Original article

https://doi.org/10.6065/apem.2448070.035
Ann Pediatr Endocrinol Metab 2024;29:365-370

Annals of Pediatric Endocrinology & Metabolism
apem

Pituitary abnormalities in patients with pediatric growth hormone deficiency in a single tertiary center

Hyeon Jun Jung[1], Jeong Rye Kim[2], Jeesuk Yu[1]

[1]Department of Pediatrics, Dankook University Hospital, Dankook University College of Medicine, Cheonan, Korea
[2]Department of Radiology, Dankook University Hospital, Dankook University College of Medicine, Cheonan, Korea

Purpose: There is controversy as to whether brain magnetic resonance imaging (MRI) should be performed on all children with growth hormone deficiency (GHD) including those judged to have mild GHD. This study was aimed to determine the frequency of pituitary or intracranial abnormalities in pediatric GHD and to identify risk factors that may predict pituitary or intracranial abnormalities.
Methods: A total of 95 pediatric GHD patients were included. Their medical records and brain magnetic resonance (MR) images were reviewed retrospectively.
Results: Abnormal pathogenic MR images were found in 14 patients (14.7%), including 10 (10.5%) with pituitary hypoplasia and 4 (4.2%) with pituitary stalk interruption syndrome. Serum levels of insulin-like growth factor-I (IGF-I), IGF-I standard deviation score (SDS), insulin-like growth factor binding protein 3 (IGFBP3), and growth hormone (GH) peak level of GH stimulation test were statistically significantly lower in the group with abnormal brain MRI. The frequency of abnormal MRI was statistically significantly higher in the complete GHD group. IGF-1 SDS showed the highest area under the curve which can predict the presence of brain abnormality with a sensitivity of 85% and a specificity of 71.4%, if IGF-1 SDS was less than -1.365. IGF-1, IGFBP3, and GH peak levels also showed good sensitivity of over 80% for predicting brain abnormalities with cutoff values of 70.285 ng/mL, 1,604 ng/mL, and 4.205 ng/mL, respectively.
Conclusion: The sensitivity and specificity of each cutoff value of IGF-1, IGF-1 SDS, IGFBP3, and GH peak levels were good and statistically significant in predicting brain MRI abnormalities. However, it was insufficient to predict all brain abnormalities with these variables. Therefore, we would like to recommend performing a brain MRI if a child is diagnosed with GHD.

Keywords: Growth hormone deficiency, Magnetic resonance imaging, Insulin-like growth factor-I, Standard deviation score

Highlights

- In this study, the incidence of abnormal pathogenic MR images in children with GHD was 14.7%, of which 10.5% had pituitary hypoplasia and 4.2% had pituitary stalk interruption syndrome.
- IGF- 1 SDS had the highest area under the curve predicting brain abnormalities with a cutoff value of -1.365, and IGF-1, IGFBP3, and GH peak levels also showed good sensitivities of over 80% in predicting brain abnormalities with cutoff values of 70.285 ng/mL, 1,604 ng/mL, and 4.205 ng/mL, respectively.
- Although the cutoff values of IGF-1, IGF- 1 SDS, IGFBP3, and GH peak levels were statistically significant in predicting brain MRI abnormalities, these variables alone were not sufficient to predict all brain abnormalities, so we would recommend brain MRI when children are diagnosed with GHD.

