (process number 1.938.354). A sample of cone-beam computed tomography (CBCT) of subjects with Treacher Collins Syndrome and non-syndromic Pierre Robin Sequence was selected from the files from a single center. The sample size calculation was based on a standard deviation for mandibular ramus height of 2.0mm[30], a minimum intergroup difference of 2.0mm, an alpha value of 5% and a statistical power of 80%. The sample size for each group was 17 subjects.

The inclusion criteria were the diagnosis of either TCS or PRS confirmed by the team of geneticists; and age varying from 7 to 20 years. The exclusion criteria consisted of history of previous facial surgical intervention, except palate repair; history of previous facial orthopedic treatment; inadequate quality of CBCT, including motion or metal artifacts or excessive artifacts.

Group TCS was composed by 17 subjects (7 male, 10 female) with a mean age of 11.5 years (SD=4.4) (Figure 1). Group PRS was composed by 17 subjects paired by age and sex with Group TCS (mean=11.6; SD=4.2) (Figure 2). CBCT exams from all subjects were analyzed using Mimics Innovation Suite 17.0 (Materialise, Leuven, Belgium). “Thresholding” tool was used in order to achieve differentiation between bone and soft tissue. For bone segmentation, a Hounsfield Units threshold varying from +226 to +17079 HU was used. The mandible of each subject was digitally isolated from the skull. Seven landmarks were assigned on the right and left side of mandible (Figure 3). Eight mandibular dimensions were measured (Figure 4).

Statistical Analysis

The sample normal distribution was tested using Shapiro Wilk test. Intragroup side comparisons were performed using paired t-tests or Wilcoxon tests. For intergroup comparisons, the less and more affected sides of TCS were considered separately. Intergroup comparisons were performed using one-way ANOVA and Tukey test or Kruskal-Wallis tests. The significance level considered was 5%. All the analyses were performed using SPSS IBM (16.0, SPSS, Chicago, I11).

Error Analysis

The study error was conduct remeasuring 9 patients from each group of the sample that were randomly selected in both groups, by two examiners after a 30-day interval. Inter and intra-examiner reproducibility was calculated using intraclass correlation coefficient (ICC) and Bland-Altman plots.

RESULTS

Variables had an excellent intra-examiner agreement, with intraclass correlation coefficients varying from 0.932 to 0.997 (Table I). The variable with the greatest limits of agreement was the right gonial angle for both intra-examiner (-4.00 and 5.04) and inter-examiner assessments (-3.27 and 14.19).

Group TCS showed mandibular asymmetries for 5 out of 8 variables. Significantly decreased condyle height, mandibular ramus width and height, mandibular effective length, mandibular body length and mandibular ramus/body ratio were found at the more affected side compared to the less affected side in TCS subjects (Table II). The asymmetries varied from 1.28mm (mandibular body length) to 6.66 (mandibular effective length).

The comparison between right and left mandibular sides in Group PRS showed no differences for most variables. Only the condyle height (C-E) showed a statistical significant asymmetry in patients with Pierre Robin Sequence (Table III). However, the difference of 1.35mm was not considered clinically relevant.

Intergroup comparisons revealed that both sides of group TCS showed significantly smaller condyle width and height, ramus width, mandibular effective length and mandibular body length compared to group PRS (Table IV). The more affected side of TCS showed a smaller ramus height than Group PRS. The gonial angle was greater in both sides of TCS compared to PRS. Mandibular ramus/body ratio demonstrated no differences between groups.

DISCUSSION

Two-dimensional methods for craniofacial assessment have limited ability to evaluate three-dimensional relationships. Conventional cephalometry has also the disadvantages of structure enlargement, distortion and overlap[31]. Cone beam computed tomography (CBCT) had succeeded in capturing the third dimension[32,33] and measurements are precise and accurate[34-36]. In our study, the most of three-dimensional measurements demonstrated excellent intra and inter-examiner reproducibility. The sharper and more detailed CBCT images compared to two-dimensional radiographs[32,33] in CBCT scan contributed to an adequate reproducibility. Only the gonial angle and the left condyle height measurements presented regular inter-examiner agreement. These measurements included the condylion landmark. Considering the high degree of variability in the morphology of the mandibular condyle[37] and its volumetrically smaller size[37,38] in TCS, the possible explanation for the measurement variability was the deformities observed in mandibular condyle of group TCS. The advantage of three-dimensional measurements of the mandible is the possibility to evaluate sagittal, transversal and vertical changes in patients with craniofacial anomalies. On the other hand, the method is time consuming due the need of segmentation.

Mandibular asymmetry was a relevant finding in subjects with TCS. In accordance with previous reports[38,39], this study also found a wide range of mandibular dysmorphia and asymmetry. The abnormalities included reduced ramus width, shorter ramus length and deformities in head shape and neck length of the condyle. Absence of condyles was also observed in agreement with Marsh et al[38]. In other words, the asymmetry was found in all regions of the mandible, especially in the condyle. In contrast, Sanchez et al.[40] reported that some TCS patients presented a symmetrical

mandibular hypoplasia. Travieso et al.[37] found similar left and right condylar volumes in TCS, even though a condylar deformity ranging from complete agenesis to varying degrees of hypoplasia. The degree of asymmetry is an important consideration for surgical treatment and TMJ reconstruction[37] and should be evaluated individually. The condyle morphological anomalies can also influence the temporomandibular joint, increasing the frequency of TMJ dysfunction and ankylosis in TCS patients[41].

On the other hand, subjects with PRS showed a more symmetrical mandible. Mandibular symmetry in PRS was not extensively studied previously. The major studies of facial morphology in PRS was conducted using two-dimensional methods. A previous study comparing the right and left sides of the mandible in patients with PRS reported a 5.34% difference in volume and 2.8% difference in mandibular length[42]. The present study found significant difference between right and left condyles height, with an average difference of 1.35mm that is not clinically relevant.

Treacher Collins Syndrome and Pierre Robin Sequence revealed different patterns of mandibular hypoplasia. A hypoplasia of mandibular ramus and condyles was observed in TCS compared to PRS. These results are in accordance with previous reports showing significantly smaller mandibular condyle[37] and shorter ramus height in TCS[30]. Mandibular body length was significantly shorter for TCS compared to PRS. These findings are in accordance to previous studies reporting that TCS had a smaller mandibular length compared to non-syndromic individuals[1,38,43]. TCS also presented a more obtuse gonial angle compared to PRS pointing that the former shows a more extreme vertical pattern than the last. The dimensions of mandible are smaller in TCS than PRS and the two conditions differ greatly in shape. Previous studies also showed that subjects with PRS have a horizontal mandibular hypoplasia[43]. Mandibular hypoplasia in both craniofacial anomalies might be consequence of an insufficient migration of cranial-neural crest cells into the first branchial arch during the 4th week[44]. Studies have shown that TCOF1 mutations in TCS do not affect neural crest cell migration but decrease neural crest cells overall[45]. Another difference between TCS and PRS is that Treacher Collins Syndrome appears to have a stable mandibular deformity over the years, while in Pierre Robin sequence facial growth seems to attenuate mandibular deficiencies in a catch-up growth pattern[46,47].

The shape and size of the mandible showed to be an adequate reference for differential diagnosis between TCS and PRS. An extreme mandibular asymmetry is observed in TCS. Hypoplasia of the mandibular condyles was never observed in PRS

while was frequent in TCS. The sample wide age range was a limitation of this study. However, groups were paired by sex and age for adequate comparisons. Future studies should compare facial growth longitudinally in TCS and PRS.

CONCLUSION

Treacher Collins Syndrome presented a smaller, vertical and more asymmetrical mandible compared to non-syndromic Pierre Robin Sequence.

