Growth Hormone and Craniofacial Changes: Preliminary Data From Studies in Turner’s Syndrome

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ABSTRACT. Normal craniofacial and dental growth and development is dependent on growth hormone (GH) and insulin-like growth factor I (IGF-I). Deficiencies of either during childhood cause diminished growth of the maxilla and (to a greater degree) the mandible. Dental development/eruption also is compromised. Conversely, excessive GH/insulin-like growth factor I causes overgrowth, with the mandible again more affected than the maxilla. Replacement therapy in deficiency conditions generally normalizes craniofacial growth. Systemic GH also has been used in other disorders for which overt deficiency of GH has not been demonstrated. One such condition, Turner’s syndrome, is now widely treated with GH. Although systemic GH in Turner’s syndrome has been shown to positively affect stature, the effects on craniofacial growth and dental development/eruption are largely unknown. To explore these issues, standardized lateral radiographs of seven untreated patients with Turner’s syndrome were analyzed and revealed hypoplasia of the cranial base, maxilla, and mandible. Dental development/eruption of patients with Turner’s syndrome was found to be significantly advanced (by 0.63 years), relative to control subjects, in a separate study. Annual radiocephalometric measurements of 19 patients with Turner’s syndrome treated with GH were compared with nonaffected control subjects over 1 year of treatment. Compared with age-matched historic control subjects, all maxillary—and most mandibular—growth measures were within 2 standard deviations of control. However, in our patients with Turner’s syndrome, we found two measures of mandibular growth that deviated by more than 3 standard deviations from control. These data, although preliminary and only encompassing a short period, indicate that mandibular growth may be more affected than is maxillary growth by GH treatment and should be monitored over long-term-therapy. Pediatrics 1999;104:1021–1024; growth hormone, Noonan’s syndrome, Turner’s syndrome, facial growth, craniofacial growth.

ABBREVIATIONS. GH, growth hormone. IGF-I, insulin-like growth factor I. SD, standard deviation. SDS, standard deviation scores. rGH, recombinant growth hormone

As with somatic growth, normal craniofacial and dental growth and development are dependent on a normal hormonal milieu.1 Deficiencies in growth hormone (GH) or insulin-like growth factor I (IGF-I) during childhood cause diminished growth of the facial bones, including the maxilla and the mandible,2 and compromise dental development and eruption. Conversely, excessive GH, as seen in gigantism, causes craniofacial overgrowth, with the mandible being more affected than the maxilla. It is interesting to note that the mandible, in contrast to the long bones, remains able to respond in length to excessive GH throughout life, as evidenced by the significant mandibular overgrowth characteristically seen in acromegaly.

Many other statural disorders present clinically with characteristic cranial features. One of the most common of these conditions was described more than 60 years ago by Dr Henry Turner. He described a distinct entity involving the combination of short stature, sexual infantilism, webbed neck, and cubitus valgus.3 This clinical entity, later called Turner’s syndrome, also was found to include gonadal dysgenesis. Twenty years after the initial description, Ford et al4 discovered the chromosomal basis of Turner’s syndrome—only one normal X chromosome. The other X chromosome was missing or abnormal, and mosaicism also may be present. This somewhat common syndrome, having an approximate incidence of 1 in 2500 live female births, is confirmed currently only by chromosome analysis. The partial or total absence of a second sex chromosome is at present characterized by four features: 1) female phenotype, 2) short stature, 3) sexual infantilism, and 4) various somatic abnormalities. Among the somatic abnormalities are delayed skeletal maturity; deviations in skeletal morphology (ie, cubitus valgus, pes cavus, etc); and soft tissue abnormalities (ie, webbed neck, epicanthal folds, etc).

Abnormalities of the orofacial region, including teeth, also have been reported. The first extensive dental examinations of patients with Turner’s syndrome were performed by Filipsson et al5 who reported a tendency for advanced dental age, decreased tooth size, general facial hypoplasia, and mandibular retrognathia. Subsequent studies added high palatal vaults, decreased tooth size, cranial base hypoplasia, short tooth roots, anterior open bite, lateral crossbite, and bilateral palatal bulges to the clinical spectrum.6,7 A recent study2 of patients with Turner’s syndrome (7 to 16.7 years of age), subdivided according to karyotype, found that patients with mosaic and isochromosomes for the long arm of X karyotypes demonstrated the same pattern of malocclusion, but with decreased severity compared with XO patients.