Received: 29 March 2024
Revised: 23 August 2024
Accepted: 30 August 2024

Address for correspondence:
Jeesuk Yu
Department of Pediatrics, Dankook University Hospital, Dankook University College of Medicine, 119 Dandae-ro, Dongnam-gu, Cheonan 31116, Korea
Email: dryujs@dankook.ac.kr
https://orcid.org/0000-0003-0020-2000

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

ISSN: 2287-1012(Print)
ISSN: 2287-1292(Online)

©2024 Annals of Pediatric Endocrinology & Metabolism

Introduction

Short stature is generally defined as height less than 2 standard deviations below the age- and sex-specific average or less than the 3rd percentile.[1] There are various causes of short stature, one of the most common being growth hormone deficiency (GHD), with a reported prevalence of 1: 3,480 to 1: 8,646 in the general population.[2-4] The annual incidence of GHD was previously reported as 1 in 30,000 births, with approximately half of those patients having idiopathic GHD.[5]

Because growth hormone (GH) is secreted in a pulsatile pattern, it is necessary to perform a growth hormone stimulation test (GHST) in addition to clinical and biochemical indicators to diagnose GHD.[6-9] Although most GHD is classified as idiopathic, it is important to perform brain imaging to detect pituitary abnormalities or intracranial tumors before starting GH treatment. Brain magnetic resonance (MR) imaging plays an important role in the evaluation of pituitary gland abnormalities, detecting pituitary hypoplasia, aplasia, pituitary stalk interruption syndrome (PSIS), and intracranial tumors such as craniopharyngioma or germinoma.[10,11]

Sellar or brain MR imaging is recommended for all children with GHD.[12] However, MR imaging requires sedation and considerable expense. There is controversy regarding brain MR imaging on all GHD children, including those judged to have mild disease based on height standard deviation scores and GHST results. Hwang et al.[13] found that more than half of children with nonacquired GHD had abnormal MR images. Alba et al.[12] recommended brain imaging in children with GHD because the severity of GHD does not predict abnormalities on brain MR images. Meanwhile, Mamilly et al.[14] reported that the incidence of abnormal brain MR images was significantly higher in children with a GH peak level less than 5 mg/mL in the GHST and in those with multiple pituitary hormone deficiency.

The purpose of this present study was to determine the frequency of pituitary or intracranial abnormalities in pediatric GHD patients and to identify predictive risk factors of such abnormalities.

Materials and methods

This retrospective study was based on a review of medical records of pediatric GHD at a single tertiary center. The patients were diagnosed and treated at the Pediatric Endocrinology Clinic of Dankook University Hospital between March 2008 and April 2022. Patients whose height was less than the 3rd percentile at the time of GHST and who underwent sellar or brain MR imaging after being diagnosed with GHD were included in the study. Included pediatric GHD patients showed GH peak levels less than 10 ng/mL in at least 2 GHSTs. During recent periods at our institution, only 2 GHSTs were performed routinely, with GHD diagnosed when peak GH values were less than 10 ng/mL in both tests. In the past, GHD was diagnosed when GH peak value was less than 10 ng/mL in 2 or more of 3 GHSTs.

GHST was performed using medications available at the time, including insulin, L-dopa, clonidine, L-arginine, and glucagon. In tests using insulin, 0.1 unit/kg was injected intravenously, and GH was measured at 0, 15, 30, 45, 60, 90, and 120 minutes. In tests using clonidine or L-dopa, GH was measured every 30 minutes for 2 hours. Clonidine was administered orally at 0.15 mg/m^2. L-dopa was administered orally at 125 mg for patients weighing less than 15 kg, 250 mg for patients weighing between 15 kg and 35 kg, and 500 mg for patients weighing more than 35 kg. In tests using L-arginine, 0.5 g/kg (maximum dose 30 g) was diluted in 0.9% saline solution and infused intravenously for 30 minutes. GH was measured at 0, 15, 30, 60, 90, and 120 minutes. In tests using glucagon, 0.03 mg/kg (maximum dose 1 mg) was injected intramuscularly, and GH was measured at 30-minute intervals for 3 hours. Serum GH levels were measured by electrochemiluminescence immunoassay (ECLIA).

