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Idiopathic Short Stature Phenotypes among Korean Children: Cluster Analysis

Hyo-Kyoung Nam,[1] Hye Ryun Kim,[2,*] Kee-Hyoung Lee[2] and Young-Jun Rhie[3]

[1]Department of Pediatrics, Korea University Guro Hospital, Korea University College of Medicine, Seoul, Korea
[2]Department of Pediatrics, Korea University Anam Hospital, Korea University College of Medicine, Seoul, Korea
[3]Department of Pediatrics, Korea University Ansan Hospital, Korea University College of Medicine, Gyeonggi-do, Korea

Idiopathic short stature (ISS) is a heterogeneous group and their responsiveness to growth hormone treatment varies among individuals. The aim of this study was to identify homogeneous phenotypes to better assess response before the initiation of treatment. We focused on person-centered approaches using a latent profile analysis. Clinical data of 218 children (127 boys and 91 girls) aged 4-15 years were obtained from the "LG Growth Study" which is a non-interventional Korean multicenter registry for growth hormone treatment. Growth hormone dose, first-year difference in height standard deviation score (Δheight SDS), mid-parental height SDS, and initial bone age were inputted into the model. The distribution of scatter plot was clearly distinguished at the chronological age of 8.83 years, Δheight SDS of 0.82 and mean GH dose of 0.36 mg/kg/week. The latent profile analysis revealed three distinct phenotypes names as follows: younger good responder (n = 56), older good responder (n = 111), and older poor responder (n = 51) groups. Despite more than twice the mean growth hormone dose, the older poor responder group showed the least improvement in the mean Δheight SDS. The pretreatment height velocity and peak growth hormone level were lower for the older poor responder group compared with those of the older good responder group. The statistically optimal cutoff point for predicting poor response was 3.41 cm/year for pretreatment height velocity and 9.18 ng/mL for peak growth hormone level. This study offers a new multidimensional approach to enable personalized growth hormone treatment optimization according to ISS phenotypes.

Keywords*:* children; cluster analysis; growth hormone; idiopathic short stature; phenotype
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Introduction

Idiopathic short stature (ISS) is defined as a height below –2 standard deviations with no detectable structural or functional causes. ISS is of unknown etiology and affects a heterogeneous group of children with variable responses to growth hormone (GH) (Pedicelli et al. 2009). Partial GH insensitivity and partial GH deficiency (GHD) were not easily differentiated and were classified as ISS (Cohen et al. 2008).

Although the GH response is well-known in the ISS group, responsiveness varies among individuals. Thus, there have been many attempts at enhancing individualized GH treatment in terms of safety, efficacy, and cost. Previous studies have evaluated the efficacy of GH by comparing subgroups or by using limited parameters. Growth prediction models have also been suggested using several parameters. However, they required parameters that were unavailable at the initiation of treatment or did not make predictions among children with ISS (Wikland et al. 2000; Loftus et al. 2017).

We switched from a "variable-centered" to a "person-centered" approach to understanding the characteristics of ISS. Clustering methods are useful for grouping subjects into profiles that summarize shared aspects of a disease within a heterogeneous group (Brusco et al. 2017). It has already been used in studies of respiratory diseases (Haldar et al. 2008; Herr et al. 2012; Dumas et al. 2016), but has never been applied to children with ISS.

Therefore, we aimed to identify distinct ISS phenotypes using a latent profile analysis (LPA) and to predict optimal personalized GH responses among children with ISS prior to treatment initiation.

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Correspondence: Young-Jun Rhie, Department of Pediatrics, Korea University Ansan Hospital, College of Medicine, Korea University, Goryeodae-ro 73, Seongbuk-gu, Seoul 02841, Korea.
e-mail*:* human21@korea.ac.kr
*Present address: Woorisoa Children's Hospital, Seoul, Korea.

