UNIVERSIDADE DE SÃO PAULO
HOSPITAL DE REABILITAÇÃO DE ANOMALIAS CRANIOFACIAIS

ALEXANDRE DE ALMEIDA RIBEIRO

3D tomographic analysis of the pharyngeal airway in Treacher Collins Syndrome and its relation with the skeletal pattern

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Análise tomográfica 3D da via aérea faríngea na Síndrome de Treacher Collins e sua relação com o padrão esquelético.

Tese em formato alternativo apresentada ao Hospital de Reabilitação de Anomalias Craniofaciais da Universidade de São Paulo para obtenção do título de Doutor em Ciências da Reabilitação, na área de concentração de Fissuras Orofaciais e Anomalias Relacionadas.

Orientadora: Profa. Dra. Ivy Kiemle Trindade-Suedam

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“There is no way to happiness; Happiness is the way”

Autor desconhecido

ABSTRACT

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Introduction: Treacher Collins syndrome (TCS) is a rare (1:50.000 live births) and severe anomaly of craniofacial development. It arises mainly from mutations in TCOF1 gene mapped at chromosome 5 and affects the development of first and second branchial arches. Maxillomandibular hypoplasia is among the main craniofacial characteristics. **Objectives:** This study aimed at investigating the skeletal craniofacial and pharyngeal morphologies of individuals with TCS, by means of cone beam computed tomography (CBCT) and to compare these data with those from a control population. **Methods:** CBCT scans of 26 individuals had the pharyngeal volume (V) and minimal cross-sectional area (mCSA) evaluated. The study group (TCS) was composed by CBCT scans of individuals (n=13) with TCS (7 males and 6 females; 20.2±4.7y). Control group (CG) was composed by CBCT scans of non-syndromic subjects (n=13) with the same type of skeletal pattern (2 males and 11 females; 26.6 ± 5.4y). Cephalometric data of maxillomandibular position, maxillomandibular dimensions and growth pattern were assessed. Statistics included Student t test and Pearson Correlation Coefficient ($p \leq 0.05$). **Results:** Pharyngeal V and mCSA of TCS were smaller, although not significantly. Minimum CSA was located at the oropharyngeal level on the great majority of the cases. The jaws of TCS were significantly retropositioned and reduced, especially the mandible. It was observed a hiperdivergent growth pattern in TCS subjects. **Conclusion:** TCS is a skeletal class II high angle craniofacial malformation with reduced pharyngeal dimensions when compared with a control group. The micro and retrognathia seem to affect negatively the pharyngeal dimension of TCS population.

Keywords - Mandibulofacial Dysostosis, Micrognathism, Cleft Palate, Cephalometry, Cone-Beam Computed Tomography.

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1 INTRODUCTION AND RATIONALE

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Treacher Collins syndrome (TCS), also known as mandibulofacial dysostosis or Franschetti-ZwahlenKlein syndrome, is a rare and severe congenital disorder of craniofacial development with an estimated prevalence of 1:50.000 live births (Plomp et al, 2016; Posnick and Ruiz, 2000). The condition is most derived from a mutation in TFOC1 gene, of the chromosome 5. Whereas 40% of the cases are originated from a pre-existent familiar condition, the situations originated from a *de novo*, or spontaneous, gene alteration, account for 60% of the affected individuals (Trainor et al, 2009; Trainor and Andrews, 2013). The modification in genetic information causes a deficit in the recruitment of neural crest cells, which impairs the development of the first and second branchial arches along the embryogenesis period. Gene mutation was identified to have an autosomal dominant inheritance with a strong penetrance but with a great range of phenotypic expressivity (van Gijn, Tucker and Couborne, 2013). As derivatives from branchial arches, the substantial characteristics of TCS arise from the underdevelopment and dysmorphology of the craniofacial aspects, especially mandibular, maxillary and zygomatic bones (Posnick and Ruiz, 2000; Plomp et al, 2016; Esenlik et al, 2017).

Most of the skeletal malformations are relatively stable from infancy to adulthood (Posnick and Ruiz, 2000; Plomp et al, 2016; Esenlik et al, 2017). Hypoplasia of the mandible and zygomatic arches, coloboma and hypoplasia of the lower eyelids, total or partial absence of the external ears, stenosis of auditory canal, hypoplasia of ossicles of the middle ear, narrowing of dental arches and macrostomia are amongst the most common clinical characteristics aroused from the malformation (Figure 1 from the Study #1). In general, clinical features have a symmetric manifestation and a variability of functional outcomes, such as dysphagia, glossoptosis, visual deficiency and hearing impairments. The presence of a cleft palate is not rare, with prevalence rates reaching 24-28% of the affected subjects (Cobb et al, 2014).

Besides the underdevelopment of the craniofacial structures, mandibulofacial dysostosis also leads to the stenosis of the nasomaxillary complex, atresia of

choanas and nasal obstructions. These conditions frequently leads to an increased risk for breathing disorders such as chronic upper respiratory tract infections and obstructive sleep apnea (Plomp et al, 2012; Plomp et al, 2016). In fact, TCS individuals have the respiratory issues amongst their leading clinical complaints.

Studies based on cephalometric analysis have long demonstrated the correlation of craniofacial pattern with the airways (Alves et al, 2012; Lopatiene et al, 2016). Similarly, studies on TCS constantly correlated the hypoplasia of maxillomandibular complex with the constricted upper airways morphology. These findings have been largely discussed in several manuscripts based on non-syndromic populations and seem to be a definitive topic (Posnick and Ruiz, 2000; de Oliveira et al, 2007; Chong et al, 2008; Plomp et al, 2012; Cobb et al, 2014; Ma et al, 2015; Ma et al, 2015; Plomp et al, 2016; Esenlik et al, 2017). However, little has been investigated about the craniofacial pattern and facial growth of TCS individuals and its relation with the upper airways morphophysiology. Previous study has shown an increased facial convexity in children with TCS when compared to non-syndromic subjects (Esenlik et al, 2017) and clinical observation shows that this pattern is maintained throughout the growth of the individual.

The underdevelopment of the face can be explained by two distinct aspects, as follows: 1) Genetic background - since craniofacial growth is a genetically predetermined (Trainor et al, 2009; Trainor and Andrews, 2013; van Gijn et al, 2013), it can be assumed that such condition is stablished in the very first moments of facial embryogenesis and remains through life; 2) Part–counterpart principle - besides the intrinsic growing properties, maxillary (part) and mandibular (counterpart) development must be matched to result in a normal occlusion. It means that, if the mandible is genetically determined to be hypoplasic and retruded, such as in TCS, the maxilla will not grow properly as well; besides, maxillomandibular growth is related to the cranial base growth. In other words, as the cranial base elongates, this anteroposterior movement will also contribute to the horizontal growth of the maxilla and the mandible (Enlow and Moyers, 1971; Cobourne and DiBiase, 2011). Indeed, in non-syndromic individuals, the dynamic of facial development has long been stablished to be a cranial base driven feature. However, as stated previously, TCS has great impact on the final craniofacial morphology of the affected individuals and it

is speculated that this facial dismorphology consequently leads to a reduction is the upper airways dimensions.

As stated before, TCS individuals have in the respiratory issues one of their main complaints. In a non-syndromic population, it has been demonstrated that the pharyngeal dimensions of skeletal class II individuals are reduced when compared to normal growth pattern (Grauer et al, 2009; Oh et al, 2011; Alves et al, 2012; Flores Mir et al, 2013; Lopatiene, Dabkute and Juskeviciute, 2013; Lopatiene et al, 2016; Schorr et al, 2016). Previous studies from our group have also demonstrated that the pharyngeal volumes and minimal cross-sectional areas are also reduced in individuals with cleft lip and palate (CLP) (Trindade-Suedam et al, 2017.

It is our hypothesis that this condition is also observed in the TCS population. The main objectives of the present studies are to characterize the upper airways dimensions and the craniofacial aspects of this syndrome, trying to establish if this particular craniofacial architecture may influence the upper airways of this population. It is expected that this investigation contributes to a better understanding of the craniofacial conditions associated with this singular and rare craniofacial anomaly.

Figure 1 – Facial characteristics of an individual with Treacher Collins Syndrome (Frontal and lateral views)

2 OBJECTIVES

2 OBJECTIVES

This study aimed at investigating the pharyngeal dimensions of non-operated individuals with Treacher Collins Syndrome and its relation with the skeletal craniofacial morphology, by means of cone beam computed tomography.

The present investigation was composed by two complementary studies, as follows:

Study 1: *"Cephalometric characterization of Treacher Collins Syndrome individuals".* The objective of this study was to perform a cephalometric analysis on a sample of individuals diagnosed with Treacher Collins Syndrome using lateral cephalograms in order to characterize the craniofacial morphology and the skeletal growth pattern of this population.

Study 2*:* *"Three-Dimensional Upper Airways assessment on Treacher Collins Syndrome".* This is a subsequent study in which a three-dimensional analysis of the pharyngeal airway of Treacher Collins Syndrome individuals was performed and compared with a group of non-syndromic individuals presenting the same type of skeletal pattern. It was also intended to compare the cephalometric data between these groups. Finally, a correlation between upper airway dimensions and the cephalometric characteristics were also assessed, trying to understand how these particular features influence the upper airways dimensions of TCS individuals.

3 STUDY #1

3 STUDY #1

CEPHALOMETRIC CHARACTERIZATION OF TREACHER COLLINS SYNDROME INDIVIDUALS*

**To be submitted to the American Journal of Orthodontics and Dental Orthopedics. (AJODO)*

ABSTRACT

Introduction and Background: Treacher Collins syndrome (TCS) is a rare congenital craniofacial anomaly, which main clinical features are hypoplasia of maxillary and mandibular bones and zygomatic arches. Despite the extensive description of facial characteristics and functional issues, little is known about the cephalometric features of adults with TCS. **Objectives:** To assess the skeletal craniofacial characteristics of young adults with TCS by means of cone beam computed tomography (CBCT), before the rehabilitation bone surgeries. **Methods:** After strict inclusions criteria, the study was composed by thirteen lateral cephalometric scans of young adults with TCS (7 males and 6 females; mean age: 20.2±4.7y), obtained from an initial sample of 125 individuals. Cephalometric data of maxillomandibular relationship (SNA, SNB ANB and Pg-NB), maxillomandibular dimensions (Co-A, Co-Gn and LAFH) and growth pattern (SN.SGn, SN.GoGn, FMA and SN.PP) were assessed on lateral cephalograms obtained from CBCT scans. Means and standard deviation were calculated for each variable and descriptive analysis was performed. **Results:** The maxilla and the mandible of individuals with TCS are considerably retruded in relation to the cranial base when compared to the general population. This is especially observed in the mandible. The maxillomandibular complex is smaller in the sagittal aspect. Combined, the retruded and hypolastic mandible help to explain the much greater ANB angle of TCS as compared to a Class I patient, resulting in a severe skeletal class II malocclusion condition. **Conclusion:** TCS is a high angle growth pattern craniofacial malformation. The knowledge of the cephalometric characteristics leads to a better craniofacial morphological understanding, which positively impacts on the treatment outcomes, and, consequently on the functional rehabilitation of this anomaly.

