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ORIGINAL ARTICLE

Ontogenetic changes of craniofacial complex in Turner syndrome patients treated with growth hormone

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Abstract
Objective The present study assessed changes of craniofacial complex in Turner syndrome (TS) patients treated with growth hormone (GH) during development. The objective was to examine the growth rate and pattern of craniofacial structures and to establish effects of GH on craniofacial development.
Materials and methods The study population consisted of 15 TS patients treated with GH aged 5–18.5 years (13.3± 4.4) and corresponding control group of 45 females aged 6.8–18.7 (11.4±2.6). According to the stage of cervical vertebral maturation, subjects were categorized into pre-growth (5 TS and 15 controls) and growth (10 TS and 30 controls) subgroups. The cephalometric analysis comprised angular and linear variables, measured on lateral cephalometric radiographs.
Results The mandibular corpus/anterior cranial base ratio increased significantly only in controls during development. In growth period, ramus/corpus ratio was significantly larger in TS group. SNA and SNB angles were significantly smaller in TS growth subgroup compared to corresponding controls. Among other variables, no statistically significant differences were revealed.
Conclusions In TS patients treated with GH, growth capacities of cranial base and maxilla are adequate which can be attributed to GH treatment. Shape of mandible is altered due to decreased growth of corpus and overdeveloped ramus. Both maxillary and mandibular retrognathism are becoming more expressed during development.
Clinical relevance Favorable influence of GH on craniofacial complex growth rate and altered growth pattern revealed in this study should be considered while planning both orthodontic treatment and retention.

Keywords Turner syndrome · Growth hormone therapy · Craniofacial development · Bimaxillary retrognathism

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Introduction

Turner syndrome or Ullrich–Turner syndrome (TS) is a relatively common sex chromosome abnormality with a prevalence of 53 per 100,000 live-born females [1]. The syndrome may be caused by complete absence—monosomy (45,X) or structural aberrations of one of the X chromosomes. The most common structural aberrations are X-isochromosome (46,X,i(Xq)), X-ring (46,X,r(X)), and X-deletion (46,XX,del(Xp)). Likewise, it can be expressed in mosaic forms, with a second cell line carrying numerical (46,XX/45,X) or structural X chromosome aberrations, causing more moderate phenotypic appearance. In Serbian population, the most common karyotype is monosomy X (present in 48.4 % patients), with the missing paternal X chromosome [2], followed by structural aberrations of X chromosome (38.7 %), and mosaic karyotype (9.7 %) [3].

The main characteristics of TS are short stature, gonadal dysgenesis and a variable spectrum of typical phenotypic

features, including micrognathia, high-arched palate, low set and malformed ears, pterygium colli, broad chest, cubitus valgus, congenital lymphedema, congenital heart disease, renal abnormalities, etc. [4]. Though the pathogenesis of the disorder is still not entirely understood, there are several factors assumed to be responsible for the development of TS features, chromosome imbalance and dosage effect (haploinsufficiency) of growth and lymphogenic genes being among the most important [5].

It is well-known that haploinsufficiency of pseudoautosomal gene SHOX (the short stature homeobox gene) causes growth failure [6, 7]. Moreover, SHOX is expressed in two major regions: (a) the limb, which explains the immediate role in final height, and (b) the first and second pharyngeal arches which explains the craniofacial disorders in TS patients [8]. Namely, the structures involved in micrognatia, high-arched palate, and sensoneural deafness originate from the mesenchyme of the first and second pharyngeal arches. Cephalometric studies have reported distinct craniofacial features in young and adult patients with TS [9–16]. These studies have shown increased cranial base flexion with reduced posterior and total cranial base length, bimaxillary retrognathism and posteriorly rotated maxilla and mandible, as well as short mandible [9–16]. The study of prenatal cranial base complex reported its abnormal shape: larger cranial base angle, retrognathic maxilla, smaller anterior and posterior cranial fossa, and smaller maxillary complex [17].