Brain MR images were classified as normal, incidental, or abnormal pathogenic findings according to the following criteria.[14-16] Incidental findings were lesions that were unlikely to affect GH secretion, such as pineal cysts, Rathke's cyst, and nonspecific white matter changes. Abnormal pathogenic findings included ectopic posterior pituitary gland, small or interrupted pituitary stalk, hypoplastic pituitary gland, and hypothalamic-pituitary tumors such as craniopharyngioma or germinoma. In this study, cases that showed normal or incidental findings on brain MRI were classified as the normal MRI group, and those that showed abnormal pathogenic findings on brain MRI were classified as the abnormal MRI group. Pituitary size measurements and their interpretations followed the criteria suggested by Sari et al.[17]

Age, sex, height, weight, serum levels of insulin-like growth factor-I (IGF-I) and insulin-like growth factor binding protein 3 (IGFBP3) and each standard deviation score (SDS), bone age, and GH peak levels during GHST were reviewed. Height SDS and weight SDS were calculated based on the latest version of the Korean National Growth Charts released in 2017.[18] Serum levels of IGF-1 and IGFBP3 were measured immediately before GHST, and their standard deviation scores were calculated based on the paper by Hyun et al.[19] Both IGF-1 and IGFBP3 levels were measured by ECLIA.

In addition, subjects in which all GH peak levels did not exceed 3 ng/mL during GHST were defined as the complete GHD group, and the frequency of MRI abnormalities was compared with the group in which the GH peak level was 3 ng/mL or more at least once. We also compared the frequency of MRI abnormalities in the group with no GH peaks exceeding 5 or 7 ng/mL and those with one or more GH peaks exceeding 5 or 7 ng/mL. In addition to setting age as a continuous variable, we divided the subjects into specific age groups to detect potential correlations between age and MRI abnormalities. Bone age was identified by 1 pediatric radiologist and 1 pediatric endocrinologist and was confirmed by the pediatric endocrinologist.

1. Ethical statement

This study was approved by the Institutional Review Board of Dankook University Hospital (approval number: DKUH 2022-10-045). The requirement for informed consent was waived due to the retrospective nature of the study.

2. Statistical analysis

Statistical analyses were conducted using SPSS Statistics version 28 (IBM Corp., Armonk, NY, USA). Chi-square test was used to analyze whether there were differences in the frequency of MRI abnormalities between patients with partial GHD and patients with complete GHD according to each criterion. The frequencies of abnormal MRI findings according to sex, premature birth, small for gestational age (SGA) at birth, and age group were analyzed using the chi-square test and Fisher's exact test. Preterm was defined as gestational age less than 37 weeks. SGA was defined as birth weight below the 10th percentile for gestational age. Independent samples T-tests were performed to compare age, height, height standard deviation score (SDS), weight, weight SDS, serum levels of IGF-1, IGF-1 SDS, IGFBP3, and IGFBP3 SDS, and GH peak levels between the abnormal MRI group and the normal MRI group.

Table 1. Clinical characteristics of study subjects (N=95)

Characteristic	Value
Sex, male:female	56:39
GA, AGA:SGA	73:21[†]
Birth, term:preterm	76:16[‡]
Age (yr)	7.92±3.27
Bone age (yr)	6.56±3.23
Height SDS	-2.64±0.63
Weight SDS	-1.75±0.95
IGF-I (ng/mL)	141.57±78.49
IGF-I SDS	-0.87±0.7
IGFBP3 (ng/mL)	2,146.17±619.63
IGFBP3 SDS	-0.94±1.04
GH Peak level (ng/mL)	6.38±2.45
IGHD:MPHD	94:1
Brain MRI, normal:abnormal	81:14
GHD, partial:complete GHD	
With cutoff value of 3 ng/mL	89: 6
With cutoff value of 5 ng/mL	81:14
With cutoff value of 7 ng/mL	67: 28

Values are presented as number or mean±standard deviation.
Preterm was defined as gestational age less than 37 weeks.
GA, gestational age; AGA, average for GA; SGA, small for GA; SDS, standard deviation score; IGF-I, insulin-like growth factor-I; IGFBP3, insulin-like growth factor binding protein 3; IGHD, isolated growth hormone deficiency; MPHD, multiple pituitary hormone deficiency; MRI, magnetic resonance imaging; GHD, growth hormone deficiency.
[†]One subject was discarded from statistics because birth weight could not be confirmed. [‡]Three subjects were discarded from statistics because gestational ages could not be confirmed.

