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CASE

Untreated Hypopituitarism Due to Absence of the Pituitary Stalk with Normal Adult Height

Report of Two Cases

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Patients with congenital multiple pituitary hormones deficiency (MPHD) occasionally present with pituitary stalk interruption and ectopic posterior lobe on magnetic resonance imaging (MRI). Very rarely normal adult height despite growth hormone deficiency (GHD) has been described in these patients. We report two patients with evidence of congenital MPHD, who remained untreated until adulthood. They both failed to develop spontaneous puberty, and they demonstrated very low growth velocity until adulthood when they continued to grow, with a final height of 176 and 169 cm when they sought medical attention in our department at the age of 45 and 33 yr, respectively. At that time a hypoplastic pituitary, absence of pituitary stalk, and ectopic posterior pituitary lobe were found on MRI, and the laboratory investigations, including dynamic tests for pituitary hormone reserve, revealed MPHD with severe GHD. In conclusion, these cases illustrate that very rarely patients with untreated MPHD can reach normal adult height. Some postulations about the pathophysiology of this phenomenon are discussed.

Key Words: Multiple pituitary hormone deficiency (MPHD); final height; growth-hormone deficiency; growth factors.

Introduction

Congenital hypopituitarism is a rare disorder consisting of multiple deficiencies of hormones of the anterior lobe (MPHD). Imaging of the hypothalamic pituitary area varies from normal or even hyperplastic pituitary *(1)* to hypoplastic pituitary, absence of the stalk, and posterior lobe ectopia *(2)*. Mutations of the genes of specific pituitary transcription factors are responsible for many cases of congenital MPHD *(3)*. Whatever the cause, it may lead to clinical signs at birth (hypoglycemia, prolonged jaundice, and micropenis) and severe growth retardation, evident during early childhood. Growth hormone deficiency (GHD) plays a predominant role among other factors (low T4 and sex steroids levels) in the low growth velocity, and the reduced growth spurt during puberty *(4)* of these patients. Indeed, treatment with GH restores these abnormalities and results in final height close to target height of the patients *(5)*.

Occasionally, untreated patients with MPHD who achieve normal final adult height despite severe GH deficiency have been described *(6,7)*. Usually these are patients with MPHD secondary to hypothalamic damage (i.e., craniopharingiomas, amartomas, etc.) *(8–11)*. Obesity due to hypothalamic damage and the concomitant hyperinsulinemia are implicated in the pathopysiology of this phenomenon *(7, 12)*. In patients with congenital MPHD however, the phenomenon is extremely rare *(13–16)*. It is possible that, due to the extreme symptoms and clinical signs, treatment is usually provided in infancy or early childhood, so there is a little documentation about the natural history of untreated congenital MPHD.

In this report, we describe two patients with untreated congenital MPHD, absence of pituitary stalk, and ectopic posterior lobe, who reached normal adult height.

Case 1

A 45-yr-old male first presented in 1987 in our department for evaluation of hypopituitarism. His medical history revealed that he was a child of healthy and unrelated parents. His father was 173 cm, and his mother was 158 cm (target height of the patient, i.e., midparental height corrected for sex and secular change of +4.5/generation, 176 cm). No family history of an endocrine disorder that might suggest a genetic syndrome is reported. He was born full-term with unknown birth weight. His mental and psychosocial development were normal. He finished high school and he was working as a secretary. He reported that he had always been

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Table 1
ITT+LHRH+TSH Test of Patient #1 When He Was 45 Yr Old