Keywords - Mandibulofacial Dysostosis, Micrognathism, Cleft Palate, Cephalometry, Cone-Beam Computed Tomography.

INTRODUCTION

Treacher Collins syndrome (TCS) is a rare congenital craniofacial anomaly with an estimated prevalence varying from 1:25.000 to 1:50.000 live births[1-3]. Determined predominantly from an autosomal dominant mutation in TFOC1 gene of chromosome 5, the condition is characterized by a high genetic penetrance and a significant inter and intra-familial phenotypic variability [3-5].

From a pathogenic point of view, it is clear that the genetic mutation impairs the growth and proliferation of the neural crest cells during embryogenesis[5,6]. The insufficient number of neural cells affects the formation of first and second branchial arches and their derivatives, causing the underdevelopment and dysmorphology of craniofacial bones, especially mandible and maxillary complex[6] (Figure 1).

Of symmetric impairment, individuals with this syndrome may present severe facial convexity, retrognathic and hypoplastic mandible, malocclusion, anterior open bite, total or partial absence of the ears, atresia of choanas and coloboma of the lower eyelids[7-14]. The morphological alterations of the face arise fundamentally from the hypoplasia of mandible, maxilla and zygomatic bones. Association with cleft palate is not uncommon, with prevalence ranging from 28% to 40%[13]. Dysfunctions derived from malformation may include dysphagia, glossoptosis, and speech and hearing impairments[1-14]. The upper airways are also affected, with patients generally suffering from different degrees of respiratory issues, including recurrent infection of the UAW and the obstructive sleep apnea (OSA)[2,7,11-13].

Despite the extensive description of facial characteristics and functional issues, little is known about the cephalometric features of TCS. Presumably, final rehabilitation of this condition involves a combined surgical orthodontic approach for

improvement of facial aesthetics and recovery of orofacial functions[1,2,7,9,10,14]. A better understanding of the craniofacial architecture, from the perspective of orthodontics and maxillofacial surgery, would be of fundamental importance for a comprehensive treatment.

Considering the limited information available on the cephalometric pattern of adults with TCS and the heterogeneity of the groups evaluated, the objective of the present study was to characterize the skeletal pattern of young adults with TCS prior skeletal rehabilitation procedures.

MATERIAL AND METHODS

This study was approved by the Institutional Review Board of the Hospital for Rehabilitation of Craniofacial Anomalies (HRAC) from University of São Paulo (USP), protocol number 440.749-SVAPEPE-CEP (ANEXO 1).

One hundred and twenty five patients being diagnosed with TCS were under regular treatment at HRAC/USP at the time of data collection. Pre-established inclusion criteria were: young adults with TCS, having CBCT scans on i-CAT computed tomography scanner, with a field of view greater than 13 cm, in which the pituitary saddle, the 4th cervical vertebra and the hyoid bone were present, allowing the complete assessment of the pharyngeal length. Exclusion criteria were: subjects with TCS having a cleft palate, children or elderly subjects, patients already submitted to orthognathic surgeries, and, the presence of hypertrophic tonsils or adenoids. This resulted in thirteen scans that met the inclusion criteria, as seen on Figure 2.

All CBCT scans were obtained at the Hospital for Rehabilitation of Craniofacial Anomalies database (HRAC, University of São Paulo, Bauru-SP, Brazil). Images were obtained for surgical planning purposes by means of i-CAT Next Generation scanner (ISI-i-CAT Imaging System, beam cone, Next Generation i-CAT, Hatfield, PA), with the specifications: FOV ≥ 13cm, 26.9 sec (exposure time), 120 kV, 37 mA, and a resolution of 0.25 voxels or greater. Images were saved as a DICOM files (Digital Imaging and Communications in Medicine) and analyzed using Dolphin Imaging 11.8 software (Dolphin Imaging, Chatsworth, California, USA). Standardization of head positioning was based on axial plane (line passing through the most inferior point of mastoid processes on both sides), coronal plane (Frankfort horizontal) and sagittal plane (line passing through the tip of nasal bone and the most inferior point of foramen magnum), as seen on Figure 3.

For cephalometric measurements, lateral cephalograms from 3D images were created out of sagittal plane. Seven angular and four linear measurements were assessed using fifteen craniofacial landmarks, described on Tables 1 and 2 and seen on Figure 4. These measurements were divided into 3 specific variables: maxillomandibular sagittal position, maxillomandibular dimensions and growth pattern. All data was assessed twice by the same trained operator (orthodontist) with a minimum interval of thirty days between each assessment.

Intra class correlation coefficient (ICC) was used to assess intra examiner agreement[15], which adopts the following score: ICC <.40= poor agreement, ICC .40 to .75 = moderate agreement and ICC > .75 = high agreement. Cephalometric data obtained in the present study was compared with normative data from the literature[14,16-19].

RESULTS

Considering that intra-examiner agreement was high, the mean values of both measurements were considered for descriptive analysis. Results obtained for the maxillomandibular sagittal position, the maxillomandibular dimensions and the growth pattern are described on Table 1. Thirteen young adults (20.2±4.7y, 7 males, 6 females), diagnosed with TCS composed the sample size.

Regarding *maxillomandibular sagittal position*, the mean values (SD) of SNA and SNB angles, for the adult individuals with TCS, were reduced when compared with normative data from the general adult population and corresponded to 79.2±5.4° and 70.0±7.0°, respectively. An increased mean value for ANB was obtained when compared to the normative values (9.2±3.3°). Pg-NB was reduced when compared to data control (-3.7±3.2mm)

Anteroposterior *maxillomandibular dimensions* were also reduced in relation to normative values and corresponded to 72.6±6.0mm for the maxilla and 64.2±2.1mm for the mandible. Lower anterior facial height was greater than standard values (69.1±9.1mm).

With respect to the *growth pattern*, results were greater than the values observed for the general adult population and corresponded to 80.3±7.9° (SN.SGn), 50.5±8.6° (SN.GoGn) and 40.6± 7.2° (FMA). SN.PP values were greater than the standard population (17.2±6.6).

DISCUSSION

The findings of the present study indicate that the maxilla and the mandible of individuals with Treacher Collins Syndrome are considerably retruded in relation to the cranial base when compared to the general population. This is especially observed in the mandible and is in accordance with clinical observation. Furthermore, the maxillomandibular complex is smaller in the sagittal aspect. This is also observed in the mandibular symphysis, which is more posteriorly positioned than expected. Likewise, the relation between the maxilla and the mandible is altered and this anteroposterior discrepancy is mainly due to the retruded mandible, as the cephalometric findings suggest. Combined, the retruded and hypolastic mandible help to explain the much greater ANB angle of TCS as compared to Class I patients, resulting in a severe skeletal class II malocclusion condition.

In respect to pogonion point, it presented posteriorly positioned in relation to the reference line NB. According to Posnick and Ruiz[7], the chin in TCS individuals is dysplastic and characterized by increased vertical length and horizontal retrusion. This particular data has been described as a singular mandibular feature of TCS individuals[10]. Accordingly, the mandibular symphysis of this population behaviors like a “independent” part of the mandible, improving its retrognathic pattern, as pointed out by the blue arrow on Figure 4.

According to several authors[1,2,7,8,11,12], the dimensional reduction of the mandibular complex on TCS can impact negatively the dimension of the upper airways. In fact, in non-syndromic populations, mandibular class II malocclusion subjects are more likely to present diminished airways when compared to class I or class III malocclusion ones[20-22].

In terms of craniofacial growth, despite the diminutive aspect, TCS patients evaluated in this study present a dolichocephalic pattern. The growth trend metrics altogether make the TCS patients likely to present a hyperdivergent pattern. In accordance with previous studies[9-12,14], they also reflect the downward and backward shift of the mandible, which comes to reinforce the tendency of lower-anterior facial height (LAFH) excess, observed in the present sample.

Besides the mandible, it was observed that the maxilla also presents a considerable clockwise rotation in relation to the cranial base, observed using the SN.PP angle. This is an considerable result when compared to normative data and even in relation to skeletal class II subjects[23] or high angle pattern individuals[24]. Additionally, it is in accordance with the clinical report of Chung, Cangialosi and Eisig[14], which have described a similar value for the same parameter. The steepness of the occlusal plane is a particular feature of TCS cephalometrics and it might contribute to the construction of the high angle craniofacial design. Interestingly, despite the phenotypic variability[4-7], the vertical growth pattern, together with the skeletal class II malocclusion, stand as regular features of TCS population.

One important limitation of this study was the sample size. Although thirteen subjects seem a limited number, it is important to emphasize that this a rare syndrome and restricted inclusion criteria were established in the present study. Another point must be stressed out, i.e., although being a considerable element on craniofacial analysis, teeth measurements, such as positions and angulations, were not evaluated in this study. It relied on the presence of orthodontic brackets at the time of image acquisition as the majority of patients were under orthodontic treatment. At this point, teeth, especially incisors, have already changed its positions.

Despite being clinically recognized by the retrognathic mandible[1-14], it can be stated, based on the results obtained, that TCS individuals also present a vertical growth pattern. Since facial growth has a genetic predetermined trend[4,5], we may assume such condition to be stable from infancy to adulthood[7,25,26], especially the mandibular plane and palatal plane angles[14].

It is important to mention that the dimensional reduction of the maxillomandibular complex associated with its retropositioning, characteristics detected by this investigation, can lead to respiratory issues, including obstructive sleep apnea[2,11,12,27-30]. This is the focus of an ongoing investigation from our group.

Finally, it is our understanding that the knowledge about the skeletal pattern and the growth trend of this population is crucial for the final rehabilitation of the individuals. A well succeed rehabilitation will aim, among others, at functional improvement of the skeletal architecture and occlusion, with positive impression on the upper airways physiology.

