Craniofacial and occlusal features of individuals with Turner Syndrome: A cephalometric study

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Craniofacial features of 18 individuals with Turner Syndrome (TS) were compared with age and gender matched healthy individuals. Dental history, panoramic radiograph, dental casts and cephalometric measurements were assessed. The dental casts analysis showed a significantly higher PH/PW ratio in individuals with TS under GH therapy compared to healthy individuals (p=0.004; paired t-test). This data objectively supported the definition of a high-narrow palate. The ANB angle and the Wits index were similar in the two group, showing a skeletal class I malocclusion. The vertical characteristics did not differ between the two groups, showing a mesofacial growth pattern. Our results showed similar cephalometric characteristics in individuals with TS treated with GH and healthy controls.

The Turner Syndrome (TS) was first described in 1938 as "A syndrome of infantilism. congenital webbed neck and cubitus valgus" by Henry Turner, who reported the presence of short stature, *Pterygium colli*, *Cubitus valgus*, primary amenorrhea and sexual infantilism, due to hypopituitarism, in 7 adult women. TS is a chromosomal disease associated with the partial deletion or monosomy of the X chromosome. The X chromosome monosomy is responsible for less than half of the TS diagnosis; many of them are mosaicism or related to abnormal X or Y chromosome (deletion, isochromosome X, dicentric chromosome). The TS shows different somatic manifestations, but some phenotypic features are common in many TS individuals including short stature, gonadal dysgenesis, lymphedema and congenital heart diseases. The TS is characterized by skeletal dysplasia, mild epiphyseal dysplasia and typical bony alterations (1). Other features include *Cubitus valgus*, webbed neck, widely spaced nipples and developmental delay (2). The 10–20% of girls with TS develop scoliosis; kyphosis and/or vertebral wedging are also common (3-10).

Short stature is probably the most common, readily recognizable clinical feature of TS. Therefore, the treatment of girls with TS with growth hormone (GH) has become a common therapy in many countries to promote the growth during the childhood and increase the adult stature (4).

Congenital heart diseases are the first cause of death for girls with TS (11). In fact, 65-70% of patients show aortic structural abnormalities, leading to aortic dissection in patients with Turner syndrome. Moreover, bicuspid aortic valve, ectasia of the transverse aortic arch, aortic coarctation, aberrant right subclavian artery are frequent findings in girls or women with Turner syndrome (12).

In the medical literature, most of data regard the oro-dental features of TS girls or women with no GH therapy (13-20). Few studies evaluate cranio-

Key words: Turner Syndrome, occlusion

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0393-974X (2020)

facial characteristics of TS girls or women under GH therapy (21-30). Giving the lack of data on this topic, the aim of this case series was to describe the craniofacial characteristics of 18 Italian girls with TS in comparison with 18 Italian healthy girls.

MATERIALS AND METHODS

Study population

This study was conducted on outpatients attending the Unit of Special Needs Dentistry and Pediatric Dentistry, Department of Biomedical and Neuromotor Sciences, University of Bologna, Italy. The dental records of the individuals with NS attending the Unit of Special Needs Dentistry between January 2015 and January 2019 were recruited. Individuals with NS were referred from the Unit of Rare Disease, Syndromology and Auxology of the St. Orsola-Malpighi Polyclinic, Department of Medical and Surgical Sciences (DIMEC), University of Bologna, Italy. The following inclusion criteria were applied: documented genetic diagnosis of TS, growth hormone (GH) therapy for at least two years, Italian origin and nationality of both parents, availability of good quality orthopantomogram, lateral cephalogram and dental casts. Individuals with a previous orthodontic treatment were excluded. As a control group, for each child with TS, one age and gender matched healthy subject was found. The following inclusion criteria were applied: Italian origin and nationality of both parents, normal, or only minor deviations from normal occlusion; availability of good quality orthopantomogram, lateral cephalogram and dental casts. The exclusion criteria were the following: chronic diseases except for allergy; medical condition associated with oral diseases; history of surgical/medical treatments that might have affected the craniofacial development (e.g. cancer therapies); craniofacial anomalies; dental agenesis; supernumerary teeth; extracted permanent teeth; history of orthodontic treatment; bad quality radiographs.