Methods

Subjects

This study used data from the LG Growth Study (LGS). This retrospective and prospective multicenter registry study included five cohorts: the GHD, ISS, small for gestational age (SGA), Turner syndrome, and chronic renal failure groups (Chung et al. 2018). Children who were at least 2 years of age were enrolled in this study. Six-month interval follow-up data from the day of registration until 2 years after epiphyseal closure were obtained prospectively, and pre- and post-treatment data before registration were also collected retrospectively. The children were treated with four recombinant human GH (rhGH) products (LG Chem Ltd., Korea): three rhGH formulations requiring daily administration (Eutropin® inj., Eutropin®AQ inj. and Eutropin®Pen inj.) and one rhGH formulation requiring weekly administration (Eutropin®Plus inj.) used in Korea.

Data from a total of 1,612 children who were initially enrolled with GHD (n = 1,297) and ISS (n = 315) were available in the LGS database between November 2011 and March 2017. When GH stimulation test was indicated, appropriate tests among insulin-induced hypoglycemia, L-dopa, clonidine, L-arginine or glucagon were chosen. Children with a peak GH level below 10 ng/mL (as a Korean insurance criterion) with at least two GH stimulation test results were classified as GHD in the LGS database. However, based on the result of recent studies (GH Research Society 2000; Wagner et al. 2014; Murray et al. 2016), we used a revised cutoff of 7 ng/mL in this study.

Among them, 404 children remained after excluding those whose initial height was above the third percentile or whose peak GH was below 7 ng/mL on two tests, or whose initial heights and heights after 1 year were not available. There were 13 children younger than 4 years and two children older than or equal to 15 years; namely, these 15 children were also excluded (Fig. 1). After the cluster analysis, a total of 218 children who had all four parameters, including mid-parental height standard deviation score (SDS), first-year difference in height SDS (*Δ*height SDS [0-12 months]), total GH dose, and initial bone age (BA), were included.

In summary, 127 boys and 91 girls aged 4 to 15 years who were treated with GH for more than 12 months were included in this study (Fig. 1). After excluding outliers, the children were assigned to three groups as follows: younger good responders, older good responders, and older poor responder (Fig. 2).

Methods

We obtained data regarding gender, chronological age (CA), pubertal status, height, weight, body mass index (BMI) (kg/m^2), and mid-parental height. The height, body weight, and BMI were expressed as SDS values using the Korean Growth Standard for the same age and gender. Pretreatment height, pretreatment height velocity (HV), mean GH dose (mg/kg/week), and 6-month interval post-treatment data were also obtained. HV was calculated using the following formula: HV (cm/year) = change in height from the baseline / (date of measurement – date of baseline height measurement + 1) × 365. Change (*Δ*) in a variable induced by GH treatment was obtained as the difference between two values. We also reviewed BA, BA advancement (BA-CA), hemoglobin, glucose, aspartate transaminase, alanine transaminase, total cholesterol, blood urea nitrogen, creatinine, free T4, thyroid stimulating hormone, insulin-like growth factor (IGF)-I, IGF-binding protein 3 (IGFBP-3), and pretreatment GH stimulation test results.

Written informed consent was obtained from patients and their parents/legal guardians prior to enrolment at each institute. The present study protocol was reviewed and approved by the Institutional Review Board of Korea University Guro Hospital (IRB no. 2017GR0352). This study was conducted in accordance with the Declaration of Helsinki.

Statistical analysis

Statistical data analyses were performed using SAS® version 9.4 (SAS Institute, Inc., Cary, NC, USA). In addition, R version 3.4.1 (The R Development Core Team, Vienna, Austria) and the *mclust*

