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Case Series

Paediatrics Section

Spectrum of Growth Hormone Disorders in Children: A Case Series of 5 Cases

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ABSTRACT

Growth Hormone Deficiency (GHD) is one of the most important treatable endocrine causes of short stature. A problem anywhere in the Growth Hormone (GH) - Insulin-Like Growth Factor-1 (IGF-1) axis can lead to short stature. Childhood GH deficiency can be congenital, acquired, or idiopathic. Hereby, the authors present a case series consisting of five cases of short stature, aimed to provide an overview of the spectrum of GH-related disorders. All five patients presented to the Paediatric Endocrinology Outpatient Department of a tertiary care Institute with complaints of not gaining height. The patients in present case series had significant short stature (Z score for height <-3 SD (Standard Deviation) in each case). These patients were suspected of having GH deficiency based on clinical presentation and investigations. After a proper diagnostic work-up and GH stimulation tests, cases 1 to 4 were found to have GH deficiency. The 5th case was suspected of having Laron Syndrome based on high GH levels and low IGF-1. There were subtle differences in the spectrum of GH deficiency. The 1st case had Multiple Pituitary Hormone Deficiency (MPHD). Cases 2 to 4 had Isolated Growth Hormone Deficiency (IGHD). Case 2 had findings of pituitary stalk interruption on brain imaging. We found a genetic association in the 3rd case, while the 4th case had almost normal brain imaging. Cases 1 to 4 received GH therapy, and all showed appreciable height gain. These subtle differences can sometimes make the diagnosis difficult, and often a different approach to treatment is required.

Keywords: Diagnosis, Genetic, Panhypopituitarism, Short stature

INTRODUCTION

Growth Hormone (GH) is the most important hormone responsible for linear growth in children. GH has a limited role in intrauterine growth. The major effect of GH on linear growth starts after infancy. GH is secreted from the anterior pituitary in a pulsatile fashion, with GH-Releasing Hormone (GHRH), which is secreted from the hypothalamus, having a positive control over GH secretion. GH acts on the liver to produce IGF-1, which acts on the type-1 IGF receptors on the growth plates, resulting in height gain [1]. GH also directly affects cartilage cells in the growth plates of long bones, in addition to the production of local IGF-1. A problem anywhere in the GH-IGF1 axis can lead to significant short stature. Childhood GH deficiency can be congenital, acquired, or idiopathic. GH deficiency can be isolated or associated with deficiencies of other pituitary hormones (panhypopituitarism) [2]. Rarely, other disorders of the GH-IGF1 axis, like Laron syndrome, can also cause severe short stature [3].

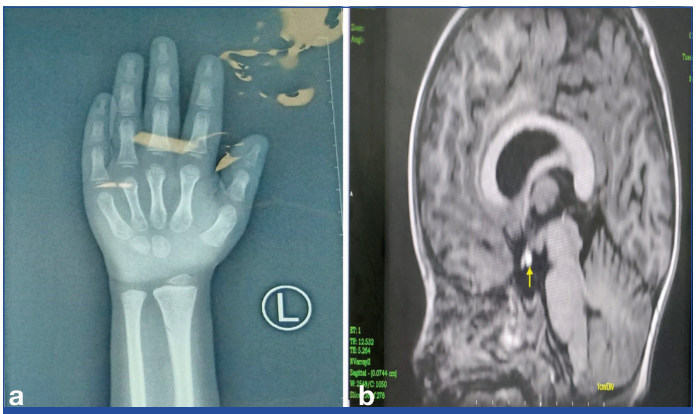
The present case series aimed to provide an overview of short stature in children due to different spectrums of GH-related disorders.

CASE SERIES

Case 1

A six-year eight-month-old male child presented to the Paediatric Endocrinology Outpatient Department with the chief complaint of not gaining weight and height for the last three years. General physical and systemic examinations were normal. Birth history was normal, and there was no history of Neonatal Intensive Care Unit (NICU) admission. Patients anthropometric findings were suggestive of short stature. Anthropometric data were analysed using the MedEClasses Endocrinology application on Android [4].