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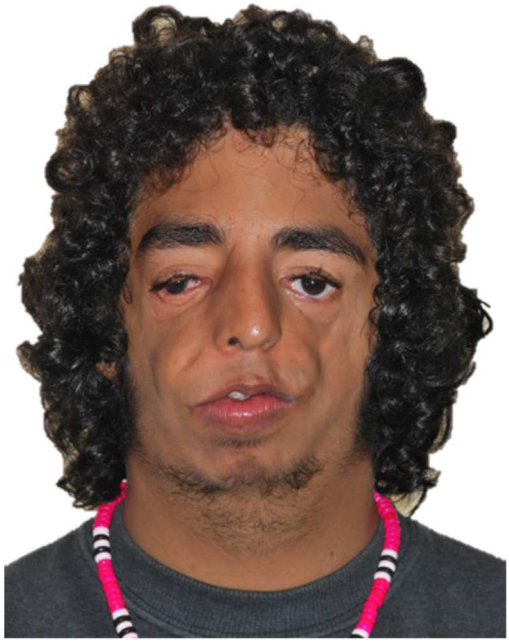


Fonte: HRAC-USP

Figure 1 – Facial characteristics of an individual with Treacher Collins Syndrome (Frontal and lateral views)

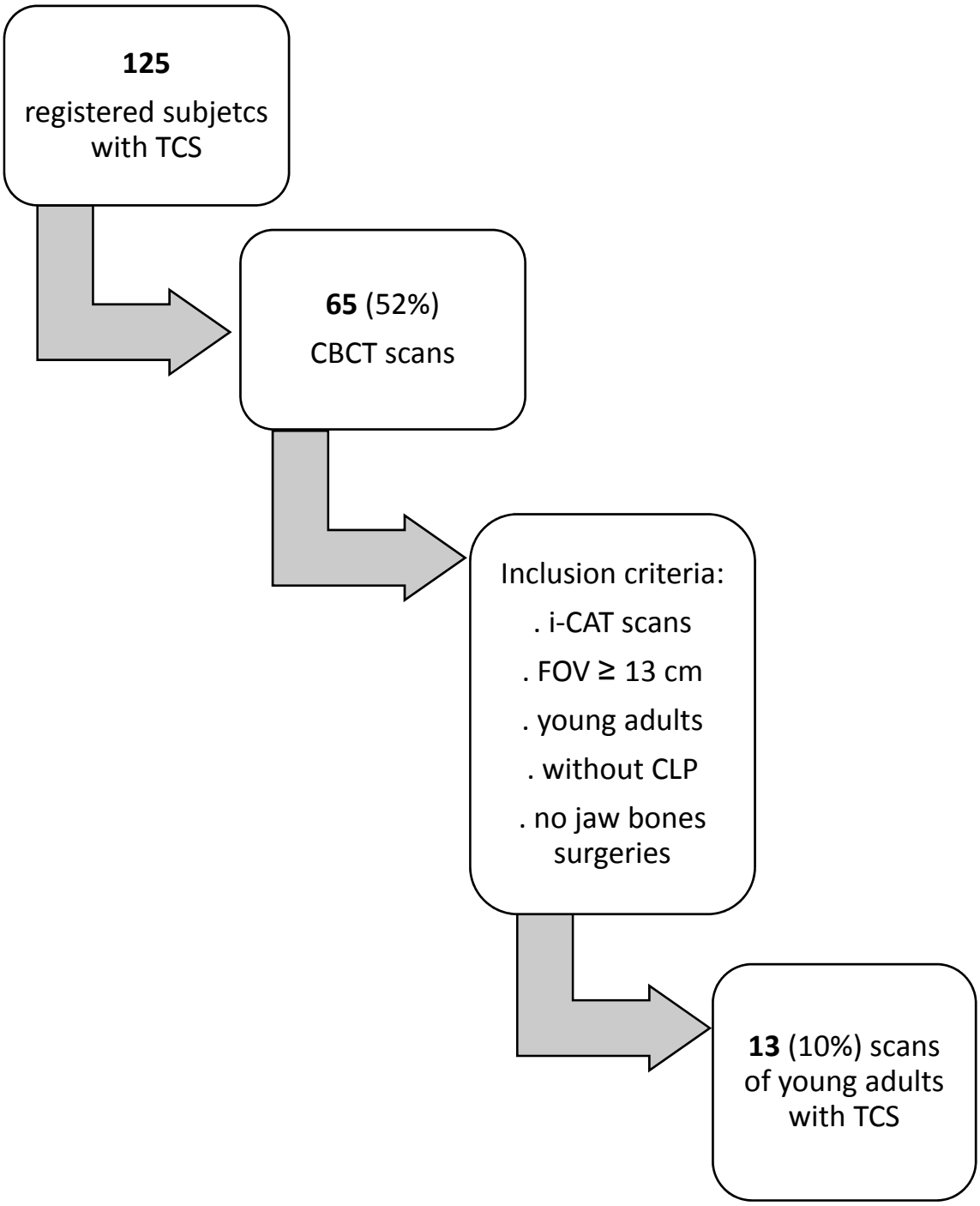
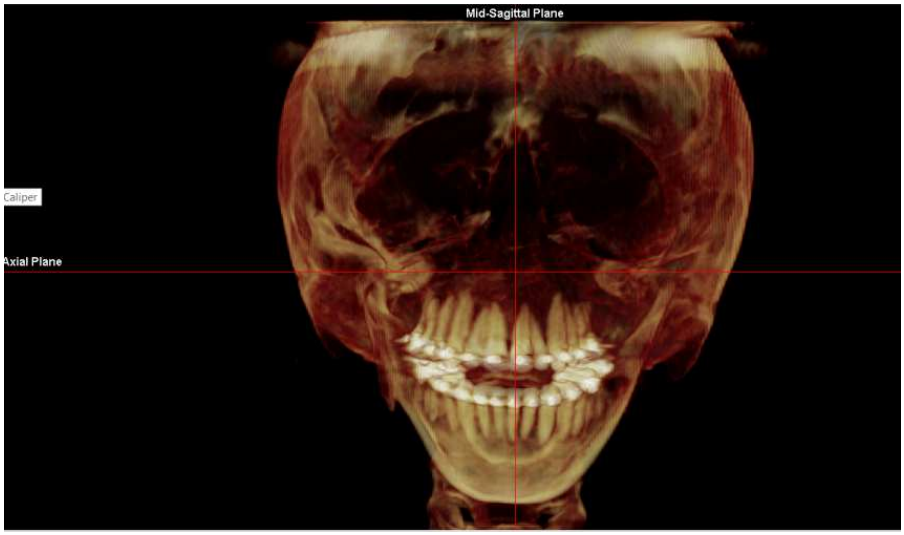
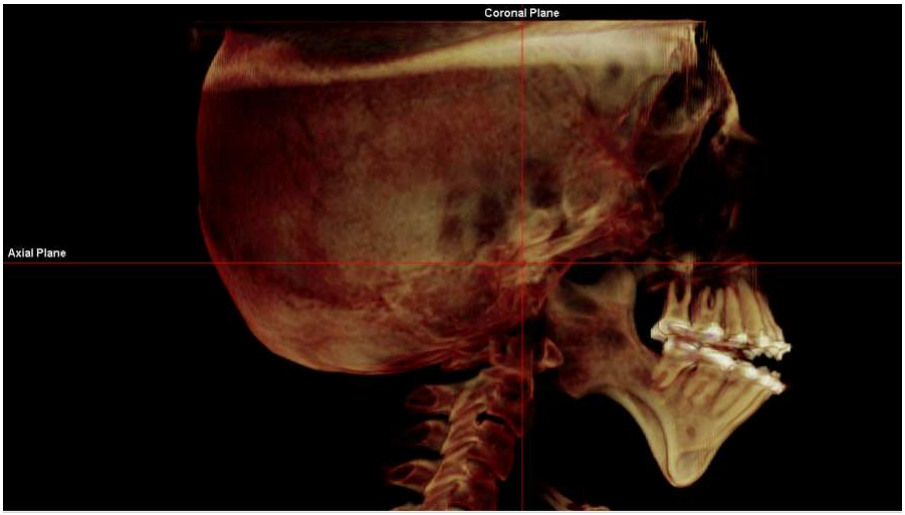


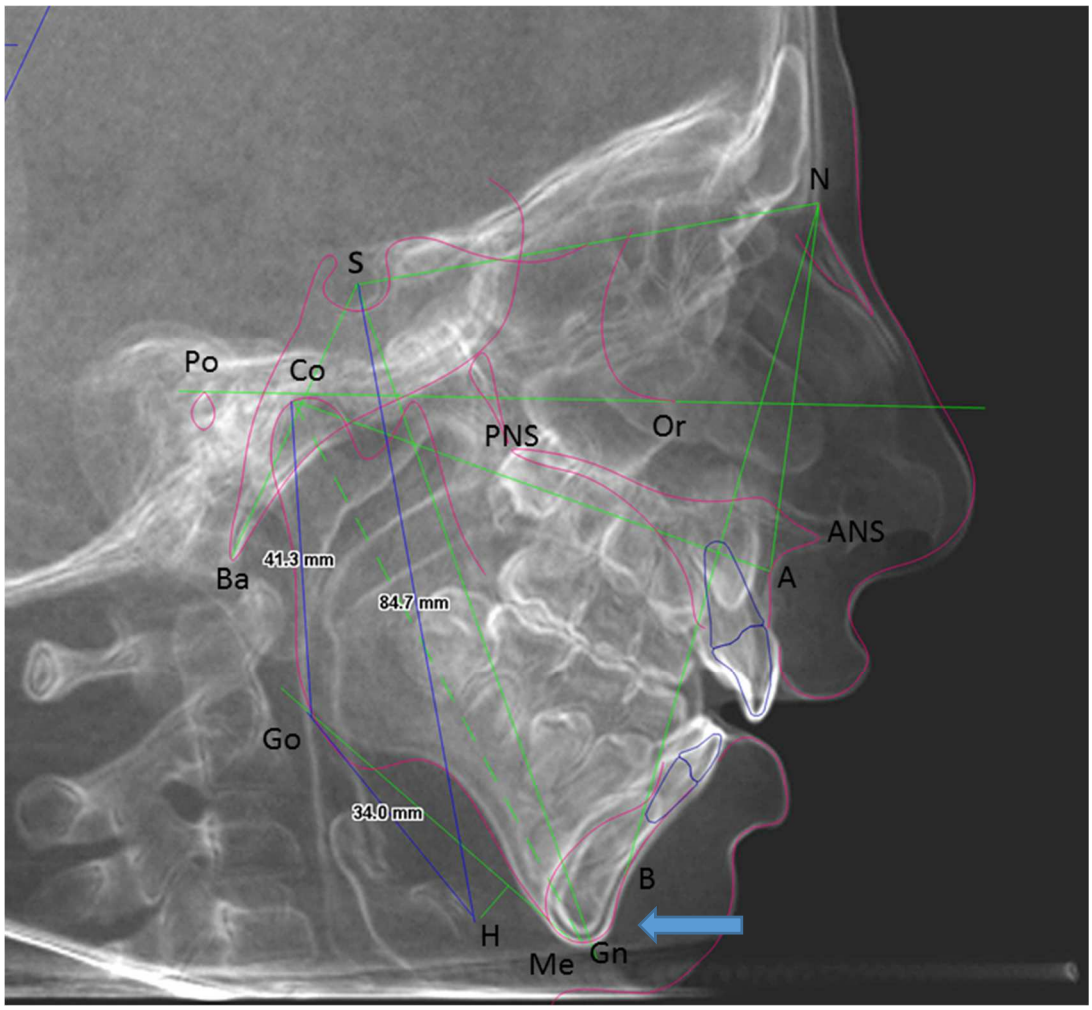
Figure 2 - Process of sample selection.





Fonte: HRAC-USP

Figure 3 – 3D head positioning prior to cephalometric assessment.



Fonte: HRAC-USP

Figure 4 – Cephalometric landmarks

Table 1 - Definitions of all cephalometric landmarks and planes at the sagittal aspect.