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FIGURES

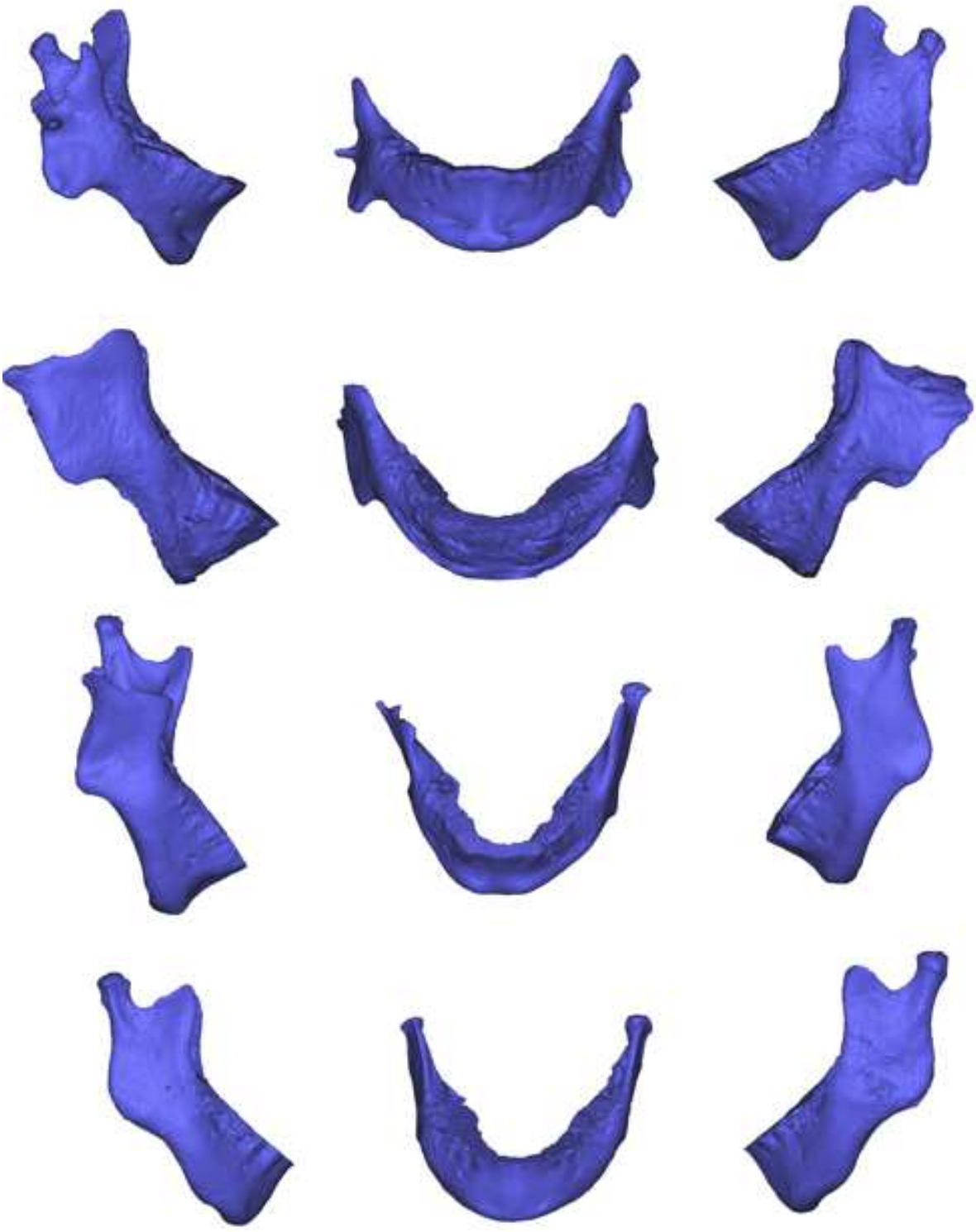

Figure 1: Right, frontal and left side views of the mandible in Group TCS.

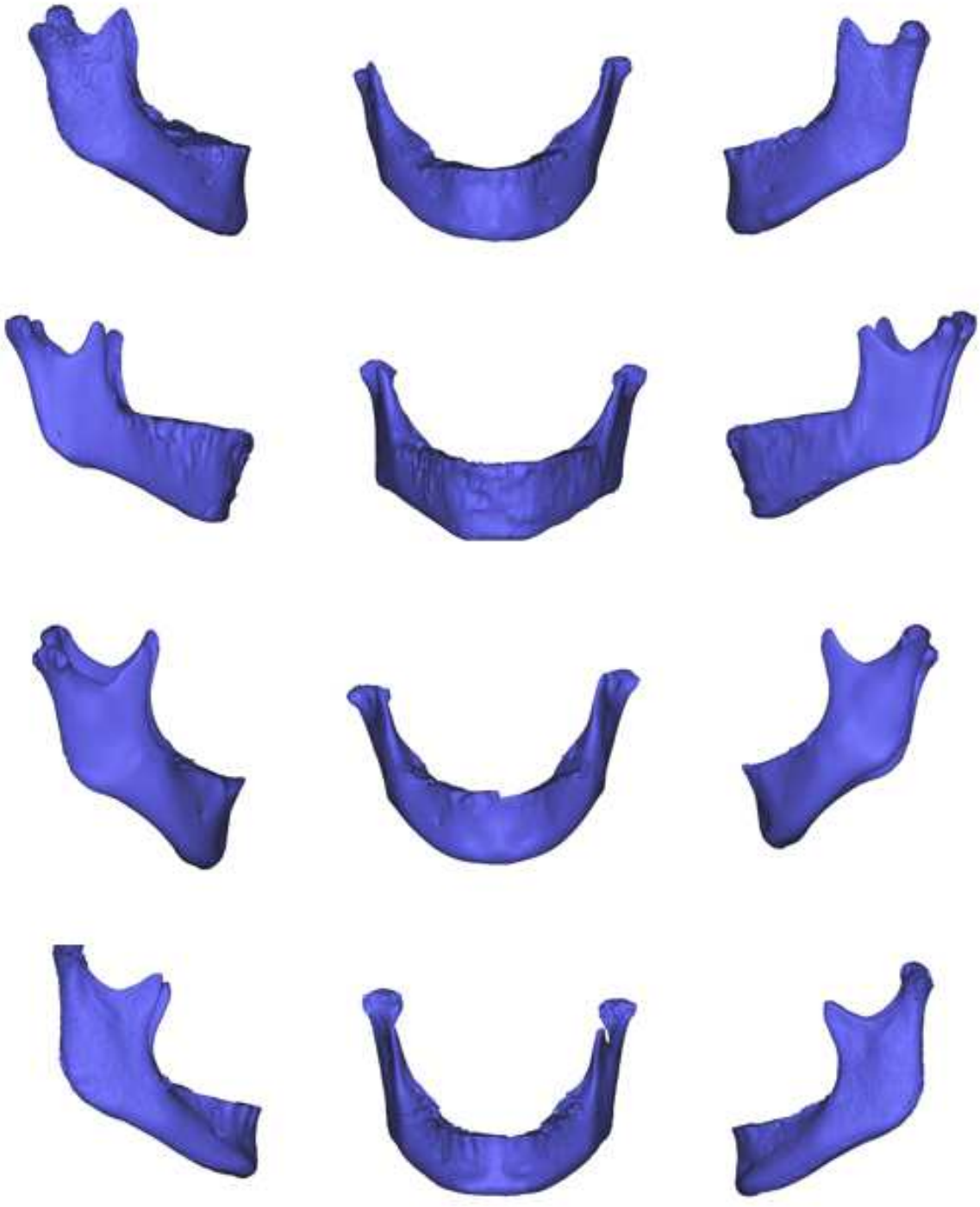

Figure 2: Right, frontal and left side views of the mandible in Group PRS.

