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Comparison of Growth Hormone Treatment in Patients with Idiopathic Short Stature and Idiopathic Growth Hormone Deficiency

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After recombinant human growth hormone (rhGH) was introduced in the treatment of patients with growth hormone deficiency (GHD) and idiopathic short stature (ISS), many studies have addressed the effect of GH treatment and changes in the height standard deviation score (SDS) after GH treatment. However, few studies comparing the effect of GH in Korean patients with idiopathic GHD and ISS have been designed. Therefore, this study focused on the difference in effect of GH treatment between the two groups. We retrospectively reviewed the height SDS of 34 patients with idiopathic GHD and 12 patients with ISS. The mean ages of the patients with idiopathic GHD and ISS were 9.84±2.09 and 10.72±1.48 years, respectively. All patients were treated with GH for 1 year and body parameters were recorded before and after the GH treatment. Change in height SDS in patients with idiopathic GHD was significantly higher than that in patients with ISS (0.62±0.33 vs. 0.40±0.27, p=0.03). However, body mass index, insulin-like growth factor-1, and insulin-like growth factor binding protein-3 were not significantly different between the two groups after GH treatment. These results suggest that GH treatment has a more powerful effect on increasing height SDS in patients with idiopathic GHD than in patients with ISS.

Key Words: *Growth hormone; Idiopathic short stature; Deficiency*

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INTRODUCTION

Growth is regulated by an interaction of genetic, hormonal, and nutritional factors. Any error in these factors can cause growth disorders. Growth disorders in children include growth hormone deficiency (GHD), idiopathic short stature (ISS), Noonan syndrome, Prader-Willi syndrome, Turner syndrome, and chronic renal insufficiency.[1] Growth hormone plays an important role in growth control, and normal human growth requires appropriate interaction between the proper production of growth hormone and the target organ. For more than 50 years, growth hormone was used only in patients with severe GHD until recombinant human growth hormone (rhGH) was developed in 1985.[2] The introduction of rhGH treatment triggered more widespread treatment of patients with GHD. GHD is diagnosed when the peak growth hormone concentration is less than 10 ng/mL on more than two growth hormone provocation tests.[3] GHD can be categorized into congenital GHD, organic GHD, and idiopathic GHD.[3]

Short children without any signs of GHD who were not born small for gestational age or who have no other chronic diseases are defined as having ISS.[4] Because the causes of ISS are regarded as a combination of a decrease of sensitivity and inappropriate secretion of growth hormone, it is thought that growth will be improved with growth hormone supplementation. After the introduction of rhGH treatment, this treatment was also widely used to treat patients with ISS as well as patients with GHD.[5]

Many studies have been conducted to estimate the effect of growth hormone treatment in patients with GHD and ISS. However, there are not many conventional studies comparing the effects of growth hormone on Korean children with idiopathic GHD and ISS.[6-9] Therefore, we carried

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out a study on the clinical effects of growth hormone in Korean patients diagnosed with idiopathic GHD or ISS.

MATERIALS AND METHODS

1. Patients

This retrospective study was done by reviewing the medical records of patients with idiopathic GHD or ISS at Chonnam National University Hospital from January 2007 to March 2013. The clinical diagnosis of GHD was verified by severe short stature (height less than the 3rd percentile) and peak growth hormone response less than 10 ng/mL after growth hormone provocation tests. ISS (height less than the 3rd percentile) was defined when the patient had short stature without genetic factors or other physical problems but the peak growth hormone response was more than 10 ng/mL. These two groups were treated with growth hormone for 1 year. Patients with chromosomal abnormality, organic lesions on brain magnetic resonance imaging, or a systemic disease or syndrome that causes growth disorders were excluded. Patients with Tanner stage 2 or more were also precluded.

2. Methods

Body parameters of patients with idiopathic GHD and ISS were recorded at the visit to our center. We checked chronological age, bone age (BA), height standard deviation score (SDS), body weight, body mass index (BMI), birth weight, gestational age, and midparental height (MPH) at the point of diagnosis. BA was evaluated by the Greulich-Pyle method.[10] Hormone concentrations of insulin-like growth factor-1 (IGF-1) and insulin-like growth factor binding protein-3 (IGFBP-3) were also estimated. After 1 year of growth hormone treatment, the values of height SDS, BMI, IGF-1, and IGFBP-3 were monitored. MPH was the average height of the parents plus 6.5 cm in boys and minus 6.5 cm in girls. Height SDS was calculated as the patient's height minus the average height for the same age and sex divided by the standard deviation.

