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The Comparison of the Effects of Short-Term Growth Hormone Treatment in Patients with Achondroplasia and with Hypochondroplasia

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Abstract. The effects of recombinant human growth hormone (rhGH) treatment for three years were compared in patients with achondroplasia (ACH) and hypochondroplasia (HCH), whose diagnosis had been confirmed by DNA analysis of the fibroblast growth factor receptor 3 gene. Height SDS (H-SDS) and height velocity SDS (HV-SDS) using the standard for ACH significantly improved during three-year treatment as compared with that before treatment in both ACH and HCH except HV-SDS in the third year. The improvement was much greater in HCH than in ACH. The mean increase H-SDS using the standard for ACH in three years in ACH (from −0.2 SD to 0.1 SD) is almost negligible but that in HCH (from 1.2 SD to 2.6 SD) can be estimated as effective clinically. It can be concluded short-term GH treatment in HCH is effective to increase growth rate and H-SDS, but it has little effect in ACH. Further studies would be required to confirm the other beneficial effects of GH treatment such as increase in bone mineral density in ACH and HCH and the effect on the final height.

Key words: Achondroplasia (ACH), Hypochondroplasia (HCH), Growth hormone (GH) treatment
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ACHONDROPLASIA (ACH) and hypochondroplasia (HCH) are the most common forms of chondrodysplasia. These disorders are inherited as an autosomal dominant. The pathogenesis is a defect in enchondral ossification. As with disturbance of long bones, vertebrae and base of skull, ACH is characterized by short-limbed marked short stature (rhizomelic short stature), a relative macrocephaly with prominent forehead, midface hypoplasia, lumbar lordosis, a trident configuration of hands and hydrocephalus during growth development caused by narrowing of the foramen magnum. In addition to prepubertal growth failure, ACH patients show decreased pubertal growth spurt. Adult height for Japanese patients without any treatment is approximately 130 (118–145) cm for males and 120 (112–136) cm for females [1, 2].

HCH is clinically milder than ACH. Patients with HCH also show short-limbed short stature, near-normal appearance, various degrees of lumbar lordosis. Appan *et al.* [3] reported that spontaneous growth in patients with HCH does not show pubertal growth spurt evidently and that final height in boys with HCH ranges from 145.0 cm to 165.0 cm and in girls ranges from 133.4 cm to 150.6 cm. It is possible to distinguish HCH from ACH to a certain degree on the basis of the characteristic clinical phenotype.

Recently, it has become clear that these common skeletal dysplasias are caused by mutations in the fibroblast growth factor receptor 3 (FGFR 3) gene mapped to chromosome 4p16.3 [4–7]. ACH is caused by a point mutation in the transmembrane domain of FGFR 3, whereas HCH is caused by a

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missense mutation in the tyrosine kinase domain of FGFR 3 [8, 9]. Although the gene mutation is not detected in all patients with HCH, some HCH patients are differentiated from ACH patients accurately by analyzing the gene mutation [10].

There have been several reports that short-term growth hormone (GH) treatment in patients with ACH and HCH increased their growth rates [11–17]. However, the efficacy of GH treatment in these disorders is still unclear. In this study, we compared the short-term effects of GH treatment between ACH patients and HCH patients definitively diagnosed by the FGFR 3 gene mutation.

Table 1. Clinical characteristics and summary of GH treatment

	ACH [n=11]	HCH [n=4]
Height of father/mother [cm]	174/156.8※	171/161.7
Height at birth [cm]	48.0±1.6 [n=9]	48.6±0.9 [n=4]
Age at start of GH treatment [years old]	7.1±2.5 (3.7~11.8)	4.9±2.8 (3.1~9.0)
GH treatment periods [years]	4.2±2.3 (0.6~8.1)	4.8±2.2 (2.7~7.5)

※One mother with ACH (125 cm) in a patient with ACH is excluded.
( ) shows the ranges.

Methods and Subjects

Subjects are eleven children (7 males and 4 females, aged from 3.7 to 11.8 years old) with ACH, four children (3 males and 1 female, aged from 3.1 to 9.0 years old) with HCH. The diagnosis of all subjects was performed by the FGFR 3 gene analysis. All patients with ACH and with HCH showed the G380R and N540K mutations in FGFR3 gene, respectively. Fifteen patients with ACH or HCH had received only recombinant human GH (rhGH). Five patients with ACH and two patients with HCH received rhGH at a dose of 0.5 IU/kg/week, and five patients with ACH and two patients with HCH received it at a dose of 1.0 IU/kg/week. One patient with ACH commenced GH treatment at a dose of 0.5 IU/kg/week, withdrew for a while and them resumed it at a dose of 1.0 IU/kg/week.