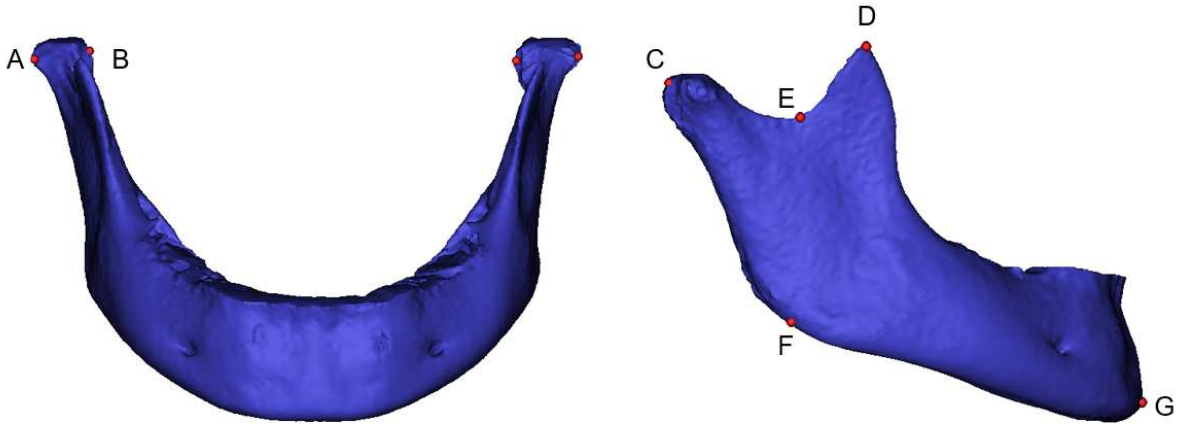

Figure 3 - Cephalometric landmarks. A. Lateral surface of the condyle; B. Medial surface of the condyle; C. Condylion; D. Coronoid; E. Mandibular notch; F. Gonion; G. Pogonion.

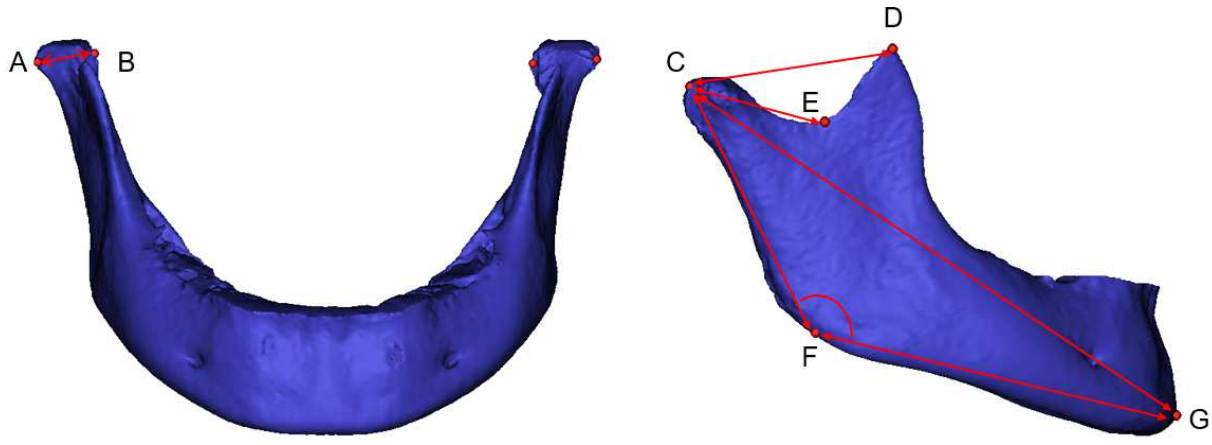

Figure 4 - Cephalometric variables. A-B: condyle width; C-E: condyle height; C-D: ramus width; C-F: ramus height; F-G: mandibular body length; C-G: mandibular effective length; C-F-G: gonial angle; C-F/F-G: ramus/body ratio.

TABLES

Table I. Intra and inter-examiner reability (intraclass correlation coefficients and Bland-Altman).

INTRA-EXAMINER ERROR						INTER-EXAMINER ERROR				
MEASUREMENTS	**Measurement 1**	**Measurement 2**	**ICC**	**Bland-Altman**		**Examiner 1**	**Examiner 2**	**ICC**	**Bland- Altman**	
RIGHT SIDE	**MEAN (SD)**	**MEAN (SD)**		**Lower**	**Upper**	**MEAN (SD)**	**MEAN (SD)**		**Lower**	**Upper**
Condyle width A-B (mm)	12.02 (4.30)	11.90 (4.70)	0.976	-1.79	2.03	12.02 (4.30)	12.32 (3.65)	0.875	-4.16	3.56
Condyle height C-E (mm)	19.19 (4.72)	18.82 (4.82)	0.969	-1.81	2.57	19.19 (4.72)	18.77 (4.46)	0.952	-2.24	3.10
Ramus width C-D (mm)	28.96 (5.44)	28.17 (6.10)	0.932	-3.11	4.68	28.96 (5.44)	29.09 (6.41)	0.902	-5.28	5.02
Ramus height C-F (mm)	41.11 (9.64)	41.17 (9.29)	0.994	-2.03	1.91	41.11 (9.64)	40.73 (9.32)	0.955	-5.15	5.93
Mandibular body length F-G (mm)	69.48 (7.72)	69.22 (7.78)	0.995	-1.21	1.74	69.48 (7.72)	68.26 (6.87)	0.955	-2.32	4.78
Mandibular effective length C-G (mm)	100.43 (12.6)	99.98 (12.38)	0.996	-1.68	2.58	100.43 (12.60)	96.74 (10.28)	0.912	-2.57	9.95
Gonial Angle C-F-G (º)	129.52 (7.13)	129.00 (7.04)	0.944	-4.00	5.04	129.52 (7.13)	124.06 (6.96)	0.607	-3.27	14.19
Ramus/body ratio C-F/F-G	0.59 (0.10)	0.59 (0.10)	0.985	-0.04	0.03	0.59 (0.10)	0.59 (0.12)	0.894	-0.10	0.09

INTRA-EXAMINER ERROR						INTER-EXAMINER ERROR				
MEASUREMENTS	**Measurement 1**	**Measurement 2**	**ICC**	**Bland-Altman**		**Examiner 1**	**Examiner 2**	**ICC**	**Bland- Altman**	
LEFT SIDE	**MEAN (SD)**	**MEAN (SD)**		Lower	Upper	MEAN (SD)	MEAN (SD)		Lower	Upper
Condyle width A-B (mm)	12.34 (3.96)	12.30 (3.87)	0.956	-2.23	2.32	12.34 (3.96)	12.19 (3.85)	0.979	-1.38	1.69
Condyle height C-E (mm)	18.03 (5.42)	17.98 (5.68)	0.961	-3.01	3.10	18.03 (5.42)	18.94 (3.71)	0.742	-7.26	5.43
Ramus width C-D (mm)	28.90 (5.32)	28.29 (6.09)	0.932	-3.35	4.56	28.9 (5.32)	29.40 (6.25)	0.947	-4.07	3.06
Ramus height C-F (mm)	43.98 (7.52)	43.69 (7.19)	0.977	-2.78	3.36	43.98 (7.52)	41.74 (7.76)	0.913	-2.32	6.79
Mandibular body length F-G (mm)	68.25 (9.80)	68.10 (9.55)	0.997	-1.25	1.56	68.25 (9.80)	67.23 (7.58)	0.940	-4.56	6.60
Mandibular effective length C-G (mm)	101.13 (12.45)	100.55 (12.33)	0.995	-1.55	2.70	101.13 (12.45)	96.04 (10.93)	0.887	0.01	10.15
Gonial Angle C-F-G (º)	128.11 (7.04)	127.53 (6.25)	0.951	-3.34	4.50	128.11 (7.04)	122.41 (5.99)	0.634	-0.33	11.75
Ramus/body ratio C-F/F-G	0.65 (0.09)	0.64 (0.08)	0.941	-0.05	0.06	0.65 (0.09)	0.62 (0.09)	0.755	-0.08	0.14

Table II. Comparison between the more and less affected sides in group Treacher Collins Syndrome (Paired t-test/Wilcoxon test).