Systemic administration of exogenous GH has been used as replacement therapy to normalize the stature of GH-deficient patients. This replacement therapy also increases craniofacial growth, although the degree to which this increase results in normalization of the maxillo-mandibular relationship has been shown to be quite variable among individuals.8

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GH-deficient patients also demonstrate delayed dental development, and GH replacement therapy generally serves to normalize dental development in these patients as well. More recently, GH has been used to increase the stature of patients with Turner’s syndrome. Although these patients generally exhibit normal levels of circulating GH, augmentation of this hormone’s levels has been used and proven successful in increasing height.

This article presents a brief summary of some of our studies on the craniofacial manifestations of Turner’s syndrome and our preliminary results of the effects of treatment with recombinant GH.

RESEARCH STUDIES

Cephalometric Analysis of Children With Turner’s Syndrome

Objective
The objective of a study by Jones and Simmons (Indiana University School of Dentistry) was to analyze retrospectively a historic sample of patients with Turner’s syndrome (as well as patients with the Turner’s syndrome mosaic karyotype and Noonan’s syndrome) compared with locally derived age-matched control subjects.

METHODS
The craniofacial morphology of 7 children (6 to 19 years of age) with Turner’s syndrome (45,XO) was compared with that of same-age control subjects of normal chromosomal makeup by cephalometric analysis of standardized lateral cephalometric radiographs. Variants of Turner’s syndrome also were examined—2 patients with XX;XO mosaic genotype and 1 patient with Noonan’s syndrome (NS-46,XX). Eleven cephalometric points were used (Indiana University Digitizing Program), and 20 linear and angular measurements were made to assess size and position of the maxilla and mandible as well as dimensions of the cranial base and facial height computed as standard deviation scores (SDS).10

RESULTS AND DISCUSSION
All patients had small posterior cranial base lengths and maxillary and mandibular skeletal positions that were retrusive. Fifty-seven percent had SDS ≤2 for facial depth, maxillary skeletal position, and posterior cranial base length; and 29% had SDS ≤2 for total cranial base length. Overall, effects in the maxilla were consistently retrusive and tipping up posteriorly; in the mandible, a decrease in corpus length; and in cranial base, a short posterior cranial base length and slightly short total cranial base length. The maxillary to mandibular skeletal relationship was normal. The other 12 measurements showed no consistent deviation from control. These results are in accord with other reports on patients with untreated Turner’s syndrome.11,12 One of the 2 patients with mosaic karyotype and the 1 with Noonan’s syndrome showed deviations characteristic of the 45,XO patients, whereas the other patient with mosaic karyotype did not differ from normal. The difference in the 2 patients with mosaic karyotypes may be accounted for by a difference in their percentage of mosaicism. Midtbø et al12 recently evaluated the craniofacial morphology of 33 patients with Turner’s syndrome, 7 to 16.7 years of age, by standard cephalometric methods. As with our results, they found that the Turner’s syndrome morphology was characterized by a “flattened cranial base angle, a marked reduction in posterior cranial base length, facial retragnathism, and short and posteriorly rotated jaws.” They also subdivided their sample according to karyotype and found that the same morphologic pattern was associated with all the karyotypes, but the deviations were most pronounced in the patients with monosomy X (45,X). Our results indicate that patients with structural and/or numerical aberrations of the X chromosome develop a specific pattern of craniofacial abnormalities with deviations in the cranial base, maxilla, and mandible in the sagittal and vertical planes. Midtbø et al12 have suggested that these “deviations originate in the fetal period, when the primary cartilages form the craniofacial skeleton.”