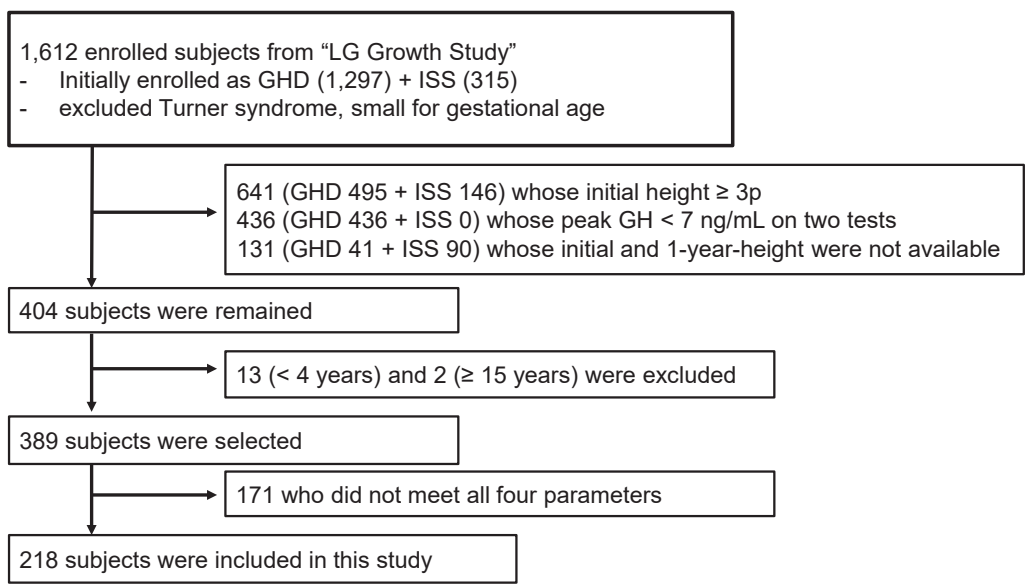

Fig. 1. Flow chart of subject inclusion in this study.
A total of 218 children aged 4 to 15 years who were treated with GH for more than 12 months were included in this study. The four parameters were mid-parental height SDS, first-year height SDS, total GH dose, and initial bone age.
GH, growth hormone; GHD, growth hormone deficiency; ISS, idiopathic short stature; SDS, standard deviation score.

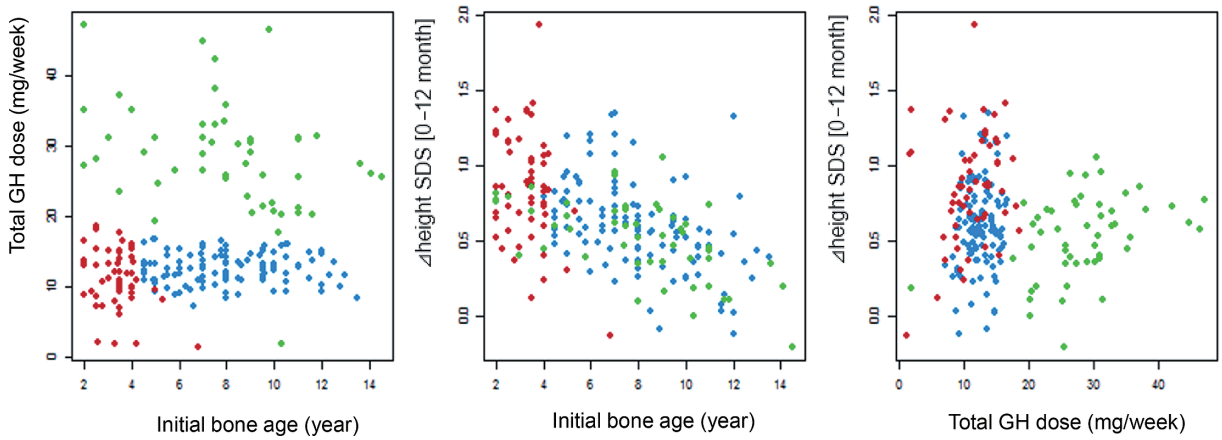

Fig. 2. Clinical and biochemical phenotypes of idiopathic short stature.
Children were assigned to three groups (younger good responders [red dots], older good responders [blue dots], and older poor responders [green dots]).
⊿height SDS [0-12 months], first-year difference in height SDS; GH, growth hormone; SDS, standard deviation score.

package version 5.4 were used to perform cluster analyses. To select the best profile, we applied various conditions and clustering methods (LPA and K-means) (Brusco et al. 2017). LPA was selected to identify distinct ISS phenotypes. As the objective of this study was to identify homogeneous ISS phenotypes to better assess GH response before the initiation of GH treatment, we focused on individual characteristics (CA, baseline height SDS, mid-parental height SDS, and ⊿BMI SDS), phenotypic characteristics (pretreatment HV, BA, and BA-CA), and GH treatment (total GH dose and ⊿height SDS). We chose four variables that included mid-parental height SDS, ⊿height SDS [0-12 months], total GH dose, and initial BA.

