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Three-Dimensional Upper Airway Assessment in Treacher Collins Syndrome

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Abstract

Objectives: The purpose of this investigation was to assess the *pharyngeal dimensions* and the *craniofacial morphology* of individuals with Treacher Collins syndrome (TCS) when compared to vertical skeletal class II individuals. It is our hypothesis that the upper airways of individuals with TCS are reduced in view of the skeletal pattern and the maxillomandibular dysmorphologies.

Materials and Methods: Cone-beam computed tomography scans of 26 individuals had the pharyngeal volume (V) and minimal cross-sectional area (mCSA) evaluated. Study group (TCS) was formed by 13 scans of patients with TCS (7 males and 6 females; 20.2 $\pm$ 4.7 years). Control group (CG) assembled 13 scans of nonaffected individuals with the same type of skeletal pattern (2 males and 11 females; 26.6 $\pm$ 5.4 years). Cephalometric data of maxillomandibular position, maxillomandibular dimensions, and growth pattern were assessed. Statistical analysis ($P \leq .05$) 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 was mostly at the oropharyngeal level. Individuals with TCS presented retrognathic chin, reduced maxillomandibular dimensions, and increased clockwise rotation of the palatal plane. Maxillary and mandibular lengths were correlated with pharyngeal V and mCSA.

Conclusions: The pharyngeal dimensions of individuals with TCS are impacted by the micrognathia and retrognathia. In association with the skeletal pattern, the reduction of the airways, although not statistically significant, may explain the increased prevalence of airways disorder in this syndrome.

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. This syndromic condition is mostly derived from mutations of the gene *TCOF1*, mapped at the chromosome 5 (Trainor et al., 2009; Trainor & Andrews, 2013, van Gijn et al., 2013; Kadakia et al., 2014). Its main clinical features include hypoplasia of maxilla, mandible, and zygoma (Posnick & Ruiz, 2000; de Oliveira Lira Ortega et al., 2007; Cobb et al., 2014). It is estimated that approximately 46% of the individuals with TCS have some degree of airway obstruction (Plomp et al., 2012; Plomp et al., 2016), ranging from mild obliteration to severe and life-threatening obstructive sleep apnea (OSA).

Despite the great phenotypic variability (Posnick & Ruiz, 2000; Chong et al., 2008; Kapadia et al., 2013; Chung et al., 2014; Cobb et al., 2014; Ma et al., 2015a; Ma et al., 2015b; Esenlik et al., 2017), craniofacial analysis of young adults with TCS brings up the hyperdivergent type and the skeletal class II malocclusion as standard features of this syndrome. Moreover, different studies on nonsyndromic populations (Grauer et al.,

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2009; Alves et al., 2012; Flores-Mir et al., 2013; Wang et al., 2014; Lopatiene et al., 2016a; Lopatiene et al., 2016b) have shown that the skeletal class II malocclusion and the high angle growth pattern are among the predisposing factors for pharyngeal obstruction, recurrent respiratory infections, and the occurrence of OSA.

The influence of craniofacial form on the airway morphology of individuals with syndrome has long been studied, but no conclusive data could be noticed. In general, it is speculated that TCS individuals have reduced upper airway volume caused by the shortening and the retrognathic position of the mandible (Ma et al., 2015b; Plomp et al., 2016), leading to facial convexity and dysfunctional occlusion (Chong et al., 2008; Kapadia et al., 2013, Chung et al., 2014).

Despite the evidence of these findings, the role of craniofacial pattern and malocclusion on pharyngeal volume of TCS remains unclear. Can hyperdivergent growth and skeletal class II malocclusion influence the pharyngeal dimensions of individuals with TCS as they do for nonsyndromic individuals? In face of the question, the purpose of this investigation was to assess the *pharyngeal dimensions* and the *craniofacial morphology* of individuals with TCS when compared to control vertical skeletal class II individuals. It is our hypothesis that the upper airways in individuals with TCS may be reduced, in view of the hyperdivergent skeletal pattern and the maxillo-mandibular dysmorphologies.