Given that the main characteristic of TS patient is short stature, this feature has been extensively studied [8, 18, 19]. A noticeable failure of intrauterine growth, slightly reduced height with progressive reduction in childhood, and no evidence of pubertal height spurt have been established [18]. In order to increase growth velocity and final adult height, it is recommended to treat TS patients with recombinant human growth hormone (GH) [20, 21]. GH therapy has an impact on craniofacial growth in boys with idiopathic short stature [22], growth hormone-deficient children [23], children born small for gestational age [24], children treated with total body irradiation [25], and TS girls [26]. GH treatment resulted in increase in growth of the craniofacial skeleton, especially in maxillary base length and mandibular ramus height [22–26] and anterior rotation of the mandible [22].

However, data on growth pattern of craniofacial complex in TS patients treated with GH are still scarce. Therefore, the present study was directed at assessing the craniofacial complex changes in TS patients treated with GH during development. The objective was to examine the growth rate and pattern of the craniofacial structures in different skeletal maturation stages and to establish effects of GH on craniofacial development.

Subjects and methods

Study subjects

The study population consisted of TS patients treated with GH. The diagnosis was established by karyotype analysis performed on peripheral blood lymphocytes. The patients were treated with GH, as soon as they have dropped below the tenth percentile of the normal female growth curve, with starting daily dose of 0.045–0.05 mg GH/kg body weight and the dose was adapted according to patient's growth response. At the Department of Orthodontics, School of Dentistry, University of Belgrade, all the subjects have undergone clinical orthodontic examination and required treatment. Inclusion criteria were: occlusion which was not impaired by missing teeth, orthodontic treatment which did not involve functional appliance, lateral cephalometric radiographs of good quality, Caucasian origin, and similar socio-economical background. The records of female patients (46,XX), matching the TS patients by age and inclusion criteria, were selected from the files at the Department of Orthodontics as the controls. Modified version of the cervical vertebral maturation method by Tiziano Baccetti [27] was used to subdivide subjects, from both study and control group, into two subgroups. According to the stage of cervical vertebral maturation, subjects were categorized into pre-growth (cervical stage 1 and 2) and growth (included cervical stage 3, 4, and 5) subgroups.

Of all TS patients that had been treated at The Department of Orthodontics, 15 met the inclusion criteria. The control group consisted of 45 females. The TS patients were 5–18.5 years old at the time of examination (mean 13.3± 4.4 years), the control group 6.8–18.7 (mean 11.4±2.6). Pre-growth subgroups consisted of 5 TS and 15 control patients, while growth subgroups had 10 and 30 patients in TS and control group, respectively.

All subjects involved in this study were a part of research conducted at The Department of Orthodontics, School of Dentistry, University of Belgrade in cooperation with Institute for Mother and Child Healthcare of Serbia "Dr Vukan Cupic" in Belgrade. The research design was approved by the Ethics Committee of the School of Dentistry, Belgrade, Serbia. Informed consent was obtained from all patients, parents, or legal guardians for the use of diagnostic records (study casts, panoramic radiographs, lateral cephalometric radiographs, facial photographs, etc.) for research purposes.

Cephalometric analysis

Variables of interest, measured on lateral cephalometric radiographs, were used to describe growth rate and pattern

of craniofacial complex by ratios and angles. The cephalometric analysis consisted of angular and linear measurements. The reference points used are presented in Fig. 1 and the planes, lengths, and angles in Fig. 2. All investigated variables are listed in Table 1. Subjects from both groups had the lateral cephalometric radiographs taken under standardized conditions. Each lateral cephalometric radiograph was numbered randomly in order to eliminate observer bias.