TCS GROUP						
MEASUREMENTS	**Less affected side**		**More affected side**		**95% IC**	**p**
	Mean	**S.D.**	**Mean**	**S.D.**		
Mandibular condyles						
Condyle width A-B (mm)	9.21	2.69	9.50	3.99	-2.04; 1.46	0.727
Condyle height C-E (mm)	16.27	4.62	13.97	3.15	0.29; 4.32	0.02$^{\beta}$*
Mandibular ramus						
Ramus width C-D (mm)	26.68	2.87	24.43	3.30	0.59; 3.92	0.0112*
Ramus height C-F (mm)	39.76	5.84	33.37	8.62	2.41; 10.36	0.00362*
Mandibular body						
Mandibular body length F-G (mm)	63.29	7.42	62.01	6.69	-1.96; 4.53	0.027$^{\beta}$*
Mandible						
Mandibular effective length C-G (mm)	94.36	10.17	87.70	11.94	3.19; 10.12	<0.001*
Gonial angle C-F-G (º)	131.95	7.02	131.36	8.30	-3.71; 4.89	0.775
Ramus/body ratio C-F/F-G	0.63	0.079	0.54	0.12	0.016; 0.17	0.071

(*) Statistically difference.

(β) nonparametric analysis.

Table III. Comparison between right and left sides in group Pierre Robin Sequence (Paired t-test/Wilcoxon test).

GROUP PRS						
MEASUREMENTS	**RIGHT SIDE**		**LEFT SIDE**		**95% IC**	**p**
	Mean	**S.D.**	**Mean**	**S.D.**		
Mandibular condyles						
Condyle width A-B (mm)	14.89	2.65	14.78	2.42	-0.54; 0.77	0.644
Condyle height C-E (mm)	22.06	3.07	20.71	3.27	0.48; 2.22	0.00471*
Mandibular ramus						
Ramus width C-D (mm)	31.06	5.50	30.48	5.86	-0.38; 1.53	0.217
Ramus height C-F (mm)	44.77	6.77	44.71	7.07	-1.47; 1.60	0.644
Mandibular body						
Mandibular body length F-G (mm)	73.06	5.85	72.83	5.87	-0.74; 1.21	0.617
Mandible						
Mandibular effective length C-G (mm)	105.26	9.32	104.83	8.70	-0.50; 1.35	0.345
Gonial Angle C-F-G (º)	125.26	5.22	124.94	5.93	-1.38; 2.02	0.695
Ramus/body ratio C-F/F-G	0.61	0.06	0.61	0.08	-0.03; 0.02	0.818

(*) Statistically difference.

Table IV. Intergroup comparisons (One-way Analysis of Variance and Tukey/Kruskal-Wallis test).

MEASUREMENTS	GROUP TCS Less affected side		GROUP TCS More affected side		GROUP PRS		p
	Mean	S.D.	Mean	S.D.	Mean	S.D.	
Mandibular condyles							
Condyle width A-B (mm)	9.21^{B}	2.69	9.50^{B}	3.99	14.84^{A}	2.45	<0.001*
Condyle height C-E (mm)	16.27^{B}	4.62	13.97^{B}	3.15	21.39^{A}	3.06	<0.001*
Mandibular ramus							
Ramus width C-D (mm)	26.68^{B}	2.87	24.43^{B}	3.30	30.77^{A}	5.61	$<0.001^{\beta *}$
Ramus height C-F (mm)	39.76^{A}	5.84	33.37^{B}	8.62	44.74^{A}	6.76	<0.001*
Mandibular body							
Mandibular body length F-G (mm)	63.29^{B}	7.42	62.01^{B}	6.69	72.94^{A}	5.79	<0.001*
Mandible							
Mandibular effective length C-G (mm)	94.36^{B}	10.17	87.70^{B}	11.94	105.05^{A}	8.970	<0.001*
Gonial Angle C-F-G (º)	131.95^{B}	7.02	131.36^{B}	8.30	125.10^{A}	5.34	0.011*
Ramus/body ratio C-F/F-G	0.63^{A}	0.08	0.54^{B}	0.12	0.61^{AB}	0.067	0.011*

(*) Statistically difference.

(β) nonparametric analysis.

3.2 ARTICLE 2

Article 2 presented in this Dissertation was written according to Clinical Oral Investigations instructions and guidelines for article submission.

Manuscript title: Comparison between Treacher Collins Syndrome and Pierre Robin Sequence: a preliminary cephalometric study

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ABSTRACT

Objective: The aim of this study was to compare the dentoskeletal pattern of Treacher Collins Syndrome and non-syndromic Pierre Robin Sequence.

Methods: Group TCS was composed by 9 subjects (4 male, 5 female) with a mean age of 12.9 years (SD=4.8). Group PRS was composed by 9 subjects paired by age and sex with Group TCS. CBCT derived cephalometric images taken before the orthodontic treatment were analyzed using Dolphin Imaging (Dolphin Imaging 11.0 & Management Solutions, California, United States). Variables evaluating the cranial base, the maxillary and mandibular skeletal components, maxillomandibular relationship, the vertical components and the dentoalveolar region were measured. Intergroup comparisons were performed using t tests. The significance level considered was 5%.

Results: Intergroup differences in the mandible size and growth pattern were observed. Group TCS showed a smaller mandibular length (Co-Go, Co-Gn) and a higher palatal plane (SN-Palatal Plane) and mandibular plane angles (SN-Go.Gn) compared to group PRS. No differences between TCS and PRS were observed for the sagittal position of the maxilla, maxillomandibular relationship and dental components.

Conclusion: Treacher Collins Syndrome presented a decreased mandible and a more severe vertical growth pattern compared to Pierre Robin Sequence.

Clinical Relevance: Cephalometric differences are important in order to clarify differential diagnosis and support clinical and surgical interventions.

Keywords: Cephalometry. Analysis. Pierre Robin Syndrome. Mandibulofacial dysostosis.

INTRODUCTION

Treacher Collins Syndrome (TCS) is an autosomal dominant syndrome [12,34] and includes a group of defects closely related to the head and neck, arising from abnormalities in the development of craniofacial structures derived from the first and second branchial arches [25]. These abnormalities affect mandible and bring convex profile, lack of chin projection, redundant presence of submental soft tissues and Angle Class II malocclusion as a result of jaw deformity [36,38] and can contribute to glossoptosis and airway obstruction [36]. TCS midface length is reduced compared with controls without anomalies [7]. Decreased anterior, posterior and total cranial base lengths and reduced cranial base angle is observed in TCS [16]. Maxillary and mandibular length are shorter than subjects without syndromes [5]. Both maxilla and mandible are retropositioned in relation to the cranial base [16]. Gonial angle is increased [16].