	–30	0	15	30	45	60	75	90
Glu (mg/dL)	65	68	38	23	25	35	39	61
GH (ng/mL)	<0.5	<0.5	<0.5	<0.5	<0.5	<0.5	<0.5	<0.5
F (μg/mL)	2.1	3.4	4.8	6.1	4.3	4.2	4.4	4.7
ACTH (pg/mL)	<20	<20						
FSH (mIU/mL)	<1.5	<1.5		<1.5		<1.5		
LH (mIU/mL)	3.1	2.2		2.3		2.4		
TSH (mIU/mL)	5.4	5.5		14.5		21.5		

much shorter than his peers at school and he had not developed spontaneous puberty. At age 16 yr his height was 147 cm while by the age of 20 yr he was nearly 159 cm, with no signs of puberty. No details about endocrinological investigation are given but at that time the patient recalls that he was prescribed testosterone enanthate im (250 mg/mo). He was under this treatment for about 2 yr, when he developed secondary sexual characteristics. After this period he discontinued the treatment for unknown reasons. He claimed that without any treatment, he gradually gained about 15 cm of height during the following 6 yr. He has not been followed since the age of 22 yr until when at 44 yr he developed symptoms of renal failure. He was admitted in the surgery ward of our hospital where retroperitoneal fibrosis was diagnosed and the patient underwent uneventfully abdominal surgery. One year later, when he was 45 yr old he was admitted for the first time to our department.

On physical examination he looked younger than his age. His IQ score was normal. His height was 176 cm (identical to target height and with +0.5 SD score for the Greek nationwide references), he weighed 57 kg and his body mass index was 22 kg/m^2. His blood pressure was 130/80 mmHg, and his heart rate was 72 beats/min. He presented with eunuchoid habitus. His sitting height was 104 cm, his span was 174 cm. His voice was high-pitched. He had Tanner stage P1G1. No gynecomastia was detected. Thoracic kyphoscoliosis was present. No abnormalities of heart, lung, or abdomen were revealed.

Routine biochemical evaluation was normal except a mild elevation of the creatinine level (creatine:1.4 ng/dL). Endocrine evaluation disclosed undetectable testosterone (<50 ng/dL) with inappropriately low serum gonadotropin, which did not respond to LHRH stimulation indicating gonadotroph deficiency, low T4 levels (5.5 μg/dL) and slightly elevated TSH with a delayed response to TRH stimulation consistent with tertiary hypothyroidism, whereas the serum prolactin level was within the normal range (12.5 ng/dL). Blunted response of GH and cortisol to insulin tolerance test (ITT), indicating somatotroph and corticotroph deficiency respectively was also noted (Table 1).

A CT scan of the pituitary at that time revealed a hypoplastic pituitary gland. The patient was started on hormonal substitution therapy with levothyroxine 100 μg/d, hydrocortisone 10-5-0 mg daily, and testosterone enanthate 250 mg/mo and, since then, he is followed-up in our outpatient clinic. He responded well to treatment. In 2003 an MRI of the hypothalamic–hypophyseal was performed for the first time, which showed a small anterior pituitary remnant on the sella floor, absence of pituitary stalk, and an ectopic neurohypophysis (Fig. 1).

Case 2

A 33-yr-old male was first admitted in our department in 1989 for evaluation of delayed puberty. His medical history revealed that he was born full-term with breech delivery. His birth weight was 3600 g. He experienced normal psychosocial and mental development. He reported being shorter than his peers until he was 16 yr old, but since that age he claimed continuous growth in height until the age of 30 yr, when he reached his final adult height of 169 cm. He never developed signs of puberty.

At physical examination he looked younger than his age. His height was 169 cm (–0.5 SD score for the Greek nationwide references), and his body mass index was 21 kg/m^2 with eunuchoid habitus. His father was 170 cm tall. There was no information about his mother's height. He had Tanner stage P1G1. His voice was high-pitched. Mild gynecomastia and thoracic kyphoscoliosis were present. He had normal IQ level. No abnormalities of heart, lung, or abdomen were present. Routine laboratory evaluation was normal. The X-ray of the left hand and the wrist showed a bone age of 14 yr *(17)*. Endocrine evaluation including stimulation tests (Table 2) revealed deficiency of gonadotrophs (testosterone <50 ng/dL), somatotrophs, and corticotrops, tertiary hypothyroidism, (T4 4.6 μg/dL), whereas serum prolactin level was within the normal range (8.6 ng/dL).

