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The Effect of Growth Hormone on Craniofacial Growth and Dental Maturation in Turner Syndrome

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ABSTRACT

Serial cephalometric and panoramic radiographs from a mixed longitudinal group of 28 subjects with Turner syndrome (TS), age 4.4–19.0 years, were evaluated for annualized growth increments of the craniofacial complex and dental development and were compared with a longitudinal control group from the Burlington growth study. The short and retrognathic face characteristic of the syndrome was due largely to the increased cranial base angle, decreased posterior face height, and decreased mandibular length, all of which were significantly different from the controls. Although increases in statural height occurred in the TS children who were treated with human growth hormone (GH), there was little or no effect on growth of the jaws, particularly in the older subjects, and the characteristic facies of the syndrome persisted. Dental development was advanced in all TS subjects, and GH administration had no effect on the rate of dental development.

KEY WORDS: Craniofacial growth, Growth hormone, Turner syndrome, Dental development.

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Turner syndrome (TS) is an X chromosome abnormality of females, occurring in approximately 1 in 2500 live female births. These patients present with varying degrees of dysmorphic features. Virtually all patients develop short stature, and common dysmorphic features include epicanthal folds, low posterior hairline, short webbed neck, and cubitus valgus¹ ([Figure 1](#) ). Organ system problems include ovarian dysfunction, structural renal abnormalities, and congenital heart malformations, including bicuspid aortic valve and coarctation of the aorta.² Comparison of craniofacial proportions with normal children shows retarded development of the cranial skeleton, reduced size of the craniofacial complex, retrognathic profile, and increased incisor overjet. Decreased overbite and Class II dental and jaw relationships usually are present, and an increased incidence of anterior open bite and lateral crossbite has been observed. Common intraoral findings include posterior crossbite, narrow high-arched palate, early eruption of permanent teeth, reduced tooth size, and an increased tendency toward idiopathic root resorption.³

Loss of all or part of an X chromosome causes Turner syndrome. Common karyotypes include 45,X, 46X,i(X) and 45,X/mosaic.⁴ The 45,X karyotype is the most common, occurring in 50–55% of all cases, with 46X,i(X) karyotype (isochromosome X) occurring in approximately 15% of cases. Mosaic subjects have 2 or more separate cell lines, eg, 45,X/46,XX, 45,X/46,XY, or 45,X/47,XXX.⁵

The chromosomal basis for most of the phenotypic features of TS is an insufficiency of genes that reside on the X chromosome. In normal 46,XX females, one X chromosome is inactivated shortly after fertilization through the process of lyonization. Although one X chromosome is inactivated, some of its genes remain active, including several in the pseudoautosomal region of the short arm. Absence of the SHOX gene, which is expressed at high levels by adult bone marrow and fibroblasts⁶ and in the limbs and first and second pharyngeal arches during human embryonic development,⁷ appears to be responsible for short stature in Turner syndrome subjects.

The phenotype for TS subjects is variable, with dysmorphic features ranging from profound to subtle. As a general rule, the more normal cells a subject has, the fewer TS-like characteristics are seen, but the severity of clinical expression does not correlate one-to-one with karyotype. Facial characteristics range from near-normal appearance to severe malocclusion and obvious jaw deficiencies. In untreated Turner syndrome patients, the face and facial bones usually are proportionately smaller than normal, the cranial base angle is increased, and the jaws are retrognathic.⁸ Orthodontists need to be aware that some girls who present for treatment of malocclusion may have a previously undiagnosed Turner syndrome and should keep the facial characteristics in mind during diagnostic evaluation.

The psychological and sociological impact of reduced statural height in childhood, adolescence, and adulthood is the driving force behind growth hormone treatment in Turner syndrome. Although girls with TS are generally not growth hormone deficient, they grow in response to supplemental growth hormone administration.⁹ The goal is normalizing the stature to within the population range. Short stature in TS was first successfully treated with cadaver growth hormone extracts in 1960. Due to limited availability, cost, and safety issues, biosynthetic growth hormone (recombinant human growth hormone, rGH) was developed and became available in 1985. With this increase in availability, larger and more complex research studies have shown that growth hormone supplementation increases growth velocity and improves final statural height.¹⁰