Pierre Robin Sequence (PRS) is a congenital craniofacial anomaly composed by the triad of mandibular micrognathia, glossoptosis and upper airway obstruction, frequently associated with cleft palate [10,32]. The incidence is 1:8500 to 1:14,000 [4,30]. Previous studies showed a persistent bimaxillary hypoplasia, Angle Class II malocclusion [8, 9, 13, 24] and facial profile more convex in individuals with PRS, due to the lack of anterior projection mandible [27]. When compared to control groups without anomalies, PRS shows smaller cranial base length, shorter maxillary and mandibular length, bimaxillary retrognathism, increased palatal and mandibular plane inclinations and more open mandibular flexure [37]. In patients who presented cleft palate, the short and retruded maxilla, due to surgical palate repair and/or from inherent growth disturbance from the clefting process, can normalize maxillomandibular relationship [2,33]. Mandibular body length and height, ramus length and width, anterior basal thickness and chin thickness are smaller too [37].

The recognition of phenotypic differences between TCS and PRS is important for an adequate differential diagnosis and treatment planning. No previous studies have compared TCS and PRS by means of cephalometric evaluations. Therefore, the aim of this study was to compare the dentoskeletal pattern of Treacher Collins Syndrome and non-syndromic Pierre Robin Sequence. The hypothesis was that both type of craniofacial anomalies have similar dentoskeletal features.

METHODS

This retrospective study was approved by the Institutional Research Ethics Committee of Hospital for Rehabilitation of Craniofacial Anomalies – University of São Paulo (process number 1.938.354). A sample of cone-beam computed tomography (CBCT) exams of subjects with Treacher Collins Syndrome and non-syndromic Pierre Robin Sequence was collected from the files of a single center. The sample size calculation was based on a standard deviation for SNB of 5.10º [16], a minimum intergroup difference of 5º, an alpha value of 5% and a statistical power of 80%. The sample size for each group was 17 subjects.

The inclusion criteria were: diagnosis of TCS or PRS confirmed by the team of geneticists; age varying from 7 to 20 years. The exclusion criteria consisted of history of previous facial surgical intervention, except palate repair; history of previous facial orthopedic treatment; associated syndromes.

A group composed by 17 subjects (7 male, 10 female) with Treacher Collins Syndrome and mean age of 11.5 years (SD=4.4) was collected. From this group, 6 CBCT were excluded due to cranial base image absence and 2 due to lack of occlusion during the exam. The final sample comprised 9 subjects (4 male, 5 female) with a mean age of 12.9 years (SD=4.8) (Figure 1). Group PRS was composed by 9 subjects (4 male, 5 female) with non-syndromic Pierre Robin Sequence paired by sex and age (mean=13.1; SD=5.4) with Group TCS (Figure 2).

Using the software Dolphin Imaging *(Dolphin Imaging 11.0 & Management Solutions, Califórnia, Estados Unidos),* CBCT exams from all subjects were reconstructed using tool *Building X-ray* to generate lateral cephalometric radiographs. Cephalometric analysis was performed at the same software. Initially, the head position was standardized with the bi-orbital and Frankfurt planes parallel to the horizontal plane in the frontal and lateral views, respectively. The midline of the cranial base was positioned parallel to the vertical plane in the head superior view. Fourteen cephalometric variables were measured on the reformatted lateral cephalometric image (Table 1).

Statistical Analysis

Sample normal distribution was verified using Shapiro Wilk test. Intergroup comparisons were performed using independent t tests or Mann-Whitney test. The significance level considered was 5%. All the analyses were performed using SPSS IBM (16.0, SPSS, Chicago, I11)

Error Analysis

Five patients from each group was randomly selected and remeasured by the same examiner after a 30-day interval. Random and systematic errors were assessed using Dahlberg and t tests (< 0.05).

RESULTS

The random errors ranged from 0.26 to 3.84 (SN and U1-Palatal Plane, respectively). Systematic errors were found for SNA, SNB, SN-Palatal Plane, SN.Go.Gn and Na-Me measurements (Table II).

Table III show intergroup comparisons. No difference between TCS and PRS was found for the length and sagittal position of the maxilla. The ramus height (Co-Go) and the mandibular effective length (Co-Gn) were significantly smaller in Group TCS compared to Group PRS. No intergroup differences were noted to maxillomandibular relationship. TCS subjects displayed an increased palatal plane (SN-Palatal Plane) and mandibular plane angles (SN-Go.Gn) than Group PRS. Cranial base lengths and the inclination of maxillary and mandibular incisors were similar in both groups.

DISCUSSION

Previous cephalometric studies assessed subjects with Treacher Collins Syndrome or Pierre Robin Sequence in comparison with patients without craniofacial anomalies [5, 16, 33, 37]. No previous study compared cephalometric features of TCS and PRS. CBCT-derived cephalometric images were reliable showing precision and

accuracy for cephalometric measurements [18, 19, 23]. Measurements from lateral cephalograms from CBCT were comparable with measurements obtained directly from dry skulls and from conventional cephalograms [18, 19, 23]. Previous studies used reformatted CBCT images for evaluating facial morphological features [11, 17, 39, 40]. In our study, five out of 14 variables showed a systematic type of error, all including the cranial base. Considering that CBCT-derived images showed greater precision in the landmark definition [23], the possible explanation for the measurement variability was the deformities observed in the cranial base of group TCS. In TCS, the sella is anomalously positioned and the triangle Ba-S-N is extended vertically [14]. The sphenoethimoidal region is positioned posteriorly, closer than normal to the sella, and the cranial base is significantly misshapen [14]. Additionally, Frankfurt plane could not be used as a reference in this study due to severe deformities observed in the orbital cavity [26, 29].

No cranial base differences were observed between TCS and PRS. These results are in accordance with previous studies that found a retruded cranial base, a decreased cranial base length and a closed cranial base angle both in TCS and PRS [16, 21, 35, 37]. In TCS, kyphosis of cranial base related to a deficient growth at the spheno-occipital synchondrosis was reported [3, 7, 14, 15]. In PRS, a shorter cranial base length was found previously [37].

The sagittal position and the length of maxilla were similar between groups. Both TCS and PRS showed a retruded maxilla (Table III). These results are in conformity with previous studies showing a midface deficiency in both TCS and PRS subjects [5, 16, 17, 21, 35, 37]. According to Shen [35], a possible reason for the maxillary hypoplasia is the surgical repair of the cleft palate during infancy or an intrinsic growth deficiency. The literature reported a small mandible in TCS and PRS [16, 22 36, 37]. Despite both craniofacial anomalies are characterized by a micrognathia, this study found significant differences between groups. Group TCS showed a smaller mandible length compared to PRS. The study by Lu et al. [22] reported that the mandible hypoplasia in TCS occurs in both vertical and horizontal dimensions, whereas PRS display a horizontally deficient mandible compared to subjects with isolated cleft palate. Although the differences found in mandibular length, the anteroposterior position of the mandible was similar between groups (Table III).

The literature show that both TCS and PRS present a hyperdivergent growth pattern [11,27,33, 37]. In our study, a more severe vertical growth pattern was found in

TCS in comparison to PRS. According to Rogers [33], the extreme vertical pattern observed in Treacher Collins syndrome with a very obtuse gonial angle contributes to attenuate the decreased anteroposterior expression of the mandible. These features explain the anterior open bite (Figure 1), incompetent lips, and impaired chewing and speech frequently observed in TCS [5,36].

