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ORIGINAL ARTICLE

Long-term follow-up data of patients with Multiple Pituitary Hormone Deficiency

Seguimiento a largo plazo de pacientes con Deficiencia Hormonal Hipofisiaria Múltiple

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What do we know about the subject matter of this study?

Multiple pituitary hormone deficiency (MPHD) is a differential diagnosis that should be considered to determine the underlying etiology in cases of hypoglycemia, cholestasis, or jaundice in newborns. Its exact prevalence is not known, but it is estimated to be about 1/8000 worldwide.

What does this study contribute to what is already known?

The long-term follow-up of 45 patients with multiple pituitary hormone deficiencies (MPHD) shows that the most common hormone deficiencies are Growth Hormone (GH) and Thyroid-Stimulating Hormone (TSH), and additional hormone deficiencies may occur even years after the diagnosis. In the presence of pituitary structural anomalies in patients diagnosed with growth hormone deficiency, indefinite follow-up is required to detect the development of MPHD.

Abstract

The deficiency of two or more pituitary hormones is called multiple pituitary hormone deficiencies (MPHD). Its prevalence is estimated to be about 1/8,000 worldwide. **Objective**: To present the diagnosis processes, clinical findings, and long-term follow-up of patients with MPHD. **Patients and Method**: Between 1999 and 2015, patients diagnosed with MPHD were evaluated. Clinical presentation, anthropometry, imaging studies, and clinical evolution were analyzed. Hormone status was evaluated, including growth hormone (GH), thyroid-stimulating hormone (TSH), adrenocorticotropic hormone (ACTH), follicle-stimulating hormone/luteinizing hormone (FSH/LH), and prolactin (PRL). Data were assessed using the student's t-test and the Mann-Whitney U test. Spearman's correlation was used for correlations. A p-value < 0.05 was considered statistically significant. **Results**: Forty-five patients were included; 55.6% were male, the mean age at presentation was

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5.6 ± 3.9 (0-14.4) years, and the median bone age was 3.5 ± 2.3 (0.5-11) years. At admission, GH deficiency was found in 88.9% of the cases, TSH deficiency in 77.8%, ACTH deficiency in 33.3%, FSH/LH deficiency in 22.2%, and PRL deficiency in 17.8%. During the follow-up, 62% of the cases added other hormone deficiencies. The mean follow-up period was 9.18 ± 3.6 (3.02-17.2) years. **Conclusion**: Patients with MPHD have very different clinical presentations, with GH and TSH deficiency being the most common in this study. Additional hormonal deficiencies can occur even years after the initial diagnosis and our results demonstrate that genetic height potential is achieved with GH treatment.

Introduction

The deficiency of two or more pituitary hormones is called multiple pituitary hormone deficiencies (MPHD), and the deficiency of all pituitary hormones is called panhypopituitarism. Its exact prevalence is not known, but it is estimated to be about 1/8000 worldwide[1].

The most important and most common initial sign of congenital hypopituitarism is hypoglycemia. These patients usually present severe and resistant hypoglycemia and related neonatal emergencies, such as seizures, apnea, and cyanosis. Cases with congenital hypopituitarism are usually of normal height and weight at birth. In childhood, somatic growth retardation and proportional short stature are common, which are evident at the end of the first year of life[2]. In some cases, the clinical findings may be nonspecific, and it can be misdiagnosed if it is not suspected.

Although complications such as hypoglycemia, hyponatremia, and recurrent sepsis are observed in 52% of patients with hypopituitarism, only 23% of them are diagnosed in the neonatal period, demonstrating the difficulty of diagnosis in this period[3]. Delay in the diagnosis of hormone deficiencies is an important cause of morbidity and mortality.

Based on the history and clinical findings, if pituitary insufficiency is suspected, simultaneous measurement of hormone levels released from the pituitary gland, target organs, and appropriate dynamic testing should be performed. Patients diagnosed with MPHD are generally on follow-up throughout their lives to detect additional pituitary hormone deficiencies[4].

The objective of this study was to present the diagnosis processes, clinical findings, and long-term follow-up data of MPHD patients on follow-up in a single center.

Patients and Method

Patients

Between January 1999 and November 2015, 66 cases diagnosed with MPHD who were on follow-up were analyzed retrospectively. A total of 45 cases were included in the study, excluding those cases whose records were inaccessible or who did not continue their follow-up.

