Cephalometric Predictors of Clinical Severity in Treacher Collins Syndrome

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Background: The aim of this study was to identify cephalometric measurements associated with clinical severity in patients with Treacher Collins syndrome.
Methods: A retrospective single-institution review of patients with Treacher Collins syndrome was conducted. Preoperative cephalograms and computed tomographic scans ($n = 30$) were evaluated. Fifty cephalometric measurements were compared to age-specific normative data using analysis of variance. These cephalometric measurements and the patient's Pruzansky classification were correlated to clinical severity using Spearman analysis. Clinical severity was defined as severe (required tracheostomy), moderate (obstructive sleep apnea, oral cleft, or gastrostomy-tube), or mild (absence of listed comorbidities). Cephalometric measurements with a strong correlation ($r > 0.60$) were identified as predictors of clinical severity.
Results: Cephalograms of the study population contained 30 measurements that were found to be significantly different from normative data ($p < 0.01$). These measurements were related largely to maxillary/mandibular projection, maxillary/mandibular plane angle, mandibular morphology, facial height, facial convexity, and mandible/throat position. Ten of these 30 statistically significant measurements in addition to Pruzansky classification were found to be strongly correlated ($r > 0.60$) to clinical severity. These measurements include the following: mandibular projection/position (sella-nasion-pogonion, $r = -0.64$; hyoid-menton, $r = -0.62$); posterior facial height (posterior facial height/anterior facial height, $r = 0.60$; condyle-gonion, $r = -0.66$); maxillary/mandibular plane angle (sella-nasion–mandibular plane, $r = 0.62$; Frankfort horizontal–mandibular plane, $r = 0.61$; sella-nasion–palatal plane, $r = 0.69$; sella-nasion-symphysis, $r = -0.69$); and Pruzansky classification ($r = 0.82$).
Conclusion: Specific cephalometric measurements of increased mandibular retrognathia, decreased posterior facial height, more obtuse maxillary/mandibular plane angle and more obtuse symphysis notch angle are strongly correlated to increased clinical severity in patients with Treacher Collins syndrome. (*Plast. Reconstr. Surg.* 140: 1240, 2017.)

Treacher Collins syndrome is a complex and uncommon craniofacial deformity that affects multiple craniofacial organ systems of the first and second pharyngeal arches, including the eyelids, ears, nose, maxilla, palate, and mandible. This autosomal dominant disorder has an incidence of one in 50,000 live births[1] and has been described as one of the most challenging craniofacial conditions to repair.[2] Treatment requires a multidisciplinary approach and, depending on the clinical severity, patients may require multiple interventions throughout and beyond facial growth and development.[3–7]

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Although numerous studies have described bony and soft-tissue deformities associated with Treacher Collins syndrome,[8–16] limited information is available regarding how specific and quantifiable anatomical aberrations correlate with patient dysfunction.[14,15,17] Moreover, many diagnostic classification schemes used for Treacher Collins syndrome are nonspecific to the disease or have not been correlated to clinical severity. We hypothesize that the bony dysmorphology expressed in Treacher Collins syndrome is progressive in clinical severity; therefore, specific bony deformities may be used to predict the expressivity of the condition. This study aims to identity cephalometrically viewed craniofacial bony aberrations that are statistically associated with increasing clinical severity in this challenging patient population.

PATIENTS AND METHODS

An institutional retrospective review of all patients diagnosed with Treacher Collins syndrome was performed after institutional review board approval was obtained. Clinical and surgical history was documented for each patient. Study inclusion required a cephalometric radiograph to have been obtained before surgical correction of the facial skeleton, specifically, mandibular or maxillary surgery. Surgical interventions preceding imaging, but acceptable for inclusion, were as follows: tracheostomy; orbitozygomatic bone grafting; and soft-tissue manipulation such as cleft lip/palate repair, eyelid and ear reconstruction, and fat grafting. If a computed tomographic scan meeting these inclusion criteria was obtained, a lateral cephalogram was generated from the study. Patients were divided into three evenly distributed age groups, based on their age at the time of imaging: infancy (0 to 2 years), adolescence (5 to 12 years), and young adulthood (15 to 21 years) (Table 1).

Cephalometric analysis was performed using lateral cephalograms to evaluate maxillary-mandibular relationships, vertical plane angles, facial heights, facial convexity, and soft-tissue measurements (Fig. 1). (**See Table, Supplemental Digital Content 1**, which shows cephalometric parameters. Abbreviations and definition of each cephalometric parameter measured are listed, ***http://links.lww.com/PRS/C466***.) Standard measurements were performed on Dolphin Imaging Software (Dolphin Imaging & Management Solutions, Chatsworth, Calif.); additional morphology was studied through manual tracings on Dolphin, collected by a single orthodontist and assessed by a second examiner. Any discrepancies in cephalometric tracings were discussed between orthodontists and a consensus was achieved. In the presence of asymmetry, the lateral cephalogram was traced twice and the deficient side was evaluated using posteroanterior radiographs. Twenty-six angular, five ratio, and 19 linear measurements were used for the cephalometric analysis. Vertical plane angles and facial height–related measurements were excluded from the infant group, who underwent general anesthesia and therefore had open-mouth posture during computed tomographic scanning. Cephalometric parameters were studied among age groups using analysis of variance and later compared to age- and sex-matched Bolton and Moyers normative data,[18] when available, using the independent *t* test (Table 2).