3. Statistical analysis

Categorical data were indicated as number (percentage) and continuous data were indicated as mean±standard deviation. We used the Mann-Whitney U test to compare the groups for continuous variables. A p value of less than 0.05 was considered statistically significant. Data were analyzed by using the Statistical Package for Social Sciences software package for Windows (version 19.0; SPSS Inc., Chicago, IL, USA).

RESULTS

The clinical characteristics of the patients with idiopathic GHD and ISS are summarized in Table 1. The total

TABLE 1. Clinical characteristics of the patients at the start of the study and after 1 year of growth hormone (GH) treatment

	GHD patients	ISS patients	p value
At birth			
Gestational age (wk)	39.48±1.95	39.83±0.57	NS
Weight (kg)	2.98±0.44	3.16±0.43	NS
At study start			
Number	34	12	
Male (%)	23 (67.6)	7 (58.3)	
Age (yr)	9.84±2.09	10.72±1.48	NS
Bone age (yr)	8.67±2.21	9.63±1.61	NS
CA-BA (yr)	0.88±0.69	0.57±0.69	NS
Height SDS	−2.55±0.56	−2.60±0.74	NS
Weight	26.33±6.99	27.63±8.73	NS
BMI (kg/m^2)	17.22±2.53	16.99±3.53	NS
MPH (cm)	164.49±6.64	162.42±7.07	NS
Peak GH (ng/mL)	6.04±2.87	22.99±12.54	<0.01
IGF-1 (ng/mL)	140.79±67.47	165.02±68.26	NS
IGFBP-3 (ng/mL)	2,426.88±756.13	2,707.02±1,049.97	NS
After 1 yr GH			
Height gain (cm)	8.86±1.86	7.68±1.44	NS
Height SDS	−1.93±0.59	−2.20±0.69	NS
Change in height SDS	0.62±0.33	0.40±0.27	0.03
BMI (kg/m^2)	17.49±2.73	17.38±3.53	NS
IGF-1 (ng/mL)	331.51±139.06	261.92±116.71	NS
IGFBP-3 (ng/mL)	2,924.75±568.22	3,126.48±521.89	NS

Values are presented as mean±SD. GHD: growth hormone deficiency, ISS: idiopathic short stature, CA: chronological age, BA: bone age, SDS: standard deviation score, BMI: body mass index, MPH: midparental height, IGF-1: insulin-like growth factor-1, IGFBP-3: IGF binding protein-3.

number of patients was 46 (30 males and 16 females), of whom 34 patients were in the idiopathic GHD group (23 males and 11 females) and 12 patients were in the ISS group (7 males and 5 females). The mean age of the patients with idiopathic GHD was 9.84±2.09 years and that of the patients with ISS was 10.72±1.48 years, but the results of the Mann-Whitney U test showed that these values were not significantly different. BA in patients with idiopathic GHD was delayed by 0.88±0.70 years compared with chronological age (CA), and BA in patients with ISS was delayed by 0.57±0.68 years compared with CA. However, the values of CA minus BA (CA-BA) in the two groups were not significantly different. Height SDS in patients with idiopathic GHD was insignificantly higher than that in patients with ISS (−2.55±0.56 vs. −2.60±0.74, respectively). The mean weight in patients with idiopathic GHD and ISS was 26.33±6.99 kg and 27.63±8.73 kg, respectively. Mean BMI in patients with idiopathic GHD and ISS was 17.22±2.53 kg/m^2 and 16.99±3.53 kg/m^2, respectively. Peak growth hormone after the growth hormone provocation test at the diagnosis of idiopathic GHD was significantly lower than that at the diagnosis of ISS (6.04±2.87 ng/mL vs. 22.99± 12.54 ng/mL, respectively, $p<0.01$). The other body parameters including gestational age and MPH, IGF-1, and IGFBP-3 were not significantly different between the two groups (Table 1).