Table 1 shows the clinical characteristics and the summary of GH treatment in these subjects. The patients were sporadic except one patient with ACH who had a mother with ACH. Height at birth of all subjects which could be examined was within normal range. ACH patients were significantly older than HCH patients. All patients with ACH have been observed in the first year, 10 patients in the second year and 8 patients in the third year after the commencement of GH treatment. All patients with HCH have been observed for three years on rhGH. Three patients with ACH entered puberty in the third year of GH treatment. None of the patients with HCH entered puberty during three-year GH treatment.

In patients, whose treatment periods were 0.6 and 2.7 years, projected height and height velocity (HV) to 1.0 and 3.0 years, respectively, were used for calculation. Height SD score (H-SDS) and HV-SDS were calculated using standardized height and HV for Japanese normal healthy children [18] or for patients with ACH [1]. Bone age (BA), bone mineral density (BMD; ΣGS/D [mm Al]), insulin like growth factor-I (IGF-I) were determined before and during three-year GH treatment. BA was determined according to a Computer Aided Skeletal Maturity Assessment System (CASMAS) [19, 20]. BMD of the 2nd metacarpal bone of the left hand was evaluated according to the Computer Aided Bone Density Assessment System (CABDAS) based on Digital Image Processing (DIP) method [20]. The BMD was corrected for BA.

Data are presented as mean ± standard deviation (SD). Statistical analyses were performed using Student's t-test and paired t-test. P value of less than 0.05 was considered as significant.

Results

Figure 1 shows the longitudinal growth chart during GH treatment [1, 18]. Obviously the patients with HCH are taller than those with ACH. Figure 2 shows HV in the patients with ACH and HCH. Mean HV in ACH group increased from 4.1 ± 1.0 cm/year before treatment to 5.1 ± 0.7 cm/year in the first year, to 5.2 ± 0.5 cm/year in the second year and to 4.7 ± 1.2 cm/year in the third year of treatment. In ACH, HV in the first and second years was significantly greater than that before treatment. Mean HV