Results

A total of 95 pediatric GHD patients were included in the study. Clinical characteristics are described in Table 1. There were 56 males (59%). The average chronologic age at the time of GHST was 7.92 years and the average bone age was 6.56 years. The average GH peak level was 6.38 ng/mL. We attempted to include all pediatric GHD patients who met the inclusion criteria, regardless of isolated GHD or multiple pituitary hormone deficiencies (MPHD), but only one patient (1.1%) had MPHD (Table 1). Abnormal pathogenic MR images were found in 14 patients (14.7%), including 10 patients (10.5%) with pituitary hypoplasia and 4 patients (4.2%) with pituitary stalk interruption syndrome (PSIS). In the normal brain MRI group (n=81; 85.3%), there were normal brain structures (n=66), Ranthke's cleft cyst (n=5), arachnoid cyst (n=5), choroid fissure cyst (n=2), pineal gland cyst (n=1), hippocampal sulcus remnant cyst (n =1), and deep concave contour of sellar turcica (n=1). Regardless of brain abnormalities, no patient showed any specific neurologic signs or symptoms.

Based on the GH peak level shown during GHST, patients were divided into partial GHD and complete GHD groups and compared to determine a difference in the frequency of MRI abnormalities. At this time, the GH peak level, which is the standard value for complete GHD, was defined as 3, 5, or 7 ng/mL (Tables 1 and 2). Among 81 patients with normal MRI, only 2 (2.5%) had GH peak values less than 3 ng/mL, and 20 patients (24.7%) showed GH peak values less than 7 ng/mL. Among 14 patients with abnormal MRI, 4 (28.6%) had GH peak values less than 3 ng/mL, and 8 patients (57.1%) showed GH peak values less than 7 ng/mL. Regardless of the criteria thresholds for complete GHD, the frequency of abnormal MRI was significantly higher in the complete GHD group (Table 2).

We compared age, height, height SDS, weight, weight SDS, IGF-I, IGF-I SDS, insulin-like growth factor binding protein 3 (IGFBP3), and IGFBP3 SDS, bone age, and peak GH level between the normal and abnormal MRI groups to identify risk factors that predict abnormal brain MR images. Serum levels of IGF-I, IGF-I SDS, GH peak, and IGFBP3 were significantly lower in the abnormal brain MRI group. Factors of age, sex, bone age, height SDS, weight SDS, and IGFBP3 SDS did not differ between groups (Table 2). When analyzing only children with a history of full-term birth or average birth weight for gestational age (AGA), serum levels of IGF-I, IGF-I SDS, GH peak, and IGFBP3 SDS in children with a history of full-term birth and serum levels of IGF-I and IGF-I SDS, GH peaks of GHST, IGFBP3, and IGFBP3 SDS in children with a history of AGA were significantly lower in the abnormal brain MRI group (Supplementary Tables 1-4).

Receiver operating characteristic analysis was used to determine the optimal cutoff values for factors predicting the presence of abnormal MR images. IGF-I SDS showed the highest area under the curve (AUC) value of 0.838, followed

by IGF-1 (0.818), GH peak level (0.722), and IGFBP3 (0.646). These results imply that IGF-I and IGF-I SDS are the best factors for predicting abnormal brain MR images. In predicting abnormal brain MR images in pediatric GHD, the IGF-I value was 70.285 and the IGF-I SDS was -1.365, showing a sensitivity greater than 85% and a specificity greater than 64%, respectively (Table 3, Fig. 1).