In order to determine the number of latent profiles, models with different numbers of latent profiles were compared using the Bayesian information criterion; larger values indicate a better model in this study and the model with the highest Bayesian information criterion (-3140 with a three-group model between 0-12 months of GH treatment) was selected (Fraley and Raftery 1999). After excluding the outliers, the three-group model was chosen. The distribution of scatter plot was clearly distinguished at the CA of 8.83 years, BA of 7.00 years, ⊿height SDS [0-12 months] of 0.82 and mean GH dose [0-12 months] of 0.36 mg/kg/week. Therefore, we named the groups as the younger good responder (younger than 8.83 years of age and better improvement in height SDS even with GH dose of less than 0.36 mg/kg/week), older good responder (older than 8.83 years of age and better improvement in height SDS even with GH dose of less than 0.36 mg/kg/week), and older poor responder (older than 8.83 years of age and poor improvement in height SDS despite with high GH dose of more than 0.36 mg/kg/week) groups according to characteristics shown in Fig. 2.

A one-way analysis of variance or Kruskal-Wallis test was performed to compare the clinical characteristics and laboratory findings of the three groups. The chi-square test or Fisher's exact test was used to compare categorical variables. Data were expressed as the mean ± standard deviation or number (percentage). The area under the receiver operating characteristic curve (AUC) was generated and the optimal cutoff values of baseline characteristics were determined as the points at which the sum of the sensitivity and specificity were maximized. Values with $P < 0.05$ were considered statistically significant.

Results

Comparison of characteristics between selected and included subjects

The proportions of boys and prepubertal subjects, mid-parental height SDS, baseline CA and BA, height SDS, weight SDS, BMI SDS, and height velocity were similar between the selected (n = 389) and included subjects (n = 218). The peak GH level, baseline IGF-I SDS, IGFBP-3 SDS, mean GH dose, and ⊿height SDS were also similar between the two groups.

The included subjects comprised 218 children (127 boys and 91 girls) and more than half of the children (n = 94, 64.8%) were prepubescent. The mean CA was 8.58 ± 2.93 years, and the mean height SDS was –2.46 ± 0.54 at the baseline. The mean pretreatment HV was 4.99 ± 2.01 cm/year, and the peak GH level was 10.82 ± 6.43 ng/mL. The mean GH dose for 12 months was 0.31 ± 0.16 mg/kg/week (Table 1).

Comparison of baseline clinical characteristics and laboratory findings among the three groups

Based on the results of LPA, 56 children were younger good responders, 111 were older good responders and 51 were older poor responders.

The proportions of boys and prepubertal subjects were similar among the three groups. Children classified as younger good responders were the youngest (5.35 ± 0.95 years, $P < 0.001$) and the shortest (–2.66 ± 0.67, $P = 0.017$), and their mid-parental height SDS (–0.74 ± 0.77, $P = 0.010$) were the highest among the three groups. Pretreatment HV was the lowest at 3.99 ± 2.07 cm/year in the older poor responder group ($P = 0.018$). The mean peak GH level and baseline IGFBP-3 SDS were the lowest at 8.72 ± 2.28 ng/mL (vs. 11.12 ± 5.70 ng/mL vs. 11.65 ± 7.77 ng/mL, $P = 0.007$) and –0.47 ± 1.36 (vs. 0.90 ± 2.01 vs. 0.17 ± 1.78, $P = 0.008$), respectively, in the older poor responder group

Table 1. Comparisons of characteristics between selected and included subjects.

