Growth hormone therapy in achondroplasia

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Achondroplasia is the most common form of short-limbed dwarfism. Adult height is as short as 118–145 cm for men and 112–136 cm for women (1). The social disadvantages and psychological problems of extremely short stature place much pressure on patients and their parents to seek growth-promoting medications. Recently, surgical lengthening of the lower limbs has been performed to increase overall height and improve body proportion, but surgical procedures require long-term hospitalization and involve serious complications, such as postoperative infection, bone fractures and deviations of the bone axis (2, 3). The prospects of synthetic GH offer a new aspect of treatment.

Patients and methods

Three boys and three girls with typical features of achondroplasia were studied. All patients were prepubertal before GH therapy. The conduct of this study was approved by the Hiroshima Red Cross Hospital Committee for the Protection of the Rights of Human Subjects, and informed consent was obtained from the patients and their parents. The diagnosis of achondroplasia was established on the basis of typical clinical features, such as short-limbed dwarfism, large head with a prominent forehead and midface hypoplasia, bowed legs and trident hand, and typical radiological findings, such as large skull with relatively small base, narrow foramen magnum and decreased lumbosacral interpedicular distance, (4). All patients were able to stand and walk unaided. None had a history of neurological or respiratory dysfunctions, such as obstructive sleep apnea. The fathers of Cases 2 and 3 have achondroplasia. None received any treatment before entry into this study.

The GH response to L-dopa (250 mg/m² po) and...
arginine (0.5 g/kg iv) infusion was studied. Blood count, urinalysis, routine laboratory tests, TSH, thyroxine (T₄), triiodothyronine (T₃), anti-GH antibody and plasma insulin-like growth factor I (IGF-I) were determined before and every 3rd month during GH treatment. Plasma IGF-I was measured by a commercial radioimmunoassay (RIA) kit (Nichols Institute, San Juan Capistrano, CA) before December 1989. Thereafter, it was measured by a commercial RIA kit (CIBA Corning, Tokyo, Japan). The samples were measured after acid ethanol extraction. Commercial RIA kits were used to determine GH, TSH, T₃ and T₄. Anti-GH antibody was measured by a polyethylene glycol procedure using multiple dilutions of the patients' serum.

Ventricular size, size of foramen magnum, spinal canal stenosis, etc. were evaluated by plain X-ray, computed tomography or magnetic resonance imagings taken before therapy and then yearly during therapy. Bone age was not evaluated because of the possibility that achondroplasia may have altered the radiographic parameters used to assign bone age, making such determination difficult to interpret (5).

The patients received 0.5 U·kg⁻¹·week⁻¹ of recombinant GH (Genotropin®, Kabi, Stockholm, Sweden) in six divided doses per week by subcutaneous injection.

Results

Clinical and laboratory data of the patients during GH therapy are shown in Table 1. In Case 3, the l-dopa and arginine infusion tests showed a blunted response (peak GH values were 5.5 and 5.3 μg/l, respectively). The plasma IGF-I was low (530 U/l).

Height velocity was accelerated during the 1st year of GH therapy but declined progressively during the 2nd and 3rd year. However, one patient (Case 1) who received GH therapy for 4 years had good growth. The sitting height/height ratio did not change throughout GH therapy (0.65 ± 0.03, 0.65 ± 0.02 and 0.64 ± 0.02 at year 0, 1 and 2, respectively). All patients except Case 2 were prepubertal during GH treatment.

The plasma IGF-I level increased to 88–376 μg/l after GH therapy. There was no anti-GH antibody formation during GH therapy. No significant changes were observed in thyroid function tests or in routine laboratory tests before and during GH treatment. Computed tomography and magnetic resonance findings were as follows. Three of six patients had mild ventricular enlargement and a small foramen magnum when compared to normal standards (6). None had spinal canal stenosis or atlantoaxial dislocations. These findings did not change and new findings were not observed during GH treatment. No adverse effects were observed.

Discussion

In this study, one patient with obesity and normal birth had impaired GH secretion, which may, in part, be due to

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<th>Table 2. Summary of reports on growth hormone (GH) therapy in achondroplasia and hypochondroplasia</th>
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<td><strong>First author (reference)</strong></td>
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<td><strong>Escamilla (11)</strong></td>
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<td><strong>Horton (16)</strong></td>
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* A, achondroplasia; H, hypochondroplasia.
* Case 1 in this study.
* Case 2 in this study.
chronic somatostatin, which is the inhibitory factor of GH secretion, hypersecretion and/or reduced pituitary GH pool in obesity (7, 8). Obesity is a common problem in achondroplasia (9). Moreover, obstructive sleep apnea, which occurs in achondroplasia, impairs sleep-related GH secretion (10), although none of our six patients had obstructive sleep apnea.

There are several reports on GH therapy in achondroplasia or hypochondroplasia (Table 2) (5. 11–16) but no reports on the effect of long-term GH treatment on final height. The efficacy of short-term GH therapy was reported in some children with achondroplasia or hypochondroplasia (5. 11–16). An initial acceleration of growth was seen, but thereafter the growth waned. In this study, height velocity was accelerated during the 1st year of GH treatment but declined progressively during the subsequent years in achondroplasia; the magnitude of this height velocity was similar to that in hypochondroplasia (15), in Turner’s syndrome (17), in GH-insufficient children (18) and in normal short children (19). Decreased effectiveness of GH treatment according to the duration of treatment might be due to resistance of the tissues against GH and/or IGF-I. However, the mechanism of this phenomenon is not clear at present. There was considerable variation in clinical response within the treated cases. One patient with achondroplasia showed good growth during 4 years of GH therapy. Therefore, some patients with achondroplasia may respond well to long-term GH therapy. As with Turner’s syndrome, a greater dose of GH may be needed in order to promote growth.

It is not known whether GH therapy exaggerates ventricular enlargement, a small foramen magnum or stenosis of the vertebral canal, but these are difficult to assess retrospectively. Before GH treatment is initiated, it is necessary to explore these possible complications by magnetic resonance imagings. Growth hormone therapy may be beneficial for some children with achondroplasia before surgical lengthening of the lower limbs is performed. although to date surgical procedures are not considered to be the best treatment because of long-term hospitalization, postoperative infection, bone fractures and deviations of the bone axis (2, 3). Further studies are required to evaluate the efficacy of long-term GH therapy on adult height and body proportions and the optimal effective dosage and safety of GH in a large number of achondroplasia and hypochondroplasia cases.

References


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