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). Researchers signed a liability form for image handling.

One hundred twenty-five patients being diagnosed with TCS were under regular treatment at HRAC/USP at the time of data collection. Inclusion criteria preestablished include adults with TCS and having cone-beam computed tomography scans on i-CAT computed tomography scanner, with a field of view greater than 13 cm, in which the pituitary saddle, the fourth cervical vertebra, and the hyoid bone were present. Exclusion criteria include individuals with TCS having a cleft palate, children (in the mixed dentition phase) or elderly patients (older than 65 years), 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 (CG) from a maxillofacial private practice was also assessed and was composed of 13 nonsyndromic dolichocephalic skeletal class II individuals matched (ANB and FMA) with those in the TCS group. Control group selection was based on cephalometric assessment performed by 1 single operator. Inclusion criteria were defined as individuals having the ANB and FMA angles greater than 4° and 30°, respectively.

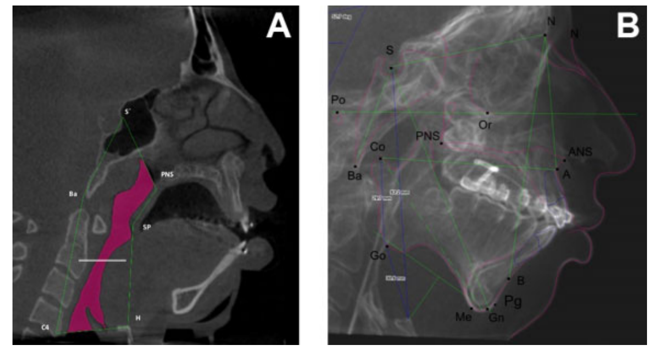

Figure 1. A, The 6 anatomical landmarks that form the polygon to assess the pharyngeal dimensions. Ba indicates basion; S', anterosuperior edge of the pituitary saddle; C4, anterior limit of the fourth cervical vertebra; H, anterior limit of the hyoid bone, SP, inferior limit of soft palate; PNS, posterior nasal spine. B, The craniofacial points used for the cephalometric measurements.

Cone-beam computed tomographies from the control and TCS groups 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, Pennsylvania), with the following specifications: FOV $\geq$ 13 cm, 26.9 seconds (exposure time), 120 kV, 37 mA, and a resolution of 0.25 voxels or greater. Images were saved as DICOM files (Digital Imaging and Communications in Medicine) and analyzed with Dolphin Imaging 11.8 software (Dolphin Imaging, Chatsworth, California). 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 1A). Once outlined, the pharyngeal airway was segmented from the surrounding tissues in a semiautomatic manner, followed by manual refining, which consisted in depuration of areas not software noticed in the axial, sagittal, and coronal planes. Up next, a 3-dimensional (3D) image of the airway was rendered and had its pharyngeal volume (V) and minimal cross-sectional area (mCSA) calculated (Figure 2).

The location of the CSA was determined based on the study by Yoshihara et al. (2012). The pharynx was divided into 3 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 the sagittal plane. Seven

