Original Article

Clinical and Biochemical Phenotype of Indian Children with Different Types of Idiopathic Growth Hormone Deficiency and their Association with Pituitary Height on MRI

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Abstract

Background and Objectives: Differentiation of growth hormone deficiency (GHD) into various types has been made based on peak stimulated growth hormone levels and other hormone axis involvement. The data regarding how this classification is associated with variation in clinical and biochemical phenotype and how these findings associate with pituitary morphology remains sparse, especially in the Indian population. Therefore, we aimed to ascertain the differences in the pattern of auxological, clinical features including pituitary hypoplasia, and endocrinological profile among patients with severe GHD, partial GHD, and MPHD in the Indian population and to evaluate the association of pituitary height with various clinical and hormonal parameters. **Materials and Methods:** We conducted a cross-sectional study in 100 patients with idiopathic GHD. Patients were grouped into severe GHD, partial GHD, and MPHD to observe the differences in clinical, biochemical, and MRI findings. The pituitary height findings were correlated clinical and biochemical presentation. **Results:** MPHD subjects had a significantly higher frequency of breech delivery, neonatal jaundice, neonatal hypoglycemia, and micropenis. A significant difference was observed in the chronological age, bone age retardation (CA-BA), height SDS, weight SDS, peak GH response, IGF-1, IGF-1 SDS, and prevalence of pituitary hypoplasia, pituitary height, and pituitary height SDS among these three groups. In the composite population of GHD, pituitary height SDS was correlated with peak GH, basal IGF-I SDS, and body height SDS. **Conclusion:** The clinical and biochemical phenotype differs significantly among the various types of GHD. Pituitary height correlates with these findings and is helpful in further assessment of these patients.

Keywords: Growth hormone deficiency (GHD), phenotype, pituitary height

Introduction

Short stature and growth retardation are among frequent cause for concern among the pediatric and has an estimated prevalence of 2.8%–7% in the Indian population.[1] There are numerous causes of short stature and growth retardation, including genetic syndromes, systemic illness, endocrine causes, and idiopathic short stature. Growth hormone deficiency (GHD) is an established endocrinological cause of short stature and indicates a growth hormone-related growth failure due to specific alterations in the chain of events from growth hormone synthesis and release to its growth potentiating actions. Thus, it involves a heterogeneous group of disorders where abnormalities can occur at any level of the hypothalamic-pituitary-somatomedin axis leading to growth retardation. The incidence of GHD has been reported as 1 in 4000 to 1 in 20,000 live births.[2] Congenital idiopathic GHD (IGHD) is further classified into partial isolated GHD (partial GHD) and severe GHD (SGHD) based on peak stimulated GH level or multiple pituitary hormone deficiencies (MPHD) when associated with involvement of one or more other anterior pituitary hormones during tests. The diagnosis of GHD entails detailed clinical examination followed by biochemical testing, including growth hormone stimulation tests and insulin-like growth factor 1 (IGF-1) estimation and neuroimaging. MRI helps predict the likelihood

Access this article online

Quick Response Code:

Website: www.ijem.in

DOI: 10.4103/ijem.IJEM_55_21

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Submitted: 05-Feb-2021 **Revised:** 21-Jun-2021
Accepted: 21-Sep-2021 **Published**: 26-Oct-2021

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How to cite this article: Sharma H, Mathur SK, Purwar N, Sahlot R, Garg U, Sharma B. Clinical and biochemical phenotype of Indian children with different types of idiopathic growth hormone deficiency and their association with pituitary height on MRI. Indian J Endocr Metab 2021;25:232-9.

of other pituitary hormone deficiencies, the utility of genetic testing, and the likelihood of persistent GHD.[3]

A few studies, including some studies from India, have aimed to establish these patients' clinical and biochemical characteristics. However, these studies suffer from the lacunae of small sample size and the use of nonethnicity specific data. Therefore our objective of this study was to ascertain the differences in the pattern of auxological, clinical features including pituitary hypoplasia, and endocrinological profile among patients with severe GHD, partial GHD, and MPHD in the Indian population and to evaluate the association of pituitary height with various clinical and hormonal parameters.

Materials and Methods

Study design

The children presenting in SMS Endocrine OPD between September 2018 and December 2020, with short stature, were evaluated by complete history, including perinatal history, detailed physical examination, anthropometry, and relevant biochemical and hormonal test. After this evaluation, a total of 100 subjects were diagnosed to have GHD with the exclusion of syndromic causes, system illness, pituitary mass, post-op cases of pituitary surgery, and with history of cranial irradiation. Institutional ethical permission and written consent (from legal guardians in minor subjects) were obtained. Strict confidentiality of the data and patients was maintained.