Height gain in patients with idiopathic GHD after 1 year of growth hormone treatment was greater than that in patients with ISS (8.86±1.86 cm vs. 7.68±1.44 cm), but the difference was not significant. Height SDS in patients with idiopathic GHD after 1 year of growth hormone treatment was also insignificantly higher than that in patients with ISS (−1.93±0.59 vs. −2.20±0.68, respectively). BMI in patients with idiopathic GHD and ISS after growth hormone treatment was 17.49±2.73 kg/m^2 and 17.38±3.53 kg/m^2, respectively. The differences in IGF-1 and IGFBP-3 between the two groups after 1 year of growth hormone treatment were not significant. However, change in height SDS in patients with idiopathic GHD was significantly higher than that in patients with ISS (0.62±0.33 vs. 0.40±0.27, respectively, p=0.03).

DISCUSSION

Since growth hormone was developed in 1958, it has been used in many fields.[11] In the early days, growth hormone was used only in patients with GHD, but the indications for growth hormone use have widened. It is used in short patients with Turner syndrome, chronic renal insufficiency, and adult growth hormone deficiency. Recently, small for gestational age, Prader-Willi syndrome, and ISS patients have undergone growth hormone treatment.[12] Growth hormone can help patients with GHD to catch up with height.[3,5] Among the three types of GHD (congenital, organic, and idiopathic), organic GHD is now increasing because of the high incidence of brain tumor therapy. Brain tumors are the most common solid tumors in pediatric patients. Because of the high survival rate with complex treatment regimens with surgery, chemotherapy, and radiotherapy, the late complications of brain tumor therapy such as GHD are now increasing.[13] However, idiopathic GHD is still the most common of the three types.[13] Patients with GHD without an obvious cause of decreased growth hormone are referred to as idiopathic GHD patients. Many previous studies researched the usefulness of growth hormone treatment in patients with idiopathic GHD.[10,14,15]

The heights of patients with ISS are below the 3rd percentile and peak growth hormone concentrations of these patients after a growth hormone provocation test are more than 10 ng/mL. ISS is not a single disease entity but a multifactorial disease. The etiology of ISS was assumed to be a combination of partial growth hormone insensitivity and mild degree of growth hormone deficiency.[16,17] Whereas it was obvious that growth hormone was essential to patients with idiopathic GHD, the usefulness of growth hormone therapy in patients with ISS was debatable. The therapy was tried in many fields. Several investigators reported that growth hormone treatment improved growth velocity, but it was ultimately unhelpful because it accelerated bone maturation and puberty.[18-20] Many opposite studies, on the other hand, reported that treatment with growth hormone in patients with ISS resulted in increases in the final height as well as short-term increases.[21-27]

In our study, we compared the anthropometric measurements of patients with idiopathic GHD and patients with ISS and evaluated the effect of growth hormone therapy after 1 year of treatment. According to our results, peak growth hormone after a growth hormone provocation test at the diagnosis of GHD was lower than that at the diagnosis of ISS. This result can be easily understood from the viewpoint of the definition of GHD and ISS. GHD was defined when the peak growth hormone concentration was under 10 ng/mL in more than two growth hormone provocation tests and ISS was diagnosed when the peak growth hormone concentration was more than 10 ng/mL. Thus, the peak growth hormone concentration in patients with GHD was inevitably lower than that in patients with ISS. The change in height SDS in patients with idiopathic GHD and in patients with ISS was positive, and this result proved the short-term effect of 1 year of growth hormone treatment in patients with both idiopathic GHD and ISS. Also, the change in height SDS in patients with idiopathic GHD was significantly higher than that in patients with ISS (0.62± 0.33 vs. 0.40±0.27, p=0.03).

In this study, patients with GHD and ISS treated with rhGH showed improvement in height at 1 year of treatment. There were no cases of adverse events like intracranial hypertension, slipped capital femoral epiphysis, or type 2 diabetes mellitus. The incidences of dyslipidemia, thyroid dysfunction, joint pain, scoliosis, otitis media, and gynecomastia were not shown in this study. These findings do not indicate that growth hormone should be used routinely to treat children with short stature. Mild short stature appears to have only mild or no psychological con-

sequences and is usually not treated medically. Thus, the present study was limited to patients with height of below the 3rd percentile. Ultimately, any benefit derived from an increase in height must be weighed against the risk of adverse events, the cost, and the discomfort of growth hormone injections.

Our study had some limitations, especially the limited number of patients included in the study. In addition, the nature of the study was cross-sectional. Furthermore, because our patients were observed for only 1 year of treatment, more continuous treatment and longer follow-up is needed. More data from more patients with idiopathic GHD and ISS should be collected and continuous treatment and observation are needed.

CONFLICT OF INTEREST STATEMENT

None declared.

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