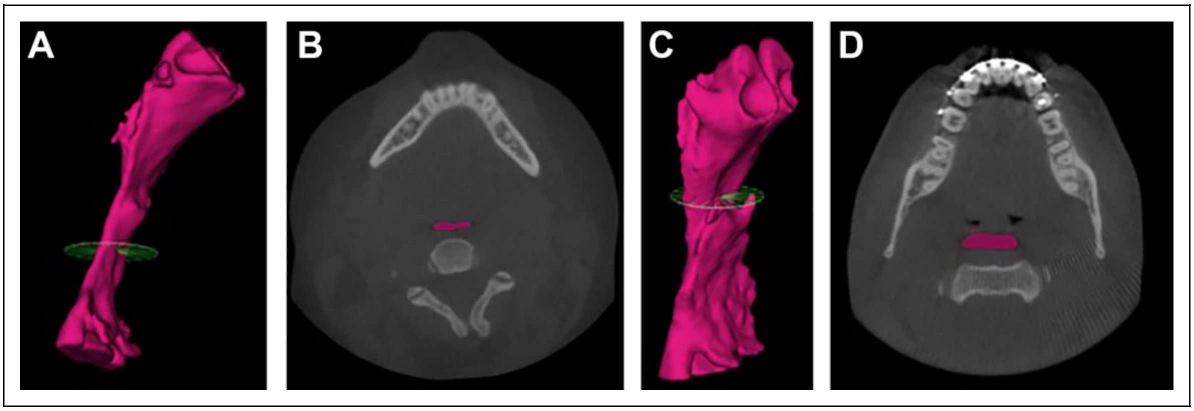

Figure 2. Three-dimensional reconstruction of the pharyngeal airway and the minimum cross-sectional area (mCSA) of representative patients of the Treacher Collins syndrome group (A and B) and the control group (C and D).

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)

angular and 6 linear measurements were assessed by means of 14 craniofacial landmarks (Figure 1B). They were segmented into 3 specific variables: m*axillomandibular sagittal position*, *maxillomandibular dimensions*, and *growth pattern*, as seen in Tables 1 and 2. All airway and cephalometric measurements were performed twice by the same trained and blinded evaluator, with a minimum interval of 30 days between them. A second blinded operator assessed 50% of the airway samples for interexaminer comparison.

Intraclass correlation coefficient (ICC) was used to assess intra- and interexaminer agreement. Descriptive statistical data of mean value and standard deviation (SD) were calculated for each parameter in controls and in the TCS group. Statistical analysis included independent sample Student 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 $r = 0$ to 0.29 were considered as indicative of negligible correlation, $r = 0.30$ to 0.49 weak correlation, $r = 0.50$ to 0.69 moderate

Table 3. Upper Airways Dimensions and Cephalometric Measurements (Means and Standard Deviation) of the Control and 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)[a]	+192
Mx/Md dimensions			
Co-A, mm	76.8 (3.3)	72.6 (6.1)[a]	−5
Co-Gn, mm	109.1 (5.0)	93.2 (12.0)[a]	−15
LAFH, mm	75.8 (4.9)	69.1 (9.3)[a]	−9
Co-Go	50.2 (5.8)	43.7 (8.8)[a]	−13
Go-Me	61.2 (3.7)	46.0 (6.5)[a]	−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)[a]	+226
FMA (°)	37.6 (7.8)	40.6 (7.2)	+8

Abbreviations: LAFH, lower anterior facial height; mCSA, minimal cross-sectional area; Pg-NB, perpendicular distance from chin point to reference line NB; SNA maxillary position; SNB, mandibular position; TCS, Treacher Collins syndrome; V, volume.
[a]Statistical significance ($P < .05$).

correlation, and $r = 0.70$ to 1.00 strong correlation (Hinkle et al., 2003).

Results

A high interexaminer agreement was found (ICC = 0.98) for the control and TCS groups. Intraexaminer agreement was also high (ICC = 0.99) in both groups. Considering this high agreement, the mean values of the most experienced evaluator were considered for analysis. The results are reported in Table 3.

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

As seen in 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 statistically increased in the 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 group were statistically reduced when compared to the CG. Growth angles (SN.SGn, SN.GoGn, SN.PP, and FMA) were increased in the TCS group, and a statistical significance was observed only for the SN.PP variable.

Strong positive correlations were found between pharyngeal V versus Co-Gn, V versus Co-Go, and mCSA versus Co-Go. Moderate positive correlations were found between pharyngeal V versus Co-A and mCSA versus Co-Gn, as seen in Figure 3. 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.

It has also been observed throughout the sample of the present study that, in 100% of the cases (TCS group), the area of the greatest pharyngeal constriction (mCSA) was located at the oropharyngeal level. These data surely relate to the severe retrognathia (Pg-NB) observed in these patients. This is in accordance with Tang et al. (2012), which indicates that the oropharynx is the main site of obstruction in individuals with OSA syndrome.