The diagnosis of MPHD was defined as a deficiency of two or more pituitary hormones that were not accompanied by other diseases that could affect the functioning of the hypothalamus and pituitary gland. Cases that developed MPHD secondary to trauma or had intracranial masses were not included in the study.

Data Collection

Demographic data, newborns' histories, anthropometric measurements during diagnosis and follow-up, pituitary hormone levels, IGF-1 and IGFBP-3 levels, GH stimulation test response, pituitary magnetic resonance images (MRI), and annual elongation rates were recorded retrospectively.

Anthropometric Measurements

Body weight was measured with a SECA scale with 0.1 kg of accuracy. Height measurement was performed by an experienced nurse using the Harpenden stadiometer (Holtain Instruments Ltd, U.K) considering as the final height the average of two consecutive measurements. The mothers' and fathers' height were measured by the same person using the same height meter. Body mass index (BMI) was calculated by dividing the body weight of the patient in kilograms (kg) by the square of her/his height in centimeters. The percentile curves created by Neyzi et al. for Turkish children were taken as reference in the evaluation of height, body weight, and BMI and in calculating the standard deviation score (SDS) of these measurements[5].

Mid-parental height formula was [(mother's height + father's height) - 13] / 2 for females, and [(mother's height + father's height) + 13] / 2 for males.

The height velocity (cm/year) was obtained using the formula [last measurement (cm) - first measurement (cm)] / [elapsed time (month)/12]. The SDS of height velocity was determined by the calculation of [(height velocity - average height velocity of the patient) / standard deviation for that age][6].

Biochemical Measurements

Growth hormone (GH) levels were measured using the Immulite 2000 System (Siemens) through chemiluminescent immunoassay method. Pharmacological stimulation tests were used, including insulin-induced hypoglycemia and induced GH response by levodopa and insulin. In patients younger than two years old, GH levels were evaluated using glucagon test or hypoglycemia. When the hypoglycemia test was contraindicated, the GH stimulation test with clonidine was used, considering values ≥ 10 ng/ml as normal, between 5.1 and 10 ng/ml as partial GH deficiency, and values ≤ 5 ng/ml as complete GH deficiency[6]. GH stimulation tests were performed with patients in a euthyroid state. During the low-dose adrenocorticotropic hormone (ACTH) stimulation test, ACTH deficiency was assessed by either a decreased serum cortisol (COR) level in the morning (< 138 nmol/l) or an altered COR serum increase (< 550 nmol/l) during insulin-induced hypoglycemia, along with an abnormally low serum ACTH concentration.

Serum Insulin-like growth factor I (IGF-1) and insulin-like growth factor binding protein 3 (IGFBP-3) levels were measured by the chemiluminescent immunoassay method using the Immulite 2000 System (Siemens). The deviation of IGF1 and IGFBP-3 levels from normal was calculated according to the study by Elmlinger et al.[7].

Imaging

Bone age determination was made by a pediatric endocrinologist according to the Greulich-Pyle radiology atlas by X-ray of the left hand and wrist. Puberty staging was determined according to Tanner and Marshall's criteria[8].

Hypothalamic-pituitary MRI was performed using a 3T scanner (Siemens, Erlangen, Germany) in sagittal and coronal planes on T1 and T2-weighted images. All images were examined by experienced radiologists and the height of the anterior pituitary, the visibility of the pituitary stalk, and the location of the ectopic posterior pituitary were carefully evaluated for central nervous system malformations.

Statistical Analysis

Data were analyzed using the SPSS software (Statistical Package for Social Sciences) (version 22.0). The arithmetic means, standard deviations, lower limit, upper limit, and significance levels (p-values) of the data obtained from the cases were determined. Values were presented as mean ± 2SD or median and range (minimum-maximum). Body weight, height, and BMI values of the cases were reported only as SDS due to the wide age range of the cases. Descriptive statistics were used for all clinical, radiological, and endocrinological values. Parametric and nonparametric data comparisons were made using the Student's T-test and Mann-Whitney-U test, respectively. Spearman's correlations were used to identify correlations between various parameters. A p-value < 0.05 was considered statistically significant.