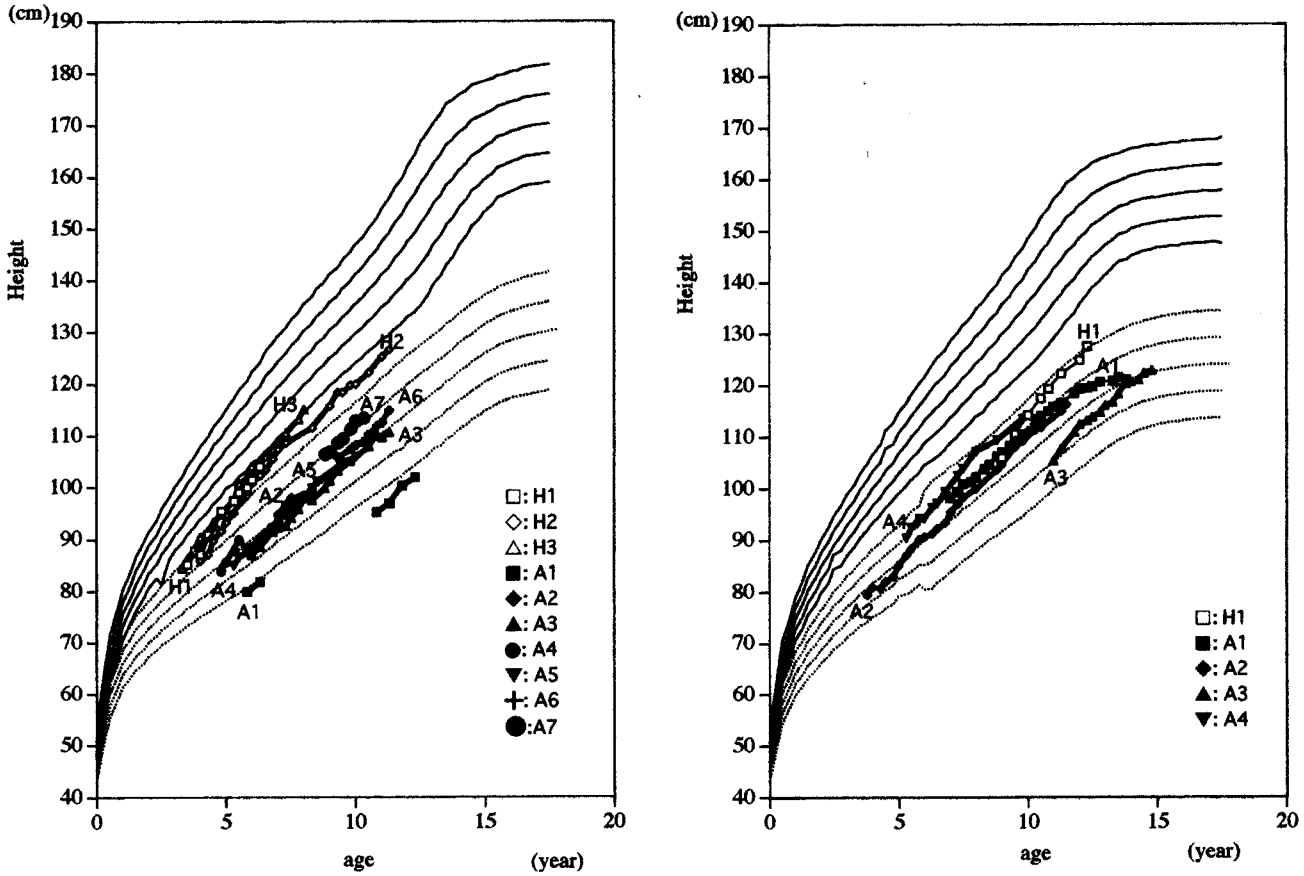

Fig. 1. Height growth data of patients with ACH and with HCH during GH treatment plotted on ACH standard curves (dotted) and Japanese normal standard curves (solid) [1, 18]. Data of patients with ACH and with HCH expressed using some open symbols (H1~H3) and some closed symbols (A1~A7), respectively. (left panel; males, 7 patients with ACH, 3 patients with HCH. right panel; females, 4 patients with ACH, 1 patients with HCH.)

in HCH group increased from 3.2 ± 1.3 cm/year before treatment to 7.9 ± 0.8 cm/year in the first year, to 6.6 ± 0.7 cm/year in the second year and to 7.0 ± 1.2 cm/year in the third year of treatment. In HCH, HV during three-year treatment was significantly greater than that before treatment. Mean HV was not significantly different between ACH group and HCH group before treatment, but it was significantly greater in HCH than in ACH during three-year treatment. Since the HCH group was younger than the ACH group, we compared the effect of GH treatment by means of HV-SDS using the standard for normal children and that using the standard for ACH (Fig. 3). Mean HV-SDS using the standard for normal children in ACH group increased from -2.5 ± 1.8 SD before treatment to -0.9 ± 1.0 SD in the first year, to -0.3 ± 0.9 SD in the second year and to -0.7 ± 2.9 SD in the third year of treatment. Mean HV-SDS using the standard for normal children in HCH group increased from -4.7 ± 2.2 SD before treatment to 1.8 ± 1.0 SD in the first year, to 0.03 ± 1.6 SD in the second year and to 1.4 ± 1.5 SD in the third year of treatment. Although HV-SDS using the standard for normal children was significantly greater in the first and second years of treatment than that before treatment in ACH, it showed much better and significant improvement during three-year treatment than that before treatment in HCH. When the HV-SDS using the standard for normal children was compared for each treatment year between ACH and HCH groups, there was a significant difference in only the first year. Mean HV-SDS using the standard for ACH increased from -0.02 ± 1.5 SD before treatment to 1.3 ± 1.0 SD in the first year, 1.5 ± 0.7 SD in the second year and 0.9 ± 1.6 SD in the third year of treatment in ACH