The investigators were two dentists trained in special needs dentistry and pediatric dentistry. The research protocol of this study was approved by the local Ethics Committee of the Bologna University Hospital Authority St. Orsola-Malpighi Polyclinic (PG. N 0019293). In full accordance with the ethical principles of the Helsinki Declaration, the written informed consent for participation and publication was obtained from the adults responsible for each individual.

Dental casts evaluation

The relationship between the upper and lower dental arch in the three planes of space (sagittal, vertical, transverse) was assessed. The Palatal Width (PW) (the distance between the upper first molars at the gingival margin) and the Palatal Height (PH) (distance between deepest point of palatal surface and line of palatal with) were measured. The palatal height index (PHI), which compares PH and PW, was calculated according to Premkumar (2011): PHI= [(PH/PW) x100].

Cephalometric assessment

Standardized lateral cephalograms were obtained using the digital radiographic equipment Planmeca Promax© (Planmeca Oy, Helsinki, Finland) with the patient in an upright position, with natural head posture and centric occlusion. The analysis of the lateral cephalograms was performed using a software for cephalometric analysis (Delta Dent) by the same investigator on the same monitor with the aid of magnification. To avoid examination bias, each radiograph was coded by another investigator with a numerical ID and the name and the date of birth of the child were not visible on the image. The calibration of distances was performed storing a millimeter scale with the images. The investigator, trained in digital cephalometric analysis, identified standard skeletal landmarks for each lateral cephalogram. These landmarks were used to define a series of linear and angular cephalometric measurements (Table Ia-Ic).

Reproducibility

Aiming to evaluate the reproducibility of the method, two independent observers performed cephalometric analysis and analysis on casts belonging to 10 patients. One of the two observers repeated the tests at day 7, following the same modalities. Intraclass correlation coefficient (ICC) measured reliability of the quantitative data. A high intra observer reproducibility was evidenced (90,4% of parameters ICC$\geq$ 0.8). A high inter observer reproducibility was evidenced ((73% of parameters ICC$\geq$ 0.8) even if lower than intra observer reproducibility.

Statistical analysis

Descriptive statistical analyses were first performed. Continuous variables were tested for distribution using the Shapiro-Wilk test. If data were normally distributed,

Table Ia. *Reference points, lines and angles in lateral cephalometric radiographic analysis: Hard and soft tissue points.*

Symbol Point and Name	Definition
Hard tissue points	
S (Sella)	The centre of the sella turcica in the pituitary fossa.
N (Nasion)	The most anterior point of the frontonasal suture.
Ba (Basion)	The lowermost point of the anterior margin of the occipital foramen.
Or (Orbitale)	The lowermost point in the lower margin of the bony orbit.
Pr (Porion)	The most superior point at the upper margin of external auditory meatus.
A (Subsupinale)	The point of the deepest concavity on the anterior outer contour of the maxilla.
B (Submentale)	The point of the deepest concavity on the outer contour of the mandibular symphysis surface.
APOcc (Anterior Point Occlusal)	The middle point of the Overjet, in occlusion.
PPOcc (Posterior Point Occlusal)	The most distal point of the occlusion, in the molar region.
Co (Condylion)	The most posterior superior point on the outline of the mandibular condyle.
Gn (Gnathion)	The most anterior and inferior point on the mandibular symphysis.
Go (Gonion)	The intersection point of the tangent to the posterior border of the ramus and the lower border of the mandible.
Me (Menton)	The most inferior point of the mandibular symphysis.
Ar (Articulare)	The intersection point between the posterior border of the mandibular condyle and the lower margin of the occipital bone.
Pg (Pogonion)	The most anterior point on the mandibular symphysis.
Pns (posterior nasal spine)	Meeting point of the hard palate with the anterior margin of the pterigo-maxillary fissure and with the soft palate.
Ans (anterior nasal spine)	The most anterior point of the anterior nasal spine.
Lia (Lower incisor apex)	The apical point of the most prominent central lower incisor.
Lie (Lower incisor edge)	The incisal margin of the most prominent central lower incisor.
Uia (Upper incisor apex)	The apical point of the most prominent central upper incisor.
Uie (Upper incisor edge)	The incisal margin of the most prominent central upper incisor.
Soft tissue points	
Pn (Pronasal)	The most anterior point on the soft tissue tip of the nose.
Col (Columella)	The lower margin of the nose.
Sn (Subnasale)	The point in the junction between the lower border of the nose and beginning of the upper lip in the mid-sagittal plane.
UL (Upper Lip)	The most anterior soft tissue point of upper lip.
Sn (Subnasale)	The point in the junction between the lower border of the nose and beginning of the upper lip in the mid-sagittal plane.
LL (Lower Lip)	The most anterior soft tissue point of the lower lip.
Pg' (Pogonion)	Soft tissue Pogonion point, the most anterior point on the chin soft tissue.