Results

Characteristics of the Patients

Of 45 patients included in the study, 55.6% (n = 25) were male, with a mean age at presentation of 5.6 ± 3.9 (0-14.4) years. 80% (n = 36) of the cases were admitted during the kindergarten/school age or adolescence period, and 20% (n = 9) during the newborn or infancy period. 76% (n = 22/29) of the cases were born by spontaneous vaginal delivery. When the neonatal period was analyzed, 11 cases (24.4%) presented jaundice, five cases (11.1%) presented cholestasis, and 12 cases (26.7%) presented hypoglycemia. Manifestations at presentation included growth retardation/short stature in 32 cases (71.1%), hypoglycemia in five cases (11.1%), cholestasis in two cases (4.4%), and thyroid function test abnormalities in two cases (4.4%), as well as polyuria-polydipsia syndrome in one case (2.2%), micropenis in one case (2.2%), undescended testicle in one case (2.2%), and primary amenorrhea in one case (2.2%). When evaluating manifestations according to age groups, the following were found: hypoglycemia and cholestasis in the neonatal period; growth retardation/short stature, hypoglycemia, cholestasis, micropenis, and abnormal thyroid function tests in infancy; growth retardation/short stature, hypoglycemia, abnormal thyroid function tests, micropenis, undescended testicle, and polyuria-polydipsia syndrome in the kindergarten/school age; and growth retardation/short stature and primary amenorrhea in adolescence.

Anthropometric Measurements

At admission, the SDS of the mean height was -3.5 ± 1.4 [-6.7-(+1.5)], with an SDS of body weight of -2.5 ± 1.6 [-6.4-(+2)], and an SDS of BMI of -0.3 ± 1.2 [-2.8-(+1.9)]. The median bone age was 3.5±2.3 (0.5-11) years. The SDS of target height, calculated based on the parent's height was -1.12 ± 0.91 [-3.44-(+1.41)].

When the cases were compared according to gender, no statistically significant differences were observed between the two groups in terms of age, height, body weight, SDS of BMI, bone age, and SDS of target height at admission ($p = 0.26$, $p = 0.95$, $p = 0.68$, $p = 0.45$, $p = 0.057$, $p = 0.55$, respectively) (table 1). The patients with short stature at presentation had an SDS of height of -3.9±1 [-6.7-(-2.5)].

Table 1. Demographic and anthropometric characteristics of the cases at admission and follow-up

	Total n = 45	Female n = 20	Male n = 25	p-value
Chronological age (years)	5.6 ± 3.9 (0-14.4)	4.8 ± 4.1 (0-14.4)	6.1 ± 3.8 (0-13)	0.26
SDS of Height (admission)	-3.5 ± 1.4 [-6.7-(+1.5)]	-3.57 ± 1 [-5.7-(-1.2)]	-3.62 ± 1 [-6.7-(+1.5)]	0.95
SDS of BMI (admission)	-0.3 ± 1.2 [-2.8-(+1.9)	0.12 ± 1.2 [-2.23-(+1.9)	-0.13 ± 1.2 [-2.8-(+1.5)	0.45
SDS of Target height	– 1.12 ± 0.91 [-3.44-(+1.41)]	-1.5 ± 0.93 [-1.98-(+1.41)]	-0.92 ± 0.9 [-3.44-(+0.51)]	0.55
Bone age	3.5 ± 2.3 (0.5-11)	3 ± 3.9 (0.5-11)	3.5 ± 1.37 (1.5-7)	0.057
Follow-up period (years)	9.18 ± 3.6 (3.02-17.2)	9.1 ± 3.1 (3.13-14.9)	9.28 ± 4.2 (3.02-17.2)	0.93
Last evaluation chronological age (years)	14.1 ± 4.8 (3-25)	15.5 ± 4.7 (5-22)	15 ± 4.9 (3-25)	0.91
SDS of Last evaluation height	-1.58 ± 0.98 [-4-(+0.42)]	-1.38 ± 0.95 [-4-(+0.42)]	-1.64 ± 1.01 [-3.67-(+0.01)]	0.51
SDS of Last evaluation BMI	0.1 ± 1 [-2.6-(+1.8)]	-0.01 ± 1.15 [-2.4-(+1.8)]	0.02 ± 1.03 [-2.6-(+1.75)]	0.34
Final/near-final height (cm)	158.9 ± 8 (141.3-178.3) n = 22	154.4 ± 5.3 (141.3-159.1) n = 10	164.95 ± 5.9 (154.9-176) n = 12	*0.001*
SDS of Final/near final height (n = 22)	-1.5 ± 0.78 [-3.2-(+0.01)]	-1.38 ± 0.8 [-3.2-(-0.65)]	-1.66 ± 0.8 [-3.04-(+0.01)]	0.37
SDS of Height increase from the start of therapy to SDS of final height (n = 22)	2.22 ± 1.07 (0.31-4.56)	2.23 ± 0.79 (1.2-4.1)	2.22 ± 1.8 (0.31-4.56)	0.51
SDS of Parental-adjusted height	-0.51 ± 0.97 [-2.1-(+1.6)]	-0.04 ± 0.9 [-0.97-(+1.09]	-0.59 ± 1.02 [-2.1-(+1.6)]	0.53
In accordance with target height (cm)	-3 ± 6.7 [-16.3-(+9)]	0.27 ± 5.5 [-6.9-(+6.5)]	-4.9 ± 7.1 [-16.3-(+9)]	0.35

