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BRIEF REPORT

Association between pituitary height and growth response to recombinant human growth hormone in prepubertal children with growth hormone deficiency

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Introduction

Growth hormone deficiency (GHD), an important cause of short stature in pediatrics, can lead to a series of adverse consequences impacting normal growth and life quality [1], although its prevalence is relatively low (about 1 in 4000 children worldwide) [2]. The occurrence of GHD is intimately linked with insufficient secretion of growth hormone (GH) from pituitary [3].

Differently from GHD, idiopathic short stature (ISS) refers to short stature without identified causes [4]. ISS is the diagnostic group that remains after excluding known conditions in children with short stature [5], and GH stimulation test is essential to discriminate GHD from ISS.

Diagnosis of GHD is complex, depending on integrated assessment of clinical manifestation, laboratory examination, as well as radiologyical evaluation. It is required to measure the body height, estimate the bone age, test the GH axis, etc. And magnetic resonance imaging (MRI) for neuroradiology evaluation of pituitary is also recommended [6].

Currently, it is widely reported that pituitary characteristics at MRI are associated with clinical diagnosis. Compared with controls or children with ISS, GHD children tend to have a smaller pituitary [7], and the pituitary is more likely to present with concave superior contour [8], especially for those with severe GHD [9]. Diagnosis model of GHD based on MRI characteristics has been established recently [10], highlighting the value of pituitary evaluation at MRI.

However, the diagnostic value of pituitary MRI still remains questioned, due to uncommon significant abnormalities of pituitary at MRI in GHD children [11]. Some researchers have investigated the association between pituitary characteristics at MRI and treatment response to recombinant human growth hormone (rhGH) replacement therapy. For example, GHD children with abnormalities at pituitary MRI (such as pituitary hypoplasia, empty sella and arachnoid cyst) tend to achieve better height gain after rhGH treatment [12]. Yet, relevant investigations are still scant.

To fill this gap in knowledge and yield more information for future studies, we undertook a retrospective cohort study, targeting prepubertal children with GHD to investigate the association between pituitary height at MRI and growth response to rhGH treatment. Furthermore, the importance of pituitary height at MRI was visualized for practical purposes.

Methods

Study design and subjects

A retrospective cohort study was conducted during the period from November 2015 to April 2021 in International Medical Services, China-Japan Friendship Hospital, Beijing, China. The conduct of this study was reviewed

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and approved by the Ethics Committee of China-Japan Friendship Hospital. The code of ethical committee was 2018-94-K68.

A total of 145 prepubertal children with short stature were enrolled in this study, involving 72 children with GHD and 73 children with ISS.

Inclusion criteria

Inclusion criteria are as follows: (1) short stature: with height z-scores < −2standard deviation (SD) based on the age- and sex-specific measures under the China criteria (2009) [13]; (2) prepubertal status: breast development Tanner stage 1 in girls and testicular volume <4 ml in boys; (3) children with GHD: peak GH response to clonidine and arginine <10 ng/ml in GH stimulation test [14]; chemiluminescence immune assay (Access Ultrasensitive hGH, Beckman Coulter, Inc. America) was used to examine the GH; (4) children with ISS: peak GH response to clonidine and arginine ≥10 ng/ml in GH stimulation test; (5) without skeletal or chromosomal abnormalities or evidence of tumor, intracranial injury or surgery.

Baseline characteristics and follow-ups

Baseline evaluations were conducted before rhGH therapy, data on clinical characteristics, laboratory biomarkers, and neuroradiological indexes of pituitary MRI were recorded. Body height and weight were measured by well-trained professionals to the nearest 0.1 cm and 0.1 kg, respectively. Body mass index (BMI) was calculated according to body weight and height. Peak GH response to clonidine and arginine and insulin-like growth factor 1 (IGF-1) ware tested. Bone age was assessed using the standards of TW3 [15]. Pituitary MRI was performed on 3.0-Tesla scanners (Philips Medical Systerm, GE Discovery MR750). Midline position of T1-weighted sagittal images with a slice thickness of 3 mm were collected and analyzed by specialized radiologists. All children were followed up until April 2021, and their information of rhGH therapy and height gain were recorded.

Statistical analyses

Statistical analyses were done using the STATA software (version 14.0, Stata Corp, TX) and two-sided P value less than 0.05 was considered statistically significant. Continuous variables were assessed for normality by use of the skewness and kurtosis test, and they were presented as mean (standard deviation) and median (interquartile range) for normally-distributed and skewed variables, respectively.

Multiple linear regression analyses were done to identify the contribution on height gain of all possible characteristics after adjusting for age and sex. Standardized and unstandardized coefficients, as well as 95% confidence interval (CI) and P value were recorded. To explain and visualize the importance of significant factors, the SHapley Additive exPlanations (SHAP) value was used via Anaconda3 (with Python version 3.6.5). SHAP values are calculated by identifying the difference between the predicted values with and without the addition of each characteristic for all combinations, and taking the average. Thus, it can reveal which characteristic have a significant influence on the contribution and visualize the results.

