Efficacy of growth hormone therapy for patients with skeletal dysplasia

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Abstract Most patients with skeletal dysplasia show severe short stature. Surgical therapy has been attempted to correct bone deformities, but therapy for improving their severe short stature has been rarely attempted. We undertook a clinical trial of growth hormone (GH) therapy for patients with skeletal dysplasia accompanying severe short stature caused by achondroplasia (ACH), hypochondroplasia (HCH), pseudochondroplasia (PSACH), spondyloepiphyseal dysplasia congenita (SED), or Schmid type metaphyseal dysplasia (MD). This study examined the efficacy of GH therapy on height increase and change of height SD score over a 1-year period in patients with skeletal dysplasia and showed a short-term efficacy for skeletal dysplasia. In ACH, HCH, and MD, GH had a significant effect on height gain. However, PSACH and SED showed no height gain efficacy; in cases of PSACH, height SD score was worse after therapy. Severe adverse events were not observed except in one SED case, in which scoliosis worsened and height did not increase. For patients with skeletal dysplasia, GH therapy is moderately effective for height gain. It is ineffective in cases with severe spinal deformities, however; although bone growth was promoted, the ligaments and matrix were too weak to support muscle tonus and the effects of gravity, resulting in worsened kyphosis and lordosis. These results clarify why GH therapy is ineffective for height gain. The pathogenic genes of skeletal dysplasia have recently been detected and consequently changes in bone formation have been investigated in detail. Careful consideration of indications for therapy and cautious observation during therapy are crucial when attempting to treat advanced bone deformities.

Keywords achondroplasia · hypochondroplasia · pseudochondroplasia · congenital spondyloepiphyseal dysplasia · Schmid type metaphyseal dysplasia

Introduction

Most patients with skeletal dysplasia show severe short stature. Up to the present, surgery has attempted to correct bone deformities but therapy for improving their severe short stature has been rarely attempted. Recently, not only for growth hormone (GH) deficiency, but also for achondroplasia (ACH), we reported the efficacy of GH therapy for height gain [1]. Administration of GH significantly increases the rate of growth among ACH patients, who have the most common cause of short-limb dwarfism; ACH ordinarily represents normal endocrine function. For other skeletal dysplasias, however, the efficacy of GH remains unknown.

Subsequently, we undertook a clinical trial of GH therapy for patients with skeletal dysplasia accompanying severe short stature caused by ACH, hypochondroplasia (HCH), pseudochondroplasia (PSACH), spondyloepiphyseal dysplasia congenita (SED), or Schmid type metaphyseal dysplasia (MD). This study examined the efficacy of GH therapy for height increase and change of height SD score over a 1-year period in patients with skeletal dysplasia accompanied by short stature. We showed a short-term GH efficacy for skeletal dysplasia.

Participants and methods

Participants

Eighty-five Japanese children with skeletal dysplasia participated in this study. Participant profiles are presented in Table 1. Oral and written informed consent was obtained from patients and their parents. All participants were prepubertal. None had received GH therapy before this study. Patients with chronic disease were excluded. Patients with height more than 2 SD
below the mean were also excluded. By GH provocative tests, the luteinizing hormone-releasing hormone loading test, thyrotropin-releasing hormone loading test, and oral glucose tolerance test, subjects with endocrinological and metabolical disorders were excluded.