BMI: Body mass index, SDS: Standard deviation score.

Hormone Deficiencies

At admission, 88.9% (n = 40) of the cases presented GH deficiency, 77.8% (n = 35) TSH deficiency, 33.3% (n = 15) ACTH deficiency, 22.2% (n = 10) FSH/LH deficiency, and 17.8% (n = 8) PRL deficiency.

During the follow-up, 62% (n = 28) of the cases developed other hormone deficiencies in addition to those present at admission. Upon the last evaluation, all cases (100%) presented GH deficiency, 93.3% (n = 42) TSH deficiency, 62.2% (n = 28) ACTH deficiency, 53.3% (n = 24) FSH/LH deficiency, and 20% (n = 9) PRL deficiency. The mean ages at which hormone deficiencies developed were 5.5 ± 3.8 (0-14) years for GH, 5.3 ± 34.5 (0-15) years for TSH, 10.6 ± 4.9 (0-16) years for ACTH, and 13 ± 5.6 (0-15) years for FSH/LH. Table 2 shows the distribution of MPHD observed at admission and during follow-up. Among the 8 (18%) patients who were diagnosed with isolated GH deficiency (IGHD) at admission, five developed TSH deficiency after 5.6 ± 4.2 (0.5-11.58) years, three developed ACTH deficiency after 6.4 ± 4 (1.25-10.7) years, and one developed FSH/LH deficiency after 2.25 years.

Biochemical Data

The median IGF-1 values of the cases at admission were 25.5 (3.26-140) ng/ml, and 93.9% of them were below -2 SDS. The median IGFBP-3 values were 1.25 (0.4-3.5) µg/ml, and 57.5% of them were below -2 SDS. In the GH stimulation test, the mean peak GH response values were 1.3 ± 1.4 (0.02-6.1) ng/ml and 1.5 ± 1.8 (0.03-6.6) ng/ml, respectively. According to the responses in the GH stimulation tests, 88.4% of the cases had complete deficiency and 11.6% had partial deficiency.

Table 2. Hormone deficiencies of cases at admission and follow-up

Hormone Deficiencies	Admission n (%)	Last Check-up % (n)
GH, TSH	12 (27)	7 (15.7)
GH, TSH, ACTH	8 (18)	9 (20)
Isolated GH	8 (18)	-
GH, TSH, PRL	4 (9)	3 (6.7)
GH, TSH, ACTH, FSH/LH	3 (7)	14 (31)
GH, TSH, FSH/LH	2 (4.5)	4 (9)
TSH, ACTH, FSH/LH	2 (4.5)	-
Isolated TSH	1 (2.2)	-
GH, FSH/LH	1 (2.2)	1 (2.2)
TSH, ACTH	1 (2.2)	-
TSH, FSH/LH, PRL	1 (2.2)	-
GH, ACTH, FSH/LH, PRL	1 (2.2)	1 (2.2)
GH, TSH, FSH/LH, PRL	1 (2.2)	2 (4.5)
GH, TSH, ACTH, FSH/LH, PRL	-	2 (4.5)
GH, ACTH	-	1 (2.2)
GH, TSH, ACTH, PRL	-	1 (2.2)

GH: Growth hormone, TSH: Thyroid-stimulating hormone, ACTH: Adrenocorticotropic hormone, FSH/LH: Follicle-stimulating hormone/luteinizing hormone, PRL: Prolactin