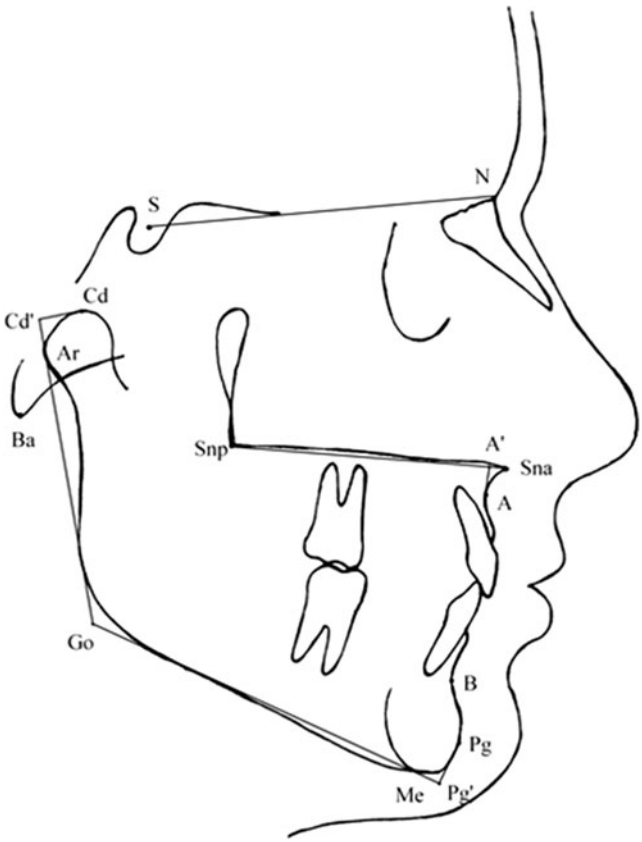

Fig. 1 Cephalometric reference points. *N* nasion—the most anterior point of the frontonasal suture in the midsagittal plane, *S* sella-midpoint of the sella, *Cd* condilion—the most posterior superior point of the condyle, *Cd′*-perpendicular construction from condilion to the ramus tangent line, *Ar* articulare—a constructed point at the intersection of the images of the posterior margin of the ramus and the outer margin of the cranial base, *Ba* basion—lowest point on the anterior margin of the foramen magnum in the medial plane, *Go* gonion—a constructed point at the intersection of the ramus tangent line and mandibular plane, *Me* menton—the most inferior point of the outline of the symphysis in the midsagittal plane, *Pg* pogonion—the most anterior point of the bony chin in the midsagittal plane, *Pg′*-perpendicular construction from pogonion to the mandibular plane, *B* point B, supramentale—the deepest point on the outer contour of the mandibular alveolar process between infradentale and pogonion, *A* point A, subspinale—the deepest midline point on the anterior outer contour of the maxillary alveolar process between the anterior nasal spine and prosthion, *A′*-perpendicular construction from point A to the palatal plane, *Sna* anterior nasal spine—the most anterior point of the tip of the anterior nasal spine in the midsagittal plane, *Snp* posterior nasal spine—the intersection of the continuation of the anterior wall of the pterygomaxillary fissure and the nasal floor

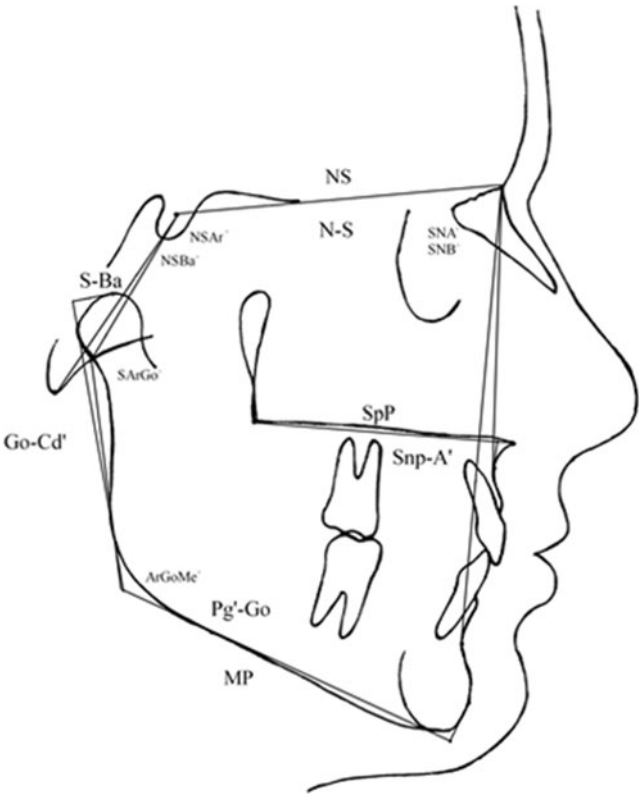

Fig. 2 Cephalometric reference planes, lengths and angles. *NS* anterior cranial baseline—line joining point *S* and *N*, *SpP* palatal plane—line joining point Snp and Sna, *MP* mandibular plane—tangent to the lower border of the mandible through point Me, *N-S* length of anterior cranial base, *S-Ba* length of posterior cranial base, *Go-Cd′* length of mandibular ramus, *Pg′-Go* length of mandibular corpus, *Snp-A′* length of maxilla, *NSBa* cranial base flexion, *NSAr* sella angle, *SArGo* articular angle, *ArGoMe* gonial angle, *SNA* maxillary prognathism angle, *SNB* mandibular prognathism angle