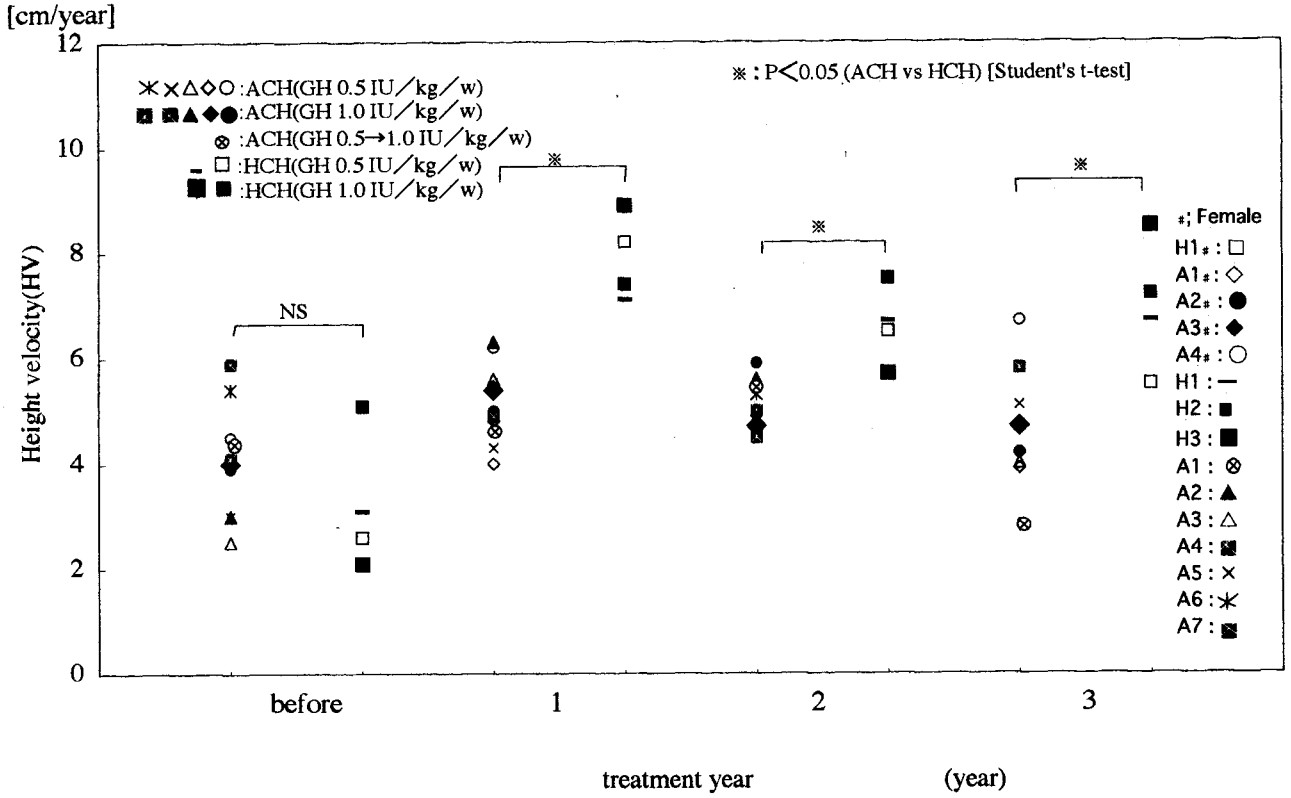

Fig. 2. Comparisons of height velocity (HV) between patients with ACH and with HCH