Table Ib. *Reference points, lines and angles in lateral cephalometric radiographic analysis: Lines or planes.*

Name and symbol	Definition
Lines or planes	
Sella – nasion line (S-N)	The anterior cranial base, the line extending from sella to nasion.
Sella – basion line (S-Ba)	The posterior cranial base, the line extending from sella to basion.
Frankfort horizontal line (FH)	The line between porion point and orbitale point.
Wits	The distance between the perpendiculars from points A and B on the maxilla and mandible, respectively, onto the occlusal plane. Sagittal relation of maxilla to mandible.
Condylion – point A line (Co-A)	The maxilla length, in the sagittal plane. The line extending from condylion to point A
Condylion – Gnathion line (Co-Gn)	The mandible length, in the sagittal plane. The line extending from condylion to gnathion.
Articulare – Gonion line (Ar-Go)	The length of the mandibular ramus. The line extending from articulare to gonion.
Gonion – Pogonion line (Go-Pg)	The length of the mandibular corpus. The line extending from gonion to pogonion.
Sella – Gonion line (S-Go)	The posterior facial height. The line extending from sella to gonion.
Nasion – Menton lines (N-Me)	The anterior facial height. The line extending from nasion to menton.
Ans-Pns	The palatale plane. The line extending from the anterior to the posterior nasal spine.
Aesthetic Line (E)	The line connecting soft tissue pogonion' to pronasal.
Overjet (OVJ)	The amount of horizontal overlap between the maxillary and mandibular incisors.
Overbite (OVB)	The amount of vertical overlap between the maxillary and mandibular incisors.
Jaraback's ratio	The relation between the anterior and posterior facial heights.
U1	The line between the upper central incisor apex and its edge.
L1	The line between the lower central incisor apex and its edge.

mean value and standard deviation (SD) were used to describe the data; if data were not normally distributed, median and interquartile range (IQR) were used. For the inferential analysis (significance tests) the unit of study was the couple of subjects. Between-groups comparisons would be performed with paired t-test if data were normally distributed and with Wilcoxon test if data were not normally distributed. The level of significance was set at 0.05. SPSS for Windows (23.0, SPSS Inc, Chicago, IL, USA) was used.

RESULTS

Eighteen Italian individuals with TS were included in the study group. The mean age was 12.8±5.4 years (range: 6-23). Eighteen Italian age and gender matched healthy individuals were included in the control group. When the comparison of the PH was done between the study group (median: 13 mm; IQR:11-17) and the control group (median:11 mm; IQR: 11-12), no statistically

Table Ic. *Reference points, lines and angles in lateral cephalometric radiographic analysis: Hard and soft tissue angels.*

Symbol	Definition
Hard tissue angles	
NSBa	The angle between nasion - sella - basion. The inclination of the cranial base.
SNA	The angle between sella - nasion line and A point. Sagittal relation of the maxilla to anterior cranial base.
SNB	The angle between sella - nasion line to B point. Sagittal relation of the mandible to anterior cranial base.
ANB	The angle of A point - nasion - B point, it measures the positions of the maxilla to mandible relative N point. Sagittal relation of maxilla to mandible.
NSAr	The sella angle. The angle between nasion – sella – articulare point. Sagittal relation of the mandible to posterior cranial base.
SArGo	The articulare angle. The angle between sella – articulare point – gonion.vIt measures the vertical growth pattern.
ArGoMe	The gonial angle. The angle between articulare – gonion – menoton. It measures the vertical growth pattern.
ArGoN	The upper gonial angle. The angle between articulare – gonion – nasion. The vertical growth of the mandibular ramus.
NGoMe	The lower gonial angle. The angle between nasion – gonion – menton. The vertical growth of the mandibular corpus.
Sum (NSAr+SArGo+ArGoMe)	The sum angle, it is the sum of the sella, articulare and gonial angles. It measures the vertical growth pattern.
SN-GoGn	The divergent angle. The angle between sella – nasion line and gonion – gnathion line. It measures the vertical growth pattern.
U1-AnsPns	The angle between the upper incisor line and palatal plane.
L1-GoMe	The angle between the lower incisor line and gonion - menton line.
U1-L1	The interincisal angle. The angle between the upper and lower central incisor.
Soft tissue angle	
ColSnUL	The naso-labial angle. The angle between the columella and subnasale – upper lip line.

