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Comparative study of growth hormone treatment in children with idiopathic short stature and growth hormone deficiency

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Introduction

ISS is a condition characterized by short stature of unknown etiology after exclusion of GHD, being small for gestational age, systemic illness, and genetic or syndromic short stature. The children with ISS present normal on GH stimulation test unlike GHD. However, the reproducibility of the GH stimulation test is low ; thus, some children's results lie at the intersection between ISS and GHD. Furthermore, children with ISS are considered to be a heterogeneous group because of the unknown etiology of their condition, and the effectiveness of GH treatment for ISS is highly variable Recently, many studies have reported that response to GH in children with ISS is dose dependent; higher doses of GH are reportedly required for patients with ISS to achieve responses similar to those seen in patients with GHD . However, it remains difficult to determine the optimal doses of GH for individual children with ISS. This study was performed to investigate the responses to GH (0.22 mg/kg/week) in children with ISS versus those with GHD and to analyze the clinical factors associated with a treatment response.

Methods

we retrospectively evaluated patients diagnosed with GHD or ISS and followed up at the pediatric endocrinology unit of Ajou University Hospital, Korea. From January 2007 to June 2012, 38 children with GHD and 22 children with ISS were included in this study. All patients were prepubertal at presentation and at the end of the study and received subcutaneous recombinant human GH, six times per week (0.23 mg/kg/week) for at least 2 years.

From their medical records, we retrieved their pretreatment auxological and laboratory data as well as the corresponding data from the 2-year period following GH treatment. Growth velocity and change in height standard deviation scores (Δ height SDS) during the first year of treatment were considered to be indicators of a response to GH . We also analyzed the pretreatment clinical and laboratory parameters to identify associations with the first-year Δ height SDS.

Statistical analyses

A *p*-value of <0.05 was considered to indicate statistical significance. Inter-group comparisons of auxological and laboratory parameters were analyzed using Student's *t*-test, and intra-group changes in the auxological parameters were analyzed using the paired *t*-test. Backward multiple regression analysis was used to evaluate the clinical factors for associations with first-year Δ height SDS. Results are described as mean ± SD unless otherwise stated.

Results

Table 1. Baseline characteristics of children with growth hormone deficiency and idiopathic short stature

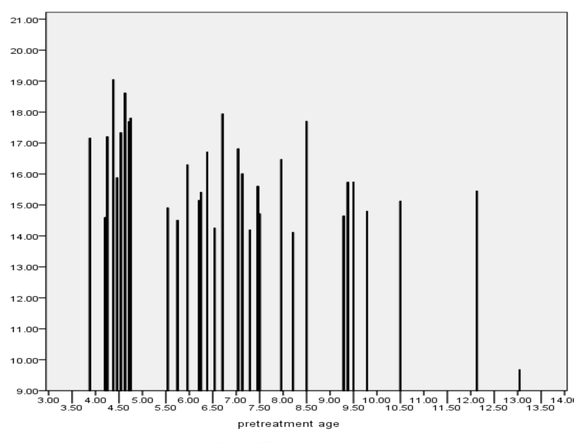
	GHD (n = 38)	ISS (n = 22)	*p – value*
M : F (%)	28 : 10 (26.3%)	14 : 8 (36.4%)	
Age (yr)	6.76 ± 2.19	6.26 ± 1.76	0.365
MPH (cm) boys	168.53 ± 2.92	167.42 ± 5.53	0.398
girls	156.49 ± 2.64	156.62 ± 2.72	0.920
MPH SDS boys	-0.86 ± 0.52	-1.06 ± 1.00	0.385
girls	-0.86 ± 0.54	-0.83 ± 0.56	0.920
Ht SDS	-2.23 ± 0.42	-2.13 ± 0.33	0.331
BMI (kg/m^2)	16.16 ± 1.90	15.59 ± 0.89	0.192
BA	5.19 ± 1.83	4.89 ± 1.58	0.524
CA – BA	1.56 ± 0.81	1.36 ± 0.53	0.309
IGF-1	132.94 ± 78.47	160.77 ± 78.48	0.191
IGFBP-3	2.31 ± 0.56	2.19 ± 0.53	0.409
IGF-1 SDS	0.04 ± 0.96	0.45 ± 0.75	0.086
IGF-BP3 SDS	-0.77 ± 0.67	-0.90 ± 0.70	0.473
peak GH (ng/ml) [a]	7.56 ± 1.93	23.44 ± 9.70	< 0.001
Insulin [a]	5.23 ± 2.64 (n=32)	15.34 ± 13.12 (n=22)	< 0.001
L-dopa [a]	6.48 ± 2.55 (n=28)	21.60 ± 8.58 (n=18)	< 0.001
Clonidine [a]	6.63 ± 2.80 (n=16)	22.73 ± 9.53 (n=4)	0.002

[a]: peak GH data was not normal distributed, statistical significance test was done by Mann – Whitney U- test.