VARIABLE	DEFINITION
Condylion (Co)	The most posterior/superior point on the condyle of the mandible
Orbitale (Or)	The most inferior point on the lower border of the orbit
Porion (Po)	The most superior point of the surface of the external auditory meatus
Sella (S)	Point at the center of sella turcica (pituitary fossa)
Pogonion (Pg)	The most anterior point of mandibular symphysis
A point (A)	The deepest point at concavity of anterior maxilla (subspinale)
B point (B)	The deepest point at concavity of mandibular symphysis (supramentale)
Menton (Me)	The lowest point on mandibular symphysis
Nasion (N)	Point at the junction of frontal and nasal bones (frontonasal suture)
Anterior Nasal Spine (ANS)	The most anterior point on maxillary bone at the inferior margin of the piriform aperture
Posterior Nasal Spine (PNS)	Posterior limit of hard palate
Gnathion (Gn)	The most anterior point on mandibular symphysis midway between Pg and Me
Gonion (Go)	The most posterior inferior point on the outline of the angle of the mandible
Mandibular plane (MP)	Plane from constructed Gonion (Go) to Menton (Me)
Frankfort horizontal (FHP)	Plane passing through points Orbitale (Or) and Porion (Po)

Table 2 – Definitions of all cephalometric measurements.

VARIABLE	DEFINITION
Mx/Md sagittal position	
SNA	Angle subtended from sella (S) by means of Nasion (N) to maxillary point A.
SNB	Angle subtended from sella (S) by means of Nasion to mandibular point B.
ANB	Angle subtended from maxillary point A by means of Nasion (N) to mandibular point B.
Pg-NB	Perpendicular distance from chin point to reference line NB
Mx/Md Dimensions	
Co-A (Maxillary unit length)	Distance between Condylion (Co) and A point
Co-Gn (Mandibular unit length)	Distance between Condylion (Co) and Gnathion (Gn)
LAFH (Lower Anterior Facial Height)	Distance between Anterior Nasal Spine (ANS) and Menton (Me)
Growth Pattern	
SN.SGn	Angle between anterior cranial base (S-N) and Y axes (S-Gn)
SN.GoGn	Angle between anterior cranial base (S-N) and mandibular plane (Go-Gn)
SN.PP	Angle between anterior cranial base (S-N) and palatal plane (ANS-PNS)
FMA	Angle between Frankfort horizontal plane (Po-Or) and mandibular plane (Go-Me)

Table 3 - Cephalometric measurements (means and standard deviation).

VARIABLE	TCS young adults (n=13)	NORMATIVE DATA (general adult population)
Mx/Md sagittal position		
SNA (°)	79.2(5.4)	82(2)[a]
SNB (°)	70.0(7.0)	80(2)[a]
ANB (°)	9.2(3.3)	2(2)[a]
Pg-NB (mm)	-3.7(3.2)	4(1,5)[a]
Mx/Md Dimensions		
Co-A (mm)	72.6(6.0)	≥80[b]
Co-Gn (mm)	93.2(11.2)	97-100[b]
LAFH (mm)	69.1(9.1)	57-58[b]
Growth Pattern		
SN.SGn (°)	80.3(7.9)	59.0(7.0)[c]
SN.GoGn (°)	50.5(8.6)	32.0(4.0)[a]
SN.PP (°)	17.2(6.6)	8.2(3.3)[d]
FMA (°)	40.6(7.2)	25.0(3)[e]

[a]Normative data from Steiner (1959), [b]Normative data from McNamara (1984), [c]Normative data from Downs (1948), [d]NormatIve data from Chung et al (2014); [e]Normative data from Tweed (1969).

4 STUDY #2

4 STUDY #2

THREE-DIMENSIONAL UPPER AIRWAYS ASSESSMENT ON TREACHER COLLINS SYNDROME

**To be submitted to the Cleft Palate-Craniofacial Journal (CPCJ)*

Objectives: Treacher Collins Syndrome (TCS) is a congenital craniofacial anomaly that presents, among its main clinical features, mandibular hypoplasia. It is our hypothesis that the upper airways of this population are reduced as a consequence of the retro andmicrognathia**:** The purpose of this investigation was to assess the *pharyngeal dimensions* and the *craniofacial morphol*ogy of TCS individuals as compared to control vertical skeletal class II subjects, by means of 3D tomographic assessment. **Design / Participants:** Cone beam computed tomography (CBCT) scans of 26 individuals had the pharyngeal volume (V) and minimal cross-sectional area (mCSA) evaluated. TCS group was composed by thirteen scans of patients with TCS (7 males and 6 females; 20.2±4.7y). Control group (CG) was composed by thirteen scans of non-affected individuals with the same type of skeletal pattern (2 males and 11 females; 26.6 ± 5.4y). Cephalometric data of maxillomandibular position, maxillomandibular dimensions and growth pattern were assessed. Statistical analysis ($p \leq 0.05$) included Student t test and Pearson Correlation Coefficient. **Results:** Although reduced, pharyngeal V and mCSA of TCS were not statistically different from the CG. On both groups mCSA were mostly at the oropharyngeal level. TCS individuals presented with retrognathic chin (Pg-NB), reduced maxillomandibular dimensions (Co-A, Co-Gn, LAFH, Co-Go, Go-Me) and an increased clockwise rotation of the palatal plane (SN.PP). Maxillary and mandibular lengths were correlated with pharyngeal V (Co-A, Co-Gn, Co-Go) and mCSA (Co-Go, Co-Gn). **Conclusions:** The pharyngeal dimensions of subjects with TCS are volumetrically smaller when compared with a group of non-syndromic individuals with class II malocclusion. This airway reduction can be explained by the hyperdivergent growth pattern and by the severe micro and retrognathia observed in the syndromic population analyzed.

Keywords - Mandibulofacial Dysostosis, Micrognathism, Cleft Palate Cephalometry, Cone-Beam Computed Tomography

INTRODUCTION

Treacher Collins Syndrome (TCS), also known as mandibular dysostosis, is a congenital craniofacial anomaly, which main clinical features are hypoplasia of maxillary and mandibular bones and zigomatic arches (Figure 1). It is estimated that approximately 46% of the subjects TCS suffer from some degree of airway obstruction[1,2], ranging from mild obliteration to severe and life threatening obstructive sleep apnea (OSA).

Previous study from our group* has shown that, despite the great phenotypic variability[3-9], craniofacial analysis of young adults with TCS brings up the hyperdivergent type and the skeletal class II malocclusion as standard features of this syndrome. In addition, it has been shown that individuals with skeletal class II malocclusion have a greater prevalence of respiratory issues as compared to class I and class III malocclusions subjects[10-13]. Moreover, different studies on respiratory disorders of non-syndromic populations[14-18] have stated that the skeletal class II malocclusion and the high angle growth pattern are amongst the predisposing factors for pharyngeal obstruction, recurrent respiratory infections and the occurrence of OSA.

In the same manner, the influence of craniofacial form on the airway morphology of syndromic subjects has long been studied[19-21] but no conclusive data has been shown. In general, it is speculated that TCS individuals have reduced upper airways volume caused by the shortening and the retrognathic position of the mandible, leading to facial convexity and dysfunctional occlusion[1-2,7-9,18-21].

**study #1*

Concurrently, a recent study from Esenlik et al[9] on TCS has correlated mandibular retrognathia, reduced posterior facial height and an obtuse maxillomandibular plane with clinical severity of the upper airways conditions, specifically, the need for tracheostomy and the occurrence of OSA. Moreover, other studies[8,19,20] on TCS subjects have reported that affected individuals present severe dysmorphologies in mandibular and midface segments, what comes to impair the upper airways dimension.

Despite the evidence of these findings, i.e, the role of craniofacial growth and malocclusion on pharyngeal volume of TCS remains unclear. Can hyperdivergent growth and skeletal class II malocclusion influence the pharyngeal dimensions of TCS subjects as they do for non-syndromic individuals? Furthermore, if so, to what extent?

It is our hypothesis that the upper airways in individuals with TCS may be reduced even more, in view of the mandibular micrognathia and retrusion, what probably implies in respiratory disorders, specially sleep-disordered breathing. As stated, the purpose of this investigation was to assess the *pharyngeal dimensions* and the *craniofacial morpholo*gy of TCS individuals as compared to control vertical skeletal class II subjects, by means of 3D tomographic assessment.

MATERIAL AND METHODS

This study was approved by the local Institutional Review Board (protocol number 440.749-SVAPEPE-CEP) of the Hospital for Rehabilitation of Craniofacial Anomalies (HRAC) from University of São Paulo (USP) (ANEXO 1). Researchers

signed a liability form for image handling. Based on the study by Cheung and Oberoi (2012)[18] and using a mean volume difference greater than 30% (5.4cm^3) and a standard deviation of 7cm^3, a sample of *28 individuals* per group was estimated.

One hundred and twenty five patients being diagnosed with TCS were under regular treatment at HRAC/USP at the time of data collection. Inclusion criteria for pre-established were: adults with TCS, having CBCT scans on i-CAT computed tomography scanner, with a field of view greater than 13 cm, in which the pituitary saddle, the 4th cervical vertebra and the hyoid bone were present, allowing the complete assessment of the pharyngeal length. Exclusion criteria were: subjects with TCS having a cleft palate, children or elderly subjects, patients already submitted to orthognathic surgeries, and, the presence of hypertrophic tonsils or adenoids. This resulted in 13 scans that met the inclusion criteria. The cephalometric characteristics of the TCS group were previously assessed on another study*.

A control group from a maxillofacial private practice (HNF) was also assessed and was composed by 13 non-syndromic subjects having the same type of malocclusion (skeletal class II) and facial morphology (dolichocephalic). CBCTs from the control and TCS groups were obtained for surgical planning purposes.

**study #1*

Images were obtained for surgical planning purposes by means of i-CAT Next Generation scanner (ISI-i-CAT Imaging System, beam cone, Next Generation i-CAT, Hatfield, PA), with the specifications: FOV ≥ 13cm, 26.9 sec (exposure time), 120 kV, 37 mA, and a resolution of 0.25 voxels or greater. Images were saved as a DICOM files (Digital Imaging and Communications in Medicine) and analyzed with Dolphin Imaging 11.8 software (Dolphin Imaging, Chatsworth, California, USA). Standardization of head positioning was based on axial plane (line passing through the most inferior point of mastoid processes on both sides), coronal plane (Frankfort horizontal) and sagittal plane (line passing through the tip of nasal bone and the most inferior point of foramen magnum).

To assess the pharyngeal dimensions on both groups, a region of interest was determined in the midsagittal plane and was delimited by the following cephalometric points: Ba (basion), S' (anterosuperior edge of the pituitary saddle), C4 (anterior limit of the fourth cervical vertebra), H (anterior limit of the hyoid bone), SP (inferior limit of soft palate) and PNS (posterior nasal spine) (Figure 2). Once outlined, pharyngeal airway was segmented from the surrounding tissues in a semi-automatic manner, followed by manual refining, which consisted in depuration of areas not software noticed in the axial, sagittal and coronal planes. Up next, a 3D image of the airways was rendered and had its pharyngeal volume (V) and minimal cross sectional area (mCSA) calculated.

The location of the CSA was determined based on the study by Yoshihara et al. (2012). Pharynx was divided into three portions, as follows: nasopharynx (portion of the pharynx located superiorly to the palatal plane, which is parallel to the Frankfort horizontal plane), oropharynx (portion of the pharynx located between palatal plane and the epiglottal plane, which were parallel to the Frankfort horizontal

plane), and, hypopharynx (portion of the pharynx located inferiorly to the epiglottal plane).