Cephalometric variables and Pruzansky-Kaban classification[19,20] were then correlated to severity of presentation in Treacher Collins syndrome using Spearman analysis. Severity was classified by clinical history and categorized into three groups: severe, moderate, and mild. The severe group encompassed all patients who underwent a tracheostomy at some point during their clinical course. The moderate group was defined by either the presence of obstructive sleep apnea, history of a cleft palate, or requirement of gastrostomy tube for feeding. The mild group included all remaining patients who did not have these comorbidities or interventions. Measurements with a strong correlation ($r > 0.60$) were identified as predictors of clinical severity.

Table 1. Distribution of Treacher Collins Syndrome Age Groups

	Infant Group	Adolescent Group	Postadolescent Group
No.	8	14	8
Age, yr			
Mean	0.62	7.91	17.04
Range	0.01–2.02	5.18–11.26	15.49–21.36
Sex			
Male	5	7	3
Female	3	7	5
No. of sides for cephalography	12	22	10

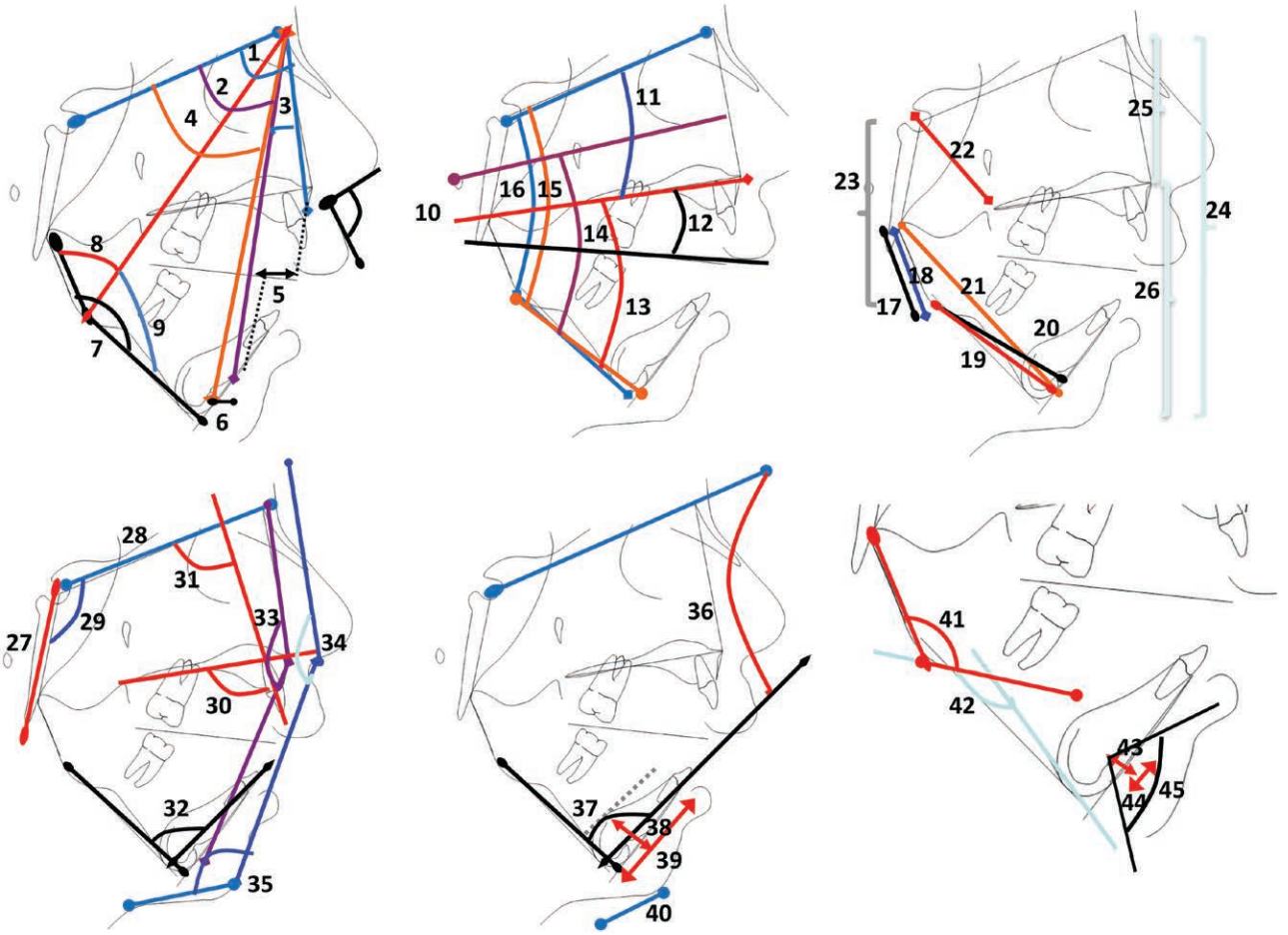

Fig. 1. Illustration of cephalometric parameters, including angular and linear cephalometric measurements. *1*, SNA (degrees); *2*, SNB (degrees); *3*, ANB (degrees); *4*, SNPg (degrees); *5*, Wits; *6*, Pg-NB; *7*, ArGoMe (degrees) (gonial angle); *8*, ArGoN (degrees) (upper gonial angle); *9*, N-Go-Me (degrees) (lower gonial angle); *10*, Ct-Sn-UL (degrees) (nasolabial angle); *11*, SN-PP (degrees); *12*, Occ-PP (degrees); *13*, PP-MP (degrees); *14*, FH-MP (degrees); *15*, Sn-Go-Gn (degrees); *16*, SN-MP (degrees); *17*, Co-Go; *18*, Ar-Go (degrees); *19*, Go-Pg; *20*, Go-B; *21*, Co-Pg; *22*, S-PNS; *23*, S-Go; *24*, N-Me (total facial height); *25*, N-ANS (upper facial height); *26*, ANS-Me (lower facial height); *27*, S-Ba; *28*, S-N; *29*, B-S-N (degrees); *30*, U1-PP (degrees); *31*, U1-SN (degrees); *32*, IMPA (degrees); *33*, N-A-Pg (degrees) (convexity angle); *34*, G-Sn-Pg′ (degrees) (soft-tissue convexity angle); *35*, Sn-Gn′-C′ (degrees) (throat angle); *36*, SN-symphysis (degrees); *37*, MP-symphysis (degrees); *38*, symphysis depth; *39*, symphysis height; *40*, Hy-Me (hyoid-menton); *41*, Co-Go-notch (degrees); *42*, antegonial notch angle; *43*, symphysis notch depth; *44*, symphysis notch height; *45*, symphysis notch angle.

Statistical significance was maintained at $p < 0.05$ for all analyses. Measurements with a strong correlation ($r > 0.60$) were identified as predictors of clinical severity (Table 3).

RESULTS

A total of 30 patients met inclusion criteria for the study. with an even distribution of male ($n = 15$) and female ($n = 15$) patients; eight patients were assigned to the infant age group, 14 patients were included in the adolescent group, and eight patients were distributed among the postadolescent age group (Table 1). Of note, two patients underwent cleft repair and four patients underwent orbitozygomatic bone grafting before their images were obtained for analysis.

Observational Findings

On computed tomographic scans, the presence of a paramaxillary cleft extending from the orbita through the posterior maxillary region and condyle area was noted. Our assessment suggests that the maxillomandibular deformity demonstrates what we have termed a "parasagittal orbitomaxillozygomatic cleft," which is aligned along the path of maximum mandibular atresia (diminished or missing coronoid, condylar processes, and rami). Another interesting finding was the classic "thumbprint" sign seen on the temporal