	Selected (n = 389)	Included (n = 218)
Sex (boys, %)	224 (57.6%)	127 (58.3%)
Prepuberty (%)	153 (61.5%)	94 (64.8%)
Baseline chronological age, years	8.54 ± 2.90	8.58 ± 2.93
Baseline bone age, years	6.81 ± 3.08	6.82 ± 3.08
Paternal height SDS	–0.88 ± 1.00	–0.95 ± 0.97
Maternal height SDS	–0.99 ± 1.07	–1.01 ± 1.08
Mid-parental height SDS	–0.90 ± 0.72	–0.95 ± 0.72
Baseline height SDS	–2.51 ± 0.56	–2.46 ± 0.54
Baseline weight SDS	–1.93 ± 1.12	–1.82 ± 1.12
Baseline body mass index SDS	–0.49 ± 1.09	–0.41 ± 1.09
Baseline height velocity, cm/year	4.85 ± 1.88	4.99 ± 2.01
Peak GH level, ng/mL	11.71 ± 8.83	10.82 ± 6.43
Baseline IGF-I SDS	–0.82 ± 0.79	–0.81 ± 0.75
Baseline IGFBP-3 SDS	0.13 ± 1.82	0.20 ± 1.81
⊿height SDS [0-6 month]	0.40 ± 0.24	0.41 ± 0.24
⊿height SDS [6-12 month]	0.25 ± 0.20	0.25 ± 0.20
⊿height SDS [0-12 month]	0.65 ± 0.33	0.65 ± 0.33
Mean GH dose [0-6 month], mg/kg/week	0.33 ± 0.21	0.30 ± 0.16
Mean GH dose [6-12 month], mg/kg/week	0.36 ± 0.22	0.32 ± 0.17
Mean GH dose [0-12 month], mg/kg/week	0.34 ± 0.21	0.31 ± 0.16

Data are expressed as the mean ± standard deviation or number (%).
GH, growth hormone; IGF-I, insulin-like growth factor-I; IGFBP-3, insulin-like growth factor binding protein-3; SDS, standard deviation score.

(Table 2).

Comparison of follow-up clinical characteristics and laboratory findings among the three groups

After the first year of GH treatment, the three groups had similar height SDS values (–1.81 ± 0.82 vs. –1.82 ± 0.56 vs. –1.80 ± 0.53, in younger good responder, older good responder, and older poor responder, respectively, P = 0.888) and BMI SDS values (–0.35 ± 0.99 vs. –0.58 ± 1.00 vs. –0.44 ± 1.04, P = 0.228). The improvement in height SDS was the highest (0.55 ± 0.26, P < 0.001 and 0.85 ± 0.37, P < 0.001) in the younger good responder group, whereas it was statistically lowest (0.34 ± 0.24, P < 0.001 and 0.53 ± 0.27, P < 0.001) in the older poor responder group at 6 months and 12 months of treatment, respectively.

The older poor responder group was treated with more than twice the mean GH dose than the younger good responder and older good responder groups (0.55 ± 0.15 mg/kg/week vs. 0.22 ± 0.07 mg/kg/week vs. 0.25 ± 0.04 mg/kg/week, P < 0.001) for 12 months. Despite the administration of the highest GH dose, the older poor responder group experienced the least improvements in IGF-I SDS (1.10 ± 1.10 vs. 1.39 ± 1.15 vs. 1.66 ± 1.27, P = 0.085) among the three groups (Table 3).

The optimal cutoff points of baseline clinical characteristics and laboratory findings

The AUCs were calculated based on the values of the older poor responder group. Table 4 shows the statistical cutoff points of baseline CA, BA, pretreatment HV, peak GH level, IGF-I SDS, and IGFBP-3 SDS. The statistically optimal cutoff point for pretreatment HV was 3.4 cm/year (AUC, 0.677; 95% confidence interval [CI], 0.499-0.855), with a sensitivity of 53.9% and a specificity of 82.5%. The

Table 2. Comparison of baseline clinical characteristics and laboratory findings among three groups.

