Achondroplasia: Effect of Growth Hormone in 40 Patients

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Abstract. We administered growth hormone (GH) to 40 patients with achondroplasia, 9 of whom were suspected to have insufficient GH secretion. The patients received 0.5 or 1.0IU/kg/week recombinant human GH. At the end of the first year, the annual height gain was significantly increased compared to before treatment. There was no difference between patients with normal or insufficient GH secretion in the annual height gain, either before or during GH treatment. The annual height gain during treatment of patients treated with GH at 0.5IU/kg/week did not differ from those treated with 1.0IU/kg/week. The annual height gain before and during GH treatment of patients in the pubertal stage was less than those in the prepubertal stage. Although the annual height gain in the second year of GH treatment was less than in the first year, it was still greater than before GH treatment. The lower limb length to height ratio was significantly increased by GH treatment. No adverse effects were observed during the treatment period of about two years.

Key words: achondroplasia, insufficient GH secretion, GH treatment

Introduction

The main concern of patients with achondroplasia is that their final height will be extremely short 1). Although the majority of patients show delayed development, particularly in motor skills, during infancy and early childhood 2), compensation is observed in almost all, with no residual psychomotor disorder in adulthood. For aesthetic, psychological and sociologic reasons, their extremely short stature with relative shortening of the limbs is their most serious anxiety. Previous studies of the growth plate in achondroplasia have revealed abnormal enchondral ossification 3)4), but its specific mechanism remains unclear. As there is presently no effective pharmacological therapy which normalizes bone growth in achondroplasia, surgical limb lengthening procedures are the only established therapy for the short stature in patients with this disease. However, as surgical limb lengthening procedures require long-term hospitalization and may result in serious complications, such as postoperative infection and fractures or deviation of the bone axis 5), the number of patients who can take advantage of this therapy is limited.

The use of growth hormone (GH) extracted from human pituitary glands was formerly restricted to short children with a demon-
strable insufficiency of GH secretion. The development of biosynthetic human GH was followed by wider application of GH for patients with conditions such as Turner's syndrome, skeletal dysplasia, intrauterine growth retardation, chronic illness and other causes of short stature, which are not considered to be associated with GH deficiency 6). While patients with achondroplasia are generally considered to have normal GH secretion, there have been no thorough investigations of hypothalamic-pituitary function (including GH secretion) in achondroplasia. It is known that most patients with this disease suffer from hydrocephalus, probably due to narrowing of the occipital foramen magnum or to spinal stenosis 7). Cerebral hypertension caused by this disorder might influence the hypothalamic-pituitary axis. It is also well known that patients with achondroplasia show delayed development, particularly of motor skills, during infancy and early childhood. These features suggest that some patients with achondroplasia might have hypothalamic-pituitary dysfunction, including abnormal GH secretion. We therefore evaluated the hypothalamic-pituitary function of patients with achondroplasia to attempt to elucidate whether poor GH secretion plays a role in the short stature of patients with this disease.

There are some recent reports describing the beneficial effects of GH therapy in hypochondroplasia 8), and some investigators have also examined the effectiveness of GH administration in achondroplasia 9)10)11). GH therapy before surgical limb lengthening procedures sometimes can markedly increase the final height.

Measurement of GH secretion in patients with achondroplasia

The subjects were 40 patients (15 males and 25 females) with achondroplasia whose ages ranged from 3 to 13 years. Their average age was 6 years, and seven patients were pubertal. Achondroplasia was diagnosed radiologically and clinically based on the typical features such as dwarfism with short limbs, which was often more pronounced in the proximal segments, large head, protruding high forehead, flattened nasal bridge, dislocation of the radial head, trident hands and hyperlordosis. Two patients had a family history of achondroplasia. As we previously reported for 22 of these patients 12), the majority showed delayed development; the average age for head control was 4.8 ±1.9 months (mean±SD), and for sitting, walking and speech it was 10.0 ±3.4, 19.8 ±3.4, and 15.7 ±7.2 months, respectively. However, no patients had a history of major neurologic dysfunction, and none showed any psychomotor disorder on admission. The mean z-scores for height on admission (−5.2±1.2) and for annual height gain before admission (−2.9±1.7) were both extremely low. The majority of patients showed increased head circumferences and enlarged ventricles. These findings suggested that a hypothalamic-pituitary disorder, including insufficient GH secretion, might play a role in the cause of the short stature of these patients, particularly in early childhood.