Table 2. Age Group Comparisons of Cephalometric Variables*

	TCS Infant	Infant Norm	Comparison	TCS Adolescent	Adolescent Norm	Comparison	TCS Postadolescent Adult	Post-adolescent-Adult Norm	Comparison	Infant-Adolescent Comparison	Adolescent-Adult Comparison	Infant-Adult Comparison
SNA, deg	76.35 ± 1.99	82.55 ± 0.21	‡	80.03 ± 1.24	80.98 ± 0.09	NS	78.75 ± 1.35	81.47 ± 0.08	NS	NS	NS	NS
SNB, deg#	59.18 ± 1.90	75.72 ± 0.25	§	69.65 ± 1.22	76.45 ± 0.18	§	68.68 ± 2.02	78.34 ± 0.13	§	§	NS	§§
ANB, deg	17.18 ± 1.19	6.87 ± 0.21	§	10.36 ± 0.66	4.54 ± 0.14	§	10.05 ± 1.08	3.12 ± 0.05	§	§	NS	§‡‡
SNPg, deg#	56.46 ± 1.95	75.93 ± 0.05	§	66.32 ± 1.30	75.24 ± 0.93	§	65.69 ± 2.20	79.37 ± 0.11	§	§	NS	§‡‡
Pg-NB#	3.68 ± 0.67	0.43 ± 0.05	§	5.77 ± 0.64	1.1 ± 0.12	§	5.87 ± 0.67	2.7 ± 0.09	§	†	NS	NS
S-PNS	NA	NA	NA	35.14 ± 1.34	47.62 ± 0.59	§	38.96 ± 1.75	53.86 ± 0.75	§	§	NS	§
Occ-PP, deg	17.77 ± 1.40	13.6 ± 0	†	17.97 ± 1.24	13.2 ± 0.44	§	11.39 ± 11.39	7.36 ± 0.66	NS	NS	‡	†‡
SN-MP, deg#	63.61 ± 2.87	35.58 ± 0.12	§	53.88 ± 2.19	35.25 ± 0.24	§	56.83 ± 2.45	32.78 ± 0.09	§	‡	NS	NS
SN-GOGN, deg#	60.44 ± 2.72	32.9 ± 0	§	51.65 ± 2.16	51.66 ± 2.16	§	53.72 ± 2.52	32.49 ± 0.11	§	†	NS	NS
FH-MP, deg#	53.37 ± 3.30	29.31 ± 0.01	§	45.92 ± 2.17	29.02 ± 0.31	§	46.34 ± 2.46	27.45 ± 0.62	§	†	NS	NS
PP-MP, deg	35.48 ± 2.33	25 ± 0	‡	39.85 ± 2.04	28.75 ± 0.25	§	37.8 ± 1.63	25.11 ± 0.18	§	NS	NS	NS
SN-PP, deg	28.14 ± 1.36	5.5 ± 0.20	§	14 ± 1.47	6.51 ± 0.16	§	19.01 ± 2.67	Tem.23	§	§	NS	‡‡
S-Go	36.2 ± 2.40	65.38 ± 0.35	§	54.89 ± 1.48	69.39 ± 1.07	§	64.12 ± 2.21	84.92 ± 1.48	§	§	‡	§‡‡
N-Me#	77.32 ± 4.53	106.42 ± 0.19	§	100.61 ± 3.16	112.99 ± 1.32	§	114.491.21	132.28 ± 2.10	§	‡‡	§	§‡‡
N-ANS	30.51 ± 1.78	45.9 ± 0	§	43.69 ± 1.36	49.69 ± 0.70	§	50.32 ± 1.13	58.31 ± 0.66	§	§	‡‡	§§
ANS-Me#	52.93 ± 3.08	63.35 ± 0.24	‡	62.41 ± 2.12	65.83 ± 0.63	NS	69.92 ± 1.48	76.22 ± 1.48	‡	‡	‡‡	§§
LFH/TFH, %	68.59 ± 0.84	45.62 ± 1.76	§	62.16 ± 1.64	49.44 ± 1.53	§	61.05 ± 0.35	47.55 ± 1.98	§	§	NS	§§
PFH/AFH, %	46.6 ± 1.51	61.46 ± 0.23	§	54.71 ± 1.15	61.32 ± 0.24	§	55.93 ± 1.57	64.19 ± 0.12	§	NS	NS	NS
B-S-N, deg	136.09 ± 2.2	129.35 ± 0.03	†	121.37 ± 1.32	129.52 ± 0.08	§	120.55 ± 3.04	129.35 ± 0.21	†	§	NS	§§
S-N	48.39 ± 2.57	72.3 ± 0.27	§	61.12 ± 1.78	74.16 ± 0.57	§	65.38 ± 1.56	81.18 ± 0.94	§	§	NS	§§
S-Ba	26.63 ± 1.11	40.51 ± 0.12	§	37.5 ± 1.24	42.37 ± 0.65	‡	38.84 ± 1.57	48.32 ± 1.61	§	§	NS	§§