Image calibration, marking of reference points and cephalometric analysis were done by the same investigator using Dolphin Imaging 11 (Dolphin Imaging Systems; Woodland Hills, CA, USA). In the case of duplicated structure, reference point was marked at the midpoint. Intra-observer reliability was assessed between repeated measurements for 15 subjects with 2 weeks interval (Chronbach's Alpha coefficient >0.95 indicated a satisfactory level of intra-observer reliability).

Statistical analysis

Since data were normally distributed (Kolmogorov–Smirnov test, $p>0.05$), parametric statistical tests were selected. Independent sample *t* tests were used to establish the statistical difference of the cephalometric measurements between study subjects and their controls (in both pre-growth and growth subgroup) and between pre-growth and growth subgroups within TS and control group. In all the statistical tests, the level of significance was set at $p<0.05$ and

Table 1 Variables investigated in the study

Cranial base	
S-Ba/N-S (%)	Posterior cranial base and anterior cranial base length ratio
NSBa (°)	Cranial base flexion
Maxillary relations	
Snp-A′/N-S (%)	Maxilla and anterior cranial base length ratio
SNA (°)	Maxillary prognathism angle
NS-SpP (°)	Angle between anterior cranial base and palatal plane
Mandibular relations	
Pg′-Go/N-S (%)	Mandibular corpus and anterior cranial base length ratio
Go-Cd′/Pg′-Go (%)	Mandibular ramus and corpus length ratio
SNB (°)	Mandibular prognathism angle
NS-MP (°)	Angle between anterior cranial base and mandibular plane
Sum of posterior angles (°)	Sum of sella (NSAr), articular (SArGo) and gonial angle (ArGoMe) according to Bjork

calculations were handled by the Statistical Package for Social Sciences, version 12.0 (SPSS Inc.; Chicago, IL, USA).

Results

Cranial base

According to the results obtained in this study, in the TS group, S-Ba/N-S ratio increased from pre-growth to growth period more than in control group. NSBa angle was slightly larger in TS pre-growth subgroup compared to the control. However, statistical tests did not reveal significant differences in variables describing cranial base between TS and controls (Table 2).

Maxillary relations

Even though Snp-A′/N-S ratio was smaller in TS pre-growth and larger in TS growth subgroup relative to the control (Table 3), the difference between groups was not statistically significant. TS patients exhibited smaller SNA angle in pre-growth period compared to the corresponding controls, although without statistically significant difference. From pre-growth to growth period SNA decreased, especially in TS group, consequently the difference between growth subgroups was significant (p=0.031) (Fig. 3). NS-SpP angle showed slight increase in vertical inclination of the maxilla in TS group, without statistical significance, and slight decrease in the control group (Table 3).

Mandibular relations

The mandibular ratio Pg′-Go/N-S increased significantly only in healthy controls during development (p=0.018; Fig. 4); whereas in TS group, the ratio remained almost unchanged. Furthermore, in growth period, Go-Cd′/Pg′-Go ratio was significantly larger in TS compared to control group (p=0.020; Fig. 5). Regarding the variables describing the growth pattern, SNB angle was smaller in TS growth subgroup compared to the corresponding control (p=0.041;

Table 2 Variables describing cranial base

Group		Turner syndrome				Control			
Variable		Mean	SD	SE	Significance (t test, p<.05)	Mean	SD	SE	Significance (t test, p<.05)
Cranial base	Subgroup								
S-Ba/N-S (%)	Pre-growth	62.14	5.54	2.48	Aa	63.76	5.47	1.46	Aa
	Growth	67.94	10.72	3.39	Aa	66.10	4.49	0.79	Aa
NSBa (°)	Pre-growth	131.30	3.31	1.48	Aa	128.32	5.43	1.45	Aa
	Growth	131.95	7.46	2.36	Aa	131.22	5.52	0.98	Aa