	Younger good responder (n = 56, 25.7%)	Older good responder (n = 111, 50.9%)	Older poor responder (n = 51, 23.4%)	*P* value
Sex (boys, %)	28 (50.0%)	69 (62.2%)	30 (58.8%)	0.331
Prepuberty (%)	29 (78.4%)	42 (60.0%)	23 (60.5%)	0.129
Baseline CA, years	5.35 ± 0.95	9.67 ± 2.39	9.76 ± 2.83	< 0.001
Baseline BA, years	3.33 ± 0.91	8.04 ± 2.35	7.98 ± 3.13	< 0.001
Baseline BA-CA, years	–2.02 ± 0.94	–1.63 ± 1.02	–1.78 ± 0.99	0.064
Paternal height SDS	–0.61 ± 1.10	–1.08 ± 0.93	–1.05 ± 0.82	0.009
Maternal height SDS	–0.90 ± 1.21	–1.12 ± 1.05	–0.87 ± 0.95	0.328
Mid-parental height SDS	–0.74 ± 0.77	–1.07 ± 0.72	–0.94 ± 0.63	0.010
Baseline height SDS	–2.66 ± 0.67	–2.42 ± 0.49	–2.33 ± 0.39	0.017
Baseline weight SDS	–2.12 ± 1.56	–1.72 ± 0.93	–1.69 ± 0.84	0.128
Baseline body mass index SDS	–0.12 ± 1.27	–0.52 ± 1.03	–0.51 ± 0.97	0.088
Baseline height velocity, cm/year	5.93 ± 2.13	4.83 ± 1.75	3.99 ± 2.07	0.018
Peak GH level, ng/mL	11.12 ± 5.70	11.65 ± 7.77	8.72 ± 2.28	0.007
Baseline IGF-I SDS	–0.70 ± 0.77	–0.78 ± 0.79	–1.01 ± 0.61	0.063
Baseline IGFBP-3 SDS	0.90 ± 2.01	0.17 ± 1.78	–0.47 ± 1.36	0.008

Data are expressed as the mean ± standard deviation or number (%).
BA, bone age; CA, chronological age; GH, growth hormone; IGF-I, insulin-like growth factor-I; IGFBP-3, insulin-like growth factor binding protein-3; SDS, standard deviation score; TSH, thyroid stimulating hormone.

statistically optimal cutoff point for peak GH level was 9.2 ng/mL (AUC, 0.652; 95% CI, 0.571-0.734), with a sensitivity of 83.0% and a specificity of 52.2%.

Discussion

A three-class model (including the younger good responder, older good responder, and older poor responder groups) was selected as the final model because the differences among the groups were explained graphically and were statistically optimal. The mid-parental height SDS and pretreatment HV were higher and the initial height SDS was lower among younger good responders. The pretreatment HV, peak GH level, and change in IGF-I SDS were lower in the older poor responder group than in the older good responder group, even though the former group received the highest dose of GH. To our knowledge, this is the first study to use a clustering approach to identify ISS phenotypes for predicting GH response before the initiation of treatment.

Although the GH response in ISS is well-known, responsiveness varies among individuals diagnosed with ISS. There have been many attempts at developing GH prediction models calculated based on the available information (Wikland et al. 2000; Ranke et al. 2017). Bakker et al. (2008) evaluated GH response among good responders and poor responders according to HV and *Δ*height SDS using data from the National Cooperative Growth Study. Most of the previous prediction models required specific parameters that were unavailable before the initiation of treatment or did not include ISS (Loftus et al. 2017).

While previous studies evaluated the efficacy of GH by comparing subgroups (e.g., GHD vs. ISS, or familial SS vs. non-familial SS) or by using a limited parameter such as HV SDS (Kaplowitz et al. 2013; Sotos and Tokar 2014; Siklar et al. 2015), several parameters were considered simultaneously in the present study.