N-A-Pg, deg#	35.12 ± 1.74	14.2 ± 0.35	§	25.74 ± 1.15	8.81 ± 0.45	§	24.41 ± 1.98	3.82 ± 0.18	§	§	NS	§§
G-Sn-Pg′, deg#	29.98 ± 2.1	12 ± 0	§	28.08 ± 1.05	12 ± 0	§	30 ± 2.61	12 ± 0	§	NS	NS	NS
Co-Go	17.73 ± 2.19	48.33 ± 0.25	§	29.41 ± 1.47	51.16 ± 0.83	§	32.13 ± 4.14	63.6 ± 1.05	§	§	NS	§§
Co-Pg	49.39 ± 3.27	101.32 ± 0.33	§	72.4 ± 2.14	107.41 ± 1.46	§	78.31 ± 4.76	127.2 ± 1.58	§	§	NS	§§
Go-B	36.53 ± 1.77	64.47 ± 0.02	§	51.18 ± 1.52	68.65 ± 0.81	§	52.57 ± 1.57	79.17 ± 0.72	§	§	NS	§§
Go-Pg	34.98 ± 1.73	66.1 ± 0	§	49.66 ± 1.64	71.46 ± 1.02	§	52.06 ± 1.68	84.5 ± 0.87	§	§	NS	§§
Ar-Go	13.1 ± 1.91	30.15 ± 0.28	§	25.44 ± 1.65	38.78 ± 0.92	§	24.63 ± 3.71	50.7 ± 0.65	§	§	NS	§*
Ar-Go-Me, deg	144.83 ± 5.43	131.63 ± 0.25	†	145.48 ± 3.89	128.85 ± 0.43	§	144.72 ± 2.73	123.68 ± 0.07	§	NS	NS	NS
Ar-Go-N, deg	54.75 ± 5.60	66.2 ± 0.21	NS	56.9 ± 3.40	58.56 ± 0.59	NS	51.36 ± 2.25	50.54 ± 0.43	NS	NS	NS	NS
N-Go-Me, deg	90.08 ± 2.86	67.68 ± 0.05	§	88.38 ± 2.19	69.6 ± 0.14	§	93.35 ± 1.92	71.6 ± 0.11	§	NS	NS	NS
Sn-Gn′-C′, deg	128.83 ± 3.50	100.00	§	118.23 ± 5.97	100.00	‡	133.88 ± 4.01	100.00	§	NS	NS	NS
Sn-Gn′/C′-Gn	3.78 ± 0.43	NA	NA	2.16 ± 0.20	NA	NA	3.55 ± 0.77	NA	NA	‡	†	‡‡
Ct-Sn-UL, deg	115.89 ± 4.51	102.00	†	107.59 ± 2.70	102.00	NS	107.03 ± 3.87	102.00	NS	NS	NS	NS
G-Sn/Sn-Me′	0.98 ± 0.04	1.00	NS	1.01 ± 0.03	1.00	NS	1.19 ± 0.05	1.00	‡	NS	‡	‡‡
U1/PP, deg	100.19 ± 3.24	101.07 ± 0.02	NS	111.2 ± 2.62	107.09 ± 0.93	NS	121.19 ± 2.40	11.7 ± 0.15	‡	‡	NS	§§
U1/SN, deg	72.06 ± 3.92	95.47 ± 0.29	§	97.21 ± 2.62	100.52 ± 0.94	NS	102.19 ± 1.75	102.59 ± 1.20	NS	§	NS	§§
IMPA	91.28 ± 1.99	89.07 ± 0.16	NS	92.56 ± 1.62	91.9 ± 0.59	NS	84.91 ± 7.15	94.26 ± 0.50	NS	NS	NS	NS
Witz	0.24 ± 1.70	−1.00	NS	0.5 ± 1.21	−1.00	NS	2.12 ± 1.48	−1.00	NS	NS	NS	NS
Antegonial angle	125.24 ± 6.93	NA	NA	136.87 ± 3.06	NA	NA	130.69 ± 4.39	NA	NA	NS	NS	NS
Co-Go-Notch, deg	119.08 ± 5.16	NA	NA	119.71 ± 3.37	NA	NA	118.36 ± 4.41	NA	NA	NS	NS	NS
Symphysis notch angle, deg	103.71 ± 3.94	NA	NA	125.43 ± 4.64	NA	NA	113.88 ± 3.58	NA	NA	†	NS	NS
Symphysis notch depth	1.8 ± 0.23	NA	NA	2.09 ± 0.29	NA	NA	2.48 ± 0.60	NA	NA	NS	NS	NS
Symphysis notch height	5.23 ± 0.52	NA	NA	8.46 ± 0.92	NA	NA	8.53 ± 2.08	NA	NA	†	NS	NS
MP-symphysis, deg	76.76 ± 2.63	NA	NA	74.63 ± 1.48	NA	NA	69.17 ± 3.42	NA	NA	NS	NS	†
SN-symphysis, deg	20.10 ± 2.81	NA	NA	34.88 ± 1.77	NA	NA	33.44 ± 3.50	NA	NA	§	NS	‡

