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ORIGINAL ARTICLE

Effect of growth hormone treatment on craniofacial growth in children: Idiopathic short stature versus growth hormone deficiency

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Background/purpose: Few studies have evaluated craniofacial growth in boys and girls with idiopathic short stature (ISS) during growth hormone (GH) treatment. The aim of this study was to evaluate the effect of GH treatment on craniofacial growth in children with ISS, compared with those with growth hormone deficiency (GHD).
Methods: This study included 36 children (mean age, 11.3 ± 1.8 years) who were treated with GH consecutively. Lateral cephalograms were analyzed before and 2 years after start of GH treatment.
Results: There were no significant differences in age and sex between ISS and GHD groups and the reference group from semilongitudinal study (10 boys and 8 girls from each group). Before treatment, girls with ISS showed a skeletal Class II facial profile compared with the GHD and reference groups ($p = 0.003$). During GH treatment, the amount of maxillary length increased beyond norm in the ISS and GHD groups in boys ($p = 0.035$) > 3 standard deviation score (SDS). Meanwhile, mandibular ramus height ($p = 0.001$), corpus length, and total mandibular length ($p = 0.007$ for both) increased more in girls with ISS than in girls with GHD. Lower and total anterior facial heights increased more in girls with ISS than in girls with GHD ($p = 0.021$ and $p = 0.007$, respectively), > 7–11 SDS.

Conflicts of interest: The authors have no conflicts of interest relevant to this article.

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Conclusion: GH should be administered carefully when treating girls with ISS, because GH treatment has great effects on vertical overgrowth of the mandible and can result in longer face.

Introduction

Growth disorders, associated with growth hormone (GH) in children, include growth hormone deficiency (GHD), idiopathic short stature (ISS), Noonan syndrome, Prader–Willi syndrome, and Turner syndrome.[1,2] Among these, ISS is defined as a height less than third percentile or two SDs (standard deviations) for age, sex, and population without evidence of nutritional, systemic chronic disease, endocrine, and chromosomal abnormalities.[3,4] The cause of ISS may be gene mutations and deletions in the SHOX gene for children, the prevalence has been estimated at 1–5%.[4,5] In addition, a karyotype should be considered in girls with no underlying specific cause of ISS to rule out Turner syndrome.[4]

As children with ISS often remain short in adult life, in 2003, the United States (US) Food and Drug Administration (FDA) approved use of GH for treatment of ISS in children whose presenting height is < -2.25 SDs for age, sex, and that height in adult life is expected to be below normal.[6] Several studies concluded that GH therapy can result in higher adult heights in some treated children.[7–9] The consensus was that the mean increase in adult height with GH therapy is 3.5–7.5 cm.[10]

However, to the best of our knowledge, few studies have evaluated craniofacial growth in ISS during GH treatment. Kjellberg et al[11] reported an enhancement of overall craniofacial growth in boys with ISS and the mandibular body length and anterior facial height of the boys treated GH were greater at the end of treatment compared with those in the reference group. However, that study had a limitation that girls with ISS were not included as subjects because most children seeking GH treatment were boys. Grimberg et al[12] reported that sex difference in short stature referrals may miss the diagnosis and treatment of diseases in girls whose growth problems are undervalued. Therefore, growth change of the craniofacial complex in girls with ISS should be determined during GH treatment.

The aim of this study was to evaluate the effect of GH treatment on craniofacial growth in children with ISS, compared with those with GHD. The investigators hypothesize that craniofacial growth pattern is significantly different between children, especially girls with ISS and those with GHD 2 years after GH treatment.

Methods

Study design/sample

The study population comprised 40 children who presented for evaluation and management of short statue with ISS or with GHD who underwent GH treatment from 2006 to 2012 at the Department of Pediatrics, Yeungnam University Hospital, Daegu, Korea.

Inclusion criteria were as follows: chronological age > 5 years old; less than third percentile or two SDs below the normal mean height for subjects of a similar age and sex or growth velocity according to the Korean population;[13] no history of GH treatment within 6 months; prepubertal stage according to Tanner stage criteria based on testicular volume in boys and breast development in girls.

Among a total of 40 children whose caregivers agreed with taking radiographs for measurements of the cephalometics, four dropped out (two from each group) 1 year after GH treatment because two refused to continue the treatment and two were lost to follow-up, 18 patients were diagnosed with idiopathic GHD and 18 patients were diagnosed with ISS. The clinical diagnosis of GHD was defined by height less than the third percentile and peak GH response < 10 ng/mL after one of three growth hormone stimulation tests using insulin, L-dopa, and clonidine. ISS was defined when patients had short stature less than third percentile without evidence of a systemic disease, nutritional, psychological of chromosomal disorder, and peak GH response more than 10 ng/mL after growth hormone stimulation tests. The patients were injected with 0.23 mg of recombinant growth hormone (rGH) /kg/week (mean dose), six times weekly for 2 years. The study protocol conforms to the Declaration of Helsinki and was approved by the Institutional Review Board of Yeungnam University Hospital, Daegu, Korea.

Reference group

The reference group consisted of healthy children with Class I molar relationships and normal occlusion selected from elementary schools in Daegu. Semilongitudinal growth study data traced and surveyed for 10 years from May 1983 by the Department of Orthodontics, Kyungpook National University Hospital, Daegu, Korea, were used. Eighteen children data were selected to fit those of the short-statured children.

Cephalometric analysis

Patients and their parents were asked if they would agree to allow measurement of their craniofacial structure by an orthodontist at the Department of Dentistry, Yeungnam University Hospital, Daegu, Korea, before undergoing GH treatment. For those who agreed, a written informed consent was obtained from each patient and parents before GH treatment. Craniofacial growth changes were evaluated using lateral cephalograms obtained before (T0) and 2 years (T1) after start of GH treatment. The lateral cephalograms were digitized using V-ceph 5.5 (Osstem, Seoul, Korea) by an observer who was blinded to the patients' clinical status. Based on the Pancherz's cephalometric method,[14] all reference planes were transferred from the T0 to T1 cephalograms according to the S (sella)-N (nasion) plane superimposition at S. This study identified nine linear and seven angular cephalometric measurements to evaluate the change of the craniofacial complex in each group during GH treatment (Figure 1).