significant difference was found (p=0.051; Wilcoxon test). The mean PW was 28.22 ± 3.31 mm in the study group and 30.22 ± 3.38 mm in the control group, without a statistically significant difference between the groups (p=0.223; paired t-test). The PH/PW ratio was significantly higher in the study group (48.11 ± 7.66) compared to the control group (37.17 ± 6.19) (p=0.004; paired t-test).

Cephalometric assessment

Cranial base characteristics:

The median SN was significantly higher in the study group compared to the control group (p=0.038; Wilcoxon test).

Sagittal characteristics:

The mean SNA and SNB were significantly lower in the study group compared to the control group (respectively p=0.018 and p=0.012; paired t-test).

When the comparisons of the parameters ANB, Wits, Co-A, Co-Gn, Ar-Go, Go-Me were done between the two groups, no statistically significant differences were found (p>0.005; paired t-test and Wilcoxon test).

Vertical characteristics:

When the comparisons of the vertical parameters

(NSAr, SArGo, ArGoMe, the sum angle, ArGoN, NGoMe, SN-GoMe, Jarabak's ratio) were done between the two groups, no statistically significant differences were found (p>0.005; paired t-test and Wilcoxon test).

Dental-basal characteristics:

The mean U1-L1 was significantly higher in the study group compared to the control group (p=0.008; paired t-test).

When the comparisons of U1-SN, L1-GoMe, OVJ and OVB were done between the two groups, no statistically significant differences were found (p>0.005; paired t-test and Wilcoxon test).

Soft-tissue characteristics:

When the comparisons of UL-E, LL-E and naso-labial angle were done between the two groups, no statistically significant differences were found (p>0.005; paired t-test and Wilcoxon test). Data in detail are shown in Table II and Table III.

Table II. *Cephalometric parameters, comparison across the study groups.*

Cephalometric parameters	Mean ± SD		p-value
	study group	control group	
Cranial base characteristics			
NSBa (degree)	133.95 ± 6.48	132.36 ± 4.95	0.414
Sagittal characteristics			
SNA (degree)	77.07±5.51	80.93 ± 2.45	0.012*
SNB (degree)	75.27 ± 3.52	77.33 ± 2.27	0.018*
Ar-Go (mm)	41.15 ± 4.67	39.12 ± 6.08	0.268
Go-Pg (mm)	67.38 ± 6.36	67.20 ± 7.04	0.935
Vertical characteristics			
NSAr (degree)	125.78 ± 4.98	123.68 ± 4.38	0.187
SArGo (degree)	145.51 ± 9.21	147.16 ± 6.84	0.546
ArGoMe (degree)	123.27 ± 5.63	122.15 ± 6.88	0.596
Sum (NSAr+ SArGo+ ArgoMe) (degree)	394.57 ± 6.65	392.99 ± 4.49	0.320
ArGoN (degree)	50.21 ± 7.12	50.34 ± 5.34	0.952
NGoMe (degree)	73.06 ± 3.96	71.80 ± 3.14	0.300
SN-GoGn (degree)	34.50 ± 5.69	32.77 ± 3.45	0.227
Jarabak's ratio (%)	62.98 ± 4.44	63.17 ± 3.67	0.887
Dento-basal characteristics			
U1-AnsPns (degree)	111.12 ± 7.48	115.05 ± 7.03	0.113
L1-GoMe (degree)	91.80 ± 6.96	95.52 ± 5.85	0.091
Interincisal angle (degree)	133.93 ± 10.32	124.8 ± 9.12	0.008*
Soft-tissue characteristics			
UL-E (mm)	-2.64 ± 3.04	-1.23 ± 1.24	0.878
LL-E (mm)	-1.31 ± 3.09	-0.99 ± 1.90	0.714
Naso-labial angle (degree)	122.57 ± 9.32	106.99 ± 10.99	p<0.001*