(*Continued*)

Table 2. (*Continued*)

	TCS Infant	Infant Norm	Comparison	TCS Adolescent	Adolescent Norm	Comparison	TCS Postadolescent Adult	Post-adolescent-Adult Norm	Comparison	Infant-Adolescent Comparison	Adolescent-Adult Comparison	Infant-Adult Comparison
Symphysis depth	8.23 ± 1.06	NA	NA	13.78 ± 1.86	NA	NA	12.28 ± 0.49	NA	NA	†	NS	NS
Symphysis height	22.5 ± 2.17	NA	NA	33.42 ± 4.23	NA	NA	35.76 ± 1.08	NA	NA	†	NS	†
Symphysis ratio	2.89 ± 0.16	NA	NA	2.48 ± 0.08	NA	NA	2.94 ± 0.13	NA	NA	†	†	NS
Hyoid-Me	13.25 ± 1.59	NA	NA	19.94 ± 0.92	NA	NA	21.57 ± 3.03	NA	NA	‡	NS	‡
N-ANS/S-PNS	1.57 ± 0.85	NA	NA	1.26 ± 0.41	NA	NA	1.32 ± 0.50	NA	NA	§	NS	†

TCS, Treacher Collins syndrome; NS, nonsignificant; NA, not available (indicates normative data were not available for comparison).
*Cephalometric measurements for each age group compared to normative age-matched controls (norm) and compared to other age groups. Results are reported as a difference between studied groups. Abbreviations are as listed in **Table, Supplemental Digital Content 1**, ***http://links.lww.com/PRS/C466***.
†$p < 0.05$.
‡$p < 0.01$.
§$p < 0.001$.
#Vertical mandibular–related measurements in infant group affected by open mouth position because of the presence of endotracheal tube.

and lower parietal bones of the skull. This finding was present on all computed tomographic scans.

When mandibular morphology was assessed, another typical feature was observed at the anterior mandible. A parasagittal triangular fossa was noted at the symphyseal area in half of the patients. The depth, height, and angulation of this "symphyseal notch" were measured.

Cephalometric Variables by Age Group

There were statistically significant changes in almost all measurements in all age groups compared with controls (Table 2).

Maxillary-Mandibular Angular Measurements

SNA angle showed significantly decreased value in only the infant group compared with the control ($p < 0.01$) and was stable during growth. SNB and SNPg angles were significantly reduced, and ANB angle was significantly increased in all Treacher Collins syndrome age groups ($p < 0.01$). These measurements increased significantly from infancy to adolescence and then remained stable, as no difference was observed between these age groups and young adults.

Vertical Plane Angles and Facial Heights

All vertical plane angles were found to be significantly increased, whereas all facial heights were found to be decreased in Treacher Collins syndrome patients ($p < 0.001$), with the exception of ANS-Me. The ratio of posterior facial height to anterior facial height was significantly decreased, but the ratio of lower facial height to total anterior facial height was significantly increased as well.

Mandibular Measurements

All mandibular lengths were significantly shorter in Treacher Collins syndrome groups ($p < 0.001$). Gonial and lower gonial angles demonstrated significantly more obtuse angle in Treacher Collins syndrome groups than in control groups ($p < 0.001$), whereas upper gonial angle was similar to controls. More than half of the patients ($n = 17$ of 30) possessed a parasagittal symphyseal notch at the anterior surface of the chin. The depth and height of this notch were increased over time, but these increases were not statistically significant. The symphyseal notch angle ($p < 0.01$), symphysis width and height ($p < 0.05$), and symphysis inclination (to cranial base) were increased from infancy through adolescence ($p < 0.001$) and then remained stable.