Results

Baseline characteristics and characteristics at the end of follow-ups

The baseline characteristics of 145 children in this study are shown in Table 1. There is no difference in body height (SD) between two groups ($P > 0.05$). Children with GHD tend to have shorter pituitary height than that of ISS, and their pituitary shape is more likely to be concave ($P < 0.05$). After median 1.5 years of follow-ups, the median height gain for children with GHD and ISS are 0.58 and 0.48 SD per year, respectively.

Identification of contributing characteristics on the height gain (SD/year) in children with GHD

Table 1 also displays the results of multivariable linear regression analyses. After adjusting for age and sex, six characteristics are significantly associated with the height gain (SD/year), including age at therapy onset, bone age at therapy onset, body height at therapy onset, BMI at therapy onset and pituitary height. Only dose of rhGH is positively associated with the height gain, while other five characteristics are negatively associated with the height gain (All $P < 0.05$).

The importance of contributing characteristics on the height gain (SD/year) in children with GHD

Figure 1 illustrates the importance of contributing characteristics using the SHAP value. The averages of absolute SHAP values indicated that pituitary height is the most important characteristic.

Discussion

In this retrospective cohort study targeting prepubertal children with GHD, we aim to investigate the association

Table 1 Characteristics of prepubertal children with GHD (compared with ISS) and multivariable regression analyses of contributing characteristics on height gain (SD/year) in children with GHD

	Children with GHD ($n = 72$)	Children with ISS ($n = 73$)	P*
Baseline characteristics			
Age (years)	7.08 (4.85, 10.15)	5.65 (4.32, 8.08)	0.027
Male (%)	39 (56.52)	30 (43.48)	0.115
Bone age (years)	6 (4, 9.5)	5 (4, 7.25)	0.147
Body height (cm)	116.95 (100.6, 131.4)	102.5 (99, 111.1)	0.028
Body height (SD)	−2.17 (−2.52, −1.6)	−2.24 (−2.53, −1.82)	0.426
Body weight (kg)	20.5 (15, 28)	17.5 (15, 22.5)	0.323
BMI (kg/m^2)	15.74 (14.88, 17.22)	15.81 (15.27, 16.85)	0.942
Peak GH (μg/L)	6.3 (4.21, 7.67)	12.61 (11.1, 15.24)	<0.001
IGF-1 (ng/ml)	129.07 (90.21, 177.91)	141.4 (85.64, 220.28)	0.540
Pituitary characteristics at MRI			
Pituitary height (mm)	2.72 (2.21, 3.34)	3.47 (2.93, 3.87)	<0.001
Pituitary shape (compare with the tuberculum sella level)			
Concave	44 (61.1%)	25 (34.2%)	
Flat	25 (34.7%)	43 (58.9%)	0.005
Convex	3 (4.2%)	5 (6.8%)	
Information of rhGH therapy and characteristics at the end of follow-ups			
Dose of rhGH (IU/kg)	0.15 (0.13, 0.19)	0.16 (0.16, 0.17)	0.149
Age (years)	8.72 (6.29, 11.69)	6.82 (5.72, 9.95)	<0.001
Body height (cm)	140.5 (123, 154)	121 (114, 127)	<0.001
Body height (SD)	−0.59 (−1.18, −0.13)	−1.45 (−1.85, −0.88)	<0.001
Height gain (SD)	1.47 (0.92, 1.93)	1.08 (0.94, 1.31)	0.063
Height gain (SD/year)	0.58 (0.39, 0.74)	0.48 (0.33, 0.66)	0.088
Multivariable linear regression analyses of contributing characteristics on height gain (SD/year) in children with GHD			
Characteristics	unstandardized; standardized coef.	95% CI	P+
Age at therapy onset (years)	−0.026; −0.311	−0.039 to −0.013	<0.001
Bone age at therapy onset (years)	−0.024; −0.293	−0.039 to −0.01	<0.001
Body height at therapy onset (SD)	−0.1; −0.324	−0.162 to −0.038	0.002
BMI at therapy onset (kg/m^2)	−0.1; −0.453	−0.131 to −0.068	<0.001
Pituitary height (mm)	−0.163; −0.574	−0.202 to −0.125	<0.001
Dose of rhGH (IU/kg)	3.294; 0.308	1.656 to 4.932	<0.001

GHD growth hormone deficiency, *ISS* idiopathic short stature, *SD* standard deviation, *BMI* body mass index, *GH* growth hormone, *IGF-1* insulin-like growth factor 1, *MRI* magnetic resonance imaging, *rhGH* recombinant human growth hormone, *Coef.* coefficient, *95% CI* 95% confidence interval, Categorical variables were presented as count (percentage).