In children with idiopathic growth hormone deficiency¹¹ and in children born small for gestational age (SGA),¹² growth hormone therapy has a significant impact on craniofacial growth. Increases in ramus height, lower facial height, and posterior cranial base lengths (S-Ar) are seen. There is an age-related effect on the posterior cranial base. In younger patients, age 4–6 years, an increased growth rate of the spheno-occipital synchondrosis is observed. When chronological age increases, growth hormone treatment has less effect on this area. It is believed that growth hormone administration primarily affects craniofacial regions where cartilage-mediated growth occurs and regions that adapt to cartilage growth.¹³

There is some question about the craniofacial effects of supplemental GH used in treatment of Turner syndrome. In a comparison of Dutch children with TS who had rGH treatment with a large cross-sectional control group, Rongen-Westerlaken et al¹⁴ found a statistically significant increase in ramus growth and anterior rotation of the mandible over a 2-year period, but they did not report either the size of the growth increments or their variability.

The dentition in untreated TS children is characterized by accelerated development, but the sequence of tooth eruption does not differ significantly from normal populations.¹⁵ No data exist regarding the effects of supplemental rGH treatment on dental development in TS subjects. In idiopathic short stature children and in hypopituitary patients (GH deficient), treatment helps to normalize skeletal growth but dental development is not significantly affected.¹⁶

The purpose of this study was to determine the effects of recombinant growth hormone administration on facial growth and dental maturation in American children with Turner syndrome.

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Subjects. The mixed longitudinal sample consisted of 28 Caucasian females (chronologic age 4.4–19.0 years) with Turner syndrome, diagnosed by lymphocyte chromosomal analysis. The percent karyotypes for the sample population were 45,X = 47%, 45,X/mosaic = 39%, and 45X,i(X) = 14%. The subjects selected for the projects were a subgroup from a larger on-going investigation at the University of North Carolina (UNC) Division of Pediatric Endocrinology. Only Caucasian subjects were selected in order to control for known racial differences in craniofacial growth and development. Of the 28 subjects, 10 were naive to GH at the initiation of the study and were treated with GH after 12 months of enrollment (naive/treated). Fifteen subjects had initiated GH treatment prior to enrolling in the study (treated), and 3 were never treated with GH (untreated). For those receiving GH, treatment consisted of 0.35 mg/kg/wk divided into 6–7 subcutaneous injections. This dosage is somewhat higher than the dose used in children with growth hormone deficiency. The age at initiation of GH therapy was 9.0 ± 3.2 years (range 2.4–9.0 years).

Radiographic evaluation. Annual lateral cephalometric, panoramic, and hand-wrist radiographs were obtained for each subject over study periods of 2–5 years. The radiographs were taken under standardized conditions, with the teeth in maximum intercuspation for the head images. All cephalometric radiographs were traced and digitized by the same investigator (AH) using the UNC 96-point model and were checked and corrected as necessary by a laboratory technician with extensive experience in digital cephalometrics. The cephalometric

analysis consisted of extensive linear and angular measurements to establish proportional relationships. The annual increment of change for each measurement was determined for each patient by subtracting the value of each previous measure to the next annual variable.

Dental age was assessed via the method established by Demirjian et al.¹⁷ Bone age was determined by analyzing the left hand against the standards of Gruelich and Pyle.¹⁸

Normative data from lateral cephalometric, panoramic, and hand-wrist radiographs were taken from a longitudinal control sample of 15 girls with skeletal and dental angle Class I relationships that had not undergone any orthodontic treatment, selected from the files of the Burlington Growth Center, Ontario, Canada.

The cephalometric and panoramic data were evaluated using the generalized estimating equations methodology (GEE, SAS Institute), Z-score description comparing the control to the Turner syndrome children, and analysis of covariance. The GEE methodology provides a method of analyzing correlated longitudinal data in which the subjects are measured at different points in time. The GEE approach was used to estimate and test the parameters of interest in the model, which were control group vs TS subjects who did and did not receive GH treatment. Z-scores were used to describe the Turner syndrome subjects naive to GH treatment at baseline. Of interest was how this group changed over the course of GH treatment. Analysis of covariance was used to determine if any parameter showed a unique effect. The variables of interest were age, cephalometric variable, and length of GH treatment.