Diagnosis

Diagnoses of patients with skeletal dysplasia were made by pediatric endocrinologists and clinical geneticists with consultation of radiologists. They were classified by clinical phenotype and radiographic findings according to classification of long bones and vertebrae [2]. The most common cause of rhizomeric dwarfism, ACH, was diagnosed by typical radiologic features such as irregularity of metaphysis, bowing of long bones, frontal bossing, trident hands, narrow foramen magnum, and small skull base. The fibroblast growth factor receptor type 3 (FGFR3) G380R point mutation, which is characteristic for ACH, was detected for all cases using polymerase chain reaction (PCR) and restriction enzyme fragment polymorphism (RFLP) as previously reported [3]. A clinically mild phenotype of ACH, HCH, was diagnosed by its mild form of deformities of the metaphysis and short stature without the G380R mutation. Radiologic features were similar to, but less severe than, those of ACH. Also, PSACH was characterized by disproportionate short stature and early-onset osteoarthritis. In radiography, epiphyseal bone deformities were emphasized; head size and facial features were normal, which were definitely distinguished from ACH. Patients with SED represented extremely short-trunked dwarfism from infancy; in this study, patients with SED tarda did not participate because it involves later onset of short stature and characteristic bone deformities. In SED, the chest was barrel shaped, accompanied with a cleft palate and myopia. Limbs were less severely affected. Radiograms showed retarded skeletal ossification, ovoid vertebral bodies, and marked severe lordosis. In MD, radiologically metaphysical deformities were found, but not with vertebrae. Coxa magna was particularly found among patients with MD.

**Table 1. Patients profiles**

<table>
<thead>
<tr>
<th>Diagnostic categories</th>
<th>Number (M/F)</th>
<th>Age (years)</th>
<th>Height Z score</th>
<th>Annual height gain (cm/year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Achondroplasia</td>
<td>73 (41/32)</td>
<td>6.2 ± 2.0</td>
<td>−4.8 ± 1.0</td>
<td>3.9 ± 1.4</td>
</tr>
<tr>
<td>Hypochondroplasia</td>
<td>4 (4/0)</td>
<td>6.4 ± 1.4</td>
<td>−3.4 ± 1.2</td>
<td>6.1 ± 1.8</td>
</tr>
<tr>
<td>Pseudoachondroplasia</td>
<td>4 (2/2)</td>
<td>3.9 ± 0.5</td>
<td>−4.4 ± 0.89</td>
<td>3.9 ± 4.2</td>
</tr>
<tr>
<td>Metaphyseal chondrodysplasia</td>
<td>4 (2/2)</td>
<td>10 ± 1.8</td>
<td>−3.2 ± 0.5</td>
<td>4.8 ± 1.7</td>
</tr>
<tr>
<td>Spondyloepiphyseal dysplasia</td>
<td>4 (2/2)</td>
<td>5.6 ± 3.9</td>
<td>−7.9 ± 1.4</td>
<td>4.8 ± 1.0</td>
</tr>
</tbody>
</table>

M, male; F, female

Evaluation of the efficacy of GH therapy

The height Z score was calculated from the age-matched standard of normal Japanese children reported by Suwa et al. [4].

In this experiment, 0.35 mg/kg/week GH was injected to participants subcutaneously; the dosage was divided into four to seven times in a week. Subjects visited the hospital before and 1, 2, 3, 6, 9, and 12 months after GH therapy began. Body measurement and blood and urine analyses were done if GH effects or side effects occurred. Additionally, insulin-like growth factor 1 (IGF-1) (by radioimmunoassay, RIA) and sex hormones such as estradiol, testosterone, dehydroepiandrosterone sulfate, luteinizing hormone, and follicule-stimulating hormone were also checked to detect onset of puberty. Carpal bone X-ray images were taken to verify bone age before and 6 and 12 months after GH therapy.

Statistical analysis

All data were analyzed by paired t test; P < 0.05 was considered significant.

Results

In ACH and HCH, GH had a significant effect on height gain as reported previously (Figs. 1, 2). In ACH, GH treatment significantly increased height, the height Z score, and annual height gain (from −5.1 ± 1.0 to −4.6 ± 1.0, and from 3.9 ± 1.2 cm/year to 7.2 ± 1.4 cm/year, respectively) after 1 year of administration. For HCH, height Z scores were improved from −3.4 ± 1.2 to −2.6 ± 0.9, but this was not significant. For MD, GH was also effective for annual height gain (height Z score changed, −3.2 ± 0.5 to −2.7 ± 0.3). However, PSACH and SED showed no height gain efficacy. In cases of PSACH, height Z score after 1 year of GH therapy was worse than before therapy (−4.4 ± 0.8 to −5.1 ± 0.7) (see Fig. 2). In SED, improvement of the height Z score was not obvious (−7.9 ± 1.4 to −7.7 ± 0.7). Severe