Discussion

In this study, the incidence of pituitary abnormalities was 14 (14.7%) of 95 pediatric GHD patients, including pituitary hypoplasia in 10 (10.5%) and PSIS in 4 patients (4.2%). Alba et al.[12] reported MRI abnormalities in 19.2% of patients with mild GHD and 24.8% of patients with severe GHD. In addition, the incidence of severe MRI abnormalities in their study was 39 of 386 pediatric GHD patients (10.1%), similar to our findings (14 of 95, 14.7%).

Because GH is secreted in a pulsatile pattern, secretion status should be assessed by the provocation test. However, diagnosis of GHD through GHST using pharmacological agents has limitations for reflecting the physiological state of GH secretion, methods for measurement of GH levels or GHST methods vary among centers, and there are also differences in GHD diagnostic criteria among centers.[20] GH secretion may be influenced by several factors, including nutrition, sex, age, and puberty.[21] In addition, GH provocation tests performed to confirm the diagnosis of GHD have disadvantages of being time-consuming, expensive, and inconvenient to patients.

Several studies have investigated the role of IGF-I in the diagnosis of GHD.[22] Since IGF-I was first identified by Salmon and Daughaday in 1957, much research has been conducted on this small peptide which has a molecular weight of 7,649 Da and consists of 70 amino acids.[23,24] We now know that IGF-I is a mediator of the anabolic and mitogenic activities of GH, and that it has a growth stimulating effect independent of GH.[25,26] Several clinical and laboratory factors have been proposed for diagnosis of GHD. Currently, the most commonly accepted biomarkers are serum IGF-I and IGFBP3 levels.[9,27-29] Past studies have shown that IGF-I levels below -2SDS have a

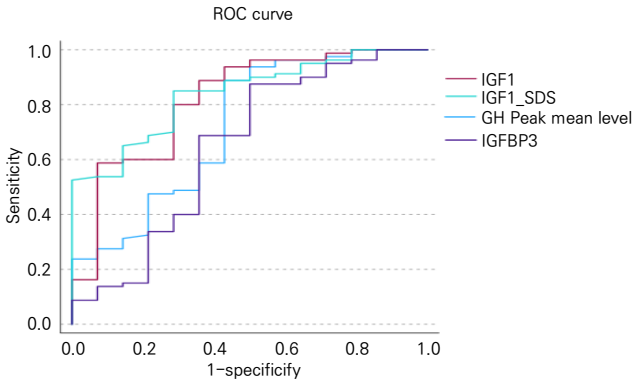

Fig. 1. Receiver operating characteristic (ROC) curves of 4 statistically significant factors for predicting abnormal brain magnetic resonance (MR) images. IGF-I SDS and IGF-1 were identified as the best predictors of abnormal brain MR images which showed an area under the curve of 0.838 and 0.818, respectively. IGF-I, insulin-like growth factor-I; SDS, standard deviation score; IGFBP3, insulin-like growth factor binding protein 3.

Table 2. Comparison of demographic and laboratory data between normal and abnormal magnetic resonance imaging groups

Variable	Normal MRI group	Abnormal MRI group	*P*-value
No. of subjects	81 (85.3)	14 (14.7)	
Sex, male:female	46:35	10:4	0.385
GA, AGA:SGA	62:18[†]	11:3	1.000
Birth, term:preterm	64:14[‡]	12:2	0.865
Age (yr)	8.03±3.28	7.27±3.28	0.421
Bone age (yr)	6.66±3.24	5.96±3.19	0.467
Height SDS	-2.58±0.5	-3.03±1.06	0.137
Weight SDS	-1.81±0.93	-1.39±1.04	0.133
IGF-I (ng/mL)	153.17±75.49	74.46±61.5	<0.001
IGF-I SDS	-0.75±0.63	-1.6±0.68	<0.001
IGFBP3 (ng/mL)	2,199.86±577.09	1,839.36±776.96	0.044
IGFBP3 SDS	-0.86±1.00	-1.42±1.19	0.063
GH peak level (ng/mL)	6.73±2.19	4.36±2.97	0.012
Complete GHD			
With cutoff value of 3 ng/mL	2 (2.5)	4 (28.6)	0.040
With cutoff value of 5 ng/mL	7 (8.6)	7 (50.0)	<0.001
With cutoff value of 7 ng/mL	20 (24.7)	8 (57.1)	0.014