The height was 95 cm (height Standard Deviation Score (SDS) -4.69), and the weight was 15 kg (-2.48 SDS). Patients height age was three years, and weight age was three years nine months (chronological age > weight age > height age). So, height was more affected than weight. Mid-parental height was 158.5 cm (father's height 160 cm, mother's height 144 cm). Routine blood investigations, blood gas, coelic profile, urine, and chest X-ray were normal. However, Thyroid Function Tests (TFT) showed normal Thyroid Stimulating Hormone (TSH)=0.9 mIU/L (normal value <5 mIU/L) and low free thyroxine (FT4)=0.54 ng/dL (Normal value=0.7 to 1.8 ng/dL) [5], suggestive of central hypothyroidism. Patients 8 am serum cortisol was 4.2 microgram/dL (Normal range is 5-23 mcg/dL), and Adrenocorticotropic (ACTH) less than 5 picogram/mL (Normal value is 7.2-63.3 pg/mL) was also low [6,7]. The baseline IGF-1 level was also 12.2 ng/mL, which is low for the age and sex (age-wise normal values to be used) [8]. The GH stimulation test (after treatment with steroid and thyroxine) with clonidine (5 microgram/kg) showed peak GH levels to be very low (30 min - 0.7 ng/mL, 60 min - 0.4 ng/mL, 90 min - 0.9 ng/mL, and 120 min - 0.8 ng/mL) (more than 10 ng/mL considered as normal) [9]. Patients left wrist X-ray showed a bone age of around three years. Contrast-Enhanced Magnetic Resonance Imaging (CEMRI) of the brain in a T1-weighted (T1W) image showed a small bright spot near the upper end of the infundibulum. The pituitary fossa was empty, suggestive of an ectopic posterior pituitary with hypoplasia/aplasia of the anterior pituitary [Table/Fig-1a,b].

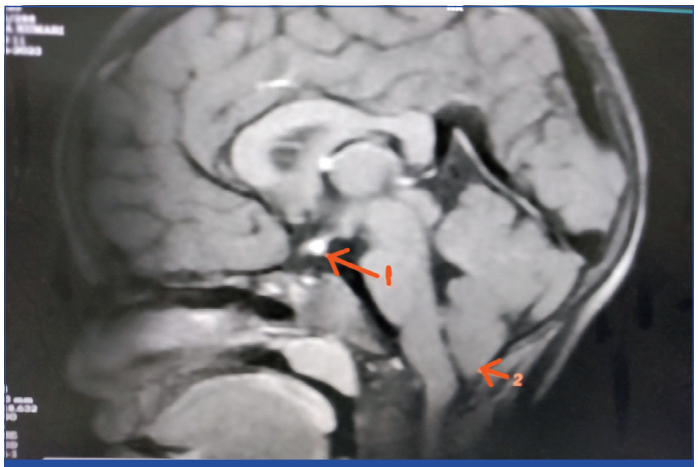


[Table/Fig-1a,b]: a) Bone age of case 1; b) MRI scan of the brain, arrow showing ectopic posterior pituitary.

Based-on clinical, laboratory, and radiological findings, the child was diagnosed as a case of MPHD. Other differentials kept were traumatic injury, neoplastic disorders, and infectious causes, which were easily ruled out based on history and investigations. Initially, treatment was started with hydrocortisone at a dose of 10 mg/day in three divided dosages (10-15 mg/m^2/day), followed by levothyroxine 50 mcg daily empty stomach (3-5 mcg/kg/day) after two weeks of starting the hydrocortisone. After one week, subcutaneous GH therapy (Norditropin) was started at a dose of 0.3 mg/day at bedtime (0.024-0.034 mg/kg/day). Height after one year of GH therapy was 106 cm (gain of 10 cm).