For cephalometric measurements, lateral cephalograms from 3D images were created out of sagittal plane. Seven angular and six linear measurements were assessed by means of fifteen craniofacial landmarks. They were segmented into 3 specific variables: ma*xillomandibular sagittal position*, *maxillomandibular dimensions* and *growth pattern*, as seen on Tables 1 and 2. All airway and cephalometric measurements were performed twice by the same trained evaluator, with a minimum interval of thirty days between them. A second operator assessed 50% of the airway samples for inter- examiner comparison.

Intraclass correlation coefficient (ICC) was used to assess intra- and inter-examiner agreement. Descriptive statistical data of mean value and standard deviation (SD) were calculated for each parameter in controls and in TCS group. Statistical analysis included independent sample Student´s *t*-test for intergroup evaluation. Correlation between the pharyngeal dimensions and cephalometric data was determined using Pearson Correlation Coefficient. In all cases, P values <.05 were considered significant.

For the Pearson correlation coefficient, values of r = 0-0.29 were considered as indicative of negligible correlation, r = 0.30-0.49 weak correlation, r = 0.50-0.69 moderate correlation, r = 0.70-1.00 strong correlation (HINKLE; WIERSMA; JURS, 2003).

RESULTS

A high inter-examiners agreement was found (ICC=0.98) for the control and TCS groups. Intra-examiner agreement was also high (ICC=0.99) on both groups. Considering this high agreement, the mean values of the most experienced evaluator was considered for analysis. The results are reported in Table 3 and in Figure 3.

Pharyngeal V (SD) of TCS and CG subjects corresponded to 17.5cm^3±8.2 and 19.9cm^3±4.7, respectively. Pharyngeal mCSA (SD) corresponded to 84.6mm^2±47.4 and 107.8mm^2±40.0, respectively. Although reduced on TCS, no significant differences were observed between groups on both variables. Location of mCSA was predominantly on the oropharyngeal level for both groups.

As seen on Table 3, maxillary and mandibular position (SNA and SNB) were similar for both groups. The same was observed for the ANB angle. Perpendicular distance from chin point to reference line NB (Pg-NB) was significantly increased on TCS group (-3.8±3.0) when compared to the CG (-1.3±2.9). Maxillary and mandibular lengths (Co-A, Co-Gn, LAFH, Co-Go, Go-Me) in the TCS were significantly reduced when compared to the CG. Growth angles (SN.SGn, SN.GoGn, SN.PP and FMA) were increased in the TCS group, and significant values was observed for the SN.PP variable.

Strong positive correlations were found between pharyngeal V *vs* Co-Gn, V *vs* Co-Go and mCSA *vs* Co-Go. Moderate positive correlations were found between pharyngeal V *vs* Co-A and mCSA *vs* Co-Gn, as seen on Figures 5 and 6. Weak correlations were observed among the other variables.

DISCUSSION

The main finding of the present study indicates that pharyngeal dimensions (V and mCSA) of TCS individuals are reduced when compared to controls. However, contrary to what was expected, there were no statistically significant differences between groups regarding these parameters, although the authors do believe that the respective reductions of 12% (V) and 22% (mCSA) are of considerable clinical relevance and may impact negatively on respiratory and sleep functions. Preliminary data from our group has shown that the quality of sleep pf TCS individuals is impaired in this population and this finding might be explained by the dimensional reduction observed in the present study.

Furthermore, it must be emphasized that, although differences between groups were not significant, the pharyngeal volume and mCSA data obtained in the TCS population is considerably reduced when compared to a cleft population, for instance (Trindade-Suedam et al 2017). Pharyngeal volume and mCSA of patients with TCS (17,5cm^3 and 84,6mm^2) are substantially smaller than that of individuals with unilateral clefts (20.8cm^3 and 149.5mm^2), especially the mCSA. This result reinforces the importance of investigating the upper airways and the sleep in this population.

The knowledge of the size of the mCSA needs special attention and is supported by Poiseuille's Law and Bernoulli's principle which state that the smaller the diameter of a tube, the greater the resistance to airflow. In other words, it means that the smaller is the pharyngeal area, the greater are the chances of a pharyngeal collapse occur during inhalation. Additionally, it must be taken into account that the

reduced muscular tonus that occurs during sleep contributes to the pharyngeal lumen reduction and consequent collapse, leading to obstructive sleep apnea.

It has also been observed throughout the sample of present study that, in 100% of the cases (TCS group), the area of the greatest pharyngeal constriction (mCSA) was located at the oropharyngeal level. No mCSAs were observed in the nasopharynx. This data surely relates to the expressive retrognathia (SN.PP) observed in these patients. In a group of subjects having a class III skeletal pattern (Trindade-Suedam et al 2017), data was differently distributed and 78% of the cases had the mCSA were at the oropharyngeal level while 22% was at the hypopharynx. This is in accordance with Tang et al, 2012 which indicates that the oropharynx is the main site of obstruction in individuals with obstructive sleep apnea syndrome.

Both groups assessed in the present study presented the same type of craniofacial skeletal pattern, i.e., a skeletal class II malocclusion and a high angle facial growth. Although the groups were matched for the skeletal pattern, the cephalometric data showed the TCS subjects as having a more severe craniofacial condition, as represented by the significant retrognathia (Pg-NB), micrognathia (Co-Gn) and hyperdivergent growth (SN.PP).

In spite cephalometric data of both groups were distinct from the normative data of class I subjects (*study #1*), it was surprising to observe no differences between groups regarding the maxillary and mandibular positions (SNA and SNB) and the maxillomandibular relationship (ANB). In fact, both groups presented a relatively well positioned maxilla (SNA) in the horizontal aspect, a similar degree of mandibular retropositioning (SNB) and a comparable severity of skeletal class II malocclusion (ANB). The fact that: 1) both groups have very similar skeletal patterns, and, 2) TCS group presented with a dimensional pharyngeal reduction in relation to

the control group, it reinforces the role of the syndrome itselft on the overall morphology and reduction of the airways of these individuals.

Although a weak correlation was observed between the pharyngeal dimensions of the TCS and the position of the mandible (SNB) or maxillomandibular relationship (ANB), the latter being increased in 10% for the TCS group, these findings must be highlighted, as the retropositioning of the mandible is considered an important predisposing factor for the upper airways collapsibility[12-18,5-7]. This may be particularly true for the TCS condition, especially if the reduction of the mCSA is taken into account.

The distance between the chin point (Pg) and the reference line NB (Pg-NB) was found to be significantly increased in TCS (192%) when compared to controls. Since CG comprised a mandibular deficient population, this result gives support to the accentuated retrognathic tendency found in TCS individuals[1-4,8-11]. According to Esenlik[4], the posteriorly displacement of the chin point is a particular dysmorphology of the symphysis in TCS individuals. It has been shown to be a complementary mandibular issue in addition to the mandibular retropositioning and micrognathia presented by SNB and Co-Gn data[4]. On the other hand, this posteriorly displacement of pogonion point does not seem to influence either the mandibular position (SNB) or the maxillomandibular sagittal relationship (ANB),

A clear topic on TCS studies[1-3,5-9], the reduction in size of maxilla and mandible, were also found in the present investigation. The maxillary and mandibular sagittal lengths were significantly reduced as compared to control group, especially the mandible, that presented a definitive micrognathia (Co-Gn, reduced in 15% and Go-Me reduced in 25%).

In spite of the smaller reduction (5%), maxillary sagittal length (Co-A) was found to be moderately positive correlated with pharyngeal V. As expected, it has also been shown that mandibular micrognathia, assessed by means of Co-Gn, is strongly correlated with the airway dimensional reduction. This information supports the importance of surgical procedures for mandibular advancement, such as distraction osteogenesys and orthognathic surgery[1-3,8-11], as predictable steps for improvement of the pharyngeal airway, the occlusion and the facial aesthetics.

From a clinical point of view, it can be noticed that the lower anterior face height (LAFH) of TCS individuals, a linear dimension associated to facial growth, is increased in relation to maxillomandibular dimensions, and some clinical observations are associated to this, as follows: (1) an anterior open bite malocclusion, (2) lips incompetence, (3) a retrognathic chin, (4) hypertonia of the mentonian muscle, and (5) the hyperdivergent growth pattern. However, when compared to CG, the LAFH was found to be significantly reduced. This is because, the LAFH is a result of the geometric arrangement of the retrognathic mandible and the hypoplastic maxilla. Given the diminutive dimensions of the maxillomandibular complex of TCS, it was not surprising to found an 9% reduction of the LAFH in relation to CG.

In a recent study on TCS[5], the authors have stated that reduction in posterior facial height, assessed by means of the vertical length of mandibular ramus (Co-Go), are amongst the main predictors of clinical severity in TCS. Indeed, the significant reduction of ramus height (Co-Go) is a characteristic of TCS also found in our study. The 13% reduction in relation to controls was strongly and positively correlated with the pharyngeal V and mCSA.

As mentioned before, although both groups had no significant differences regarding growth pattern angles, they were all increased in the TCS group. Together, these angles support the hyperdivergent growth pattern of TCS, even as compared to high angle subjects, a characteristic of clinical significance. Regarding growth pattern, another important data observed was the clockwise rotation of the palatal plane in relation to the cranial base (SN.PP). The steepness (clockwise rotation) of the maxillary plane is one hallmark of TCS and is believed to be related to the upper displacement of the posterior nasal spine and not to the lower displacement of the anterior nasal spine[3]. It is our understanding that this feature may be a maxillary compensatory mechanism caused by the mandibular ramus height reduction (Co-Go). Finally, it was expected that growth pattern could be a predictor of the pharyngeal dimensions, however, no association was found between these variables.

It must be emphasized that morphological findings[29] must be complemented by functional investigations. Instrumental evaluations such as polysomnography, acoustic rhinometry, rhinonanometry[27,30-33] and computational fluid dynamics assessment[34] could confirm the airway reductions as the main cause of the respiratory complaints referred by these individuals.

It is important to point out that body mass index and gender were variables not controlled in this study, since comprising an adequate sample of a rare syndrome is not an easy task. Another important topic refers to the control group. It is our impression that if a control group of individuals without any craniofacial condition was assessed, for instance, subjects with a normal growth and a skeletal class I malocclusion, differences on pharyngeal dimensions would be statistically detected., Finally, tongue volume and hyoid position[35,36] are variables considered by the

literature as having strong correlations with upper airway collapsibility[25,26] and must be assessed in future studies.

In summary, the results of the present study indicate that the pharyngeal dimensions of subjects with Treacher Collins Syndrome are volumetrically smaller when compared with a group of non-syndromic individuals with class II malocclusion. This airway reduction can be explained by the hyperdivergent growth pattern and by the severe micro and retrognathia observed in the syndromic population analyzed. In turn, considering that reduced pharyngeal volumes, reduced pharyngeal cross-sectional areas and mandibular retropositioning represent risk factors for airway obstruction, it can be stated that this syndromic population are more prone to develop obstructive sleep apnea.