Values are presented as number (%) or mean±standard deviation.
Preterm was defined as gestational age less than 37 weeks.
GA, gestational age; AGA, average for GA; SGA, small for GA; SDS, standard deviation score; IGF-I, insulin-like growth factor-I; IGFBP3, insulin-like growth factor binding protein 3; GH, growth hormone; GHD, GH deficiency.
[†]One subject was discarded from statistics because birth weight could not be confirmed. [‡]Three subjects were discarded from statistics because mom's gestational age could not be confirmed.

Table 3. Sensitivity, specificity, and AUC for each cutoff value of IGF-I, IGF-I SDS, GH peak level, and IGFBP3 for predicting abnormal brain MR images

Variable	Cutoff value	Sensitivity (%)	Specificity (%)	AUC
IGF-I (ng/mL)	70.285	88.8	64.3	0.818
IGF-I SDS	-1.365	85	71.4	0.838
GH peak level (ng/mL)	4.205	88.8	57.1	0.722
IGFBP3 (ng/mL)	1,604	87.5	50	0.646

AUC, area under the curve; IGF-I, insulin-like growth factor-I; SDS, standard deviation score; GH, growth hormone; IGFBP3, insulin-like growth factor binding protein 3.
IGF-1 SDS and IGF-1 were identified as the best predictors of abnormal brain magnetic resonance (MR) images with the cutoff value of -1.365 and 70.285 ng/mL, respectively.

good specificity of about 90% and a sensitivity of about 70%, indicating a high predictive value for GHD. However, levels outside this range cannot rule out GHD.[20]

There is controversy as to whether brain MR imaging should be performed in children judged to have mild GHD based on height SDS and GHST results. Alba et al.[12] suggested that the severity of GHD does not predict the presence of intracranial or pituitary abnormalities. Mamilly et al.[14] reported that the incidence of pituitary abnormalities was significantly higher in pediatric patients with GH peak levels less than 5 ng/mL on GHST and with multiple pituitary hormone deficiency. Our findings showed that, regardless of the set criterion values for complete GHD as less than 3 or 5 or 7 ng/mL, the frequency of abnormal MR images was significantly higher in the complete GHD group (4 of 6, 67%, $P<0.05$; 7 of 14, 50%, $P<0.001$; 8 of 28, 29%, $P<0.05$, respectively) (Table 2). In addition, patients with pituitary abnormalities showed significantly lower IGF-I, IGF-I SDS, and IGFBP3 levels ($P<0.05$). Among the predictive factors, IGF-I SDS showed the highest AUC and can predict the presence of brain abnormality with a sensitivity of 85% and a specificity of 71.4%, if IGF-I SDS was -1.365 (Fig. 1). In addition to IGF-I SDS, serum levels of IGF-I, GH peak level, and IGFBP3 showed good sensitivity greater than 80% for predicting brain abnormalities with cutoff values of 70.285 ng/mL, 4.205 ng/mL, and 1,604 ng/mL, respectively (Table 3). However, even if the sensitivity and specificity of each of the above variables are positively significant, it was not possible to detect all brain abnormalities using these variables. Therefore, if a child is diagnosed with GHD, we recommend performing a brain MRI.

This study has several limitations. Because this study was based at a single tertiary center and included only patients with short stature defined as that less than the 3rd percentile, the sample size was not large and did not include patients with brain tumor, a common acquired cause of GHD. On the other hand, this study was consistent as it drew only from patients treated at a single tertiary center. This ensures that all patients were evaluated using similar measurements and diagnostic criteria, improving study consistency.