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Tabulated data for the control and TS subjects are shown in [Table 1](#) as the median dimensions and Z-scores for selected measurements and angles. For this table, because of the lack of significant differences related to treatment, data for naive (untreated) and GH-treated subjects were combined. It can be seen that, in general, the TS children differed from the controls particularly in their decreased distance from sella turcica to posterior nasal spine and articulare (S-PNS, S-Ar), short mandibular body (Go-Gn), and increased cranial base angle (N-S-Ba). Both maxillary length (PNS-ANS) and mandibular ramus height (Ar-Go) were increased relative to the controls. The decreased SNA angle, therefore, could be attributed to a maxilla of normal length that was positioned somewhat posteriorly ([Figure 2](#)). The even more decreased SNB angle and the increased ANB angle were due to a horizontally short mandible with normal ramus height that also was positioned posteriorly and superiorly on the skull. The short and retrognathic face characteristic of the syndrome can be seen to be due largely to the increased cranial base angle, decreased posterior face height, and decreased mandibular length, all of which are significantly different from the controls (GEE, $P < .0001$).

Statistical analysis did not reveal significant differences in growth increments between the GH-treated and untreated TS subjects. Because growth was observed over only a short period for most of the subjects before GH treatment was instituted, however, the variability in responses and small sample size limited our ability to discern the effects of treatment vs no treatment.

Annualized increments of growth for selected craniofacial dimensions in TS subjects treated with GH are shown in comparison with the control population in [Figure 3](#). For each graph, the mean and 1 standard deviation (SD) above and below the mean for the control population are represented as wide, solid black lines, with the intervening area shaded. Growth increments for each TS individual are plotted as a function of age. Growth increments for individual patients were quite variable but were similar to the controls, with most being within 1 SD of the mean of the control group.

When cephalometric variables were plotted against age, little or no change occurred during the period of study in cranial and cranial base variables or in jaw relationships. Growth of the mandible did occur, however. In [Figure 4](#), an increase with age in S-Go and Gn-Ar dimensions is demonstrated.

Dental ages over time for individual TS subjects with and without GH treatment vs controls are displayed in [Figure 5](#). Dental age in the Turner syndrome subjects was always advanced relative to chronologic age, and administration of rGH had no effect on the rate of dental maturation.

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Although growth hormone therapy in Turner syndrome increases statural height toward or within the normal population range, it does not correct the craniofacial growth deficiencies that produce the characteristic facies of the syndrome. It is known that growth hormone, directly or indirectly through its modulation of gene products, 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.¹⁵ The difference in craniofacial and general body effects is due largely to the different timing of endochondral bone growth in the 2 regions.

The primary growth cartilages, the first skeletal components to appear in early embryonic life, control growth in the cranial base and the limbs. The mechanism of growth in the synchondroses of the cranial base and the epiphyseal plates of the limbs is the same, ie, growth of the cartilage followed by its transformation into bone as maturing cartilage is replaced with bone. The timing is quite different in the craniofacial and limb areas, however. Growth of the cranial base parallels growth of the brain and is largely complete by age 6, while growth

in the limbs because growth at the s-e and i-s synchondroses peaks at the early cessation of growth at the synchondroses of the cranial base means that, by the time treatment of short stature in TS patients typically begins, there is no longer the possibility of a significant response in that area.

Forward growth of the maxilla occurs by 2 mechanisms. First, the nasomaxillary complex is pushed forward by growth at the sphenothmoidal (s-e) and (less importantly) interethmoidal (i-s) synchondroses. This lengthens the anterior cranial base and moves the entire midface more anteriorly. Second, the maxilla and associated structures are pulled forward by further development of the soft tissue complex in which they are embedded, and growth at the posterior and superior sutures moves the nasomaxillary complex away from the cranial base. The first mechanism is quite important up to age 6, when growth at the s-e and i-s synchondroses is completed; the second mechanism accounts for almost all maxillary growth thereafter.