Sample size calculation

An estimated sample size of 97 was calculated with a precision of 0.1 and 95% confidence interval, taking the prevalence of pituitary hypoplasia at 56.8%, as per a previous study by Acharya *et al*.[4]

Anthropometric and pubertal evaluation

The same trained clinician made all measurements at the time of initial diagnosis. The height was measured without footwear to the closest 0.1 cm using a mobile stadiometer (SECA Int., Hamburg, Germany) with the back lined up with a stadiometer and the head held in Frankfurt horizontal plane. The weight was recorded to the closest 0.1 kg using a standardized electronic scale, with patients dressed in minimal light clothing. The measurements were taken thrice, and the mean of recordings was taken as final. Midparental height (MPH) was calculated based on the height of the parents (mother's height + father's height)/2, −6.5 cm for girls, and +6.5 cm for boys). All measurements were plotted on IAP growth charts.[5,6] Height was recorded as a standard deviation score (SDS) as per the formula: Height SDS = (Measured height − Mean height for age)/SD for age. In boys, testicular volume was assessed by comparative palpation with the Prader orchidometer to the nearest milliliter. The pubertal stage was recorded according to tanner staging.

Diagnosis of GHD

Patients were considered for evaluation of GHD if they had a normal initial investigative workup for other causes as per GH research society guidelines.[3] After confirmation of euthyroid and eucortisolemic status and exclusion of other causes of short stature, patients were evaluated for the presence of GHD by two different GH stimulation tests (GHST), i.e., clonidine stimulation test and glucagon stimulation performed in a sequential manner to confirm GH deficiency. Sex steroid priming was done prior to provocative GH testing, in prepubertal boys older than 11 and prepubertal girls older than 10 years, as per guidelines of the pediatric endocrine society.[7]

A peak serum GH level more than or equal to 10 ng/ml at any time point during a GHST was considered normal, excluding the diagnosis of GHD. A peak serum GH level less than 10 ng/ml in both tests was considered diagnostic for GHD.

Assessment of other pituitary axes

All patients were evaluated for the involvement of other pituitary axis using hormone assays (serum cortisol, plasma ACTH, serum T4, TSH, 8:00 am). The testing for GHD in subjects with preexisting central hypothyroidism and central hypocortisolism was delayed until euthyroidism and eucortisolism were achieved. Evaluation of gonadotroph axis (serum LH, FSH, testosterone, and GnRH stimulation test using triptorelin 0.1 mg, when deemed necessary) was performed if the subjects did not enter puberty by the age of 14 years (boys) and 13 years (girls). Documentation of the 24-hour urine output followed by a serum and urine osmolality measurement were performed to evaluate posterior pituitary dysfunction, as required. Subjects with other pituitary axis involvement were defined as having multiple pituitary hormone deficiencies, while those without any other hormone involvement were defined as having isolated GHD.

Based on the results of the endocrinological evaluation, patients were divided into three groups: 1) patients with MPHD (MPHD group), defined as GH peak concentration <10 ng/ml accompanied by at least one other anterior pituitary deficit; 2) patients with severe GHD (SGHD group) GH peak <5 ng/ml; 3) patients with partial GHD (PGHD group) defined as GH peak >5 ng/ml, but <10 ng/ml. This study defined SGHD as a GH peak <5 ng/ml.[8,9] The flow diagram for patient selection and GHD diagnosis is presented in Figure 1.

Serum Cortisol, LH, FSH, TSH, FT3, FT4, testosterone, and ACTH levels were determined using a commercial chemiluminescent kit (SIEMENS ADVIA Centaur XPT Immunoassay System, USA). Serum growth hormone and IGF-1 were determined using a commercial chemiluminescent kit (IMMULITE/IMMULITE 1000 solid-phase, enzyme-labeled chemiluminescent immunometric assay. IGF-1 was expressed as standard deviation score (SDS) according to the formula: IGF-1 SDS = (Measured IGF-1 − Mean IGF-1 for age)/SD for age and were calculated according to chronological age (CA).

Radiological evaluation

Bone age (BA) of all patients was estimated from an X-ray of the distal end of the nondominant hand's forearm, and BA was calculated using Tanner Whitehouse 2 system.