In summary, the incidence of pituitary abnormalities in pediatric GHD was 14.7% in this study. IGF-I SDS and IGF-I were the best predictors of abnormal brain MR images, with cutoff values of -1.365 and 70.285 ng/mL, respectively. However, neither IGF-I SDS nor IGF-I were sufficient to replace brain MRI in predicting brain abnormalities.

Notes

Supplementary Materials: Supplementary Tables 1-4 can be found via https://doi.org/10.6065/apem.2448070.035.
Conflicts of interest: No potential conflict of interest relevant to this article was reported.
Funding: This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.
Data availability: The data that support the findings of this study can be provided by the corresponding author upon reasonable request.
Author contribution: Conceptualization: JY; Data curation: HJJ; Formal analysis: HJJ, JRK; Methodology: HJJ, JRK, JY; Writing - original draft: HJJ; Writing - review & editing: JY
ORCID
Hyeon Jun Jung: 0000-0003-2794-2228
Jeong Rye Kim: 0000-0001-6762-4174
Jeesuk Yu: 0000-0003-0020-2000

References

1. Ranke MB. Towards a consensus on the definition of idiopathic short stature. Horm Res 1996;45 Suppl 2:64-6.
2. Lindsay R, Feldkamp M, Harris D, Robertson J, Rallison M. Utah Growth Study: growth standards and the prevalence of growth hormone deficiency. J Pediatr 1994;125:29-35.
3. Bao XL, Shi YF, Du YC, Liu R, Deng JY, Gao SM. Prevalence of growth hormone deficiency of children in Beijing. Chin Med J (Engl) 1992;105:401-5.
4. Vimpani GV, Vimpani AF, Lidgard GP, Cameron EH, Farquhar JW. Prevalence of severe growth hormone deficiency. Br Med J 1977;2:427-30.
5. Parkin JM. Incidence of growth hormone deficiency. Arch Dis Child 1974;49:904-5.
6. Winer LM, Shaw MA, Baumann G. Basal plasma growth hormone levels in man: new evidence for rhythmicity of growth hormone secretion. J Clin Endocrinol Metab 1990;70:1678-86.
7. Carel JC, Tresca JP, Letrait M, Chaussain JL, Lebouc Y, Job JC, et al. Growth hormone testing for the diagnosis of growth hormone deficiency in childhood: a population register-based study. J Clin Endocrinol Metab 1997;82:2117-21.