Subgroups marked with the same superscript letters are not statistically significantly different. Upper case letters indicate statistically significant differences in variables within the row between Turner syndrome and control group (in pre-growth and growth subgroups, separately). Lower case letters indicate statistically significant differences within the column between pre-growth and growth subgroups in each group

Table 3 Variables describing maxillary relations

Group		Turner syndrome				Control			
Variable		Mean	SD	SE	Significance (t test, $p<.05$)	Mean	SD	SE	Significance (t test, $p<.05$)
Maxillary relations	Subgroup								
Snp-A′/N-S	Pre-growth	67.02	2.63	1.17	Aa	68.81	4.53	1.21	Aa
	Growth	69.91	3.68	1.23	Aa	68.06	2.86	0.51	Aa
SNA (°)	Pre-growth	79.94	4.62	2.07	Aa	82.66	4.39	1.17	Aa
	Growth	77.49	5.99	1.89	Aa	81.25	4.18	0.74	Ba
NS-SpP (°)	Pre-growth	7.96	0.71	0.32	Aa	8.50	2.82	0.75	Aa
	Growth	9.87	5.07	1.60	Aa	8.19	4.10	0.72	Aa

Subgroups marked with the same superscript letters are not statistically significantly different. Upper case letters indicate statistically significant differences in variables within the row between Turner syndrome and control group (in pre-growth and growth subgroups, separately). Lower case letters indicate statistically significant differences within the column between pre-growth and growth subgroups in each group

Fig. 6), while among other variables no statistically significant differences were revealed (Table 4).

Discussion

This comparative study was designed to assess growth rate and pattern of craniofacial structures during development in Turner syndrome patients treated with growth hormone and to compare them with growth features of healthy controls. Initially, the idea was to compare TS patients treated with GH with those who never underwent GH therapy and with healthy females in order to precisely determine the effects of GH on craniofacial development. However, GH treatment is accessible to a large number of TS patients and it was barely achievable to find enough TS subjects who did not receive GH. Thus, it has been decided to compare data of TS patients treated with GH with healthy controls, while the literature provided the insight into craniofacial features exhibited by non-GH treated TS patients.

In order to best evaluate developmental changes, groups were subdivided consistent with the skeletal maturity. Skeletal age was determined according to cervical vertebral maturation stage [27] on the basis of the information derived from a single cephalogram, avoiding an additional X-ray exposure. The ratios between linear dimensions of craniofacial structures and anterior cranial base length were used to describe the changes in craniofacial morphology, as the growth of craniofacial structures depends on cranial base growth [28].

Cranial base development

TS patients treated with GH and controls had similar growth rate and pattern of cranial base. The growth rate of posterior cranial base of TS patients was slightly higher than the