***** *statistically significant; paired t-test.*

Table III. *Cephalometric parameters, comparison across the study groups.*

Cephalometric parameters	Median (IQR)		p-value
	study group	control group	
Cranial base characteristics			
S-N (mm)	64.45 (63.35; 67.97)	62.30 (59.95; 66.20)	0.038*
S-Ba (mm)	39.45 (37.30; 42.77)	39.95 (35.17; 45.23)	0,95
Sagittal characteristics			
ANB (degree)	2.45 (-0.17; 4.42)	3.5 (2.3; 3.9)	0,319
Wits (mm)	-1.70 (-5.35; 0.95)	-1.45 (-1.72; -0.50)	0,465
Co-A (mm)	78.60(73.32; 81.42)	76.25 (73.05; 80.9)	0,776
Co-Gn (mm)	102.10 (98.60; 111.10)	99.00 (93.55; 107.67)	0,133
Dento-basal characteristics			
OVJ (mm)	4.3 (3.47; 5.27)	3.95 (3.07; 5.55)	0,486
OVB (mm)	1.05 (-2.92; 2.62)	2.05 (0.67; 3.50)	0,179

* *statistically significant; Wilcoxon test.*

DISCUSSION

This study included 18 individuals with TS under growth hormone therapy and a control group of age and gender matched healthy individuals. The craniofacial features were objectively described using dental casts and lateral cephalograms (31-44).

Previous studies, focused on the cranio-facial features of TS untreated with GH therapy, showed common characteristics. Mitbø et al. (1996) in two studies on 33 children with TS, reported a short posterior cranial base, retrognathic and posteriorly rotated maxilla and mandible. While the corpus and the total lenght of the mandible were found to be reduced, the length of the maxilla was normal. Moreover, they showed an increased anterior and lateral open-bite, a lateral cross-bite and Angle class II malocclusion. Svanberg et al. (2016) found similar results, studying 10 women with TS without GH: bimaxillary retrusion, posterior-rotation of the maxilla and a skeletal class II malocclusion. One-hundred-eight patients with TS were studied by Rizell et al. (2013): bimaxillary retrusion, bimaxillary posterior-rotation and short posterior cranial base and posterior facial height were described according to Jensen (1985) and to Rongen-Westerlaken et al. (1992) (45-50).

To the best of our knowledge, only two studies evaluated the occlusal features of TS without GH therapy. Szilágyi et al. (2000) studied 29 women with TS and reported Angle class II malocclusion, later cross-bite, anterior open and deep bite and a high narrow palate. Lopez et al. (2002) clinically assessed a high narrow palate in 23 women from Argentina. In the present study, the dental casts analysis showed a significantly higher PH/PW ratio in individuals with TS under GH therapy compared to healthy individuals. This data objectively supported the definition of a high-narrow palate. Oral habits, as oral breathing and non-nutritive sucking can interfere with the palatal growth. No data regarding oral habits were collected in the present study (45-52). This limitation may be taken into consideration in the interpretation of the results.

The GH therapy in individuals with TS is worldwide approved and its efficiency in increasing adult stature is demonstrated. However, few studies described the craniofacial features of individuals with TS treated with GH. Thirteen girls with TS under GH therapy, compared to 13 girls with TS without GH therapy, showed higher anterior and posterior facial heights, and longer mandibular rami and body and maxilla length. While the linear measurements were increased, the angular measurements and facial

height ratio did not show statistically significant difference. Davidopoulou and Chatzigianni (2017) showed that GH therapy had a major effect on the vertical growth of mandible with an anterior rotation, while the anterior and posterior cranial bases were not influenced. Rongen-Westerlaken et al. (1993) examined 19 children with TS before and after 2 years of GH therapy and demonstrated a significant growth of the mandibular rami and the anterior rotation of the mandible. Simmons et al. (1999) examined 19 girls with TS after 1 year of GH therapy and showed significant increased linear measurements of the mandible (53-60).