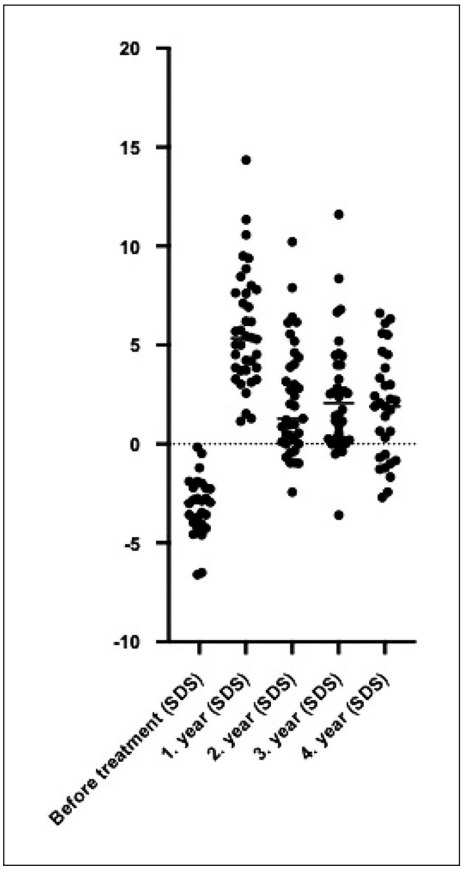

Figure 1. SDS of annual height velocity values of the patients before and after treatment.

Annual Height Velocity

The mean annual height velocity and the SDS height velocity values of the cases with GH deficiency were 3.1 ± 1.5 (0-5.5) cm and -2.9 [-0.1-(-6.6)] SDS, respectively, before GH treatment. These values were 11.4 ± 3.1 (7.9-23) cm and +5.3 [+1.1-(+14.3)] SDS in the first year of GH treatment (figure 1). The SDS of height velocity values of the cases, which were on follow-up up to nine years under GH treatment, ranged from +1 to +2 from the second year to the ninth year of treatment. According to the puberty status of the cases at the beginning of the treatment, the mean SDS of height velocity in the first four years was compared. Although the SDS of height velocity values of pubertal cases were higher in all years compared with prepubertal cases, this difference was statistically significant in the third year ($p = 0.018$).

Radiological Data

Pituitary MRI was performed in 43 cases, showing normal imaging results in 14% (n = 6) of the cases. Pituitary hypoplasia was detected in 62.7% (n = 27/43) of the cases. 10 cases presented pituitary hypoplasia accompanied by ectopic neurohypophysis, and five cases presented ectopic neurohypophysis and infundibulum agenesis along with pituitary hypoplasia. Other MRI findings included empty sella (11.6%, n = 5), isolated ectopic neurohypophysis (4.7%, n = 2), pituitary microadenoma (4.7%, n = 2), and septo-optic dysplasia (n = 1). Pituitary hypoplasia was observed in three of the eight cases diagnosed with IGHD at admission. Two cases presented pituitary hypoplasia along with ectopic neurohypophysis and one case presented pituitary hypoplasia, ectopic neurohypophysis, and infundibulum agenesis. Also, in another case diagnosed with IGHD, the pituitary MRI findings were normal at admission.

Clinical Follow-up

Among the cases, 40% (n = 18) presented diseases and/or complications related to MPHD, including osteoporosis in six cases, dyslipidemia in five cases, undescended testicles in five cases, chronic liver disease in one case, and diabetes insipidus in one case.

The mean follow-up period was 9.18 ± 3.6 (3.02-17.2) years, and the mean chronological age at the last follow-up evaluation was 14.1 ± 4.8 (3-25) years. At the last follow-up evaluation, the SDS of height was

-1.58 ± 0.98 [-4-(+0.42)], the SDS of body weight was -0.8 ± 1.2 [-4.5-(+1.4)], and SDS of BMI was -0.3 ± 1.4 [-2.8-(+1.9)]. Age, follow-up period, height, body weight, and SDS of BMI were similar in both genders at the last follow-up evaluation (Table 1).

The SDS of the median final height of 22 patients who reached the final/near-final height was -1.5 ± 0.78 [-3.2-(+0.01)], and the SDS of the median target height of these patients was -1.29 ± 0.74 [-3.44-(+0.5)]. In 77.3% of the cases, the final/near-final height was above -2 SDS, and in 90% of them, the target height was compatible with the SDS. There was a positive correlation between final height and SDS of parental target height (R = 0.626, $p = 0.003$), and a negative correlation between total height increase and SDS of height, IGF-1, and IGFBP-3 levels before GH treatment (R = -0.671, $p = 0.001$; R = -0.605, $p = 0.013$; R = -0.645, $p = 0.009$, respectively).