All cephalometric variables showed a wide range of standard deviation due to the morphological variation in both TCS and PRS. Sample age range could have contributed to the variation. However, previous cephalometric studies also showed the same high standard deviation, especially for TCS craniofacial pattern [1, 16]. The limitation of this study was the reduced sample size that can hide real differences between groups. For this reason, our study can be considered preliminary and the results should be analyzed with caution. On the other hand, previous studies with TCS and PRS had usually small samples [1, 26,31, 35, 39] considering both are rare craniofacial anomalies. Future studies with a larger sample should be performed to confirm these results.

CONCLUSION

Treacher Collins Syndrome presented a decreased mandible and a more severe vertical growth pattern compared to non-syndromic Pierre Robin Sequence.

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FIGURES

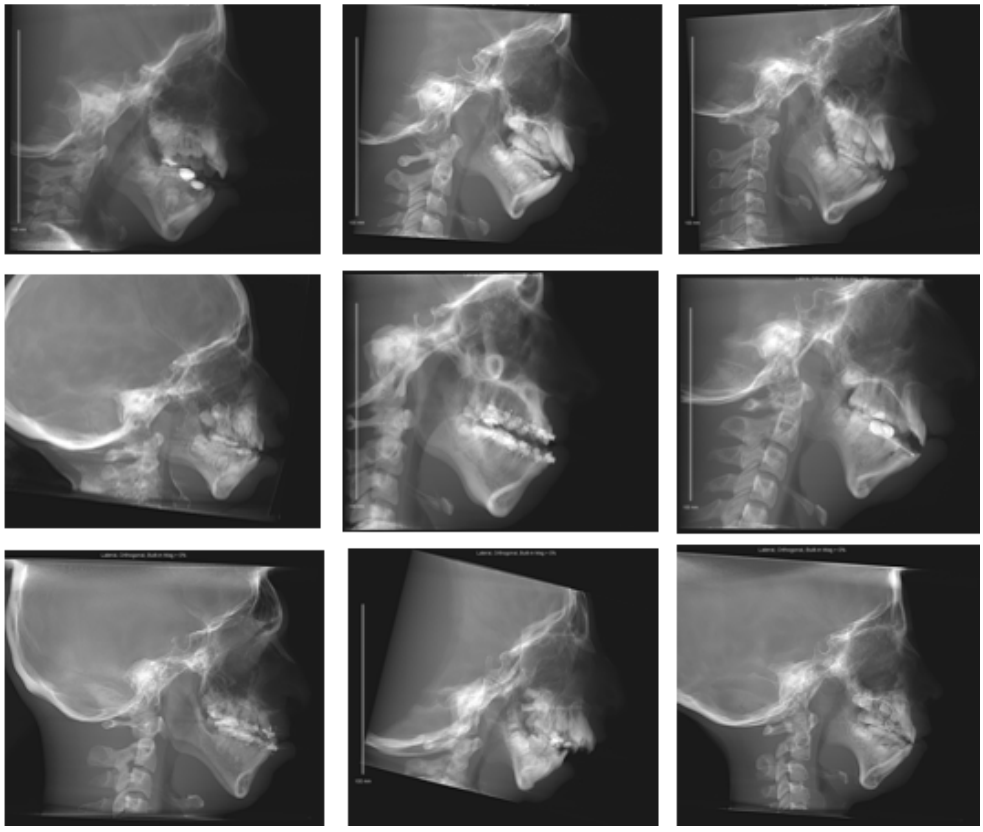

Figure 1. Reconstructed lateral cephalographs from CBCT of Group TCS.

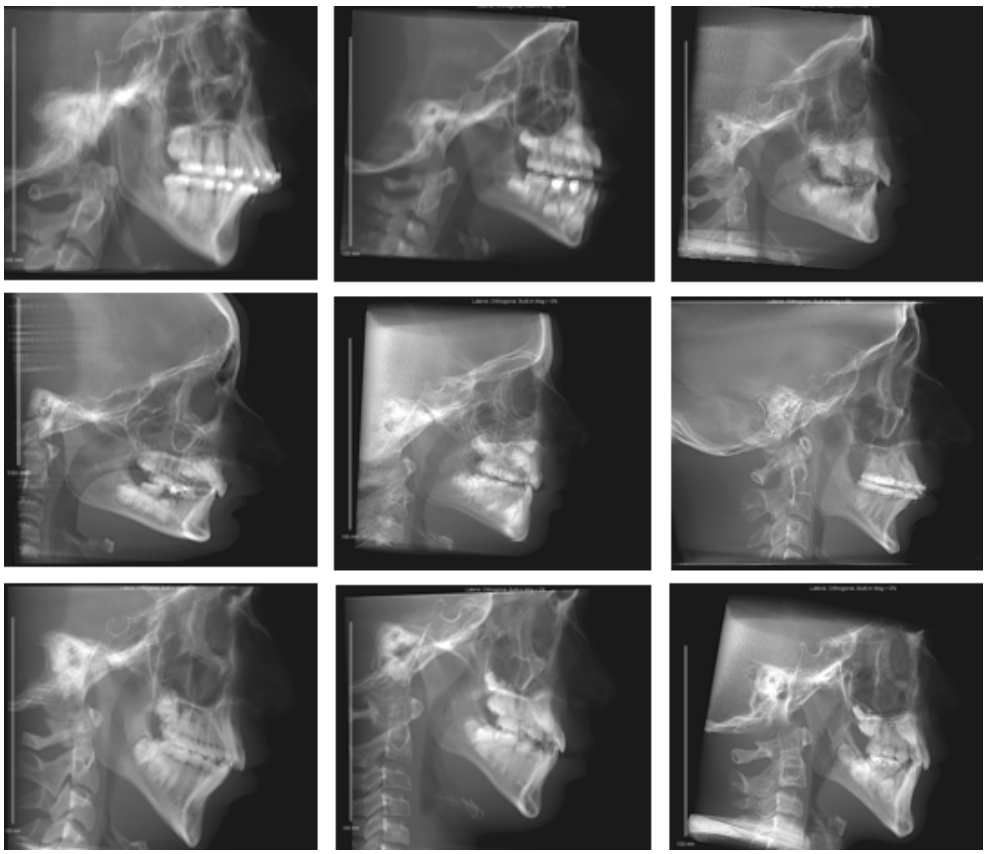

Figure 2. Reconstructed lateral cephalographs from CBCT of Group PRS.

Table I. Cephalometric landmarks and variables.

LANDMARKS	A point (A)
	B point (B)
	Basion (Ba)
	Anterior nasal spine (ANS)
	Condylion (Co)
	Gnathion (Gn)
	Gonion (Go)
	Lower incisor (L1)
	Menton (Me)
	Nasion (N)
	Orbitale (Or)
	Pogonion (Pg)
	Porion (Po)
	Posterior nasal spine (PNS)
	Sella (S)
	Upper incisor (U1)
CEPHALOMETRIC VARIABLES	
Cranial base components	S-N (mm)
	SN-Basion (º)
Maxillary skeletal components	SNA (º)
	ANS-PNS (mm)
Mandibular skeletal components	SNB (º)
	Co-Gn (mm)
	Co-Go (mm)
Maxillomandibular relationship	ANB (°)
Vertical components	SN-Palatal Plane (º)
	SN-Go.Gn (º)
	ANS-Me (mm)
	Na-Me (mm)
Dentoalveolar components	U1-Palatal Plane (º)
	IMPA (º)

Table II. Random and systematic errors (Dahlberg and t tests).