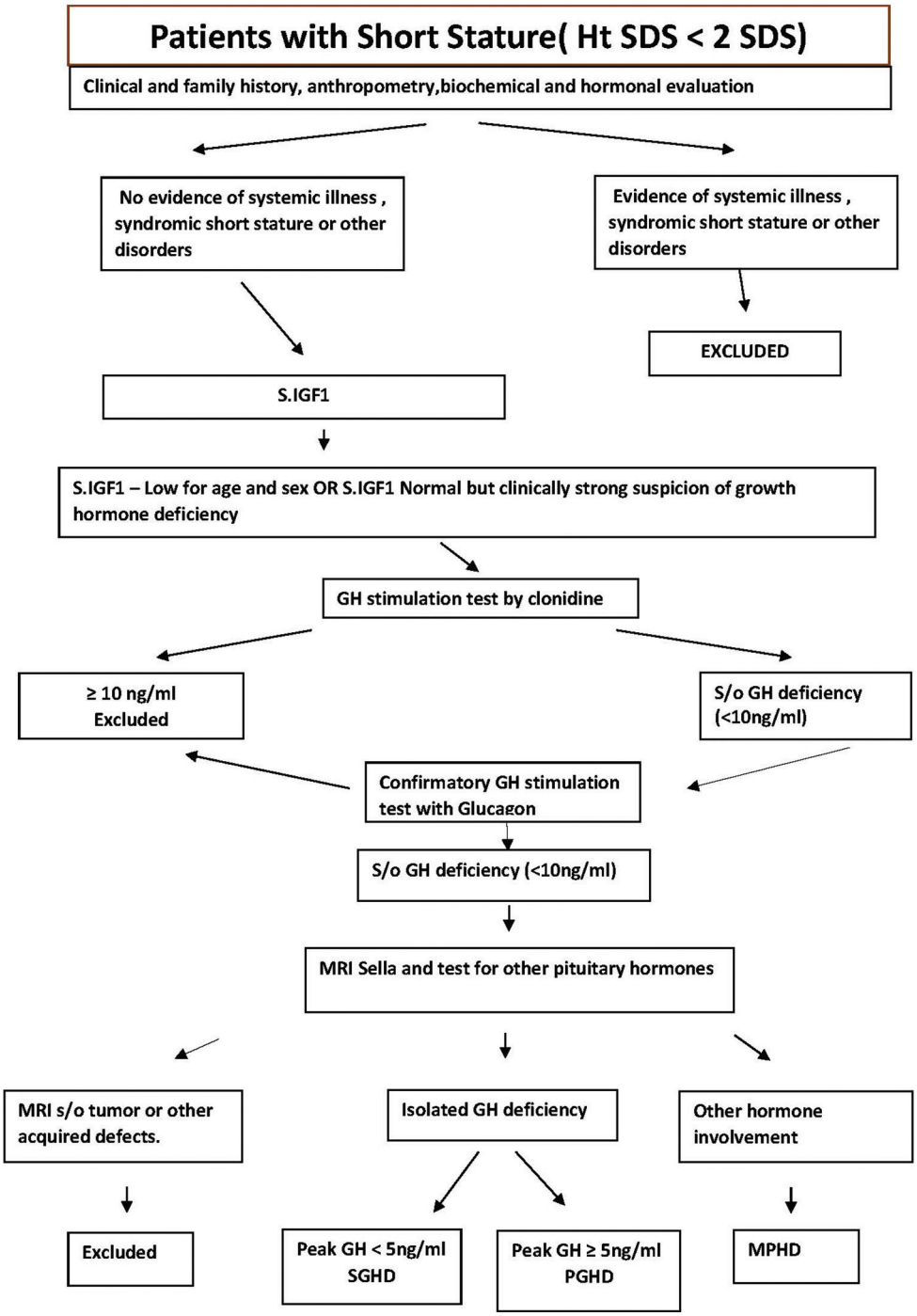

Figure 1: Flow diagram for patient selection and GHD diagnosis

All subjects with a diagnosis of GHD underwent neuroimaging in the form of 3T magnetic resonance imaging (MRI) [Phillips Ingenia] of the sellar, suprasellar region, and brain for associated anomalies. The same experienced radiologist performed the images' assessments, and measurements were done to the nearest single decimal point using the inbuilt software. The height of the pituitary gland was estimated in the midline sagittal plane in a line perpendicular to the floor of the sella turcica to the highest point of the superior gland surface, which was located at the point of insertion of the pituitary stalk, with a pituitary height SDS <−2 compared with normal age-matched controls being designated as pituitary hypoplasia.[10,11] Radiological empty sella was defined when the pituitary gland was not visible, but the cerebrospinal fluid cavity invaded the sella. For statistical purposes, pituitary height in empty sella was taken to be 0.1 mm (lowest measurable unit). The coefficient of variance was 3.8% (determined using a phantom).