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Dental Age in Patients With Turner’s Syndrome

Objective
The effect of GH therapy on dental age has been studied in GH deficient individuals, but not in patients with Turner’s syndrome. Because dental age usually is normal or advanced before intervention in Turner’s syndrome, we are interested in the effects of GH augmentation in these patients. As a first step in evaluating these issues, McNairy et al13 (University of North Carolina Schools of Dentistry and Medicine, Chapel Hill, NC) sought to determine whether a difference existed between the dental age and chronologic age of our Turner’s syndrome population and a cohort control population. To test this hypothesis, an accurate, reproducible assessment of dental age was necessary.

A computer program, Bio Age (Sonart, Montreal, Canada), has been marketed with claims of accuracy in determining dental age. We used this program to determine whether the program’s control population was comparable with our control population. Comparison of our results with previous studies, which suggest that dental development is advanced in patients with Turner’s syndrome, would demonstrate whether this computer program is a valid tool for assessing dental age in patients with Turner’s syndrome. A finding of validity would support the use of this technique in studying the longitudinal effects of GH therapy on dental development in these patients.

METHODS
Standard panoramic radiographs taken with a Siemens Orthopos (Madison, WI) machine were used to assign a developmental stage to each tooth of the mandibular left quadrant (as defined by Demirjian).14 Demirjian defined eight stages, A to H, beginning with the first appearance of calcification to the closure of the root apex. The stages are based on developmental criteria (amount of dentinal deposit, shape change of the pulp chamber, etc) rather than on changes in size. The stage assigned to each tooth then was entered into the Biological Age computer program, which calculated a dental maturity score and corresponding dental age. The sample population included three different control girls at each chronologic age from 6 to 19 years (a total of 42 patients) and 53 different patients with Turner’s syndrome from the same general chronologic age range as the normal girls. The data were analyzed.
using the SAS computer package (SAS Institute, Cary, NC). The mean difference between the dental and chronologic ages was determined individually for the patients with Turner’s syndrome and the control patients using paired $t$ tests. The mean difference for the patients with Turner’s syndrome then was compared with the mean difference for the control patients using an unpaired $t$ test. The level of significance was set at 0.05.

**RESULTS AND DISCUSSION**

For the control population, there was no significant mean difference between dental and chronologic ages. In the Turner’s syndrome population, however, the dental age was significantly advanced (mean difference, 0.63 years) relative to the chronologic age (Table 1).

The mean differences between dental age and chronologic age varied significantly between the normal and Turner’s syndrome groups (unpaired $t$ tests, $P = .002$). Because no mean difference was found between the dental and chronologic ages in the control population, we found Demirjian’s computer program to be a valid method for assessing dental age in this group. These findings are consistent with those from past studies (e.g., Filipsson et al) that showed a tendency for earlier eruption of permanent teeth in patients with Turner’s syndrome. Thus, it appears that the computerized method of calculating dental age is valid also for use with patients who have Turner’s syndrome.

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**GH Effects on Facial Morphology of Patients With Turner’s Syndrome**

**Objective**

Patients with Turner’s syndrome have deficient growth of the long bones resulting in short stature. Studies have shown that as a group these patients have deficient growth of the maxilla and extremely deficient growth of the mandible, resulting in a retrognathic relationship. GH has been used recently to increase the length of the long bones in patients with Turner’s syndrome. The purpose of a study by Stecker and Simmons (presented at the University of North Carolina, 1997) was to determine the effect of GH on craniofacial growth as assessed by standardized lateral cephalometric radiographs taken at the beginning of the study and again 1 year later.

**METHOD**

The study participants included 19 patients with Turner’s syndrome, ranging 4 to 16 years of age and all on systemic recombinant growth hormone (rGH) treatment. All radiographs were traced by one investigator and verified by another. The tracings, including 75 points, were digitized, and a computer was used to calculate differences in 32 linear measures and 23 angular measures describing the maxilla, mandible, dentition, and facial height between initial and 1-year values for each patient. An average difference for each measure was calculated for all patients. A historical control of the same age range was used as a measure of normal early growth (Riolo et al). Significance was assessed at $P < .01$.