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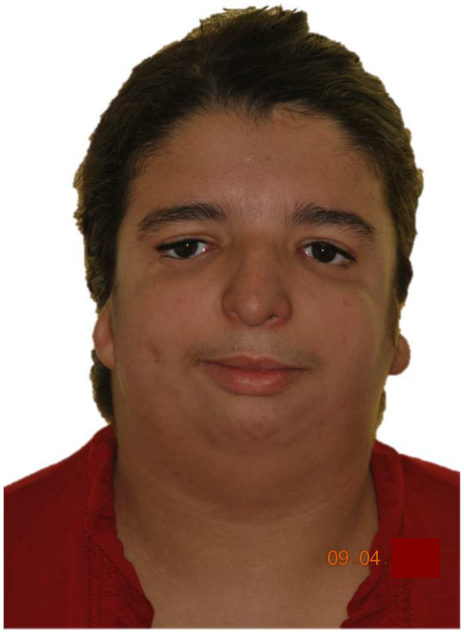


Fonte: HRAC-USP

Figure 1 – Facial characteristics of an individual with Treacher Collins Syndrome (Frontal and lateral views)

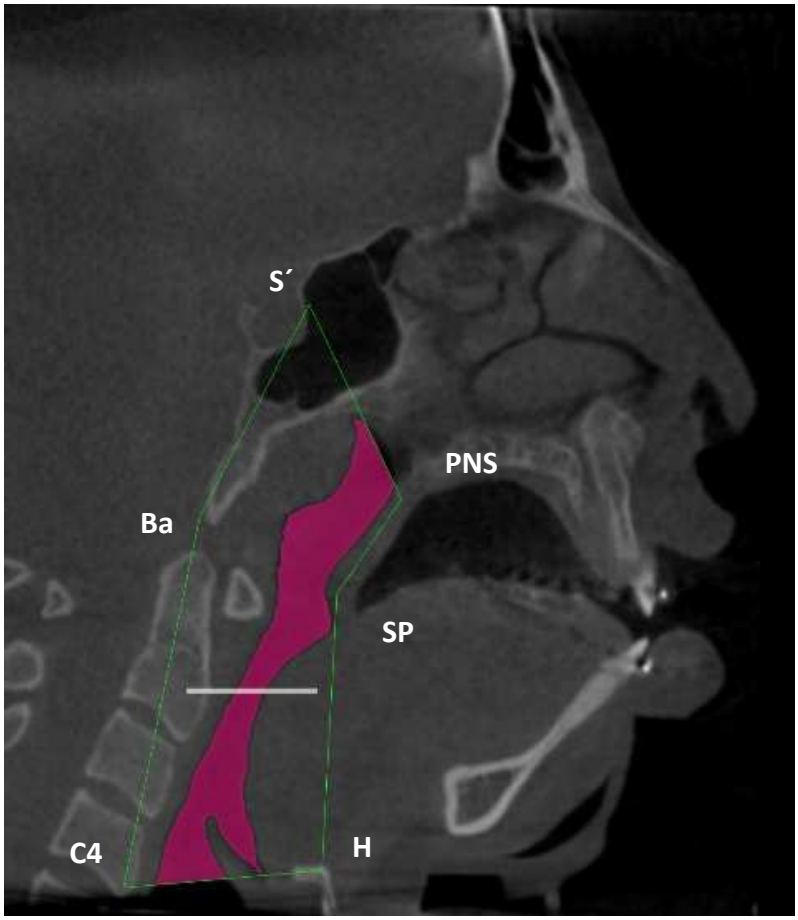


Figure 2 – The six anatomical landmarks that form the polygon to assess the pharyngeal dimensions. Ba: basion; S´: anterosuperior edge of the pituitary saddle; C4: anterior limit of the fourth cervical vertebra; H: anterior limit of the hyoid bone, SP: inferior limit of soft palate; PNS: posterior nasal spine. Fonte: (HRAC-USP)

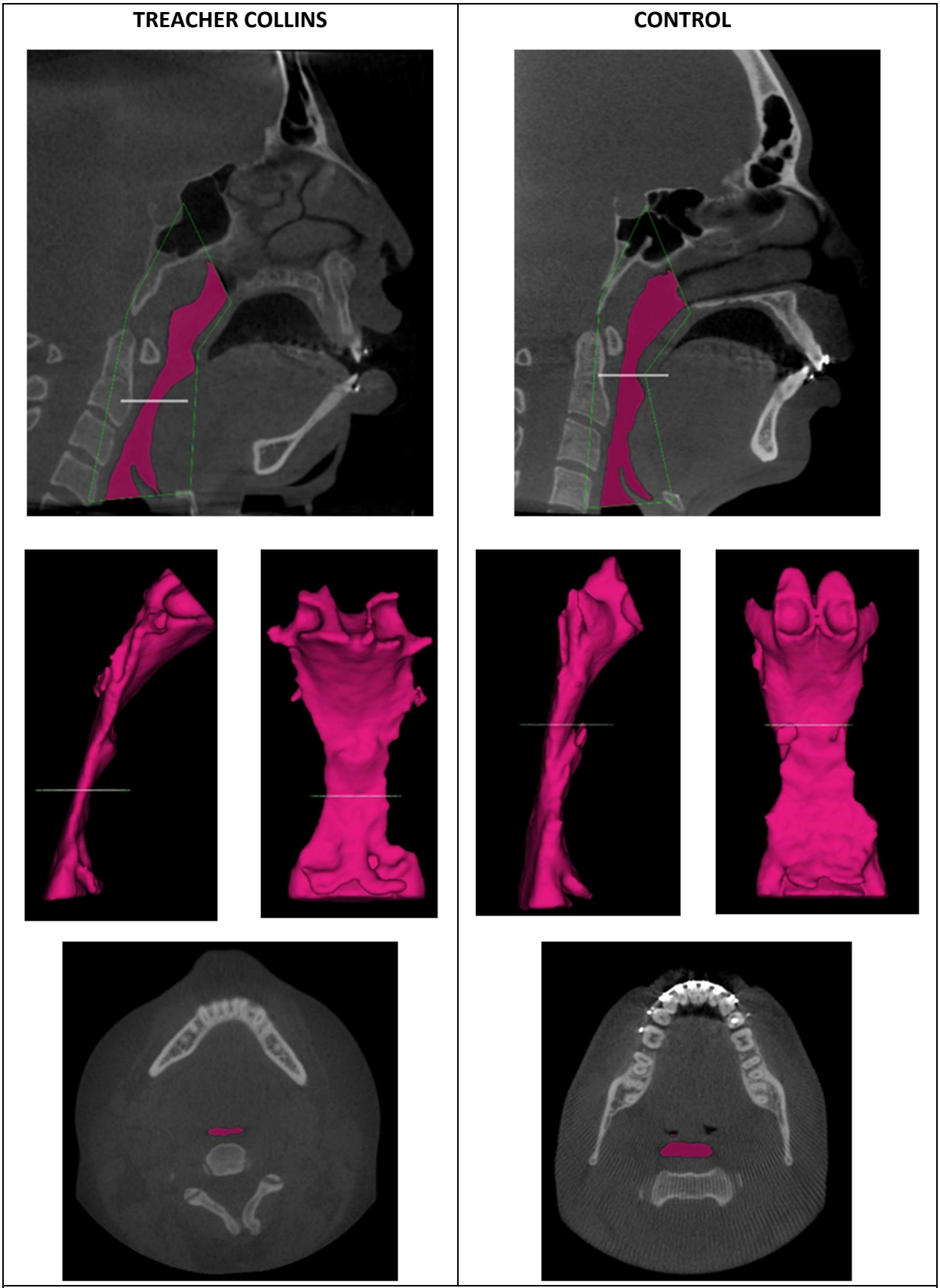


Figure 3 – Tomographic images of two representative patients of Treacher Collins Syndrome group and Control group, illustrating the 3D reconstruction of the pharynx and the minimum cross-sectional area. (Fonte: HRAC-USP)

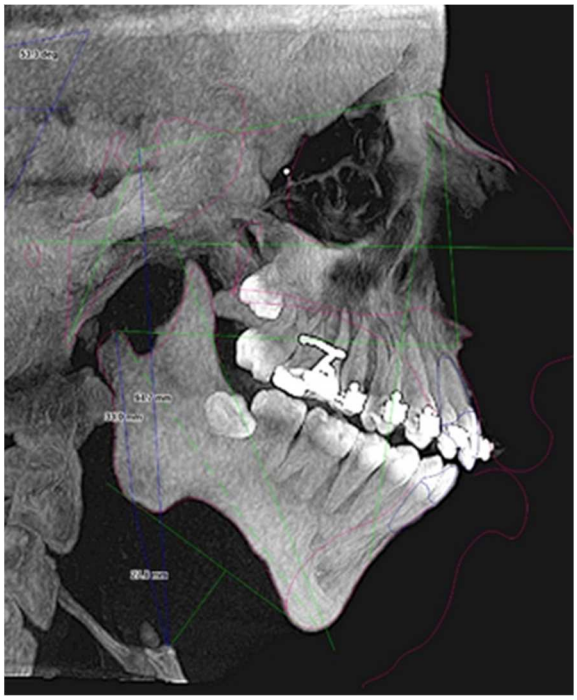
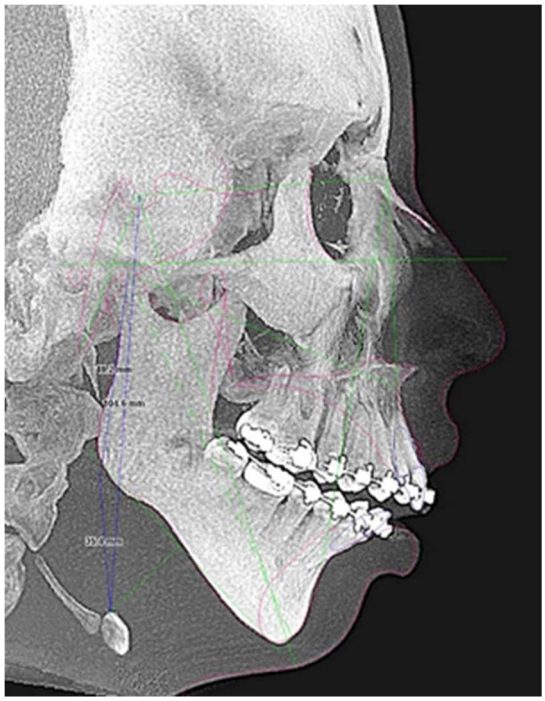
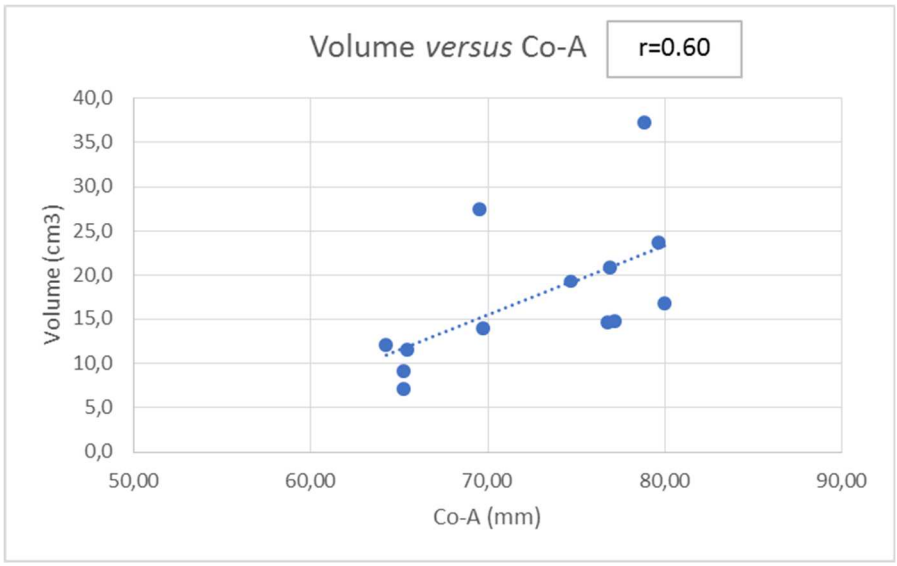
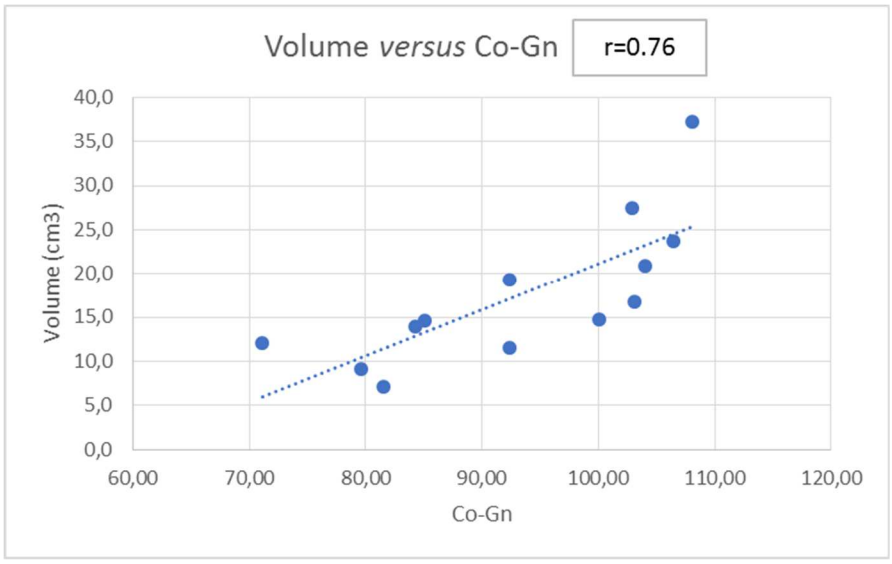
TREACHER COLLINS	CONTROL
	