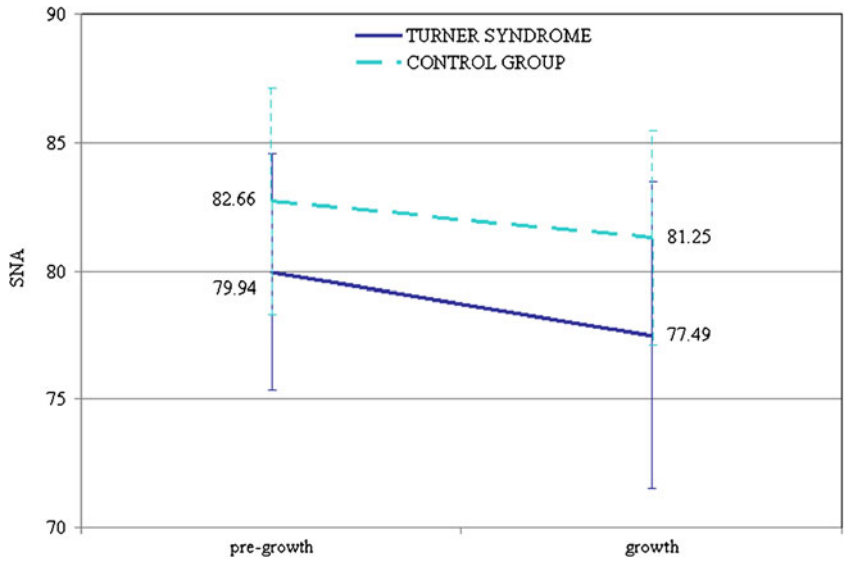

Fig. 3 The change of SNA angle during development

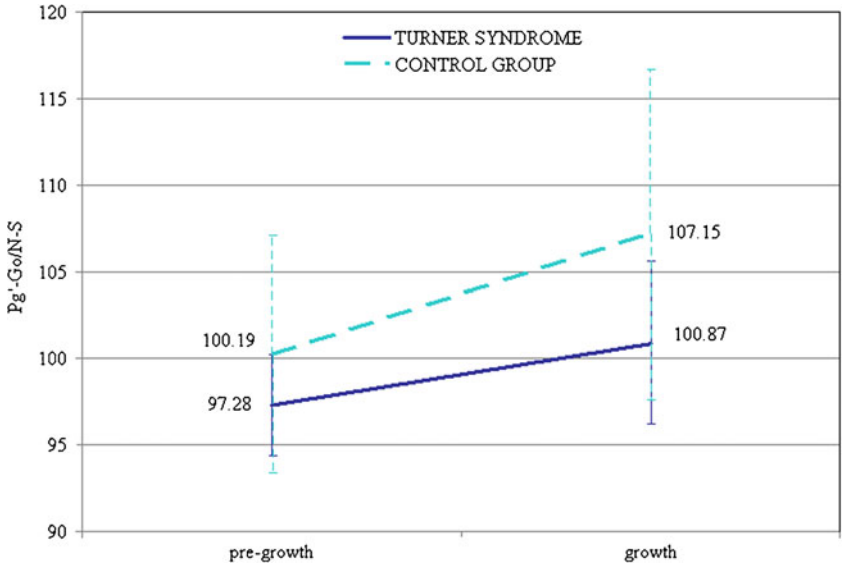

Fig. 4 The change of mandibular base and anterior cranial base length ratio (Pg′-Go/N-S) during development

growth rate of healthy controls, ensuring similar ratio of posterior and anterior cranial base length (S-Ba/N-S) in growth peak period in the groups. In contrast, studies on TS patients who did not receive GH treatment showed growth retardation of posterior cranial base [12, 14–16]. According to these studies, anterior cranial base was normally developed, while posterior cranial base length exhibited shortening. Normally developed posterior cranial base in TS patients found in the present study can be attributed to GH treatment, known to cause an overall increase of the craniofacial skeleton growth [22]. Furthermore, the basal angle (NSBa) was similar between groups in the two observed periods of growth. Previous cephalometric studies have found flattened cranial base angle in TS patients, though they referred to an unspecific growth period [14–16], adult TS population [11, 13], and fetuses with greater phenotypic anomalies than children born with TS only [17]. It can be speculated that cranial base angle might increase by the time full maturity is established, leading to a flattened cranial base.

Maxillary development

The development of maxilla in TS patients treated with GH differed only in growth pattern when compared to healthy controls, while growth rate was comparable between groups. In the course of the development, maxillary growth was to some extent accelerated in TS group. Therefore, the ratio of maxilla and anterior cranial base length (Snp-A′/N-S) was larger in TS group than in control group in the growth peak period, even though statistically significant difference could not be found. Some studies investigating TS patients who did not receive GH have found maxilla to be underdeveloped [14, 17], while others have reported normally developed maxilla [12, 15]. In a study that assessed the correlation of craniofacial