Discussion

This study presents clinical and laboratory characteristics, frequency and temporal progression of pituitary hormone deficiencies, long-term follow-up data, and treatment outcomes of 45 cases with congenital MPHD. These cases generally presented normal weight and height at birth, and their medical history highlights the presence of jaundice, cholestasis, and hypoglycemia. Also, it varies according to the age at admission, the most common manifestation was short stature, and new hormone deficiencies were added to the hormonal deficiencies present at the time of admission. Our study showed that 86% of the cases presented pituitary anatomical defects and GH deficiency was detected in all of them. The SDS of the height of 90% of the cases reaching the final/near-final height was compatible with the SDS of the target height.

The clinical presentation of MPHD is known to lack specificity and can vary significantly depending on factors such as the age at presentation and the degree and severity of hormone deficiencies[1]differentiation and maturation may lead to combined pituitary hormone deficiency (CPHD. In addition, the overlap of signs and symptoms of different hormone deficiencies causes difficulties in the diagnosis and management of MPHD[9]. MPHD is a differential diagnosis that should be considered to determine the underlying etiology in cases of hypoglycemia, cholestasis, or jaundice.

In our study, a quarter of our cases had a history of hypoglycemia. In a study of five cases by Cavarzere et al., early-onset and severe neonatal hypoglycemia was reported in all cases[10], emphasizing that clinicians examined the cases for metabolic disease and endocrinological tests and, although only two cases were diagnosed and treated in the neonatal period with these findings, the remaining three cases were diagnosed at the age of two, five, and eight years due to short stature[10].

Similarly, in our study, one patient initially referred to neurology due to drug-resistant seizures was later diagnosed with hypoglycemia during the follow-up. Despite referrals, the family did not seek endocrinology consultation, resulting in a diagnosis of short stature 10 years later. Another patient, who presented hyperbilirubinemia and cholestasis in the neonatal period but was not suspected of ACTH deficiency, was diagnosed in the etiological evaluation with hypoglycemia-induced seizures four years later. Clinicians should be careful about differential diagnosis since early diagnosis may reduce the risk of mortality in MPHD.

The mean age at presentation in our study was 5.9 (0-14.5) years and, although it was lower than the age reported in various studies, it showed a wide distribution[11-13]. The manifestations presented by the cases also varied according to age. While admissions in the neonatal and infant period were due to hypoglycemia, cholestasis, and micropenis, the most common manifestation at school age and adolescence was short stature.

The number, severity, and timing of pituitary hormone deficiencies in MPHD are widely varied; the most common hormone deficiencies are GH and TSH deficiency. It has been reported that ACTH deficiency may occur years after diagnosis and even in adulthood, and the risk of new pituitary hormone deficiency increases as the follow-up period is prolonged[11,14]. In our study, as reported in the literature, the most common and earliest detected hormone deficiencies were GH and TSH deficiencies. During the nine-year follow-up, new hormone deficiencies were added to the existing hormone deficiencies in 62% of our cases. Eight (18%) cases were diagnosed with IGHD at admission.

In a multinational prospective study, 5,805 children diagnosed with IGHD were evaluated, and it was shown that MPHD developed in 5.5% of the cases at the end of 3.5 years of follow-up[15]. In another study in which 83 cases diagnosed with IGHD in childhood were evaluated, it was observed that MPHD developed in 45% of the cases, where the high prevalence may be due to longer-term follow-up[4]. In our study, new hormone deficiencies were observed in addition to GH deficiency in cases diagnosed as IGHD at admission, approximately 12 years after the diagnosis. These findings support the necessity of lifelong follow-up of these cases for additional hormone deficiencies.

In cases diagnosed with MPHD, pituitary imaging should be performed, preferably pituitary MRI, to determine the etiology[16]. For instance, a study evaluating 184 children and adolescents diagnosed

with MPHD reported that only 5% had normal MRI findings, with pituitary stalk interruption syndrome being the most common structural anomaly[17]. Similarly, a study from Turkey revealed that among 53 children with MPHD, 40% had normal MRI findings, while pituitary hypoplasia was the most prevalent structural anomaly[1].