Cluster analysis is based on a measure of similarity. It allows the identification of subgroups that are similar to each other among the observed variables used in this analysis. The LPA was chosen because it is well designed to deal with continuous variables (Brusco et al. 2017). Although it is helpful in the identification of different phenotypes to target intervention, careful interpretation is required with

Table 3. Comparison of follow-up clinical characteristics and laboratory findings among the three groups.

	Younger good responder (n = 56, 25.7%)	Older good responder (n = 111, 50.9%)	Older poor responder (n = 51, 23.4%)	*P* value
Height SDS [12 months]	–1.81 ± 0.82	–1.82 ± 0.56	–1.80 ± 0.53	0.888
Weight SDS [12 months]	–1.51 ± 1.18	–1.36 ± 0.86	–1.29 ± 0.91	0.705
Body mass index SDS [12 months]	–0.35 ± 0.99	–0.58 ± 1.00	–0.44 ± 1.04	0.228
⊿height SDS [0-6 months]	0.55 ± 0.26	0.37 ± 0.21	0.34 ± 0.24	< 0.001
⊿height SDS [6-12 months]	0.32 ± 0.24	0.25 ± 0.17	0.19 ± 0.20	0.028
⊿height SDS [0-12 months]	0.85 ± 0.37	0.60 ± 0.29	0.53 ± 0.27	< 0.001
BA-CA [6 months], years	–1.65 ± 1.04	–1.44 ± 0.93	–1.34 ± 1.15	0.186
BA-CA [12 months], years	–1.71 ± 1.15	–1.37 ± 1.08	–1.20 ± 1.02	0.165
Mean GH dose [0-6 months], mg/kg/week	0.21 ± 0.07	0.24 ± 0.04	0.53 ± 0.17	< 0.001
Mean GH dose [6-12 months], mg/kg/week	0.22 ± 0.07	0.26 ± 0.05	0.57 ± 0.17	< 0.001
Mean GH dose [0-12 months], mg/kg/week	0.22 ± 0.07	0.25 ± 0.04	0.55 ± 0.15	< 0.001
⊿IGF-I SDS [0-6 months]	1.31 ± 0.94	1.58 ± 1.36	1.12 ± 1.00	0.217
⊿IGF-I SDS [6-12 months]	0.07 ± 1.18	0.25 ± 1.36	–0.32 ± 1.60	0.236
⊿IGF-I SDS [0-12 months]	1.39 ± 1.15	1.66 ± 1.27	1.10 ± 1.10	0.085
⊿IGFBP-3 SDS [0-6 months]	1.40 ± 1.78	0.73 ± 1.22	0.09 ± 0.84	0.008
⊿IGFBP-3 SDS [6-12 months]	–0.43 ± 1.54	0.31 ± 1.44	0.05 ± 0.64	0.079
⊿IGFBP-3 SDS [0-12 months]	1.05 ± 1.96	1.22 ± 1.34	0.69 ± 1.03	0.340

Data are expressed as the mean ± standard deviation or number (%).
BA, bone age; CA, chronological age; IGF-I, insulin-like growth factor-I; IGFBP-3, insulin-like growth factor binding protein-3; SDS, standard deviation score.

regard to whether the identified phenotypes are relevant from a clinical viewpoint.

Previous studies reported that better growth response correlated with younger age, lower baseline height SDS, higher mid-parental height SDS, and higher GH dose. A younger age at the initiation of GH treatment is widely accepted as a major determinant of growth outcome (Ranke et al. 2007). Higher mid-parental height SDS generally indicates greater genetic potential; the association between greater height gain and taller parents was positive in the first year of treatment, but became non-significant in the second year (Kaplowitz et al. 2013). In this study, the good responder group was the youngest and shortest and had the highest mid-parental height SDS values among the three groups. The clinical characteristics of the three identified phenotypes were relevant with generally known aspects.

According to the consensus on its definition, ISS also includes constitutional delay of growth and puberty. In the present study, the proportions of prepubertal subjects and baseline BA delay were similar among the three groups.