Figure 4 – Tomographic images of two representative patients of Treacher Collins Syndrome group and Control group, illustrating the cephalometric analysis.. (Fonte: HRAC-USP)





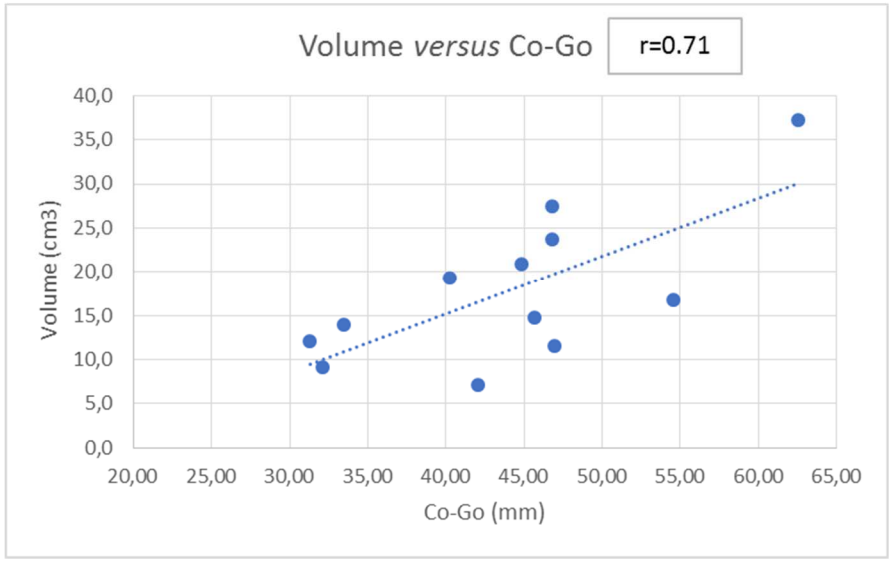
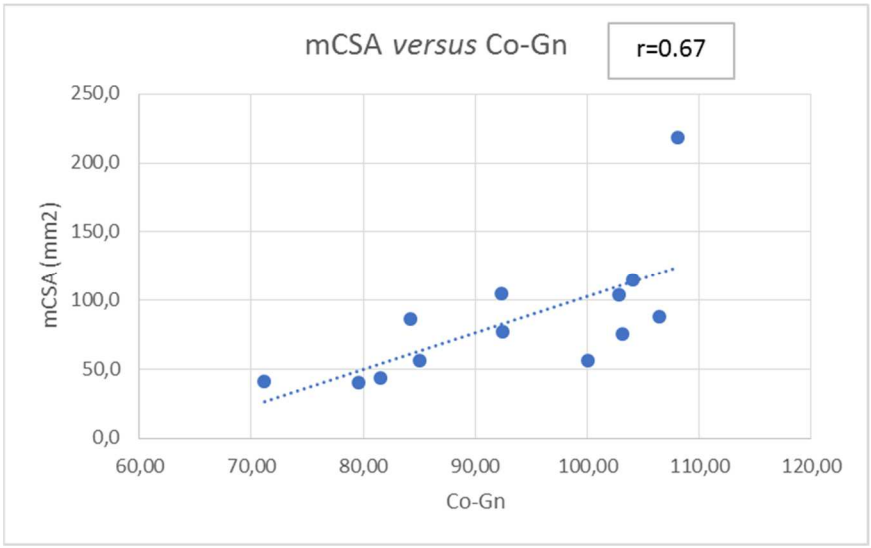


Figure 5 – Correlation between variable volume (V), expressed in cm3, and maxillary and mandibular dimensions (Co-A, Co-Gn and Co-Go).



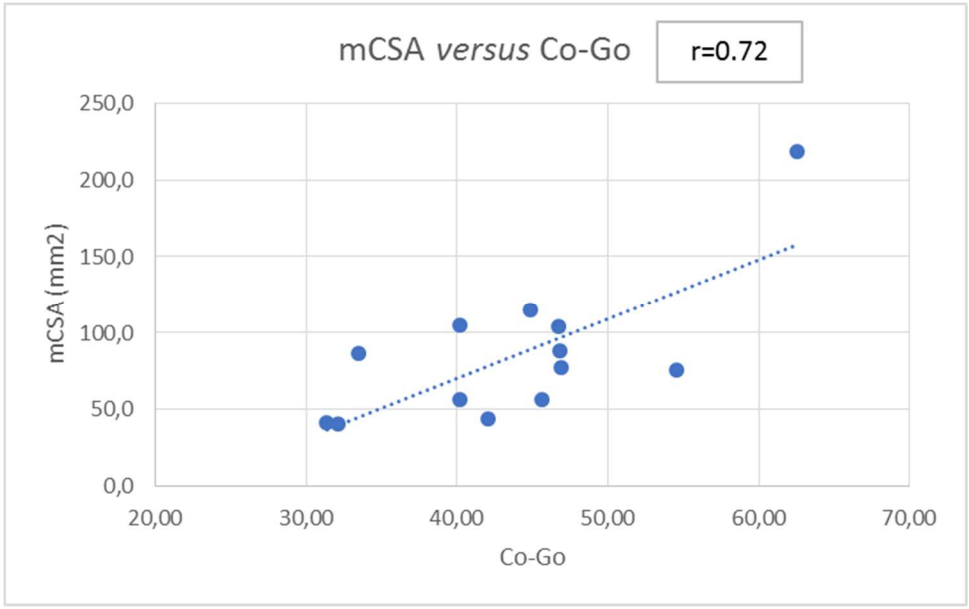


Figure 6 – Correlation between variable minimum cross-sectional area (mCSA), expressed in cm3, and maxillary and mandibular dimensions (Co-A, Co-Gn and Co-Go).

Table 1 - Definitions of all cephalometric landmarks and planes at the sagittal aspect.

VARIABLE	DEFINITION
Condylion (Co)	The most posterior/superior point on the condyle of the mandible
Orbitale (Or)	The most inferior point on the lower border of the orbit
Porion (Po)	The most superior point of the surface of the external auditory meatus
Sella (S)	Point at the center of sella turcica (pituitary fossa)
Pogonion (Pg)	The most anterior point of mandibular symphysis
A point (A)	The deepest point at concavity of anterior maxilla (subspinale)
B point (B)	The deepest point at concavity of mandibular symphysis (supramentale)
Menton (Me)	The lowest point on mandibular symphysis
Nasion (N)	Point at the junction of frontal and nasal bones (frontonasal suture)
Anterior Nasal Spine (ANS)	The most anterior point on maxillary bone at the inferior margin of the piriform aperture
Posterior Nasal Spine (PNS)	Posterior limit of hard palate
Gnathion (Gn)	The most anterior point on mandibular symphysis midway between Pg and Me
Gonion (Go)	The most posterior inferior point on the outline of the angle of the mandible
Mandibular plane (MP)	Plane from constructed Gonion (Go) to Menton (Me)
Frankfort horizontal (FHP)	Plane passing through points Orbitale (Or) and Porion (Po)

Table 2 – Definitions of all cephalometric measurements.

VARIABLE	DEFINITION
Mx/Md sagittal position	
SNA	Angle subtended from sella (S) by means of Nasion (N) to maxillary point A.
SNB	Angle subtended from sella (S) by means of Nasion to mandibular point B.
ANB	Angle subtended from maxillary point A by means of Nasion (N) to mandibular point B.
Pg-NB	Perpendicular distance from chin point to reference line NB
Mx/Md Dimensions	
Co-A (Maxillary unit length)	Distance between Condylion (Co) and A point
Co-Gn (Mandibular unit length)	Distance between Condylion (Co) and Gnathion (Gn)
LAFH (Lower Anterior Facial Height)	Distance between Anterior Nasal Spine (ANS) and Menton (Me)
Growth Pattern	
SN.SGn	Angle between anterior cranial base (S-N) and Y axes (S-Gn)
SN.GoGn	Angle between anterior cranial base (S-N) and mandibular plane (Go-Gn)
SN.PP	Angle between anterior cranial base (S-N) and palatal plane (ANS-PNS)
FMA	Angle between Frankfort horizontal plane (Po-Or) and mandibular plane (Go-Me)

Table 3 – Upper Airways Dimensions and cephalometric measurements (means and standard deviation) of the control and Treacher Collins Syndrome (TCS) groups.