Case 2

An eleven-year-three-month-old female child visited the Paediatric Endocrinology clinic with short stature. Birth history was normal with no history of Neonatal Intensive Care Unit (NICU) admission. General physical and systemic examinations were normal. Patients anthropometry showed a height of 106 cm (Height SDS=-4.69) and weight of 20 kg (Weight SDS=-2.78). Routine investigations, celiac profile, and chest X-ray were normal. Patient left wrist x-ray revealed her bone age to be around seven years ten months. Thyroid Function Tests (TFT) were normal. Serum cortisol (10.3 microg/dL) and ACTH (10.12 pg/mL) were normal. A GH stimulation test with clonidine (5 microg/kg) was done after priming with three consecutive days of oral conjugated oestrogen (2 mg). Patients basal GH level was low (0.12 ng/mL) along with low IGF-1 levels (8.6 ng/mL). GH after stimulation showed low peak GH values at 30 minutes (0.24 ng/mL), 60 minutes (0.78 ng/mL), 90 minutes (1.84 ng/mL), and 120 minutes (0.9 ng/mL). CEMRI of the brain showed a hypoplastic sella with a small anterior pituitary and ectopic posterior pituitary in the median eminence with non visualised pituitary stalk (pituitary stalk interruption syndrome), and the cerebellar tonsil appeared to be herniated into the foramen magnum [Table/Fig-2].



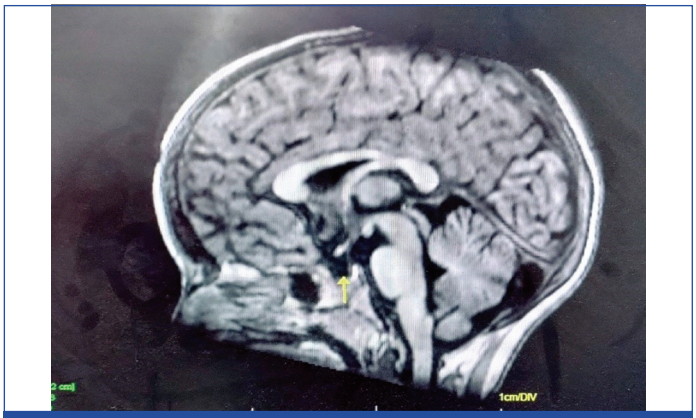
[Table/Fig-2]: CEMRI of the brain. Arrow 1 showed hypoplastic sella with small anterior pituitary and ectopic posterior pituitary in the median eminence with a non visualised pituitary stalk (pituitary stalk interruption syndrome). Arrow 2 showed the cerebellar tonsil which appears herniated into the foramen magnum.

Based on the above clinical, laboratory, and radiological features, the child was diagnosed as a case of GHD, and subsequently, subcutaneous GH was started at a dose of 0.5 mg/day at bedtime. There was a height gain of 4.3 cm in 1st six months of treatment on follow-up.

Case 3

A 10-year-old male, who had not been gaining height and weight for a long duration, visited Outpatient Department seeking possible treatment. Patients general physical and systemic examinations were normal. Anthropometry results revealed a height of 107 cm (Height SDS=-5.05) and a weight of 19 kg (Weight SDS=-2.90). The mid-parental height was 167 cm. Thyroid Function Test (TFT) results were normal, with TSH levels at 3.19 mIU/L and FT4 levels at 1.02 ng/mL. Serum cortisol levels were also normal, measuring 11.02 mg/dL. However, basal GH levels were low (0.17 ng/mL), as were IGF-1 (Insulin-like Growth Factor 1) levels (16.2 ng/mL).

To further evaluate the patient, a GH stimulation test was conducted using tab clonidine (five microgram/kg) after priming with a single Intramuscular testosterone injection (25 mg). The test showed low values at 30 minutes (0.18 ng/mL), 60 minutes (0.43 ng/mL), 90 minutes (0.38 ng/mL), and 120 minutes (0.34 ng/mL). A CEMRI of the brain revealed a partially empty sella with hypoplasia of the anterior pituitary gland [Table/Fig-3].



[Table/Fig-3]: Partially empty sella with hypoplasia of anterior pituitary.

Genetic analysis using clinical exome sequencing identified a homozygous nonsense variation in exon 3 of the Growth Hormone Releasing Hormone Receptor (GHRHR) gene on chromosome 7. This pathogenic variant is associated with the diagnosis of IGHD (Isolated Growth Hormone Deficiency) type 4 (AR) variant, OMIM#618157. The patient was confirmed to have IGHD and was initiated on subcutaneous daily GH therapy at a dose of 0.4 mg/day. After eight months of therapy, there was a remarkable gain of 11 cm in height.