In addition to these measurements, facial skeletal and soft-tissue convexity angles were significantly increased ($p < 0.001$). Another soft-tissue measurement, nasolabial angle, showed similar

Table 3. Correlation Analyses between Clinical Severity and Cephalometric Parameters and Pruzansky Scoring and Cephalometric Parameters*

Strong Correlations		Moderate Correlations		Weak Correlations	
Clinical severity					
SNPg	$r = -0.64$ $p = 0.000$	N-A-Pg	$r = 0.41$ $p = 0.003$	Ar-Go-Me	$r = 0.27$ $p = 0.039$
Hyoid-Me	$r = -0.62$ $p = 0.000$	G-Sn-Pg′	$r = 0.42$ $p = 0.002$	Antegonial angle	$r = 0.03$ $p = 0.018$
Co-Go	$r = -0.66$ $p = 0.000$	SNA	$r = -0.51$ $p = 0.000$	LFH/TFH	$r = 0.29$ $p = 0.030$
PFH/AFH	$r = -0.60$ $p = 0.000$	SNB	$r = -0.59$ $p = 0.000$	G-SN/Sn-Me	$r = 0.30$ $p = 0.025$
SN-MP	$r = 0.62$ $p = 0.000$	S-PNS	$r = -0.48$ $p = 0.001$	S-Ba	$r = -0.36$ $p = 0.009$
FH-MP	$r = 0.61$ $p = 0.000$	N-ANS/S-PNS	$r = -0.46$ $p = 0.001$	S-Go	$r = -0.34$ $p = 0.013$
SN-PP	$r = 0.69$ $p = 0.000$	SN-GoGn	$r = 0.58$ $p = 0.000$	ANB	$r = 0.32$ $p = 0.016$
SN-symphysis	$r = -0.69$ $p = 0.000$	Co-Pg	$r = -0.51$ $p = 0.000$	Occ/ANS-Me	$r = -0.32$ $p = 0.017$
SnGn/C-Gn	$r = 0.65$ $p = 0.000$	Go-Pg	$r = -0.51$ $p = 0.002$	IMPA	$r = -0.35$ $p = 0.009$
Symphysis notch angle	$r = -0.72$ $p = 0.000$	Ar-Go	$r = -0.51$ $p = 0.000$		
		B-S-N°	$r = 0.50$ $p = 0.000$		
Pruzansky scoring	$r = 0.82$ $p = 0.000$				
Pruzansky scoring					
SNPg	$r = -0.73$ $p = 0.000$	N-A-Pg	$r = -0.60$ $p = 0.000$	IMPA	$r = -0.64$ $p = 0.000$
Hyoid-Me	$r = -0.65$ $p = 0.000$	G-Sn-Pg′	$r = -0.40$ $p = 0.004$	Antegonial angle	$r = -0.34$ $p = 0.013$
Co-Go	$r = -0.77$ $p = 0.000$	SNA	$r = -0.49$ $p = 0.000$	N-Me	$r = -0.25$ $p = 0.000$
PFH/AFH	$r = -0.73$ $p = 0.000$	LFH/TFH	$r = -0.46$ $p = 0.001$	N-ANS	$r = -0.30$ $p = 0.000$
SN-GoGn	$r = 0.62$ $p = 0.000$	S-PNS	$r = -0.57$ $p = 0.000$	Symphysis notch height	$r = -0.38$ $p = 0.024$
SNB	$r = -0.70$ $p = 0.000$	N-ANS/S-PNS	$r = -0.44$ $p = 0.002$	Symphysis depth	$r = -0.31$ $p = 0.022$
SN-PP	$r = 0.70$ $p = 0.000$	ANB	$r = 0.59$ $p = 0.000$	Symphysis height	$r = -0.29$ $p = 0.027$
SN-symphysis	$r = -0.72$ $p = 0.000$	Go-B	$r = -0.50$ $p = 0.000$	U1/SN	$r = -0.37$ $p = 0.006$
SnGn/C-Gn	$r = -0.63$ $p = 0.000$	Go-Pg	$r = -0.55$ $p = 0.000$		
Ar-Go	$r = -0.70$ $p = 0.000$	Symphysis notch angle	$r = -0.48$ $p = 0.005$		
B-S-N	$r = -0.63$ $p = 0.000$	SN-MP	$r = -0.61$ $p = 0.000$		
Co-Pg	$r = -0.62$ $p = 0.000$	FH-MP	$r = 0.57$ $p = 0.000$		
		S-Go	$r = -0.50$ $p = 0.000$		
		S-Ba	$r = -0.48$ $p = 0.001$		

r, Spearman correlation coefficient.
*Abbreviations are as listed in **Table, Supplemental Digital Content 1**, ***http://links.lww.com/PRS/C466***.

mean values to controls except in young adults ($p < 0.01$).

Correlations between Clinical Severity and Cephalometric Measurements

Correlation coefficient values (r) and statistical significance are demonstrated in Table 3. Of the 50 cephalometric parameters measured, 30 showed significant correlations with the severity of presentation in Treacher Collins syndrome: 10 in addition to Pruzansky classification were strong correlations ($r > 0.60$), 11 were moderate ($r = 0.40$ to 0.60), and nine of them were weak ($r < 0.40$). When we explored the age factor in

terms of clinical severity, we did not find any relation between the age and severity.