Statistical analysis

Statistical analysis was carried out using Statistical Package for Social Sciences (SPSS) for Windows (SPSS 21.0, SPSS Inc., Chicago, IL, USA). The data were presented as number, percentages, mean (±SD), or median (IQR) as appropriate. Quantitative variables that followed normal distribution were compared using Student's *t*-test for independent samples. The normality of the data was established using the Shapiro–Wilk test. Quantitative variables that did not observe a normal distribution were compared using the Kruskal–Wallis test. Spearman rank-order correlation was employed to examine the strength and pattern of association for pituitary height and pituitary height SDS with peak GH, IGF-1, IGF-I SDS, height, and height SDS and association of peak GH with IGF-1. A *P* value of less than 0.05 was taken as statistically significant.

Results

Perinatal data, family history, and pubertal staging of patients in the three diagnostic groups are summarized in Table 1.

A total of 100 subjects were included in the final analysis. In all, 74 subjects (74%) were males, while 26 (26%) were females. A total of 42 (42%) subjects had severe GHD (27 boys, 15 girls), 24 (24%) subjects had partial GHD (17 boys, 7 girls), while the remaining 34 (34%) had GHD as a part of MPHD (30 boys, 4 girls). Compared to SGHD and PGHD, MPHD subjects had a history of significantly higher frequency of breech delivery, neonatal jaundice, neonatal hypoglycemia, and micropenis.

Clinical, auxological, endocrinological findings with pituitary height are elaborated in Table 2. We observed that the CA, bone age retardation (CA-BA), height SDS, weight SDS, peak GH response, IGF-1, IGF-1 SDS, the prevalence of pituitary hypoplasia, pituitary height, and pituitary height SDS were significantly different between these three groups. However, the distribution of BA, BMI SDS, and mid parental height was the same across all three groups. On performing the pairwise comparison, between SGHD and MPHD group, the SGHD group significantly had a younger mean CA (11.34 ± 3.74 vs 15.16 ± 3.99, *P* value = 0.001), lower weight SDS (−2.8 ± 1.63 vs − 2.1 ± 1.6, *P* = 0.04), less BA retardation (3.01 ± 1.68 years Vs 5.25 ± 2.37 years, *P* = 0.000), and higher IGF-1 SDS (−2.46 ± 0.48 vs − 2.81 ± 0.56, *P* = 0.016) than the MPHD group. Pituitary height and pituitary height SDS of patients in the MPHD group (1.865 ± 1.63 mm and − 3.7 ± 1.83, respectively) were significantly lower than in the SGHD (3.86 ± 2.35 mm, *P* = 0.00 and − 1.76 ± 1.89, *P* = 0.00, respectively). Patients with MPHD also had a higher prevalence of pituitary hypoplasia. There were no significant differences in height SDS (*P* = 0.074), peak GH value (*P* = 0.387), and IGF-1 value (*P* = 0.094) between SGHD and MPHD.

On comparison between PGHD and SGHD groups, PGHD group had higher height SDS (−2.63 ± 0.76 vs − 4.02 ± 1.43, *P* = 0.000), higher weight SDS (−1.49 ± 1.21 vs − 2.8 ± 1.63, *P* = 0.003), peak GH value (7.54 ± 1.04 ng/ml vs 2.18 ± 1.46 ng/ml, *P* = 0.000), and higher IGF-1 (125.18 ± 56.03 vs 79.6 ± 59.02 ng/ml, *P* = 0.007). Patients with SGHD had a higher prevalence of pituitary hypoplasia. There was no significant difference in BA retardation (*P* = 0.542) and IGF-1 SDS (*P* = 0.093) between PGHD and SGHD. PGHD group had an older mean CA (13.11 years ± 2.78 vs 11.34 ± 3.74 years), but the difference in distribution was not statistically significant (*P* value = 0.103). Patients with SGHD had a significantly lower pituitary height (*P* = 0.019) and pituitary height SDS (*P* = 0.036) than PGHD patients.

When PGHD and MPHD groups were compared, the PGHD group had higher height SDS (−2.63 ± 0.76 vs − 3.56 ± 1.65, *P* = 0.000), less BA retardation (2.4 ± 2.07 years vs 5.25 ± 2.37, *P* = 0.000 years), higher peak GH value (7.54 ± 1.04 ng/ml vs 2.58 ± 2.27, *P* = 0.000), higher IGF-1 (125.18 ± 56.03 ng/ml vs 56.23 ± 49.26 ng/ml, *P* = 0.000), and