Both groups assessed in the present study presented the same type of craniofacial skeletal pattern, that is, a skeletal class II malocclusion and a high angle facial growth. In addition, the 2 groups presented a relatively well-positioned maxilla in the horizontal aspect (SNA), a similar degree of mandibular retropositioning (SNB), and a comparable severity of skeletal class II malocclusion (ANB). Indeed, a weak correlation was observed between the pharyngeal dimensions of TCS group and the parameters SNB and ANB. Even so, these findings must be highlighted, as the retropositioning of the mandible is considered an important predisposing factor for the upper airways collapsibility (Oh et al., 2011; Flores-Mir et al., 2013; Cobb et al., 2014; Ma et al., 2015b; Esenlik et al., 2017).

Although the groups were matched for the skeletal pattern, the cephalometric data showed the individuals with TCS as having a more severe craniofacial condition, as represented by the statistically significant retrognathia (Pg-NB), micrognathia (Co-Gn), and hyperdivergent growth (SN.PP).

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 ($P < .05$). In association, the mandibular sagittal length was statistically reduced in relation to the CG (Co-Gn reduced in 15% and Go-Me in 25%). These particular dysmorphologies of individuals with TCS (Esenlik et al., 2017) reinforce the accentuated retrognathic tendency found in this syndromic population (Posnick & Ruiz, 2000; Kapadia et al., 2013; Chung et al., 2014; Cobb et al., 2014; Ma et al., 2015a, Ma et al., 2015b; Plomp et al., 2016; Esenlik et al., 2017).