MEASUREMENTS	Measurement 1	Measurement 2	t test p	Dahlberg
	Mean (SD)	Mean (SD)		
Cranial base components				
S-N (mm)	59.25 (5.42)	59.29 (5.1)	0.747	0.26
SN-Basion (º)	123.97 (7.58)	124.43 (8.11)	0.399	1.15
Maxillary skeletal components				
SNA (º)	79.34 (4.07)	78.25 (3.99)	0.034	1.21
ANS-PNS (mm)	48.91 (4.86)	46.6 (4.09)	0.058	2.78
Mandibular skeletal components				
SNB (º)	71.46 (6.27)	70.67 (6.59)	0.021	0.82
Co-Gn (mm)	84.38 (12.55)	84.13 (11.24)	0.833	2.45
Co-Go (mm)	41.34 (7.22)	38.35 (4.79)	0.077	3.82
Maxillomandibular relationship				
ANB (º)	7.86 (4.13)	7.58 (4.01)	0.394	0.69
Vertical components				
SN-Palatal Plane (º)	8.73 (9.88)	11.55 (9.05)	0.015	2.83
SN-Go.Gn (º)	44.91 (9.25)	48.71 (9.12)	0.001	3.10
ANS-Me (mm)	63.93 (8.96)	63.94 (8.83)	0.981	0.85
Na-Me (mm)	104.26 (10.42)	105.05 (10.46)	0.020	0.81
Dentoalveolar components				
U1-Palatal Plane (º)	109.81 (7.44)	112.08 (5.11)	0.200	3.84
IMPA (º)	83.59 (6.51)	83.26 (7.35)	0.803	2.74

Table III. Intergroup comparisons for cephalometric variables (Independent t-tests/ Mann-Whitney test).

MEASUREMENTS	GROUP TCS		GROUP PRS		95%IC	p
	MEAN	SD	MEAN	SD		
Cranial base components						
S-N (mm)	57.02	4.26	61.42	5.01	-9.04; 0.24	0.062
SN-Basion (º)	120.20	8.62	127.88	7.78	-15.88; 0.52	0.065
Maxillary skeletal components						
SNA (º)	79.12	4.26	78.83	3.18	-3.46; 4.04	0.873
ANS-PNS (mm)	49.71	2.98	48.36	5.62	-3.14; 5.85	0.532
Mandibular skeletal components						
SNB (º)	70.48	6.96	73.62	4.03	-8.82; 2.53	0.258
Co-Gn (mm)	77.52	9.98	93.67	7.96	-25.16; -7.12	0.002*
Co-Go (mm)	36.76	8.05	47.86	6.43	-18.37; -3.82	0.005*
Maxillomandibular relationship						
ANB (º)	8.63	4.23	5.20	3.07	-0.25; 7.12	0.066
Vertical components						
SN-Palatal Plane (º)	13.13	7.22	4.12	7.05	1.88; 16.14	0.016*
SN-Go.Gn (º)	50.32	7.17	38.18	7.45	4.83; 19.45	0.003*
ANS-Me (mm)	65.78	4.85	62.13	11.05	-4.88; 12.17	0.536
Na-Me (mm)	106.01	6.69	106.31	14.17	-11.37; 10.77	0.895
Dentoalveolar components						
U1-Palatal Plane (º)	112.41	7.76	107.63	6.69	-2.46; 12.01	0.181
IMPA (º)	86.18	4.94	82.10	9.78	-3.66; 11.82	0.281

(*) Statistically difference.

4 FINAL CONSIDERATIONS

4 FINAL CONSIDERATIONS

1. At the ages from 7 to 20 years, the mandible is smaller in Treacher Collins Syndrome compared to Pierre Robin Sequence. Mandibular body, ramus and condyles are all smaller in the former.

2. The degree of mandibular asymmetry is higher in Treacher Collins Syndrome;

3. Treacher Collins Syndrome presents a more severe vertical growth pattern;

4. Mandibular ramus/body ratio were similar in Pierre Robin Sequence and Treacher Collins Syndrome.

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ANNEXES

ANEXO 1 – Declaração de uso exclusivo de artigo a ser publicado em periódico de língua inglesa

DECLARATION OF EXCLUSIVE USE OF THE ARTICLE IN DISSERTATION/THESIS

We hereby declare that we are aware of the articles (Three-dimensional comparison of mandibular morphology between Treacher Collins Syndrome and Pierre Robin Sequence / Comparison between Treacher Collins Syndrome and Pierre Robin Sequence: a preliminary cephalometric study) will be included in Dissertation of the student RENATA MAYUMI KATO were not used and may not be used in other works of Graduate Programs at the Bauru School of Dentistry, University of São Paulo.

Bauru, de 20 .

_____	_____
Author	Signature
_____	_____
Author	Signature
_____	_____
Author	Signature
_____	_____
Author	Signature

ANEXO 2 - Termo de Permissão para uso de registros para fins científicos (fotografias, radiografias, tomografias e respectivos laudos odontológicos e médicos, vídeo imagens, amostra de voz/fala, registros clínicos, imagens de órgãos e espécimes para pesquisa, fins didáticos e publicação de artigos científicos)

Eu, _____, brasileir__, residente no endereço _____, na cidade de _____ - ___, RG nº_____, CPF nº _____ permito a captação, o uso e publicação de meus registros (**fotográficos, radiografias, tomografias e respectivos laudos odontológicos e médicos, vídeo imagens, amostra de voz/fala, registros clínicos, imagens de órgãos e espécimes) para pesquisa, fins didáticos e publicação de artigos científicos** especificamente relacionados ao projeto de pesquisa/ comunicação científica intitulado(a) "Caracterização maxilomandibular de indivíduos com Sequência de Robin isolada: avaliação tridimensional", sob responsabilidade das pesquisadoras Profª. Drª. Daniela Gamba Garib e Drª. Roseli Maria Zechi Ceide. Estou ciente de que não serei remunerado(a) pelo uso desses registros.

Entendo que poderei ser reconhecido(a) por terceiros e que as minhas documentações clínicas poderão ser publicadas exclusivamente para fins científicos, resguardando o sigilo das minhas informações pessoais.

Estou ciente de que, caso não aceite assinar este termo, receberei dos profissionais citados acima a mesma qualidade de atendimento e tratamento.

_____, _____ de _____ de 20___.

Assinatura: _____

Nome do Paciente:_____

Em caso de paciente menor de 18 anos:

Eu, _____, brasileir__, residente no endereço _____, na cidade de _____ - ___, RG nº_____, CPF nº _____, responsável legal pelo paciente_____, permito a captação, o uso e publicação de seus registros para fins científicos, de acordo com as condições expressas acima, que foram explicadas de forma clara.

Assinatura do responsável pelo paciente:_____

Nome do responsável pelo paciente:_____

Assinatura das Pesquisadoras Responsáveis:_____

_____

Term_Perm_Uso_Registro_V2.1 aprovado pelo CEP em 26/07/2016

USP - HOSPITAL DE REABILITAÇÃO DE ANOMALIAS CRANIOFACIAIS

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Caracterização maxilomandibular de indivíduos com Sequência de Robin isolada: avaliação tridimensional

Pesquisador: DANIELA GAMBA GARIB CARREIRA

Área Temática:

Versão: 3

CAAE: 62555716.8.0000.5441

Instituição Proponente: Hospital de Reabilitação de Anomalias Craniofaciais da USP

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 1.938.354

Apresentação do Projeto:

Terceira apresentação do Projeto de Pesquisa Guarda-chuva dos Pesquisadores responsáveis: Profª Drª Daniela Gamba Garib e Dra.Roseli Maria Zechi Ceide; com os participantes: Dr. Adriano Porto Peixoto, Dr.Cristiano Tonello, Dra.Priscila Padilha Moura e Renata Mayumi Kato. O propósito deste trabalho será realizar a caracterização das estruturas maxilomandibulares de indivíduos com Sequência de Robin isolada (SR) e compará-las com indivíduos com Disostose mandibulofacial (DMF). A amostra da pesquisa será composta por dois grupos de estudo: grupo SR, composto por 30 indivíduos com Sequência de Robin isolada de 7 a 20 anos de idade e grupo DMF, composto por 30 pacientes com disostose mandibulofacial de 7 a 20 anos. Serão utilizados exames de tomografia computadorizada de feixe cônico (TCFC) do arquivo do HRAC-USP para ambos os grupos. As TCFC do grupo SR serão complementadas ao longo do período do estudo em pacientes que serão submetidos a tratamento ortodôntico/cirúrgico ou intervenções otorrinolaringológicas que se beneficiem do exame tridimensional.