Table 1: Perinatal data, family history, and pubertal staging of patients

	Severe GHD (*n*=42)	Partial GHD (*n*=24)	MPHD (*n*=34)	Total (*n*=100)
Sex (Male/Female)	27/15	17/7	30/4	74/26
Prematurity (%)	2 (4.8%)	1 (4.2%)	1 (2.9%)	4 (4%)
Breech Delivery (%)	3 (7.1%)	0	9 (26.47%)	12 (12%)
Neonatal Jaundice (%)	2 (4.8%)	1 (4.2%)	4 (11.8%)	7 (7%)
Hypoglycemia (%)	2 (4.8%)	0	4 (11.8%)	6 (6%)
Micropenis (%)	3 (7.1%)	0	8 (23.5%)	11 (11%)
Crytorchidism (%)	2 (4.8%)	0	4 (11.8%)	6 (6%)
FAMILY HISTORY (%)	5 (11.9%)	1 (4.2%)	3 (8.8%)	9 (9%)
History of Consanguinity (%)	2 (4.8%)	1 (4.2%)	4 (11.8%)	7 (7%)
Tanner Stage				
1	23 (54.8%)	13 (54.2%)	23 (67.6%)	59 (59%)
2	8 (19.0%)	6 (25.0%)	8 (23.5%)	20 (20%)
3	7 (16.7%)	2 (8.3%)	3 (8.7%)	12 (12%)
4	3 (7.1%)	2 (8.3%)	0	5 (5%)
5	1 (2.4%)	1 (4.2%)	0	2 (2%)

Table 2: Comparison between clinical parameters, GH-IGF axis, and pituitary findings (on MRI) in different groups

	Severe GHD (*n*=42)	Partial GHD (*n*=24)	MPHD (*n*=34)	*P**
Chronological Age (years)	11.34±3.74	13.11±2.78	15.16±3.99	0.00
Bone Age (years)	8.33±4.09	10.69±2.92	9.9±3.5	0.054
CA-BA (years) difference	3.01±1.68	2.4±2.07	5.25±2.37	0.000
Height for Age *Z*-Score	−4.02±1.43	−2.63±0.76	−3.56±1.65	0.000
Weight for Age *Z*-Score	−2.8±1.63	−1.49±1.21	−2.1±1.6	0.011
BMI for Age *Z*-Score	−0.88±1.64	−0.19±1.2	−0.40±1.27	0.273
Mid Parental Height (cm)	160.6±7.6	164.25±8.95	166.37±7.16	0.055
IGF-1 (ng/ml)	79.6±59.02	125.18±56.03	56.23±49.26	0.000
IGF-1 for Age and Sex *Z*-Score	−2.46±0.48	−2.26±0.52	−2.81±0.56	0.001
Peak GH (ng/ml)	2.18±1.46	7.54±1.04	2.58±2.27	0.000
Pituitary Height (mm)	3.86±2.35	5.29±1.34	1.865±1.63	0.01
Pituitary Height for Age and Sex *Z*-Score	−1.76±1.89	0.14±1.36	−3.7±1.83	0.035
Pituitary Hypoplasia	21 (50%)	3 (12.5%)	30 (88.3%)	0.02

**P*-value was measured with the Kruskal-Wallis test to test the difference between these three groups. The test assumes that distribution is the same across all groups. A significant *P*<0.05 denotes the presence of a difference between any two groups out of three

higher IGF-1 SDS (−2.46 ± 0.48 vs − 2.81 ± 0.56, *P* = 0.000) than the MPHD group. Patients with MPHD had a higher prevalence of pituitary hypoplasia. There was no significant difference in CA (*P* = 0.308) and weight SDS (*P* = 0.217). PGHD group also had a significantly higher mean pituitary height and pituitary height SDS.

The correlation between pituitary height SDS and peak GH, basal IGF-1 SDS, and body height SDS is shown in Figure 2. Considering all the three groups of GHD together, pituitary height SDS was correlated with peak GH (r = 0.440, P =0.001), basal IGF-I SDS (r = 0.381, P =0.002), and body height SDS (r = 0.290, P =0.04). On group wise analysis, we found correlation only between pituitary height with the GH peak in SGHD (r = 0.43, *P* = 0.005) and body height SDS (r = 0.386, P =0.011), while in PGHD and MPHD groups a significant correlation was only observed with peak GH value (r = 0.365, *P* = 0.02 and r = 0.481, P =0.001, respectively) as shown in Figure 3.

Discussion

We found that patients with SGHD and MPHD had a much lower mean height, mean IGF-1, peak stimulated GH value, and mean pituitary height compared to PGHD. We observed a positive correlation between the pituitary height SDS and IGF-1 SDS, peak GH value, and body height SDS. To the best of the author's knowledge, this is the first study in the Indian population describing the association between pituitary height and peak GH value and IGF-1 SDS in GHD patients.