Hass et al. (2001) analyzed the effect of GH in 28 females with TS during their growth. The authors concluded that the results are minimal on the craniofacial growth, but their sample included: ten patients who were naive to GH at the initiation of the study and were treated with GH after 12 months of enrollment, three patient who never did the therapy and fifteen girls who had initiated GH treatment prior to enrolling in the study. A recent review by Wojcik and Ben-Skowronek (2020), reported that the exact amount and pattern of growth after GH administration is unpredictable; however, the facial convexity decreases and both the mandibular length and the posterior facial height increase (61-65).

In the present study, to assess the anteroposterior positioning of maxilla and mandible in relation to the anterior cranial base, the SNA (mean value 82°±2°) and SNB (mean value 80°±2°) **angles were calculated according to Steiner analysis (1953). In TS** group, the mean SNA (77.07°) and SNB (75.27°) were significantly lower compared to the control group (mean SNA=80.93° and SNB=77.73°), indicating a retruded position of the jaws. The cranial base measurements showed a significantly higher NS in the study group, influencing the sagittal position of the N point thus reducing the SNA and SNB angles.

The ANB (mean value 2°±2°) and WITS index (0±2 mm) exhibit the anteroposterior relationship between the maxilla and the mandible. In the present study, the ANB angle and the Wits index were similar in the two group, showing a skeletal class I malocclusion.

To evaluate the growth pattern, vertical characteristics were measured. All the parameters did not differ between the two groups, showing a mesofacial growth pattern.

The dento-basal characteristics, the OVJ and the OVB were similar in the two groups. The interincisal angle was significantly higher in the study group compared to the control group (p=0.008), but the mean value in the study group (133.93 ± 10.32) fell in the range of normality (130° ± 5°) showing a correct relationship between the upper and lower incisors. The soft-tissue evaluation showed an increased naso-labial angle in the study group compared to the control group.

The results obtained from the present study added data to the literature regarding the craniofacial characteristics of individuals with TS under GH therapy. Our results showed similar cephalometric characteristics in individuals with TS treated with GH and healthy controls. Due to the limited number of individuals included in this case series, to test this hypothesis, an analytic study with sample size calculation is needed to assure an adequate power to detect a statistically significant difference between groups if a difference is truly present (66-72).

According to the results of all the studies on TS girls untreated with GH, the growth pattern showed a tendency to a posterior rotation and retrusion of both the maxilla and the mandible, with a reduced length of the mandible, a vertical growth and a skeletal class II malocclusion. Moreover, regarding the occlusion, an anterior open bite, lateral cross bite and high narrow palate are reported.

The data, collected form the studies that evaluated the craniofacial characteristics of TS subjects under GH therapy and the results obtained from the present study, highlighted the tendency towards a normal mandibular length, a mesofacial growth pattern and a skeletal class I malocclusion. Regarding the occlusion, the palatal dimension is shown to be reduced.

It is known that growth hormone increases the expression of insulin-like growth factors (IGFs) in cartilage, and it influences skeletal growth primarily by stimulating the growth of cartilage in areas of endochondral ossification. Although growth hormone

therapy in Turner syndrome increases statural height toward or within the normal population range, the role of GH on the the craniofacial growth is unclear. It is likely that due to the timing of the growth pattern of the cranial synchondroses and endochondral ossification and the beginning of the GH therapy, the major effect of the therapy is on the mandibular growth. In fact, the tendency to a skeletal class I characteristics and a mesofacial growth pattern in girls with TS treated with GH are the results of an increased mandibular length, due to the response of the mandibular condyle cartilage to the therapy.

An early orthodontic diagnosis of narrow palatal is necessary to establish the proper treatment plan and timing of intervention. Future studies should test whether functional appliances used for skeletal class II malocclusion could increase the effect of the GH therapy in individuals with TS.

ACKNOWLEDGMENTS

The authors are grateful to all the colleagues who have made the diagnosis of Turner Syndrome. The authors have no conflict of interest to declare.

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