VARIABLES	CONTROL GROUP	TCS GROUP	%Δ
Age	26,6(5.4)	20,2(4.7)	--
Upper Airways Dimensions			
V (cm^3)	19.9(4.7)	17.5(8.2)	-12
mCSA (mm^2)	107.8(40.0)	84.6(47.4)	-22
Location of mCSA			
oropharynx (%)	92	100	--
hypopharynx (%)	8	--	--
Mx/Md sagittal position			
SNA (°)	80.0(3.8)	79.2(5.4)	-1
SNB (°)	71.9(3.0)	69.9(7.1)	-3
ANB (°)	8.4(2.1)	9.3(3.2)	+10
Pg-NB (mm)	-1.3(2.9)	-3.8(3.0)*	+192
Mx/Md Dimensions			
Co-A (mm)	76.8(3.3)	72.6(6.1)*	-5
Co-Gn (mm)	109.1(5.0)	93.2(12.0)*	-15
LAFH (mm)	75.8(4.9)	69.1(9.3)*	-9
Co-Go	50.2(5.8)	43.7(8.8)*	-13
Go-Me	61.2(3.7)	46.0(6.5)*	-25
Growth Pattern			
SN.SGn (°)	78.6(3.3)	80.3(8.0)	+2
SN.GoGn (°)	47.7(6.7)	50.5(8.8)	+6
SN.PP(°)	6.5(2.4)	21.2(4.4)*	+226
FMA (°)	37.6(7.8)	40.6(7.2)	+8

%Δ: percentual variation; Mx: maxillary; Md: mandibular; * $p<0.05$

5 GENERAL CONCLUSIONS

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The results of the present study indicate that the pharyngeal volumes and minimal cross-sectional areas of subjects with Treacher Collins Syndrome are reduced when compared with a group of non-syndromic individuals with class II malocclusion. This airway reduction can be explained by the high angle growth pattern and by the severe micro and retrognathia observed in the syndromic population analyzed. The reduced pharyngeal dimensions and the hyperdivergent growth pattern observed on the present sample are known as being risk factors for upper airway impairment, leading to obstructive sleep apnea.

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ANNEXES

ANEX 1

FOLHA DE APROVAÇÃO DO PROJETO DE PESQUISA

(PROJETO GUARDA-CHUVA)

HOSPITAL DE REABILITAÇÃO
DE ANOMALIAS CRANIOFACIAIS
UNIVERSIDADE DE SÃO PAULO
Serviço de Apoio ao Ensino, Pesquisa e Extensão
Seção de Apoio à Pesquisa

Ofício nº 72/2015-SVAPEPE-CEP

Bauru, 11 de maio de 2015.

Prezada Senhora

O projeto de pesquisa intitulado "**Vias aéreas superiores nos pacientes com fissura labiopalatina: análise tridimensional por tomografia computadorizada de feixe cônico**", de autoria de Thiago Freire Lima, foi aprovado pelo CEP em 29/10/2013. Na reunião realizada em **28/04/2015**, a alteração de pesquisador responsável para Ivy Kiemle Trindade Suedam foi **aprovada**.

Informamos que após o recebimento do trabalho concluído, este Comitê enviará um parecer final que deverá ser utilizado para publicação do trabalho.

Atenciosamente,

CD. SILVIA MARIA GRAZIADEI
Coordenadora do Comitê de Ética em Pesquisa em Seres Humanos do HRAC-USP

Ilma. Sra
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FOLHA DE APROVAÇÃO DO PROJETO DE PESQUISA (PROJETO GUARDA-CHUVA)

MINISTÉRIO DA SAÚDE - Conselho Nacional de Saúde - Comissão Nacional de Ética em Pesquisa – CONEP
PROJETO DE PESQUISA ENVOLVENDO SERES HUMANOS

Projeto de Pesquisa:
VIAS AÉREAS SUPERIORES NOS PACIENTES COM FISSURA LABIOPALATINA: ANÁLISE TRIDIMENSIONAL POR TOMOGRAFIA COMPUTADORIZADA DE FEIXE CÔNICO.

Informações Preliminares

Responsável Principal

CPF/Documento: 270.389.238-11	Nome: IVY KIEMLE TRINDADE SUEDAM
Telefone: 1432358282	E-mail: ivysuedam@fob.usp.br

Instituição Proponente

CNPJ: 63.025.530/0082-70	Nome da Instituição: Hospital de Reabilitação de Anomalias Craniofaciais da USP

Essa submissão de emenda é exclusiva do seu Centro Coordenador?

A emenda é exclusiva de seu Centro Coordenador, então as alterações realizadas em seu projeto, em virtude da emenda, NÃO serão replicadas nos Centros Participantes vinculados e nos Comitês de Ética das Instituições Coparticipantes, quando da sua aprovação.

É um estudo internacional? Sim

■ **Assistentes**

CPF/Documento	Nome
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■ **Equipe de Pesquisa**

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Área de Estudo

Grandes Áreas do Conhecimento (CNPq)

- Grande Área 4. Ciências da Saúde

Propósito Principal do Estudo (OMS)

- Ciências Básicas

Título Público da Pesquisa: VIAS AÉREAS SUPERIORES NOS PACIENTES COM FISSURA LABIOPALATINA: ANÁLISE TRIDIMENSIONAL POR TOMOGRAFIA COMPUTADORIZADA DE FEIXE CÔNICO.

Contato Científico: IVY KIEMLE TRINDADE SUEDAM

ANEX 2 - Individual and mean values (standard deviation) of the pharyngeal dimensions (area and volume) measurements of Treacher Collins Group (TCG) and Control Group (CG).

	PHARYNGEAL DIMENSIONS					
PATIENT	**AGE**		**VOLUME (cm3)**		**MINIMAL CROSS-SECTIONAL AREA (mm2)**	
	TCS (n=13)	**CG (n=13)**	**TCS (n=13)**	**CG (n=13)**	**TCS (n=13)**	**CG (n=13)**
1	17	27	23,7	20.8	87.5	112.5
2	22	30	11,5	26.2	76.3	143.4
3	26	21	19.2	19.9	104.1	94.2
4	21	25	14.5	23.9	55.5	177.5
5	20	21	16.7	18.4	75.1	95.1
6	23	22	27.4	16.8	103.3	69.7
7	18	26	20.8	28.3	114.1	149.3
8	17	36	12.0	10.1	40.7	41.8
9	18	35	14.7	17,8	56.1	120.9
10	15	33	13.9	19.8	85.7	50.5
11	15	20	9.0	18.9	40.3	85.0
12	16	23	7.1	21.9	43.2	126.4
13	31	26	37.0	16.6	218.3	135.3
MEAN	20.2	26.6	17.5	19.9	84.6	107.8
SD	4.7	5.4	8.2	4.7	47.4	40.0

ANEX 3 - Individual and mean values (standard deviation) of the cephalometric measurements of Treacher Collins Group (TCG).

VARIABLES	CEPHALOMETRIC MEASUREMENTS TCS GROUP												
SNA (°)	81,45	72,70	72,65	89,55	82,45	82,20	83,05	83,55	77,55	80,65	72,85	79,05	71,65
SNB (°)	76,20	60,95	60,40	77,65	77,20	78,20	70,10	75,45	69,60	70,85	64,30	70,85	57,40
ANB (°)	5,25	11,70	12,25	11,90	5,25	4,00	12,90	8,15	8,05	9,80	8,55	8,15	14,25
FMA (°)	38,40	52,85	51,50	35,00	45,00	38,65	35,00	35,05	33,10	41,85	39,75	31,35	49,85
SN-SGn(°)	75,50	97,80	93,25	68,95	77,40	71,20	79,80	75,60	77,20	80,10	80,05	82,45	84,85
SN-GoGn(°)	47,15	70,50	64,75	39,15	51,65	45,15	46,75	46,90	45,05	52,50	50,20	41,75	54,40
Co-A (mm)	79,70	65,50	74,70	80,00	69,55	76,90	64,30	77,20	69,75	65,25	65,30	78,85	76,80
Co-Gn (mm)	106,47	92,45	92,40	103,15	102,90	104,10	71,15	100,10	84,30	79,65	81,55	108,10	85,10
LAFH (mm)	63,10	81,25	79,15	70,10	69,00	67,40	62,45	67,70	56,30	58,05	60,10	84,15	79,55
Go-Me (mm)	54,40	37,85	49,65	45,60	49,40	52,65	37,45	53,05	51,80	41,35	38,35	47,65	38,80
Pog-NB (mm)	-4,10	-7,90	-6,00	-1,80	-7,90	-2,55	-4,10	-5,05	-1,45	-6,05	-0,55	-4,10	2,75
Co-Go (mm)	46,85	46,95	40,25	54,60	46,80	44,85	31,35	45,70	33,50	32,15	42,05	62,55	40,25
SN.PP(°)	21,95	22,15	22,35	22,55	22,75	22,95	23,15	23,35	23,55	23,75	23,95	14,05	9,00

ANEX 4 - Individual and mean values (standard deviation) of the cephalometric measurements of Control Group (CG).

VARIABLES	**CEPHALOMETRIC MEASUREMENTS CONTROL GROUP**												
SNA (^{O})	80,00	80,80	86,50	75,30	76,50	74,70	82,60	81,55	83,75	75,05	82,65	79,65	83,95
SNB (^{O})	70,30	73,70	74,00	67,45	66,30	71,10	73,65	71,75	75,80	68,80	74,40	71,35	75,45
ANB (^{O})	9,70	7,10	12,50	7,85	10,15	3,60	8,95	9,80	7,95	6,25	8,30	8,30	8,50
FMA (^{O})	38,20	41,20	47,35	36,40	44,85	38,25	19,15	50,10	33,50	33,70	35,15	31,55	39,00
SN-SGn(^{O})	78,45	76,80	78,45	82,60	83,30	76,55	73,85	84,35	74,70	81,50	77,40	76,00	77,95
SN-GoGn(^{O})	46,45	46,05	49,15	51,90	56,55	50,30	28,85	56,70	46,75	47,45	47,90	42,05	49,65
Co-A (mm)	73,20	78,40	73,55	77,85	78,50	72,60	78,40	76,05	81,05	70,75	77,35	79,50	81,30
Co-Gn (mm)	98,30	114,25	106,40	109,95	106,75	108,80	105,90	110,40	115,95	109,55	115,95	104,00	111,80
LAFH (mm)	69,75	75,00	77,10	78,50	78,75	69,20	72,45	84,25	71,90	81,55	80,35	69,45	77,35
Go-Me (mm)	55,75	60,55	59,45	63,25	60,60	65,60	60,25	60,85	69,05	61,15	67,75	61,40	59,55
Pog-NB (mm)	-2,25	-0,45	-2,15	-1,10	-1,60	2,80	-0,45	-7,30	-0,25	2,75	-0,20	0,00	-6,10
Co-Go (mm)	45,60	53,70	49,70	47,80	43,85	43,55	65,10	48,65	47,10	57,15	50,20	50,05	49,90
SN.PP(^{O})	4,75	3,85	3,40	4,20	7,90	8,60	5,30	8,05	8,25	5,50	8,20	11,35	5,10