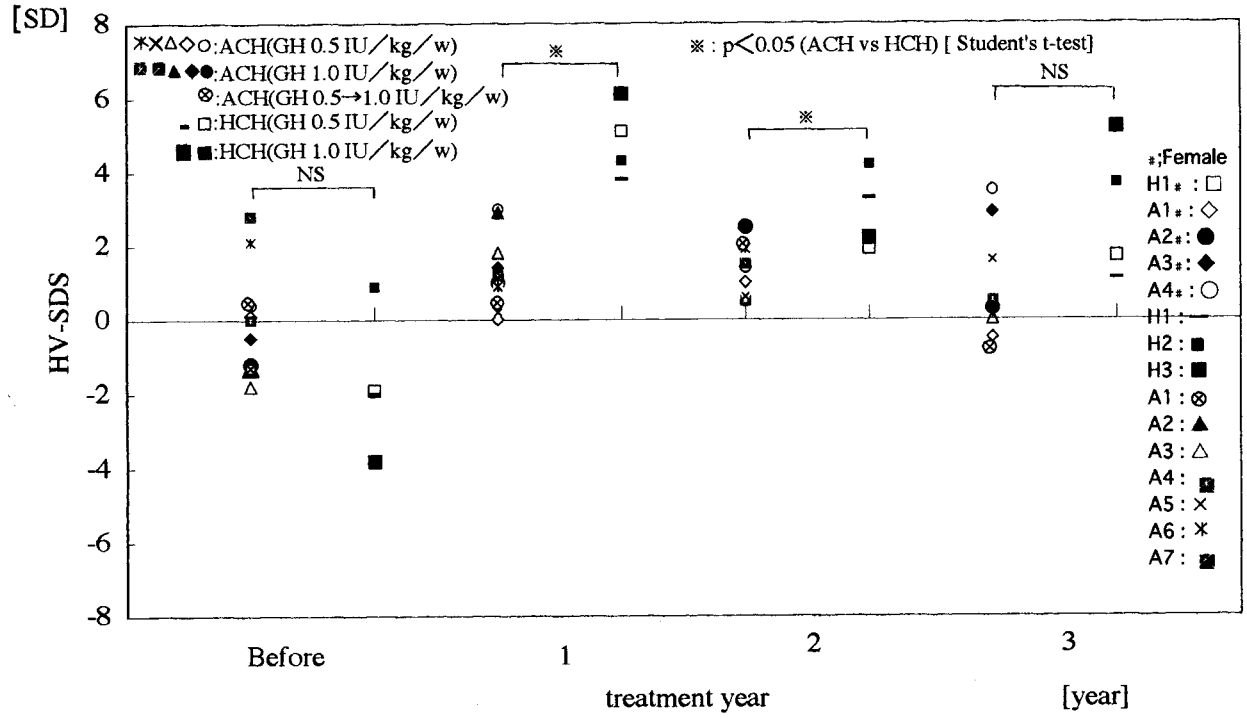

Fig. 3. Comparisons of height velocity SDS (HV-SDS) using the standard for ACH between patients with ACH and with HCH

group. Mean HV-SDS using the standard for ACH increased from -1.7 ± 1.9 SD before treatment to 4.8 ± 1.0 SD in the first year, 2.9 ± 1.1 SD in the second year and 2.9 ± 1.9 SD in the third year of treatment in HCH group. In both ACH and HCH groups, the HV-SDS using the standard for ACH was significant greater in the first and second years than that before treatment, but a much greater improvement was observed in HCH as compared with that in ACH. When the HV-SDS using the standard for ACH was compared for each treatment year between ACH and HCH groups, it was significantly greater in HCH than in ACH in the first and second years.

H-SDS using both the standard for normal children and ACH significantly improved during three-year treatment as compared with that before treatment in both ACH and HCH except in the third year in ACH (Table 2). The improvement was much greater in HCH than in ACH.

Bone age advancement was not accelerated during three-year treatment in ACH. Both BMD-SDS for chronological age and bone age increased during GH treatment in ACH but not significantly. IGF-I SDS significantly increased in the third year in ACH. Evaluation of these significant differences was not done in HCH group because of the small number (Table 2).

Discussion

HV in three patients with ACH, who entered puberty during the three-year GH treatment, changed from 4.1, 4.0 and 4.4 cm/year before treatment to 3.9, 4.7 and 2.9 cm/year in the third year of treatment, respectively. We noted that they did not show obvious pubertal growth spurt, and so we did not consider acceleration of pubertal growth on the effect of GH treatment in these patients with ACH.

Since HCH group was younger than ACH group and pubertal growth is poor in ACH, H-SDS and HV-SDS using the standard for ACH should be applied for the comparison of rhGH effects between ACH and HCH to avoid the underestimation of the effect in ACH during pubertal period. Although a significant improvement in H-SDS and HV-SDS using the standard for ACH was observed in ACH group during three-year GH treatment except HV-SDS in the third year, a much greater improvement in them was observed in HCH group. When the improvement in H-SDS was evaluated clinically using the standard for ACH, H-SDS improved by 0.2 SD on average in the first year in ACH but it did not increase in the following years. On the other hand, H-SDS improved by 0.8 SD in the first year in HCH and the improvement continued in the following years. Mean increase of H-SDS by 0.3 SD in three years in ACH is almost negligible clinically but that by 1.4 SD in three years in HCH can be estimated as effective clinically.

Seino *et al.* [17] reported that a significant dose-dependent increase in HV at doses of 0.5 IU/kg /week and 1.0 IU/kg/week in the first year of GH treatment in ACH. We could not find such a dose dependency probably due to the small number.