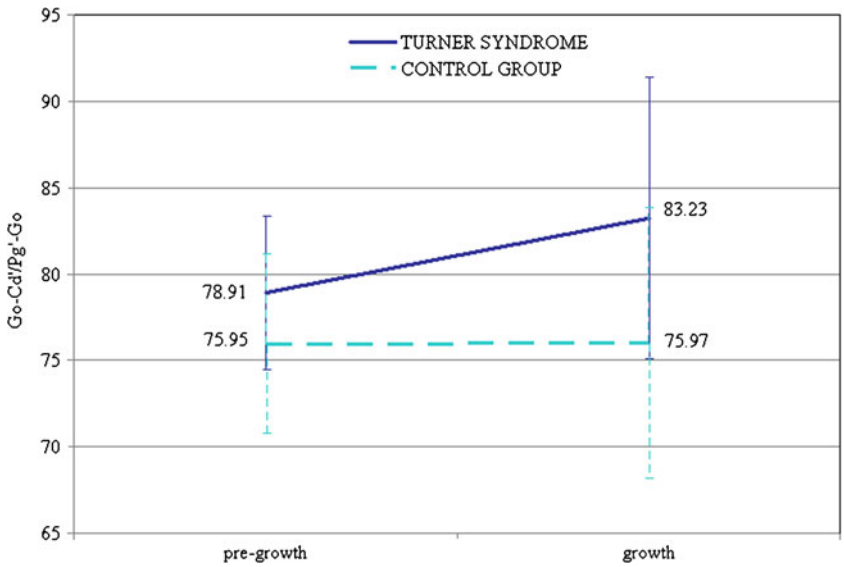

Fig. 5 The change of ramus length and mandibular base length ratio (Go-Cd′/Pg′-Go) during development

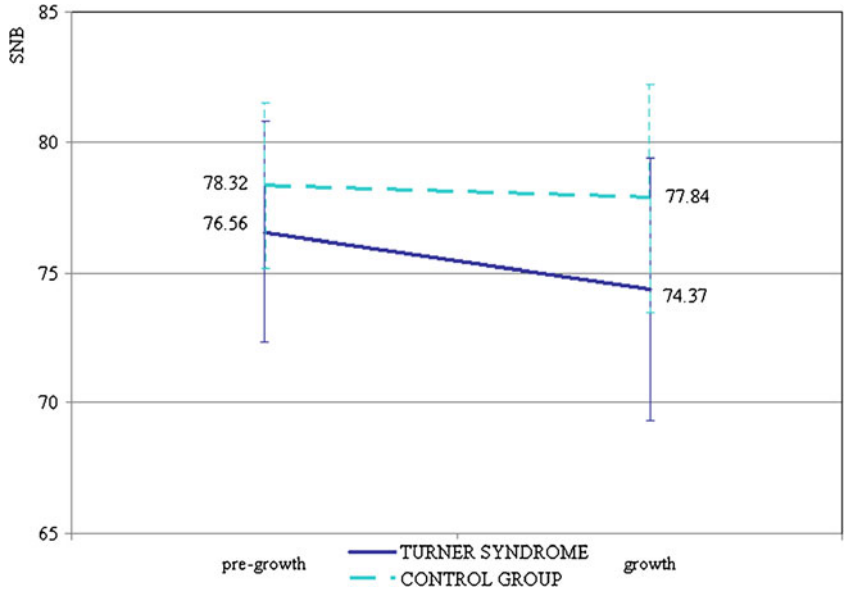

Fig. 6 The change of SNB angle during development

variables with age in untreated TS patients, Dumancic et al. showed reduced maxillary antero-posterior growth [16]. Their results are particularly useful for the present study as a reference in the evaluation of GH benefit on the craniofacial growth given that TS patients included in that study have similar geographical and genetic origin as our patients. Since GH was shown to increase the growth rate of maxillary base in treated patients [22, 23, 26], it can be assumed that it is responsible for normally developed maxilla in our TS group. Maxillary retrognathism (SNA) existed in pre-growth period in TS patients and became significant in growth peak period. This finding is in accordance with some previous studies that reported retrognathic maxilla in prenatal [17] and young TS patients [12, 14–16]. According to the results reported in earlier studies, it can be anticipated that maxillary retrognathism will become fully expressed in the adulthood [11, 13]. To conclude, during ontogenesis maxillary retrognathism increases gradually. There is a tendency towards posterior growth pattern of maxilla (NS-SpP) during growth in TS girls, although not as pronounced as found in earlier studies [12, 15, 16].