Strong correlations were observed in mandibular projection, vertical plane angles, facial heights, and Pruzansky classification. SNPg , H-Me length, PFH/AFH, ramus height, and symphysis inclination showed strong negative correlation with the severity of Treacher Collins syndrome. However, certain vertical plane angles (SN-MP, FH-MP, and SN-PP) showed strong positive correlation. In addition, lower soft-tissue facial height-to-depth ratio (Sn-Gn′/Gn′-C) was found to be related to the severity, which demonstrated increased lower height and more decreased throat depth in severe cases. Symphysis notch angle was more acute in severe cases as well.

Moderate correlations were positively correlated to measures of facial convexity (G′-Sn-Pg′ and N-A-Pg) and maxillary and mandibular projections (SNA and SNB), and mandibular lengths (Co-Pg, Go-Pg, and Ar-Go) were observed to have a negative correlation with severity. Both soft and skeletal convexity angles were positively correlated with severity. Weak correlations were seen in the gonial area (gonial and antegonial angles), posterior facial height (S-Go), cranial base angle, and posterior cranial length.

Correlations between Pruzansky Scoring and Cephalometric Measurements

See Figure, Supplemental Digital Content 2, which shows the distribution of Pruzansky classification in all Treacher Collins syndrome age groups for types I, IIA, IIB, and III, ***http://links.lww.com/PRS/C467***. Most of the patients exhibited type I in the adolescent (64.3 percent) and young adult (62.5 percent) groups, whereas type IIB was more commonly seen in the infant group (62.5 percent). Table 3 demonstrates correlation coefficient values (r) and their significance between Pruzansky scores and cephalometric measurements. Of all 50 cephalometric parameters, 34 of them showed significant correlations to the clinical severity of Treacher Collins syndrome: 12 were strong ($r > 0.60$), 14 were moderate ($r = 0.40$ to 0.40), and eight were weak ($r < 0.40$).

Strong correlations were found in mandibular projections, posterior jaw rotations, and mandibular lengths. SNB and SNPg angles and H-Me length were negatively correlated with Pruzansky scoring. SN-GoGn, SN-PP, and symphysis inclination (by protruding) showed positive correlations as well. Similar to clinical severity, a lower soft-tissue facial height-to-depth ratio (Sn-Gn′/Gn′-C) was found to be positively correlated with Pruzansky scoring. In addition, mandibular lengths (Co-Go, Ar-Go, and Co-Pg) were shorter in severe cases determined by Pruzansky scoring.

Moderate correlations were observed in other mandibular posterior rotation parameters, posterior facial heights, lower facial height–to–total facial height ratio, facial skeletal and soft convexity angles, ANB angle and other sella-related measurements (SNA, S-Ba, and U1/SN), and remaining mandibular lengths. Symphysis notch angle and symphysis height were the only symphysis area measurements that showed moderate correlation with Pruzansky classification. Weak correlations ($r < 0.40$) were found for the total and anterior facial heights, incisor mandibular plane angle, antegonial angle, and symphysis-related measurements (i.e., symphysis notch height, symphysis height, and depth).

DISCUSSION

This study assessed 50 cephalometric measurements in a cohort of 30 patients with Treacher Collins syndrome and identified 30 parameters that were statistically different from Moyers and Bolton normative data. Many of the reported measurements were consistent with findings described in other reports, including decreased cranial base angle,[9] retrusion of the maxilla[9,11] and mandible,[9–11] more obtuse plane angle of the maxilla[9] and mandible,[8–10,12,21] hypoplasia of the mandible,[9,10] reduced height of the ramus,[9,11–13,21] more obtuse gonial angle,[9,12] and increased facial convexity.[9,10] It is notable that SNA was not found to be statistically different from normative data by another large-volume study.[10] One possibility for this difference is the inclusion of only Pruzansky I or IIA mandibles[10] which would bias that study cohort to a less severely affected population compared with the population presented in this study.

Of the 30 cephalometric measurements identified to be statistically different from normative data, a subset of 10 measurements in addition to Pruzansky classification, demonstrated strong correlation ($r > 0.60$) to clinical severity. These measurements include the following: increased mandibular retrognathia (SN-Pg, Hyoid-Me, and Sn-Gn′/C-Gn′); decreased posterior facial height (Co-Go and PFH/AFH); more obtuse maxillary/mandibular plane angle (SN-MP, FH-MP, SN-PP, and SN-Sym); and an obtuse symphysis notch angle. We believe that these specific measurements shed light on the clinically relevant dysmorphology associated with Treacher Collins syndrome and may serve as a starting point to the creation

of an anatomical severity scale for Treacher Collins syndrome. A larger-scale analysis would be required to further define a severity scale and will likely require a multi-institutional cooperative.

Other proposed grading scales for Treacher Collins syndrome include a classification for malar deformities[14,17] and a comprehensive scale that incorporates a point system into eight anatomical and clinical criteria (deformities in the zygoma, lower eyelid, mandible, ear, palate, nasal root, other areas; and mutations in the *TCOF1* gene).[15] Although all of the listed classification systems demonstrate an in-depth analysis of the Treacher Collins syndrome deformity, these scales have not been supported by statistical correlation to clinical severity.