The peak GH levels of some children lie between those of GHD and ISS, because of the low reproducibility of the GH stimulation test (Fisker et al. 1998). The cutoff peak GH concentration from provocation tests varies among countries. In the 1960s, when GH provocation tests were first introduced, a peak GH level of 5 ng/mL was used to diagnose GHD. A peak GH level of 10 ng/mL is used as a Korean insurance criterion. Recent studies suggest a cutoff peak GH level of 7 ng/mL when using newer monoclonal antibody-based methods (GH Research Society 2000; Wagner et al. 2014; Murray et al. 2016). False positive rates decreased from 14.9-49% to 8.9-23.7% when a cutoff level of 7 ng/mL was used instead of 10 ng/mL (Ghigo et al. 1996). We also used a cutoff peak GH level of 7 ng/mL

Table 4. Optimal cutoff points of baseline clinical characteristics and laboratory findings.

	Cutoff point	Sensitivity (%)	Specificity (%)	AUC (95% CI)
Baseline CA, years	8.83	74.5	57.5	0.647 (0.560-0.735)
Baseline BA, years	7.00	74.5	55.7	0.639 (0.551-0.728)
Pretreatment HV, cm/year	3.41	53.9	82.5	0.677 (0.499-0.855)
Peak GH level, ng/mL	9.18	83.0	52.3	0.652 (0.571-0.734)
Baseline IGF-I SDS	-0.78	78.6	51.4	0.615 (0.524-0.706)
Baseline IGFBP-3 SDS	0.16	78.4	44.2	0.632 (0.532-0.732)

AUC, area under the receiver operating characteristic curve; BA, bone age; CA, chronological age; CI, confidence interval; GH, growth hormone; HV, height velocity; IGF-I, insulin-like growth factor-I; IGFBP-3, insulin-like growth factor binding protein-3; SDS, standard deviation score.

in order to reduce the potential overlap between ISS and partial GHD in this study.

Children with ISS are a heterogeneous population that includes different degrees of GH secretion and responsiveness. There exists an overlap between ISS and partial GH insensitivity (Pedicelli et al. 2009). As the spectrum of GH insensitivity varies, some mild types may be misrecognized as ISS (Park and Cohen 2005). The GH response in children with ISS with a GH receptor defect is usually lower than that in those with an abnormal pattern of GH secretion (Rogol et al. 2003).

Children with partial GH insensitivity have short stature with a normal or slightly increased GH level and decreased IGF-I level, and thus require a supraphysiologic GH dose (Rosenbloom 2000). In the present study, the older poor responder group had lower pretreatment HV, initial IGF-I SDS, and low but normal peak GH levels. The older poor responder group was treated with more than twice the mean GH dose (0.55 ± 0.15 mg/kg/week) than the other groups. Although they received the highest supraphysiologic GH dose, they showed the least improvement in IGF-I SDS. Regarding the aforementioned phenotype, the older poor responder group was suspected of having partial GH insensitivity.

We assessed the cutoff points of baseline characteristics to predict the GH dose and GH response before the initiation of GH treatment. The statistically optimal cutoff point for pretreatment HV was 3.41 cm/year, with a sensitivity of 53.9% and a specificity of 82.5%. The statistically optimal cutoff peak GH level was 9.18 ng/mL, with a sensitivity of 83.0% and a specificity of 52.2%. For children with pretreatment HV below 4 cm/year but who showed a low normal peak GH level of 7-10 ng/mL, we may expect a poor GH response and consider a larger than usual GH dose.

There are some limitations to the present study, including possible selection bias. While two GH stimulation tests are required to exclude GHD, the tests were not conducted among some children with ISS in this study. We had no information on compliance, which is one of the most important parameters. Further longitudinal studies will be required to ascertain whether 2-year or 3-year follow-up data coincide with 1-year data. Nevertheless, this multicenter study used a "person-centered" approach, unlike the traditional "variable-centered" approach, to enable personalized treatment optimization.

In conclusion, the cluster analysis revealed three distinct ISS phenotypes. This study offers an interesting multidimensional approach to the identification of ISS phenotypes.

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Conflict of Interest

The authors declare no conflict of interest.

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