A characteristic midface deficiency is observed in achondroplasia, the autosomal dominant genetic syndrome that produces dwarfs with a reasonably normal trunk length but very short arms and legs. In these children, the midface deficiency is due not to a small maxilla but to the failure of a reasonably normal maxilla to be translated anteriorly into a normal position because the cranial base does not lengthen as it should. The midface deficiency in Turner syndrome arises from the same cause. The dimensions of the maxilla are reasonably normal, but its position is not. As Laine et al have noted,¹⁹ palate length as measured on dental casts is normal in Turner syndrome, and [Table 1](#) demonstrates that the cephalometric measurement of maxillary length (PNS-ANS) also was close to the controls. Since the cartilage of the cranial base grows only up to about age 6, one would expect little effect on the position of the maxilla from GH administration in older children. Our sample of children who received early administration of GH was simply too small to confirm the forward movement of the maxilla that probably would occur if GH could be given early enough.

In the second phase of maxillary growth, it is possible that growth of the cartilage of the nasal septum plays some role in forward translation of the maxilla. It seems clear that, if this cartilage plays a role at all in maxillary growth, other elements in the soft tissue matrix also are important. Thus, one would not expect much, if any, effect on the maxilla from growth hormone administration after the s-e and i-s synchondroses had closed, and exactly this is observed in the Turner syndrome patients.

Growth of the cranial base also affects the position of the mandible. In [Figure 2](#), note the vertical shortening of the midcranial base, which reflects deficient growth at the sphenoccipital synchondrosis. The result is a failure to translate the area of the craniomandibular articulation downward. This produces a mandible with neither the vertical nor anterior projection that would be expected. Because of the position of the joint, an abnormally large mandible would be required to bring the chin and teeth to the normal position. In TS, the mandibular ramus grows in length to partially compensate for the vertical position of the joint, but the mandibular body length is small, and the deficiency in chin projection produced by the short mandible is magnified by the cranial base deficiency.

The prime example of endochondral ossification of a secondary cartilage is seen in the mandibular condyle. The condylar cartilage has quite a different embryologic origin than the cartilage of the cranial base synchondroses or the epiphyses of the long bones and grows on a different schedule from the cranial base cartilages. Unlike the cartilage of the epiphyseal plates (and presumably the cartilage of the synchondroses), it does not grow independently when transplanted and can regenerate if removed. In acromegaly, however, the high level of GH produced by pituitary tumors sometimes (but not always) causes renewed mandibular growth,²⁰ so in some individuals, this cartilage has the potential to respond to GH in adulthood. Why the mandible sometimes responds to GH in acromegaly and sometimes does not is not clear. The variable response in acromegaly implies that a variable response to GH might also be seen in treatment of TS. The data from this and other studies indicate that a response of the mandibular cartilage in TS patients is possible but unlikely.

In research reports, often it is important to differentiate between statistically significant and clinically significant differences. Statistically significant differences that cannot be seen clinically have little or no importance in clinical treatment. From this perspective, it makes little difference whether, on average, GH administration produces a statistically significant increase in maxillary or mandibular growth. For the maxilla, any increase is likely to be so small as to be clinically meaningless. For the mandible, the variability in response of the condylar cartilage to GH is more important than the size of average changes. Our study did not confirm the statistically significant effects on mandibular growth of TS patients reported by Rongen-Westerlaken et al.¹⁴ A larger sample probably would have shown such a difference—and yet, from the perspective of understanding the response to GH, the variability in response is the more important finding.

We conclude that, if GH administration were to have significant effects on craniofacial development in TS subjects, early initiation of treatment (before the cessation of growth at the synchondroses of the cranial base) would be required. In older children, acceleration of maxillary growth is quite unlikely. Positive effects on mandibular growth may or may not occur, but abnormally large amounts of mandibular growth would be required to overcome the effects of the cranial base deficiency. Correction of the characteristic Class II malocclusion and chin deficiency of TS patients cannot be expected from GH treatment, even if it begins very early. Fortunately, any deleterious effects on the face do not accompany the positive statural effects on these patients, and the eruption of the teeth is unaffected.