The presented study correlates cephalometric measurements to clinical severity in patients with Treacher Collins syndrome. Because of the limited radiation dose associated with cephalograms, we were able to collect a significant amount of imaging data in which linear and angular measurements could be accurately measured, with limited patient morbidity. Patients with mild expression of Treacher Collins syndrome do not commonly undergo computed tomographic analysis. Therefore, relying solely on computed tomographic data would bias the patient cohort to a more severely affected population, and a severity scale based on computed tomographic data would not be applicable to a mildly affected patient. It is notable that previously collected computed tomographic scans are easily transformed to cephalometric data using Dolphin Software. Cephalometric measurements can be compared to well-characterized normative data, available in a wide range of ages, a resource not available to computed tomographic bony analysis or three-dimensional camera imagery. Cephalometry also allowed for a comprehensive analysis of upper and lower jaw position and morphology, some of the bony structures most affected by the Treacher Collins syndrome phenotype, in addition to global changes to facial proportions. It is notable that cephalometric normative data in certain specific parameters (e.g., antegonial notch angle) does not exist. In addition, obtaining a cephalogram in children before the age of 5 becomes a challenging task because it may be hard to stabilize a child's head position during exposure. In this case, a computed tomographic scan can be obtained and cephalometric measurements performed directly from computed tomography–derived cephalograms.[22] Although the cephalometric analysis presented in this study will have limited applicability in infants and toddlers, the data presented may be a starting point for creating a similar rating scale in this young pediatric population.

The clinical severity scale used in this study was determined by consultation and agreement by two craniofacial surgeons and two craniofacial orthodontists with extensive experience in the clinical management of patients with Treacher Collins syndrome and based on a comprehensive literature review of the functional problems affecting this patient population.[3–7,23] This scale required identification of salient clinical findings that were associated with implications on function. As airway compromise is the most critical event to affect this patient population,[3–7] tracheostomy defined the highest clinical severity group. Severe airway compromise is attributable to a constellation of deformities, including lower jaw malposition, glossoptosis, and maxillary hypoplasia.[3,5,9,23] As patients who did not have a tracheostomy could still have problems with the function of the oral passage (e.g., obstructive sleep apnea, need for a gastrostomy tube),[3–7] these findings in addition to cleft palate were used to define the moderate clinical severity group. The low clinical severity group was defined simply as an absence of obstructive sleep apnea, gastrostomy tube, and cleft palate.

Recognizing the inherent challenges in identifying clinically relevant dysmorphology for a rare and complex condition, the presented scale does have limitations. The two surgical procedures used as defining criteria in the severity scale (tracheostomy and gastrostomy) do not have formalized indications. It is certainly possible that tracheostomy was performed on certain patients because of concern for the airway rather than an unstable airway. Conversely, tracheostomy may have been avoided in certain patients who were otherwise candidates for mandibular distraction. The severity scale used in this report is based on ordinal rather than interval data. As many of the older patients in this study did not benefit from preoperative polysomnography, these data were not incorporated into analysis; however, this is an area for future study. The scale is "jaw-centric" and does not take into account other parts of the craniofacial anatomy affected by Treacher Collins syndrome, including the outer ear, ear canal, eyelids, nose, zygoma, and soft-tissue envelope. Although other severity scales can certainly take these anatomical sites into account, there are no known measurement tools for these areas that are complemented by normative data. Therefore, incorporation of these anatomical areas into a severity scale would

be limited by an inability to quantify the extent of deviation from population-based normative anatomy. A severity scale that is dependent on jaw position and morphology, a critical area affected by the Treacher Collins syndrome phenotype, is well suited for correlation by cephalometric analysis. In the event that measurement tools and normative data become available for the other areas affected by Treacher Collins syndrome, additional severity scales may be constructed that incorporate these areas. Recognizing these limitations, this study did identify bone and soft-tissue abnormalities that were statistically significant and strongly correlated to clinical severity. With the exception of a novel measurement, symphysis notch angle, all listed craniofacial disproportions have been well described by other anatomical studies.

Although this is the largest scale analysis to date that assesses anatomical aberrations associated with Treacher Collins syndrome, the study is limited to 30 patients and does not qualify as a large-population study. This limitation is attributable largely to the requirement of radiographic imaging before any upper or lower jaw surgery. Many of the patients treated by our unit underwent initial surgery elsewhere which, in some cases, excluded them from analysis. Despite the moderate size of this analysis, this is the first study to identify statistically significant aberrations of craniofacial anatomy in patients with Treacher Collins syndrome that are strongly correlated to clinical severity and is the largest study of its kind. A larger scale analysis may identify other measurements not characterized by this study, and we believe that this would be possible through a multi-institutional study.

We believe the cephalometric measurements described in this article are the starting point for a more comprehensive and larger scale analysis of jaw measurements and proportions that may be used to reliably predict clinical severity in this challenging patient population. It is certainly possible that these parameters may be incorporated into a comprehensive classification system to predict prognosis and guide management in these patients. Future studies on clinical severity would benefit from quantitative analysis such as polysomnography, particularly in the background of the complex and multiple airway anomalies present in this challenging patient population.

CONCLUSIONS

Specific cephalometric measurements of increased mandibular retrognathia, decreased posterior facial height, wider maxillary/mandibular plane angle, and wider symphysis notch angle, in addition to Pruzansky classification, are strongly correlated to increased clinical severity in patients with Treacher Collins syndrome. Although age does not correlate with clinical severity, these cephalometric measurements are predictive of increased severity across all age groups.

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