There was a pituitary structural anomaly in 86% of our cases, and pituitary hypoplasia was the most common. In some studies, it has been stated that congenital anomalies of pituitary gland development are strong predictors and risk factors for progression from IGHD to MPHD, with a risk reported of 35% in pituitary hypoplasia, 45-80% in pituitary stalk interruption syndrome/agenesis, and 60% in ectopic neurohypophysis [14,18]. In another recent study, pituitary hypoplasia was reported to be the most important MRI predictor of MPHD development (OR: 9.2)[19].

In our study, in the MRI examinations of the eight cases diagnosed with IGHD at admission, the most common structural anomalies were pituitary hypoplasia and ectopic neurohypophysis, however, one case had normal MRI findings. These results highlight the importance of MRI findings for clinical interpretation, management, and follow-up of these patients and it is suggested that normal MRI findings do not exclude the risk of developing MPHD.

In our study, the SDS of mean height values of the cases at the time of presentation was higher than the studies in the literature evaluating growth and development in cases with MPHD[13,20,21]. This was attributed to the younger age at diagnosis of our cases.

Studies have reported that children with severe GH deficiency are at higher risk of developing MPHD, regardless of the underlying etiology[15]. In a previous study conducted in our clinic, it was observed that the peak GH responses obtained in stimulus tests were lower in cases with MPHD than those with IGHD, and SDS of IGF-1 was below -2 SDS in 80% of the MPHD group and 43% of the IGHD group[21]. In our study, complete GH deficiency was found in 88.4% of the cases, and IGF-1 was below -2 SDS in 90%. Although it is known that MPHD can develop in all IGHD cases, these results suggest that cases with severe deficiency should be followed more carefully.

In a study of patients diagnosed with MPHD on follow-up for 40 years, only 63% of those who received GH treatment achieved a final height compatible with parental target height[20]. Similarly, a KIGS-Pfizer International Growth Database analysis revealed that 81% of MPHD cases achieved the genetic height potential. In addition, it was stated that higher birth weight, taller parents, taller initial height, and first-year growth rate were the most important factors determining final height[13].

In our study, it was observed that 77.3% of 22 patients who reached the final/near-final height achieved growth within normal limits (>3p, >-2SDS), and 90% of them achieved the parental genetic height potential. It has been suggested that the reason for the better outcomes compared with previous studies may be due to the earlier age at diagnosis. It was observed that the most important factor determining the final height was the parental target height, and the best height increase was achieved in cases with lower SDS of height, IGF-1, and IGFBP-3 values at admission.

During the follow-up period, six cases developed osteoporosis (13.3%), five cases developed dyslipidemia (11.1%), and one case developed chronic liver disease. For this reason, physicians should be careful in terms of the possible effects of pituitary hormone deficiencies on other systems and should request the necessary examinations in the follow-up.

The main limitation of this study is the inaccessibility of medical records of all patients due to its retrospective design and the relatively low number of patients. Another limitation was the inability to perform genetic studies.

Conclusions

In our study, focusing on the long-term follow-up data of patients diagnosed with MPHD, we observed a diverse range of clinical presentations. The most common hormone deficiency was GH and TSH deficiency, with the potential additional pituitary hormone deficiencies that may develop even years after the diagnosis. In addition, our results support the need for indefinite follow-up regarding MPHD development, especially in the presence of complete GH deficiency and pituitary structural anomalies in patients diagnosed with IGHD. Finally, it has been shown that the genetic height potential is achieved to a large extent in cases diagnosed with MPHD with GH treatment and, although the best height increase is achieved in cases with low SDS, IGF-1, and IGFBP-3 values at admission, the final height determining factor is parental target height.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

Authors state that no economic support has been associated with the present study.