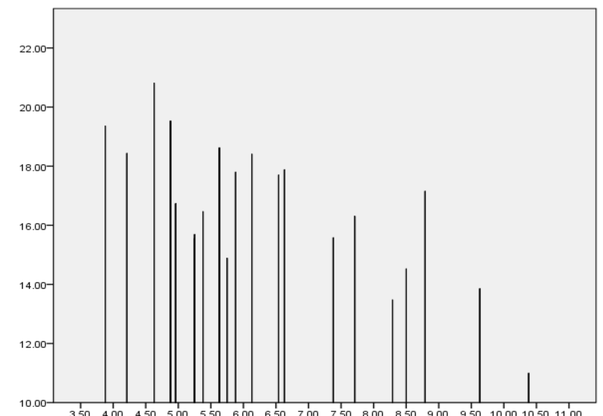
Table 2. Response to 2 years of growth hormone treatment in children with growth hormone deficiency and idiopathic short stature

	GHD (n = 38)	ISS (n = 22)	*p – value* (95% CI)
mean GH dose(mg/kg/wk)	0.22 ± 0.02	0.23 ± 0.02	0.205 (0.02 – 0.00)
Age (yr)	8.85 ± 2.23	8.39 ± 1.80	0.410 (-0.65 – 1.58)
Bone age	7.43 ± 2.14	7.14 ± 2.05	0.615 (-0.84 – 1.42)
CA - BA	1.46 ± 0.83	1.22 ± 0.84	0.295 (-0.21 – 0.68)
GV 1$_{st}$ yr (cm/yr)	8.98 ± 1.42	9.65 ± 1.42	0.082 (-1.43 – 0.08)
GV 2$_{nd}$ yr (cm/yr)	6.91 ± 0.84	7.00 ± 1.17	0.736 (-0.61 – 0.43)
Height SDS 1st yr	-1.47 ± 0.50	-1.29 ± 0.35	0.161 (-0.41 – 0.07)
Height SDS 2nd yr	-1.14 ± 0.53	-0.89 ± 0.49	0.075 (-0.52 – 0.02)
Δ Ht SDS 1$_{st}$ yr	0.76 ± 0.25	0.83 ± 0.30	0.360 (-0.21 – 0.07)
Δ Ht SDS 2$_{nd}$ yr	0.32 ± 0.18	0.40 ± 0.31	0.227 (-0.20 – 0.05)

Figure 1. Growth velocity for 2-years of GH treatment



<GHD group>



<ISS group>

After 2 years of GH treatment, growth velocity and Δ height SDS were analyzed (Table 2). There was no significant difference in the growth velocity and Δ height SDS between the two groups after GH treatment. After 2 years of treatment, the height SDS in the ISS group was increased from –2.13 ± 0.33 to –0.89 ± 0.49 ($p < 0.001$), and the height SDS in the GHD group was increased from –2.23 ± 0.42 to –1.14 ± 0.53 ($p < 0.001$). The bone age changed from 4.89 ± 1.58 to 7.14 ± 2.05 years (mean increase, 2.25 years; $p < 0.001$) in the ISS group and from 5.19 ± 1.83 to 7.43 ± 2.14 years (mean increase, 2.23 years; $p < 0.001$) in the GHD group. The difference between chronological age and bone age was 1.36 ± 0.53 to 1.22 ± 0.84 years in the ISS group ($p = 0.356$) and 1.56 ± 0.81 to 1.46 ± 0.83 years in the GHD group ($p = 0.380$). There were no sex differences in GH treatment outcomes in either group (data not shown).

The associations between pretreatment age and first-year Δ height SDS were analyzed via multiple regression. A significant negative correlation was found between age and first-year Δ height SDS in both the ISS and GHD groups (β ± standard error [SE], –0.074 ± 0.033, $p = 0.037$ and –0.039 ± 0.019, $p = 0.048$, respectively).

During GH treatment, there was no patient show significant side effect associated with growth hormone treatment, including glucose intolerance, development of tumor or cardiovascular and hormonal dysfunction etc.

Conclusion

we have demonstrated that the growth response to GH was as positive in children with ISS as it was in children with GHD during the prepubertal period. Beginning GH treatment at a younger age is a strong predictor of positive growth outcomes. Our study has several contradictory result with previous reports, further studies are needed to validate this result. Despite several limitations, we hope these data could help clinicians to assess the response to GH and make decision when to start GH in prepubertal children with ISS.

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