Table 2. The effects of rhGH in patients with ACH and with HCH before and during three years of treatment

	ACH (11)				HCH (4)			
Treatment year	before	1 year	2 year	3 year	before	1 year	2 year	3 year
H-SDS[#1] [SD]	-5.5 ± 1.0 (11)	$^{*}-5.2 \pm 0.9$ (11)	$^{*}-5.0 \pm 1.0$ (10)	-5.1 ± 1.1 (8)	-4.1 ± 0.3 (4)	$^{*}-3.4 \pm 0.4$ (4)	$^{*}-2.9 \pm 0.3$ (4)	$^{*}-2.5 \pm 0.7$ (4)
H-SDS[#2] [SD]	-0.2 ± 0.9 (11)	$^{*}0.0 \pm 0.9$ (11)	$^{*}0.1 \pm 0.9$ (10)	$^{*}0.1 \pm 1.0$ (8)	1.2 ± 0.4 (4)	$^{*}2.0 \pm 0.6$ (4)	$^{*}2.3 \pm 0.6$ (4)	$^{*}2.6 \pm 0.7$ (4)
ΔBA [years]	1.3 ± 0.1 (2)	0.9 ± 0.5 (8)	1.2 ± 0.6 (9)	1.3 ± 0.4 (10)	0.2 (1)	1.6 (1)	1.0 ± 0.1 (2)	1.3 ± 0.0 (2)
BMD-SDS[#3] for CA [SD]	-1.3 ± 1.1 (9)	-0.6 ± 1.1 (8)	-0.21 ± 1.6 (8)	0.04 ± 1.02 (9)	-0.9 (1)	-1.2 ± 1.6 (2)	-1.2 ± 2.1 (2)	0.7 ± 0.9 (4)
BMD-SDS[#3] for BA [SD]	-0.6 ± 1.0 (9)	-0.1 ± 0.8 (8)	0.3 ± 1.4 (8)	0.2 ± 0.5 (9)	0.3 (1)	-1.0 ± 1.8 (2)	-0.8 ± 2.5 (2)	0.4 ± 0.8 (4)
IGF-I SDS[#4] [SD]	-0.2 ± 0.8 (9)	-0.03 ± 0.7 (5)	0.6 ± 1.2 (5)	$^{*}0.8 \pm 0.8$ (9)	-0.03 ± 1.2 (8)	0.2 (1)	2.5 (1)	2.9 ± 0.2 (2)

[#1]H-SDS were calculated using standardized height for Japanese normal children.
[#2]H-SDS were calculated using standardized height for patients with ACH.
[#3]BMD-SDS and [#4] IGF-I SDS is based on [21] and [22] of the reference, respectively.
( ) shows the number. $^{*}p<0.05$ vs. before treatment [paired t-test].

Mean HV in HCH during GH treatment was slightly greater than that in non-GHD short children on GH treatment reported by Tanaka *et al.* [23], which were 7.2 cm/year in the first year, 6.3 cm/year in the second year and 5.7 cm/year in the third year of treatment. Since the mean age of HCH patients in this study was younger than that of non-GHD short children, HV SD scores during GH treatment were compared. The mean HV SD scores in non-GHD short children were 1.85 SD in the first year, 0.82 SD in the second year and 0.69 SD in the third year of GH treatment. These values were comparable with those in HCH patients in this study. Therefore, it is concluded that GH treatment in HCH is almost as effective as in non-GHD short stature children.

Ramaswami *et al.* [24] reported that HCH children with N540K mutation of FGFR3 gene showed severe phenotype that resembled ACH. These patients are characterized by disproportionate short stature in early childhood, but become proportionate short stature in adult. In this study, the HCH patients with the N540K mutation of FGFR3 gene showed severe short stature in early childhood, yet taller than mean height of ACH at that age. GH treatment was more effective even in this severe type of HCH patients than in ACH patients. ACH patients could be differentiated from HCH patients by the sensitivity to GH treatment as well as by the severity of short stature. The difference in rhGH effects between ACH and HCH seems to be related to the difference in chondrocyte response as well as in phenotype caused by genotype difference.

GH is a factor for not only a height increment but also increasing the amount of bone mass [25]. Osteoblasts and bone marrow cells exhibit GH and IGF-I receptors. GH directly stimulates or indirectly acts to mediate IGF-I in bone metabolism [26]. Rao *et al.* [27] reported the accumulation of bone mass in a patient with ACH at ages 9 through 12 and that of bone mass was appropriate for her physique though the BMD of the subject was lower when compared to the reference group. In this study, the mean BMD-SDS during three-year GH treatment was not significantly greater than that before treatment in ACH, though the BMD of the subject was equal to that the reference group. Therefore, further studies would be required to confirm whether this beneficial effect was gained by GH treatment in patients with ACH and HCH.

In summary, three-year GH treatment in patients with HCH was effective as that in non-GHD short children, but it has little effect in patients with ACH. Further long-term study is required to confirm the effect of GH treatment on final height in HCH. However, for the assessment of the final height effects, a natural standard growth curve needs to be established in HCH.

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