We evaluated 100 patients with a GHD, out of which 4 had a history of prematurity (2 SGHD, 1 PGHD, and 1 MPHD),12 patients had a history of breech delivery (3 SGHD and 9 MPHD), 7 had neonatal jaundice (2 SGHD, 1 PGHD, and 4 MPHD), 6 had history of neonatal hypoglycemia (2 SGHD and 4 MPHD), 11 had micropenis (3 SGHD and 8 MPHD), and cryptorchidism either unilateral or bilateral was present in 6 patients (2 SGHD and 4 MPHD). Family history was present in 9 patients (5 SGHD, 1 PGHD, and 3 MPHD), and history of consanguinity was found in 7 patients (2 SGHD, 1 PGHD, and 4 MPHD). The absence of a history of breech delivery, neonatal hypoglycemia, and micropenis among PGHD patients probably reflects that these conditions may be a measure of severity of GHD. However, a study with a more significant number of patients would be needed to confirm this finding. Among Indian studies, these findings contrast with Acharya *et al*.[4] and Dutta *et al*.,[12] who found a much higher prevalence of micropenis, family history, and history of consanguinity but the almost similar prevalence of breech delivery, jaundice, and hypoglycemia. Jagtap *et al*.[13] reported a higher prevalence of family history, breech delivery, and jaundice but a similar prevalence of neonatal hypoglycemia and micropenis. In studies from other countries, Lo *et al*.[14] reported findings similar to our study with a prevalence of prematurity, breech delivery, hypoglycemia, and a higher prevalence of neonatal jaundice. The difference may be due to the diverse ethnic population and differences in the region where the study was conducted.

While patients with MPHD are usually diagnosed at a younger age, in our study, the mean age at diagnosis was higher than both SGHD and PGHD. Most of our MPHD patients presented with gonadotropin deficiency [Supplementary Table 1], thus presenting late with delayed pubertal development as chief complaint along with short stature. This may also explain the increased BA delay and increased prevalence of micropenis compared to SGHD and PGHD.

Mean height SDS in our study (−4.02 for SGHD, −2.63 for PGHD, and − 3.56 for MPHD) is similar to what has been previously noticed by other Indian studies by Acharya *et al*.,[4] Khadilkar *et al*.,[15] and Gahlot *et al*.[16] These findings are distinct as compared to developed countries as reported by Darendeliler *et al*.,[17] Villafuerte *et al*.,[18] Lo *et al*.,[14] and Nagel *et al*.,[19] who observed a higher height SDS among these patients, and Rohayem *et al*.[20] who observed a lower height

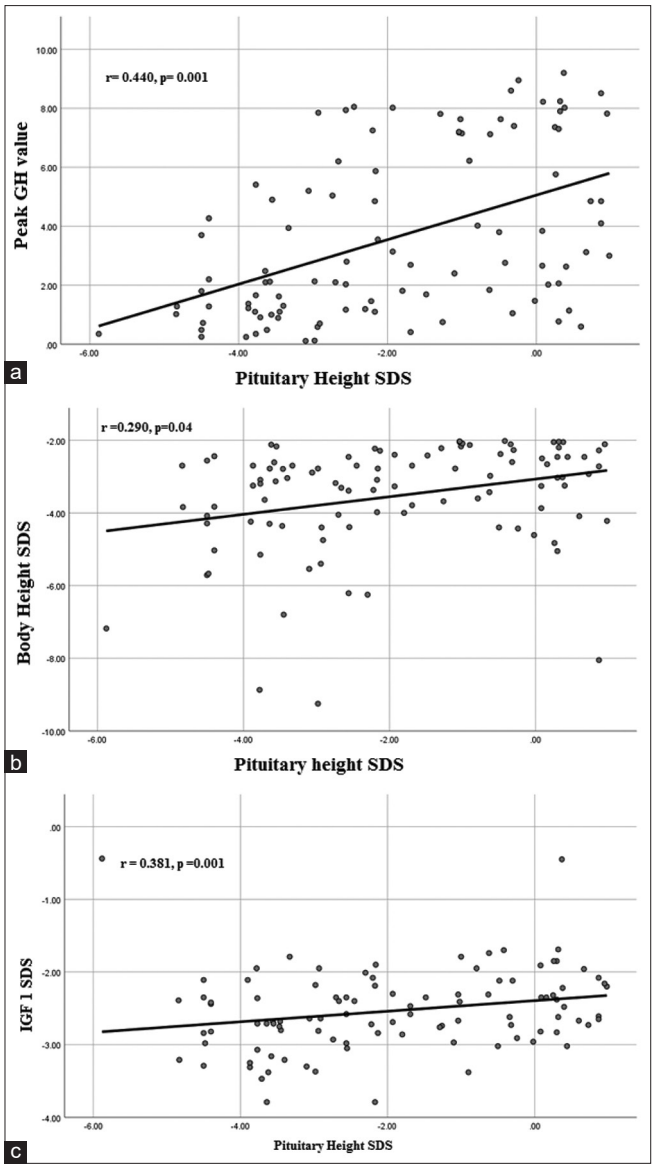

Figure 2: Correlation between pituitary height SDS and (a) Peak GH value, (b) Body height SDS, and (c) IGF-1 SDS in the composite study population