Objetivo da Pesquisa:

Este estudo objetiva descrever as características maxilomandibulares de indivíduos com Sequência de Robin isolada e compará-las com as características de indivíduos com disostose. A hipótese

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nula é que não há diferenças cefalométricas e morfológicas entre os grupos analisados.

Avaliação dos Riscos e Benefícios:

Segundo os autores:

Os Riscos do projeto: Os riscos contidos no presente estudo são inerentes aos projetos deste tipo e estão restritos à utilização de radiação para obtenção das imagens que virem a serem necessárias, já que a amostra do estudo será composta, em sua maioria, por tomografias já realizadas dos arquivos do HRAC-USP. Os benefícios gerados por TCFC adicionais, corretamente indicadas, serão maiores que riscos eventuais. Além disso, a pesquisa será realizada respeitando as normas preconizadas pela Comissão Nacional de Ética em Pesquisas em Seres Humanos, obedecendo às normas de biossegurança e mantendo o sigilo ético.

Benefícios: Os dados obtidos neste estudo poderão auxiliar na caracterização morfológica das estruturas faciais dos indivíduos com Sequência de Robin, comparados com indivíduos com DMF, possibilitando melhor ferramenta de diagnóstico. O conhecimento proporcionado pela análise das imagens da região facial e mandibular poderá ainda, auxiliar no estabelecimento do planejamento e execução de condutas terapêuticas.

Comentários e Considerações sobre a Pesquisa:

O estudo será na com imagens de TCFC de arquivo. Os autores observam que serão realizados
novos exames caso haja necessidade e justificativa clínica deles. As imagens de TCFC serão analisadas de três formas distintas: 1. Avaliação cefalométrica bidimensional utilizando a reconstrução das telerradiografias laterais; 2. Análise cefalométrica tridimensional após segmentação das imagens; 3. Análise morfológica das imagens tridimensionais segmentadas. Os softwares utilizados serão o Dolphin (Dolphin Imaging 11.0 & Management
Solutions, Califórnia, Estados Unidos) e Mimics Innovation Suite (Materialize, Leuven, Bélgica). Análise dos dados: Os dados coletados serão transferidos para o software SPSS (versão 16.0, SPSS, Chicago, I11).Será utilizado o teste Shapiro-Wilk para verificação da distribuição normal dos dados. A comparação intergrupo para as mensurações cefalométricas bi e tridimensionais será realizada pelo teste t independente. O nível de significância considerado será 5%.

O projeto havia ficado com pendência devido à inadequação listada abaixo:

1. Retirar do projeto os termos: TCLE e termo de assentimento. Resposta: TCLE e termo de assentimento foram removidos, mas ainda consta no capítulo da metodologia, na plataforma

Brasil, que o TCLE será obtido "(novos casos serão coletados somente após a assinatura do termo de consentimento livre e esclarecido)". PENDÊNCIA PARCIALMENTE ATENDIDA.
Os autores atenderam à solicitação com remoção da frase "novos casos serão coletados somente após a assinatura do termo de consentimento livre e esclarecido" do capitulo de metodologia na Plataforma Brasil. PENDÊNCIA TOTALMENTE ATENDIDA.

Considerações sobre os Termos de apresentação obrigatória:
Carta de encaminhamento dos pesquisadores aos CEP;
Formulário HRAC;
Folha de Rosto Plataforma Brasil;
Termo de Compromisso de Manuseio de Informações;
Termo de Permissão para uso de Registros para Fins Científicos;
Termo de Compromisso de Tornar Públicos os Resultados da Pesquisa e Destinação de Materiais ou Dados Coletados;
Termo de Compromisso do Pesquisador Responsável.

Recomendações:
Não se aplica.

Conclusões ou Pendências e Lista de Inadequações:
Como a pendência foi resolvida sugiro a aprovação do projeto.

Considerações Finais a critério do CEP:
O pesquisador deve atentar que o projeto de pesquisa aprovado por este CEP refere-se ao protocolo submetido para avaliação. Portanto, conforme a Resolução CNS 466/12, o pesquisador é responsável por "desenvolver o projeto conforme delineado", se caso houver alterações nesse projeto, este CEP deverá ser comunicado em emenda via Plataforma Brasil, para nova avaliação.
Cabe ao pesquisador notificar via Plataforma Brasil o relatório final para avaliação. Os Termos de Consentimento Livre e Esclarecidos e/ou outros Termos obrigatórios assinados pelos participantes da pesquisa deverão ser entregues ao CEP. Os relatórios semestrais devem ser notificados quando solicitados no parecer.

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

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Continuação do Parecer: 1.938.354

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_827392.pdf	12/02/2017 19:08:14		Aceito
Outros	oficio_resposta2.docx	12/02/2017 18:47:44	Renata Mayumi Kato	Aceito
Projeto Detalhado / Brochura Investigador	Projeto_apos_parecer2.docx	12/02/2017 18:44:42	Renata Mayumi Kato	Aceito
Outros	oficio_resposta.docx	20/12/2016 19:28:52	DANIELA GAMBA GARIB CARREIRA	Aceito
Projeto Detalhado / Brochura Investigador	Projeto_apos_parecer.docx	20/12/2016 19:28:04	DANIELA GAMBA GARIB CARREIRA	Aceito
Outros	Checklist_Prot_Pesq_107_2016.pdf	01/12/2016 11:48:55	Rafael Mattos de Deus	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	Term_Assentimento.pdf	30/11/2016 08:51:59	DANIELA GAMBA GARIB CARREIRA	Aceito
Projeto Detalhado / Brochura Investigador	projeto_uep.pdf	30/11/2016 08:51:44	DANIELA GAMBA GARIB CARREIRA	Aceito
Outros	Term_Comp_Tornar_Publico_Dest_Mat.pdf	29/11/2016 22:39:22	DANIELA GAMBA GARIB CARREIRA	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	termo_consentimento.pdf	29/11/2016 22:33:17	DANIELA GAMBA GARIB CARREIRA	Aceito
Outros	termo_permissao_uso_registro_fins_cient.pdf	24/11/2016 23:53:08	Renata Mayumi Kato	Aceito
Outros	Daniela_Term_Comp_Pesq_Resp.pdf	24/11/2016 23:42:07	Renata Mayumi Kato	Aceito
Outros	Daniela_Term_Comp_Manuseio_Inform.pdf	24/11/2016 23:38:37	Renata Mayumi Kato	Aceito
Declaração de Instituição e Infraestrutura	Daniela_Form_Cadastro_HRAC.pdf	24/11/2016 23:23:28	Renata Mayumi Kato	Aceito
Outros	Daniela_Carta_Encaminham.pdf	24/11/2016 23:22:50	Renata Mayumi Kato	Aceito
Folha de Rosto	Daniela_Folha_Rosto.pdf	24/11/2016 23:13:42	Renata Mayumi Kato	Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

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BAURU, 22 de Fevereiro de 2017

Assinado por:
Renata Paciello Yamashita
(Coordenador)

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