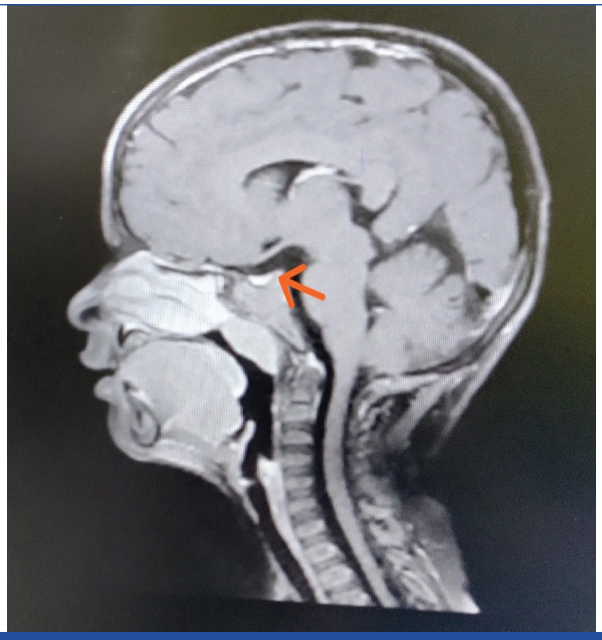
Case 4

The fourth case involves a nine-year-old male child who was brought by his parents due to concerns about his lack of height and weight gain. Upon examination, no abnormalities were found. Anthropometric evaluation showed a height of 100 cm (Height SDS=-5.157) and a weight of 15 kg (Weight SDS=-3.522). The mid-parental height was 161.5 cm, with the father's height measuring 163 cm and the mother's height measuring 147 cm.

Routine blood investigations, blood gas analysis, thyroid profile, celiac profile, serum cortisol, serum ACTH, urine examination, and chest X-ray all yielded normal results. Left wrist and hand X-ray indicated a bone age of approximately six years. A GH stimulation test was performed using clonidine (5 mg/kg). The basal GH level was 0.12 ng/mL, and IGF-1 levels were less than 20 ng/mL. GH levels after stimulation showed low peak values at 30 minutes (0.08 ng/mL), 60 minutes (0.12 ng/mL), 90 minutes (0.35 ng/mL), and 120 minutes (0.47 ng/mL). CEMRI of the brain revealed normal results, with the pituitary structures appearing normal [Table/Fig-4]. Based-on the clinical, laboratory, and radiological features mentioned above, the child was diagnosed with GHD and subcutaneous GH therapy was initiated. Patient started receiving daily GH injections at a dose of 0.4 mg/day, administered subcutaneously at bedtime. During the first year of treatment, there was a notable gain of 7 cm in height.

Case 5

A seven-year-old female presented to the Paediatric Endocrinology Outpatient Department with severe short stature, measuring 94 cm in height (height SDS=-4.34) and weighing 14 kg (weight SDS=-2.53). The child showed normal development in other aspects. Investigations for chronic diseases, metabolic disorders, and nutritional factors yielded negative results. The bone age was determined to be three years, and thyroid function was normal. A GH



[Table/Fig-4]: Near normal pituitary.

stimulation test was performed on the child, revealing a high basal GH level of 46 ng/mL and a low IGF-1 level of less than 20 ng/mL. All values of stimulated GH were high. Based on these findings, Laron syndrome (a signaling pathway defect of the GH-IGF1 axis) was suspected in the patient. Neuro imaging was not conducted, and the patient was referred to higher centres to explore the possibility of IGF-1 therapy. The present case highlighted the challenge of differentiating between Laron syndrome and GH deficiency, as they present with similar clinical features. A thorough work-up is necessary as the baseline GH levels can be normal or high in such cases, potentially delaying the diagnosis if not given proper attention. [Table/Fig-5] provides a summary of the characteristics of all five cases [8,9].