SDS (−4.1 SDS for MPHD) among these patients. Although these differences could be ascribed to ethnic variations, this could be due to the delayed presentation and lack of awareness regarding GHD in the study population.

As expected, patients with PGHD in our study had a higher mean IGF-1 (125.18 ng/ml), mean peak GH value (7.54 ng/ml), and mean IGF-1 SDS (−2.26) as compared to the other two groups. No significant difference was seen in mean peak GH and basal IGF-1 value between SGHD and MPHD groups; however, IGF-1 SDS was significantly higher for the SGHD group (−2.46) v/s MPHD group (−2.81). Khadilkar *et al*.[15] reported a similar mean IGF-1 of 84.09 ng/ml but higher mean IGF-1 SDS (−0.86) with a lower mean peak GH (0.71 ng/ml). A disparity from our result was observed by Ekbote *et al*.,[21] who reported a much lower mean IGF-1 (20 ng/ml), mean IGF-1 SDS (−3.40), and lower mean peak GH value (0.97 ng/ml) in IGHD patients. The contrast in findings may be explained by considering the fact that these studies included both IGHD and MPHD patients in the analysis and included only a small number of participants. In a study by Deal *et al*.[22] in 7039 patients with idiopathic GHD, the mean peak GH was 6.6 ng/ml, and IGF-1 SDS was − 2.0. When a distinction was made between SGHD, PGHD, and MPHD, Zimmermann *et al*.[8] and Lo *et al*.[14] reported results similar to our study. However, Nagel *et al*.[19] reported much lower values for MPHD and SGHD with mean IGF-1 SDS of − 5.0 and − 3.8 and mean peak GH (in ng/ml) value of 2.5 in both the groups. Nevertheless, the mean values for PGHD groups were similar to our study. These differences could be attributed to the difference in the mean age of the study population and different cut-offs used for diagnosis of severity.

Measuring pituitary height provides a single, useful mode for assessing pituitary size because the age-dependent changes in size have been related to changes in gland height but not gland length or width.[23] Our study also confirmed that Indian children with MPHD had significantly smaller pituitary height, pituitary height SDS, and more frequent pituitary hypoplasia compared to SGHD and PGHD patients, and patients with SGHD had a significantly smaller pituitary height and pituitary height SDS as compared to PGHD patients. Similar findings were reported by Lo *et al*.,[14] Zimmermann *et al*.,[8] and Nagel *et al*.[19] A trend for lower pituitary height in the MPHD group compared to SGHD and PGHD could be a consequence of hypoplasia and absence of pituitary cells other than somatotrophs, thus a gross lesser number of cells leading to a lower pituitary height.

Our data showed that pituitary height SDS was correlated with peak GH, basal IGF-I SDS, and body height SDS. Pituitary height on MRI has been used as a marker of the severity of GHD and shown to be correlated with IGF-I SDS, the highest peaks in tests of GH stimulation, and spontaneous GH secretion. Nagel *et al*.[19] observed that the pituitary height SDS correlates not only with IGF-I SDS (r = 0.48, $P < 0.0001$), but also with the peak values of the GH stimulation tests (r = 0.36, $P < 0.0001$). Zimmermann *et al*.[8] reported an even stronger correlation of pituitary height SDS with the GH peak after pharmacological stimulation (r = 0.75) in SGHD patients. Regarding the patients with MPHD, only a moderate positive correlation of pituitary height with the GH peak at diagnosis (r = 0.57) was seen, while PGHD groups showed no correlations. However, this contrasts with our assessment, as we found a correlation between pituitary height with the GH peak in SGHD, MPHD, and PGHD groups. We found a significant correlation between body height SDS and pituitary height in the SGHD group only. No correlation was observed between IGF-1 SDS and pituitary height SDS in any of the groups. This discrepancy may be due to ethnic variations, the smaller sample size in previous studies, the impact of other hormone involvement on body height, and the low sensitivity of IGF-1 for the diagnosis of GHD. Further studies with a higher number of patients are