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Measurement	Age 7			Age 10			Age 13			Age 17		
	Turner (n = 7)	Control (n = 16)	Z-score	Turner (n = 8)	Control (n = 16)	Z-score	Turner (n = 8)	Control (n = 15)	Z-score	Turner (n = 7)	Control (n = 15)	Z-score
S-N	68.3	65.7	1.80	70.0	65.7	1.28	71.0	68.1	0.76	72.3	70.3	0.80
S-Ba	39.2	32.0	3.19	43.5	35.0	2.45	42.6	37.8	1.79	44.5	39.7	2.16
S-Go	63.7	62.8	1.19	72.8	66.6	2.08	75.4	72.0	1.44	74.3	75.5	-0.19
S-Ar	27.1	27.8	-0.51	31.7	30.3	0.54	30.0	31.6	-0.98	32.8	32.8	-0.17
Ar-Go	42.7	36.9	2.31	46.9	38.7	2.86	50.9	42.8	3.13	46.8	45.0	0.76
S-PNS	38.6	43.1	-2.09	44.2	46.1	-0.97	43.8	49.7	-2.67	43.7	50.3	-3.00
ANS-PNS	47.5	40.9	4.18	52.0	44.3	2.52	53.1	44.8	2.78	54.3	46.5	2.58
ANS-Pg	52.4	50.4	0.91	55.8	51.8	1.14	53.4	55.7	-0.39	59.9	57.4	0.53
N-Me	102.7	98.8	1.05	113.2	105.6	1.77	111.9	110.5	0.20	115.6	113.7	0.25
Go-Gn degree	54.2	62.3	-2.74	58.6	68.3	-2.65	65.0	73.3	-1.93	69.7	77.1	-1.23
SNA	73.6	82.6	-2.25	76.5	81.5	-2.50	79.6	82.2	-0.93	78.6	81.6	-1.42
SNB	70.9	78.8	-3.16	72.1	78.9	-3.55	77.2	79.8	-1.15	76.2	79.9	-1.75
ANB	5.4	3.6	0.53	4.4	2.6	0.87	2.4	2.4	-0.26	2.4	2.5	0.83
N-S-BA	133.4	126.5	1.60	130.7	126.8	2.50	132.2	127.0	0.85	130.0	128.7	0.23

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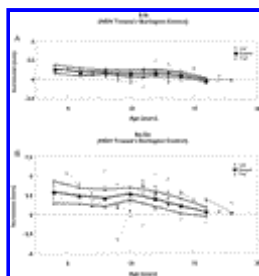
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FIGURE 1. Characteristics of Turner syndrome patients. (A) Frontal facial view demonstrating epicanthal folds; (B) frontal view showing short webbed neck; (C) frontal view demonstrating cubitus valgus.



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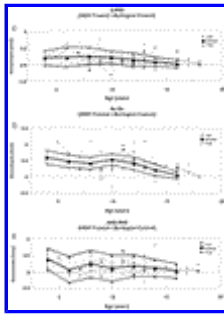
FIGURE 2. Superimposed composite cephalometric tracings for the normal controls and Turner syndrome subjects of this study, demonstrating the retrognathia associated with the syndrome



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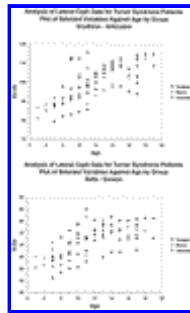
FIGURE 3. Annualized growth increments for selected dimensions in Turner syndrome patients in comparison with the control

population. For each graph, the mean \pm 1 SD for the control population is shown as the shaded area between the heavy black lines. Changes for individual TS patients are shown as the individual line segments. (A) Anterior cranial base increments (sella-nasion); (B) posterior length increments (basion-gnathion); (C) posterior face height increments (sella turcica-posterior nasal spine); (D) ramus height increments (articulare-gonion); (E) maxillary length increments (ANS-PNS). The variability in response of the TS patients, but with most changes within the range of the control population, can be seen



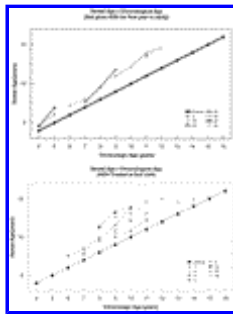
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FIGURE 3. Continued



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FIGURE 4. Changes in (A) mandibular length (Ar-Gn) and (B) posterior face height (S-Go) with age in the TS patients. Growth in these dimensions is similar in the three groups



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FIGURE 5. Dental age vs chronologic age, TS patients compared with normal controls. (A) TS patients not given GH during the first year of the study; (B) TS patients receiving GH treatment for the total duration of observation. With or without GH supplementation, dental age is advanced in the TS patients, and GH supplementation has little or no effect on the rate of dental maturation

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