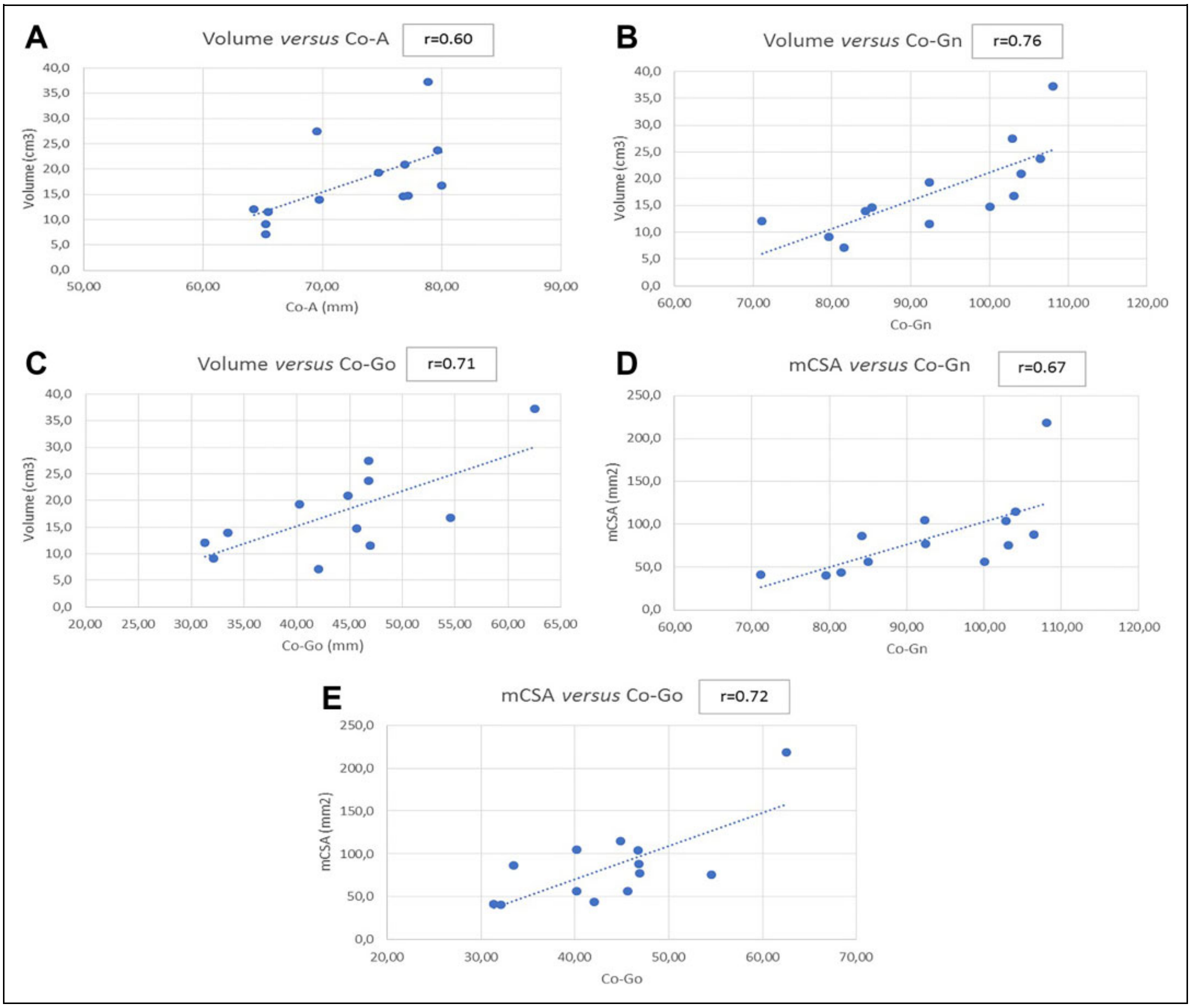

Figure 3. A-E, Positive correlations between pharyngeal airway (volume [V] and minimum cross-sectional area [mCSA]) and maxillomandibular dimensions in the Treacher Collins syndrome group.

It has also been shown that mandibular micrognathia, assessed by means of Co-Gn, was strongly correlated with the airway dimensional reduction. This information supports the importance of surgical procedures for mandibular advancement, such as distraction osteogenesis and orthognathic surgery (Posnick et al., 2000; Cobb et al., 2014; Plomp et al., 2016) for improvement of the pharyngeal airway, the occlusion, and the facial aesthetics.

The lower anterior facial height in the TCS group presented a statistically significant reduction in relation to controls. This is because this linear measurement is a result of the geometric arrangement of the retrognathic mandible and the hypoplastic maxilla seen on the syndromic group. A statistically significant reduction was also seen on the *posterior* facial height, assessed by means of the vertical length of mandibular ramus (Co-Go). The latter cephalometric measurement is among the main predictors of clinical severity in TCS (Esenlik et al., 2017). In our study, it was found to be strongly and positively correlated with the dimensional reduction observed in the pharyngeal V and mCSA.

Regarding the growth pattern angles, they were all increased in the TCS group. However, only the SN.PP angle was found to present a statistical difference between groups. Even so, these angles together characterize hyperdivergent growth pattern of the TCS group, an attribute of clinical significance. In this regard, one important observation was the clockwise rotation of the palatal plane in relation to the cranial base (SN.PP). The steepness of the maxillary plane is one hallmark of TCS and is believed to be related to the upper displacement of the posterior nasal spine (Posnick et al., 2000). 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 must be complemented by functional investigations (Pimenta et al., 2015). Instrumental evaluations such as polysomnography, acoustic rhinometry, rhinomanometry (Fukushiro & Trindade, 2005; Trindade et al., 2009; Trindade et al., 2010;

Trindade-Suedam et al., 2016; Trindade-Suedam et al., 2017), and computational fluid dynamics assessment (Farzal et al., 2016) 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 CG. It is our impression that if a CG of individuals without any craniofacial condition was assessed, for instance, individuals with a normal growth and a skeletal class I malocclusion, differences in pharyngeal dimensions would be statistically detected. Finally, tongue volume and hyoid position are variables considered by the literature (Genta et al., 2014; Schorr et al., 2016) as having strong correlations with upper airway collapsibility and must be assessed in future studies.

To sum up, results of the present study indicate that, although not statistically significant, the pharyngeal dimensions of individuals with TCS are volumetrically smaller when compared with a group of nonsyndromic individuals with class II malocclusion. This airway reduction can be explained by the hyperdivergent growth pattern and by the severe micrognathia 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 may be more prone to develop OSA.

Declaration of Conflicting Interests

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