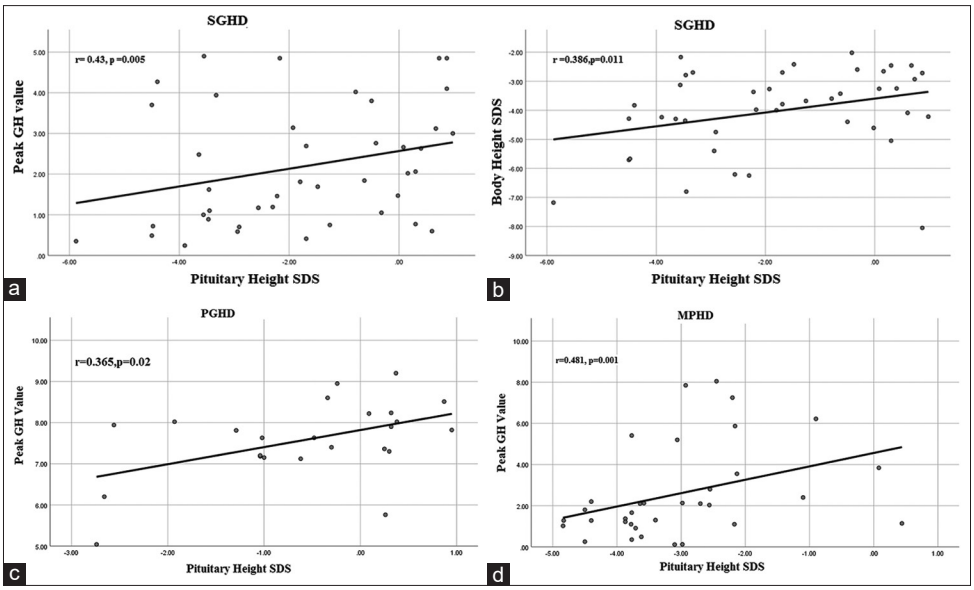

Figure 3: Correlation between pituitary height SDS and (a) Peak GH value, (b) Body height SDS in SGHD group, (c) Peak GH in PGHD group, and (d) Peak GH in MPHD group

required to confirm these results. However, these findings add to the knowledge that pituitary height provides a measure to determine the clinical severity of IGHD.

We understand that our study also has a few limitations. While various other studies have taken a variable cut off ranging from 3 ng/l to 7 ng/ml for diagnosing SGHD, we have used a 5 ng/ml peak stimulated GH value for differentiation between SGHD and PGHD. The rationale for using this limit is that 5 ng/ml at 2 SD for GH values on provocative testing of normally growing children and identifies children who will have the highest first-year growth response to GH treatment.[24] Being a clinical hospital-based study, Berksonian bias is introduced, and thus this data is not reflective of the general population. A skewed sex ratio may be a result of referral bias. Also, patients of GHD can progress to MPHD, and this could not be assessed due to the cross-sectional study design.

Our study's strengths are the relatively large sample size and the use of ethnicity-specific Indian data for pituitary height and SDS calculation. We are also the first Indian study to examine the correlation between pituitary height SDS and various clinical and biochemical parameters.

Conclusion

We observed that three groups differed significantly in CA, BA retardation (CA-BA), height SDS, weight SDS, peak GH response, IGF-1, IGF-1 SDS, pituitary height, and pituitary height SDS. We also observed that the pituitary height SDS correlated with IGF-1 SDS, peak GH value, and body height SDS. However, on the comparison between the groups, an association between only GH value and pituitary height SDS was observed in all three groups, while the association with body height SDS was observed only in the SGHD group. Based on our patients' results, we believe that meticulous assessment of auxological, clinical, and MRI findings among patients with growth hormone deficiency can facilitate their further evaluation and classification. Pituitary height assessment provides an independent measure for evaluating the severity in these patients. Future studies with a higher number of patients and a prospective design should be planned, and these will provide an even clearer picture of the differences between the various types of GHD. The addition of genetic analysis to this pool of data could provide an avenue to further our knowledge regarding GHD.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients/parents have given their consent for their/their children images and other clinical information to be reported in the journal. The patients/parents understand that their/their children names and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

Acknowledgements

We want to express our gratitude to the study participants and their families for donating time and information.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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Supplementary Table 1: Pattern of other pituitary axes involvement in MPHD

	MPHD ($n=34$)
GH +1 hormone deficiency	15
GH +2 hormone deficiency	13
GH +3 hormone deficiency	6
ACTH Deficiency	13
Thyrotropin Deficiency	21
Gonadotropin Deficiency	25