S. No.	Age/Sex	Height/Weight SDS	Basal/Stimulated GH levels (normal range >10 ng/mL) [9]	IGF levels (age-wise range of values to be used) [8]	Brain imaging	Diagnosis
Case 1	6 y 8 mnth/M	-4.69/-2.48	Low	Low	Ectopic pituitary	MPHD
Case 2	11 y 3 mnth/F	-4.89/-2.78	Low	Low	Pituitary stalk interruption syndrome	IGHD
Case 3	10 y/M	-5.05/-2.90	Low	Low	Hypoplasia of anterior pituitary	IGHD/Type 4/AR
Case 4	9 y/M	-5.16/-3.52	Low	Low	Normal brain imaging	IGHD with normal pituitary imaging
Case 5	7 y/F	-4.34/-2.53	High	Low	Not done	Laron syndrome

[Table/Fig-5]: Characteristics of all five cases [8,9].
y: Year; mnth: Month; MPHD: Multiple pituitary hormone deficiency; IGHD: Isolated growth hormone deficiency; AR: Autosomal recessive

DISCUSSION

The diagnosis of GHD should not be based on random GH values alone, as GH is secreted in a pulsatile manner. Instead, stimulated GH values should be used. A comprehensive diagnostic algorithm for children with short stature includes taking a proper history, conducting anthropometric measurements, assessing bone age, and performing investigations to rule out chronic illnesses [10]. Specialised tests for diagnosing GHD include measuring IGF-I and IGF Binding Protein 3 (IGFBP-3), performing provocative GH testing, conducting cranial imaging, and considering genetic testing if warranted [11,12]. The GH provocative or stimulation tests are the cornerstone for diagnosing GH deficiency and should be performed in all patients before initiating GH therapy. Various methods, such as clonidine, levodopa, arginine, insulin, glucagon, etc., can be used for stimulation tests. Stimulation tests using oral clonidine are relatively safe and easy to administer. It is recommended to perform sequential stimulation tests using two stimulating agents to confirm the diagnosis, unless the clinical presentation and radiological findings strongly indicate GH deficiency or the stimulated GH levels are significantly low (with a cut-off of 10 ng/mL) [9]. Sex steroid priming before GH stimulation tests, although controversial, is generally recommended for children around the age of puberty [13].

Genetic testing may be indicated in specific cases, particularly idiopathic, isolated, or familial GHD. IGHD can be classified as sporadic and familial. IGHD can be further subdivided into three categories: IA (OMIM: 262400) and IB (OMIM: 612781) with autosomal recessive inheritance, II (OMIM: 173100) with autosomal dominant inheritance, and III (OMIM: 307200) with X-linked inheritance [14].

Recombinant human Growth Hormone (rhGH) is initiated in children as soon as the diagnosis is confirmed, with a recommended dose of 0.16 to 0.24 mg/kg/week administered daily via subcutaneous injections. GH therapy leads to significant catch-up growth, and if treatment begins early, almost normal height can be achieved [15].

In a study conducted by Bajpai et al., it was demonstrated that the maximum catch-up growth occurs during the first two years of GH treatment. The study suggested that a minimum treatment duration of two years is necessary to achieve proper catch-up growth [16]. Desai MP et al., found that genetic background is more likely to be associated with congenital GHD. While genetic evaluation is not mandatory for diagnosing GH deficiency, it can be useful in cases of idiopathic and familial GHD [17]. In a case report by Boro H et al., the diagnosis and treatment of Laron syndrome were described. Laron syndrome is characterised by GH insensitivity or primary IGF-1 deficiency. The clinical presentation is similar to GHD, with features such as short stature, delayed bone age, and hypoglycemia [18]. Due to the significant variability in the presentation of different GHD patients, it is important to perform all indicated investigations before initiating treatment. Ideally, treatment should be continued until the expected height is achieved or the bony epiphyses are fused. However, if cost constraints are a concern, a minimum treatment duration of two years is required to observe any significant beneficial effects. Regular monitoring during GH therapy is also crucial [16]. An important point to consider is that initiating thyroxine supplementation without prior administration of steroids in cases of MPHD can be life-threatening [19].

CONCLUSION(S)

Growth Hormone Deficiency (GHD) is the second most common endocrine cause of short stature, following hypothyroidism, as reported in several studies. GHD can occur in isolation or be associated with a deficiency of other pituitary hormones, leading to panhypopituitarism. Well-defined guidelines exist for the evaluation of GHD, emphasising the importance of not relying solely on random GH levels for diagnosis. The present case series highlights the significance of an algorithmic approach to diagnosing short stature, the ease of GH stimulation tests, the variability of presentations among GH-deficient children, and the importance of early initiation of GH therapy. Despite all the cases presenting with short stature, authors can observe different spectrums of GH disorders in each case. It is evident that GH therapy resulted in significant height gain.

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