**SUPERMEN**

Twelve of the linear measures were increased significantly over the year of treatment, with seven (condylium–gonion, gonion–pogonion, sella–B point, condylium–gnaathion, anterio–gnaathion, pterygo–maxillary fissure at palatal plane–gonion, and nasion–articulare) associated with mandibular growth, and only one (sella–A point) associated with maxillary growth. The remaining four linear measures that were significantly increased (total face height, upper face height, mandibular incisor–nasion vertical, maxillary incisor–nasion vertical) were associated with face height and incisor inclination. The only significantly different angular measure was the ramus plane to mandibular plane angle. All these values were within 2 SDs of the historic control values except the condylion–gonion distance and the ramus plane to mandibular plane angle, which deviated by $>3$ SDs.

The results of this study indicate systemic rGH has a greater effect on growth of the mandible than of the maxilla, which may help to normalize retrognathic patients with Turner’s syndrome. Although large differences were not documented in our study period of only 1 year, Rongen-Westerlaken et al have conducted a similar study in the Netherlands of 2 years of rGH treatment, and their results agree quite closely with ours. Although no signs of acromegalic growth were noted in either study over these short treatment periods, we agree with Rongen-Westerlaken et al that additional long-term studies are needed to confirm that long-term rGH treatment does not result in relative mandibular overgrowth and a prognathic malocclusion.

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**DISCUSSION**

The results of these studies indicate craniofacial and dental growth and development are altered in Turner’s syndrome and may be changed further by growth hormone treatment. Turner’s syndrome results in diminished growth of the craniofacial complex.

This facial hypoplasia is specific in that the mandible and cranial base, both sites of endochondral growth, are affected more severely than the other facial bones. Unlike the patients with GH deficiency or insensitivity, for whom deficiency of the growth factor is the likely cause of their facial hypoplasia, patients with Turner’s syndrome exhibit apparently normal levels of GH (and presumably IGF-I), indicating a potential difference in the causative mechanism behind these effects. Even et al have demonstrated that patients with Turner’s syndrome exhibit a unique profile of bone maturation. These investigators have suggested that their reports support an insult to chondroplasia, which
could potentially account for the differential effects on craniofacial growth. Other pathologic processes appear to be at work in the calcified tissues of patients with Turner’s syndrome, as is apparent from the contradictory effects on dental crown (simpler than control) and root (greater number and complexity) morphologies noted by Midtbø and Halse.18

These differences indicate potential differences between the response of patients with Turner’s syndrome and those with GH deficiency to systemic GH. Indeed, this was observed in Turner’s original article describing this then new syndrome.3 In our study of the craniofacial growth of patients with Turner’s syndrome who received systemic GH over a 1-year period, mandibular growth was affected more by the systemic GH treatment than was maxillary growth. This discordant growth response could be beneficial in a particular retrognathic patient if the amount and direction of the mandibular growth compensated for the presenting discrepancies of that patient. It is imprudent to draw too many conclusions from this short-term study, however, and the importance of continual monitoring of craniofacial growth should not be underestimated, especially in patients expected to undergo long-term therapies.

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Methods in Determining Growth Hormone Concentrations: An Immunofunctional Assay

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ABSTRACT. Actual measurement of growth hormone (GH) levels in children suspected of having GH deficiency can confirm this diagnosis. However, there is currently no standard for the test. Although there is general agreement that in a short-statured child, a value of <10 µg/L in response to an appropriate provocative test indicates the possible need for GH replacement therapy, there is no agreement on the best testing method. Different immunoassay kits use different methods to measure serum levels and, therefore, produce different results. In this article, the evolution of assays and the reasons for disparities in results are reviewed and discussed. An immunofunctional assay using monoclonal antibodies as a new standard is described. Pediatrics 1999;104:1024–1028; growth hormone immunoassay, growth hormone binding protein, immunofunctional assay, monoclonal antibody.

ABBREVIATIONS. GHD, growth hormone deficiency; GH, growth hormone; RIA, radioimmunoassay; MOAB, monoclonal antibody; GHBP, growth hormone-binding protein; IFA, immunofunctional assay.
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