Table 4 Variables describing mandibular relations

Group		Turner syndrome				Control			
Variable		Mean	SD	SE	Significance (t test, $p<.05$)	Mean	SD	SE	Significance (t test, $p<.05$)
Mandibular relations	Subgroup								
Pg′-Go/N-S (%)	Pre-growth	97.28	2.92	1.31	Aa	100.19	6.85	1.83	Aa
	Growth	100.87	4.70	1.57	Aa	107.15	9.54	1.69	Ab
Go-Cd′/Pg′-Go (%)	Pre-growth	78.91	4.48	2.00	Aa	75.95	5.17	1.38	Aa
	Growth	83.23	8.18	2.73	Aa	75.97	7.84	1.39	Ba
SNB (°)	Pre-growth	76.56	4.21	1.88	Aa	78.32	3.18	0.85	Aa
	Growth	74.37	5.06	1.60	Aa	77.84	4.38	0.77	Ba
NS-MP (°)	Pre-growth	31.32	4.02	1.80	Aa	33.14	4.27	1.14	Aa
	Growth	34.88	8.39	2.65	Aa	33.98	6.55	1.16	Aa
Sum of post. angles (°)	Pre-growth	391.42	3.82	1.71	Aa	393.11	3.53	0.94	Aa
	Growth	395.25	8.02	2.54	Aa	393.92	6.58	1.16	Aa

Subgroups marked with the same superscript letters are not statistically significantly different. Upper case letters indicate statistically significant differences in variables within the row between Turner syndrome and control group (in pre-growth and growth subgroups separately). Lower case letters indicate statistically significant differences within the column between pre-growth and growth subgroups in each group

Mandibular development

The development of mandible differed between TS patients and healthy controls, both in growth rate and growth pattern. Lower growth rate of mandibular corpuses resulted in their underdevelopment in Turner syndromes, a finding supported by several studies [11, 12, 14–16]. On the other hand, in our TS group, higher growth rate of mandibular ramus (Fig. 5) caused its overdevelopment, which is in accordance with the results of Gron et al. [14]. Other investigators found the ramus to be of normal height [12, 15, 16] or even shorter than in controls [11]. It was shown that GH accelerates growth on mandibular condyle [22, 25, 26], consequently it could be responsible for the intensive growth of mandibular ramus in our TS patients.

Growth patterns of the mandible in sagittal and vertical planes were similar to that of maxilla. Mandibular retrognathism (SNB) of our TS patients became distinctive in the growth peak period. Retrognathic mandible has also been confirmed previously [11–16]. Taking into consideration all these results, it may be concluded that in the course of development mandibular retrognathism is becoming more pronounced. In TS group, mandible showed a tendency towards posterior growth pattern during the observed growth period. Posterior growth pattern was not as apparent as in previous studies on TS patients of various age [12, 15, 16] or adult TS patients [11, 13]. Increased vertical growth of the mandibular ramus in TS patients modified posterior growth rotation, which is in accordance with previous studies on GH effects on craniofacial growth [22].

Studies on patients with X chromosome aneuploidies (45, X and 47, XXY) showed that jaw position is affected by X chromosome aberrations [9, 11]. Even though in our TS patients both maxilla and mandible achieved normal length, GH did not seem to have any marked effect on correction of the antero-posterior position of the jaws and bimaxillary retrognathism became more apparent in the course of development. Various types of investigations on TS population [9–16] confirmed bimaxillary retrognathism. With regards to growth in vertical plane, our findings suggest that both maxilla and mandible in TS patients have tendency towards posterior growth pattern.

Conclusions

Within the limitation of this study, when comparing craniofacial complex development between TS patients treated with GH and controls, it can be concluded:

1. In the course of development, both maxillary and mandibular retrognathism are becoming more pronounced. Growth pattern is mostly influenced by X chromosome deficiency.
2. In TS patients treated with GH, cranial base and maxilla have adequate growth rates and growth capacities. However, growth of mandibular corpus is decreased, while ramus growth is enhanced.
3. Growth hormone is considered responsible for intensive growth of mandibular ramus and has a favourable influence on craniofacial complex growth rate.

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Conflict of interest The authors declare that they have no conflict of interest.

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