References

1. Bulut FD, Özdemir Dilek S, Kotan D, Mengen E, Gürbüz F, Yüksel B. Mutations Within the Transcription Factor PROP1 in a Cohort of Turkish Patients with Combined Pituitary Hormone Deficiency. J Clin Res Pediatr Endocrinol. 2020;12(3):261-8.
2. Mehta A, Hindmarsh PC, Stanhope RG, et al. The role of growth hormone in determining birth size and early postnatal growth, using congenital growth hormone deficiency (GHD) as a model. Clin Endocrinol (Oxf). 2005;63(2):223-31.
3. Mehta A, Hindmarsh PC, Dattani MT. An update on the biochemical diagnosis of congenital ACTH insufficiency. Clin Endocrinol (Oxf). 2005;62(3):307-14.
4. Otto AP, França MM, Correa FA, et al. Frequent development of combined pituitary hormone deficiency in patients initially diagnosed as isolated growth hormone deficiency: a long term follow-up of patients from a single center. Pituitary. 2015;184:561-7.
5. Bundak R, Furman A, Gunoz H, Darendeliler F, Bas F, Neyzi O. Body mass index references for Turkish children. Acta Paediatr. 2006;95(2):194-8.
6. Cianfarani S, Tondinelli T, Spadoni GL, Scirè G, Boemi S, Boscherini B. Height velocity and IGF-I assessment in the diagnosis of childhood onset GH insufficiency: do we still need a second GH stimulation test? Clin Endocrinol (Oxf). 2002;57(2):161-7.
7. Elmlinger MW, Zwirner M, Kühnel W. Stability of insulin-like growth factor (IGF)-I and IGF binding protein (IGFBP)-3 measured by the IMMULITE automated chemiluminescence assay system in different blood specimens. Clin Lab. 2005;51(3-4):145-52.
8. Marshall WA, Tanner JM. Variations in the pattern of pubertal changes in boys. Arch Dis Child. 1970;45(239):13-23.
9. Profka E, Rodari G, Giacchetti F, Giavoli C. GH Deficiency and Replacement Therapy in Hypopituitarism: Insight Into the Relationships With Other Hypothalamic-Pituitary Axes. Front Endocrinol (Lausanne). 2021;12:678778.
10. Cavarzere P, Biban P, Gaudino R, et al. Diagnostic pitfalls in the assessment of congenital hypopituitarism. J Endocrinol Invest. 2014;37(12):1201-1209.
11. Higham CE, Johannsson G, Shalet SM. Hypopituitarism. Lancet (London, England). 2016;388(10058):2403-15.
12. Haim-Pinhas H, Kauli R, Lilos P, Laron Z. Growth, development, puberty and adult height of patients with congenital multiple pituitary hormone deficiencies. Growth Horm IGF Res Off J Growth Horm Res Soc Int IGF Res Soc. 2016;27:46-52.
13. Darendeliler F, Lindberg A, Wilton P. Response to growth hormone treatment in isolated growth hormone deficiency versus multiple pituitary hormone deficiency. Horm Res Paediatr. 2011;76 Suppl 1:42-46.
14. Cerbone M, Dattani MT. Progression from isolated growth hormone deficiency to combined pituitary hormone deficiency. Growth Horm IGF Res. 2017;37:19-25.
15. Blum WF, Deal C, Zimmermann AG, et al. Development of additional pituitary hormone deficiencies in pediatric patients originally diagnosed with idiopathic isolated GH deficiency. Eur J Endocrinol. 2014;1701:13-21.
16. Hage C, Gan HW, Ibba A, et al. Advances in differential diagnosis and management of growth hormone deficiency in children. Nat Rev Endocrinol. 2021;17(10):608-24.
17. Wang F, Han J, Shang X, Li G. Distinct pituitary hormone levels of 184 Chinese children and adolescents with multiple pituitary hormone deficiency: a single-centre study. BMC Pediatr. 2019;191:441.
18. Child CJ, Blum WF, Deal C, et al. Development of additional pituitary hormone deficiencies in pediatric patients originally diagnosed with isolated growth hormone deficiency due to organic causes. Eur J Endocrinol. 2016;1745:669-679.
19. Sharma H, Purwar N, Kumar A, et al. Pituitary hypoplasia is the best MRI predictor of the severity and type of growth hormone deficiency in children with congenital growth hormone deficiency. J Pediatr Endocrinol Metab. 2021;34(7):851-858.
20. Rohayem J, Drechsel H, Tittel B, Hahn G, Pfaeffle R, Huebner A. Long-Term Outcomes, Genetics, and Pituitary Morphology in Patients with Isolated Growth Hormone Deficiency and Multiple Pituitary Hormone Deficiencies: A Single-Centre Experience of Four Decades of Growth Hormone Replacement. Horm Res Paediatr. 2016;86(2):106-16.
21. Aycan Z, Aralı Yılmaz A, Yel S, Savaş-Erdeve Ş, Çetinkaya S. Evaluation of Growth Hormone Results in Different Diagnosis and Trend Over 10 Year of Follow-up: A Single Center Experience. J Clin Res Pediatr Endocrinol. 2021;13(3):332-41.