All the patients showed normal LH and FSH response to LH-RH stimulus, TSH response to TRH stimulus, and cortisol response to insulin-induced hypoglycemia. The serum thyroxine level was also normal in all the patients. In provocation tests for GH response, three patients showed subnormal (<10ng/mL) responses to insulin-induced hypoglycemia, seven showed subnormal (<10ng/mL) responses to L-Dopa, one showed a subnormal (<10ng/mL) response to clonidine, and two patients showed subnormal (<20ng/mL) responses to GRF. The mean GH concentration during sleep (assessed by averaging ten GH level values at successive 20 minutes intervals after sleep induction) was found to be low (<5ng/mL) in six patients (Fig.1). Four patients showed subnormal responses to two different provocation tests, and one patient showed a subnormal response to three different provocation tests. The serum IGF-I level of patients with subnormal GH responses
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Fig. 1. GH Responses to Provocation Tests

to provocation tests was significantly lower than in patients with normal GH responses (Fig.2). The mean ratio of the bone age (assessed according to the Atlas of Greulich and Pyle) to the chronological age was also low (75±23%, mean±SD). In consideration of all these data, we suspected nine of the 40 patients to have insufficient GH secretion.

GH treatment in patients with achondroplasia

All 40 patients began treatment with recombinant human GH after their GH secretion was evaluated. Informed consent was obtained from the patients and/or their parents. GH was administered by subcutaneous injection at a dose of 0.5 or 1.0IU/kg/week, 6-7 times/week. In the 38 patients who received GH for more than 6 months, the annual height gain at the end of the first year was significantly increased compared to before therapy (3.8±0.9cm/year v. 6.6±1.6cm/year). At the end of the first year, there was no difference between the patients with normal or insufficient GH secretion in the mean annual height gain or its distribution, nor was there any difference between the patients treated with 0.5IU/kg/week GH and those treated with 1.0IU/kg/week GH. The annual height gain of the pubertal patients was lower than that of the prepubertal patients both before and during GH therapy.

At the end of the second year of GH therapy, although the annual height gain was lower than in the first year, it was still greater than before GH therapy (Fig.3).

The ratio of lower limb length to height was significantly increased after GH therapy (Fig.4). The ratio of arm span to height was increased but statistically of no significance. No adverse effects were observed during the treatment period of approximately two years.

Discussion

Although the short stature of achondroplasia has not been considered to be associated with GH deficiency, it is noteworthy that about a quarter of our achondroplasia patients showed evidence of insufficient GH secretion. Their developmental profiles, including the large head circumference with enlarged ventricles, also suggested that insufficient GH secretion might partly contribute to their short stature. The hypothesis is also supported by the findings that the serum IGF-
I levels of the patients with subnormal GH response to provocation tests were lower than those with normal GH secretion, and that the majority of the patients showed delayed bone age. However, there was no definite relationship between the severity of delayed development or of hydrocephalus, and GH secretion. There were also no significant differences between the patients with normal or insufficient GH secretion in the responses to GH administration. Geoldstein et al. reported that in children with achondroplasia, obstructive sleep apnea may impair sleep-related GH release 13). Our data also indicate that the nocturnal GH secretion is reduced in many patients with achondroplasia. This suggests that spontaneous GH secretion may be disturbed in some achondroplasia patients. The patients who were suspected to have insufficient GH secretion were not obese compared to the other patients except one. As obesity is a common feature in achondroplasia, further study is required to elucidate whether it is related to abnormal GH secretion, as it is in normal obese children.

It is noteworthy that GH administration increased height velocity in a large number of patients with achondroplasia during a period of at least two years with no adverse effects. This indicates that GH can promote chondrocyte proliferation and differentiation and stimulate enchondral ossification in achondroplasia. It is also interesting that the ratio of lower limb length to height was significantly increased. While there was no obvious correlation of response to GH with sex, the height velocity of patients in the pubertal stage was significantly lower than in patients in the prepubertal stage. This indicates that GH treatment should be started in early child-
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hood. Although the annual height gain during the first year of GH treatment of patients treated with GH at 0.5IU/kg/week did not differ from those treated at 1.0IU/kg/week, longer term follow-up is necessary to determine the effect of the two GH dosage. Further study is essential to establish the most effective GH administration regimen, as the response of a child to GH is determined by the pretreatment growth velocity, the dose of GH used, the frequency of administration, and the condition being treated 14). Although we did not observe any adverse effects, Okabe et al. reported the case of one patient with achondroplasia who showed atlantoaxial dislocation and neurological complications during GH therapy 9). Careful follow-up with not only routine laboratory tests, including thyroid function and glucose tolerance tests, but also orthopedic and neurological examinations, is required.

Conclusions

We found GH treatment for two years to increase the stature and improve body proportions in achondroplasia, with no adverse effects.

The most effective GH treatment regimen for achondroplasia remains to be established.

References