*P value was calculated by the t-test, Kruskal-Wallis rank-sum test or the $\chi 2$ test, where appropriate. +P values were calculated after adjusting for age and sex.

between pituitary height at MRI and growth response to rhGH treatment. The key findings of this study is that pituitary height at MRI is inversely associated with the height gain during the GH inversely in prepubertal children with GHD. And pituitary height is the most important characteristic affecting growth response to rhGH treatment.

Our findings regarding pituitary characteristics at MRI are consistent with previous investigations, that pituitary is significantly smaller in children with GHD than that of ISS [8]. The underlying mechanisms are still unclear. A possible reason might be that shorter pituitary height is related with fewer hormone-secreting cells [16]. Considering uncommon significant abnormalities in GHD children's pituitary MRI [17], quantitative measurement, like pituitary height, may be more useful than qualitative estimation in clinical practice.

Moreover, the results of our study provide more evidence on the association between pituitary characteristics at MRI and growth response to rhGH treatment. Previous explorations have found that GHD children with

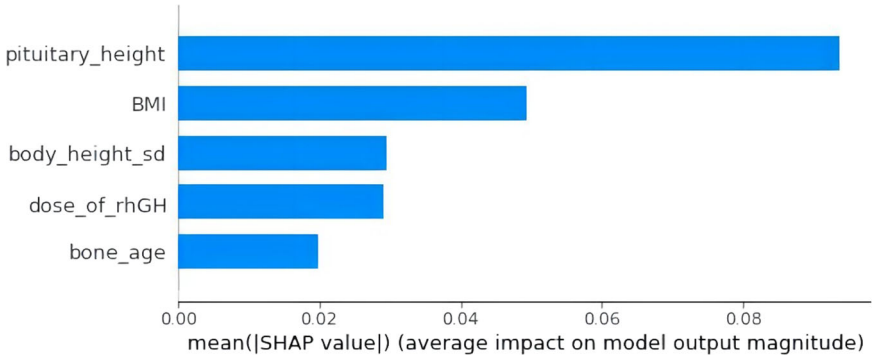

Fig. 1 The importance of contributing characteristics on height gain (SD/year) in children with GHD using the SHAP value. SHAP SHapley Additive exPlanation, BMI body mass index. Characteristic importance of linear regression by summing of SHAP value magnitudes over all children with GHD. The characteristics were listed in decreasing order by their importance. SHAP bar plot presented the mean absolute value of each characteristic

abnormalities of the pituitary at MRI tend to achieve better height gain and reach greater final height, yet GHD children with normal MRI showed no better growth respond to rhGH therapy [18]. And the abnormalities are important to predict the growth response [19]. In our study, we also find that GHD children with smaller pituitary tend to achieve more height gain per year during rhGH therapy and pituitary height can help to predict treatment response. What's more, the SHAP values indicate that pituitary height is the most important characteristic affecting height gain. Given that dose of rhGH is positively associated with height gain, children with higher pituitary height at MRI can adopt relatively higher dose of rhGH in initial therapy to achieve better height gain.

Limitations

Some limitations should be acknowledged when interpreting our findings. Firstly, all children involved in this study were diagnosed as idiopathic GHD and were all in prepubertal status, so extrapolation of our findings to the other types of GHD or pubertal children should be done with caution. Secondly, the sample size of our study was relatively small, and future long-term follow-ups with large sample size are necessary. Thirdly, the cut-off for peak GH in GH stimulation test still remains controversial in discriminating GHD from ISS. In China, it is widely accepted 10 ng/ml as the cut-off in clinical practice, which was also used in our study. Compared with 7 ng/ml, even 5 ng/ml adopted in some study [20], it may cause some overlap between GHD and ISS. Fourthly, there were age and sex differences in pituitary height of children (shown in the supplementary materials) and pituitary height can be affected by many factors. Without criteria of pituitary height SD for Chinese children, we only adjusted age and sex in our analyses. Further studies for normal children with large sample size are needed to establish the criteria and modify our findings.

Conclusions

Taken together, our findings indicate that GHD children with smaller pituitary tend to achieve more height gain per year during rhGH therapy. And children with higher pituitary height can adopt relatively higher dose of rhGH in initial therapy to achieve better height gain. Further validations are still necessary to clarify the underlying mechanisms of growth response to rhGH treatment.

Data availability

Data involved in this study are available upon reasonable request.

Author contributions Z.Z. planned and designed the study and directed its implementation. Y.Y., and X.Z. contributed to data acquisition and did the data preparation and quality control. Y.Y., and W.N. conducted statistical analyses. Y.Y., W.N., and Z.Z. wrote the manuscript. All authors read and approved the final manuscript prior to submission.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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