8. Growth Hormone Research Society. Consensus guidelines for the diagnosis and treatment of growth hormone (GH) deficiency in childhood and adolescence: summary statement of the GH Research Society. GH Research Society. J Clin Endocrinol Metab 2000;85:3990-3.
9. Stanley T. Diagnosis of growth hormone deficiency in childhood. Curr Opin Endocrinol Diabetes Obes 2012;19:47-52.
10. Maghnie M, Ghirardello S, Genovese E. Magnetic resonance imaging of the hypothalamus-pituitary unit in children suspected of hypopituitarism: who, how and when to investigate. J Endocrinol Invest 2004;27:496-509.
11. Xu C, Zhang X, Dong L, Zhu B, Xin T. MRI features of growth hormone deficiency in children with short stature caused by pituitary lesions. Exp Ther Med 2017;13:3474-8.
12. Alba P, Tsai S, Mitre N. The severity of growth hormone deficiency does not predict the presence or absence of brain magnetic resonance imaging abnormalities - a retrospective review. Eur Endocrinol 2020;16:60-4.
13. Hwang J, Jo SW, Kwon EB, Lee SA, Chang SK. Prevalence of brain MRI findings in children with nonacquired growth hormone deficiency: a systematic review and meta-analysis. Neuroradiology 2021;63:1121-33.
14. Mamilly L, Pyle-Eilola AL, Chaudhari M, Henry RK. The necessity of magnetic resonance imaging in the evaluation of pediatric growth hormone deficiency: lessons from a large academic center. Growth Horm IGF Res 2021;60-61:101427.
15. AlJurayyan RNA, AlJurayyan NAM, Omer HG, Alissa SDA, AlOtaibi HMN, AlKhalifah RAH, et al. Pituitary imaging in 129 children with growth hormone deficiency: A spectrum of findings. Sudan J Paediatr 2017;17:30-5.
16. Schmitt J, Thornton P, Shah AN, Rahman AKMF, Kubota E, Rizzuto P, et al. Brain MRIs may be of low value in most children diagnosed with isolated growth hormone deficiency. J Pediatr Endocrinol Metab 2021;34:333-40.
17. Sari S, Sari E, Akgun V, Ozcan E, Ince S, Saldir M, et al. Measures of pituitary gland and stalk: from neonate to adolescence. J Pediatr Endocrinol Metab 2014;27:1071-6.
18. Kim JH, Yun S, Hwang SS, Shim JO, Chae HW, Lee YJ, et al. The 2017 Korean National Growth Charts for children and adolescents: development, improvement, and prospects. Korean J Pediatr 2018;61:135-49.
19. Hyun SE, Lee BC, Suh BK, Chung SC, Ko CW, Kim HS, et al. Reference values for serum levels of insulin-like growth factor-I and insulin-like growth factor binding protein-3 in Korean children and adolescents. Clin Biochem 2012;45:16-21.
20. Ibba A, Corrias F, Guzzetti C, Casula L, Salerno M, di Iorgi N, et al. IGF1 for the diagnosis of growth hormone deficiency in children and adolescents: a reappraisal. Endocr Connect 2020;9:1095-102.
21. Müller EE, Locatelli V, Cocchi D. Neuroendocrine control of growth hormone secretion. Physiol Rev 1999;79:511-607.
22. Shen Y, Zhang J, Zhao Y, Yan Y, Liu Y, Cai J. Diagnostic value of serum IGF-1 and IGFBP-3 in growth hormone deficiency: a systematic review with meta-analysis. Eur J Pediatr 2015;174:419-27.
23. Salmon WD Jr, Daughaday WH. A hormonally controlled serum factor which stimulates sulfate incorporation by cartilage in vitro. J Lab Clin Med 1957;49:825-36.
24. Rinderknecht E, Humbel RE. The amino acid sequence of human insulin-like growth factor I and its structural homology with proinsulin. J Biol Chem 1978;253:2769-76.
25. Laron Z. Somatomedin-1 (recombinant insulin-like growth factor-1): clinical pharmacology and potential treatment of endocrine and metabolic disorders. BioDrugs 1999;11:55-70.
26. Sims NA, Clément-Lacroix P, Da Ponte F, Bouali Y, Binart N, Moriggl R, et al. Bone homeostasis in growth hormone receptor-null mice is restored by IGF-I but independent of Stat5. J Clin Invest 2000;106:1095-103.
27. Cohen P, Rogol AD, Deal CL, Saenger P, Reiter EO, Ross JL, et al. Consensus statement on the diagnosis and treatment of children with idiopathic short stature: a summary of the Growth Hormone Research Society, the Lawson Wilkins Pediatric Endocrine Society, and the European Society for Paediatric Endocrinology Workshop. J Clin Endocrinol Metab 2008;93:4210-7.
28. Kim JH, Chae HW, Chin SO, Ku CR, Park KH, Lim DJ, et al. Diagnosis and treatment of growth hormone deficiency: a position statement from Korean Endocrine Society and Korean Society of Pediatric Endocrinology. Endocrinol Metab (Seoul) 2020;35:272-87.
29. Clemmons DR. Value of insulin-like growth factor system markers in the assessment of growth hormone status. Endocrinol Metab Clin North Am 2007;36:109-29.