Imaging of the pituitary at that time was not available. The patient was started on hormonal substitution therapy with levothyroxine 100 μg/d, hydrocortisone 10-5-0 mg daily, and testosterone enanthate 250 mg/mo. He responded well to treatment. He was subsequently followed up regularly as an outpatient and in 2002, an MRI of the hypothalamic–hypophyseal area revealed a small pituitary remnant

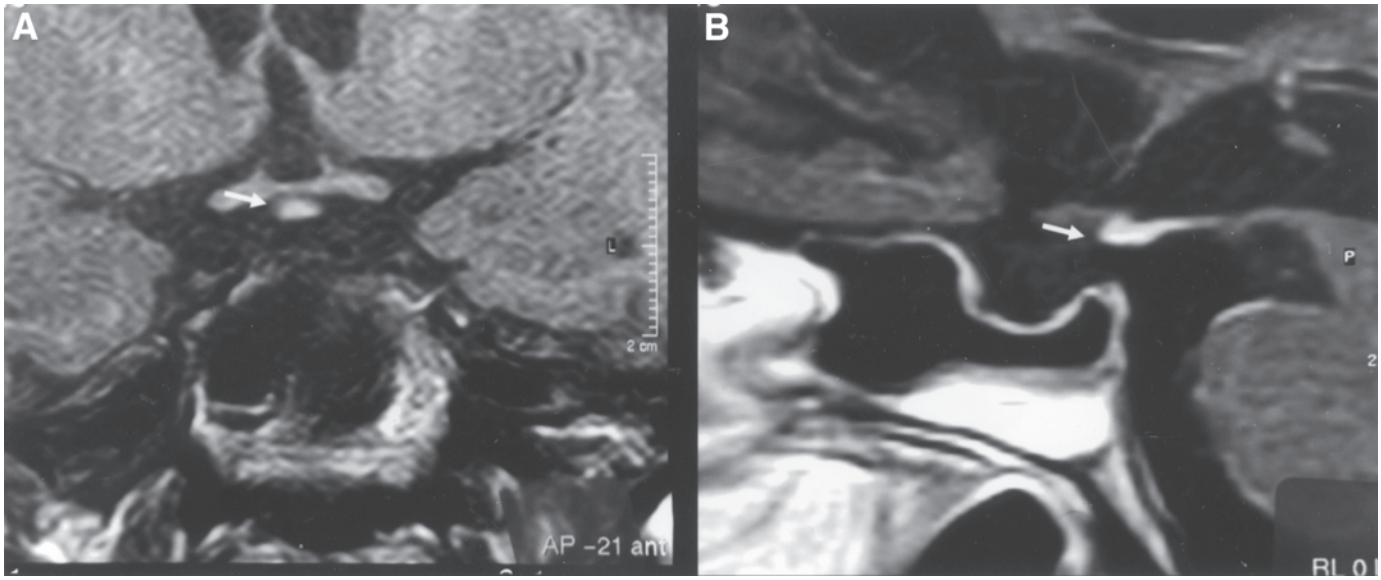

Fig. 1. Coronal **(A)** and saggital **(B)** sections of the hypothalamic–hypophyseal region showing a hypoplastic adenohypophysis, absence of the pituitary stalk, and an ectopic neurohypophysis (white arrow) of patient #1.

Table 2
ITT+LHRH+TSH Test of Patient #2 When He Was 33 Yr Old

	–30	0	15	30	45	60	75	90
Glu (mg/dL)	72	70	35	30	30	32	36	58
GH (ng/mL)	<0.3	<0.3	<0.3	<0.3	<0.3	<0.3	<0.3	<0.3
F (μg/mL)	1.9	2.1	2.3	3.1	2.5	2.6	2.3	2.1
ACTH (pg/mL)	<20	<20						
FSH (mIU/mL)	<1.5	<1.5		<1.5		<1.5		
LH (mIU/mL)	<1.0	<1.0		<1.0		<1.0		
TSH (mIU/mL)	3.9	3.8		17.5		20.5		

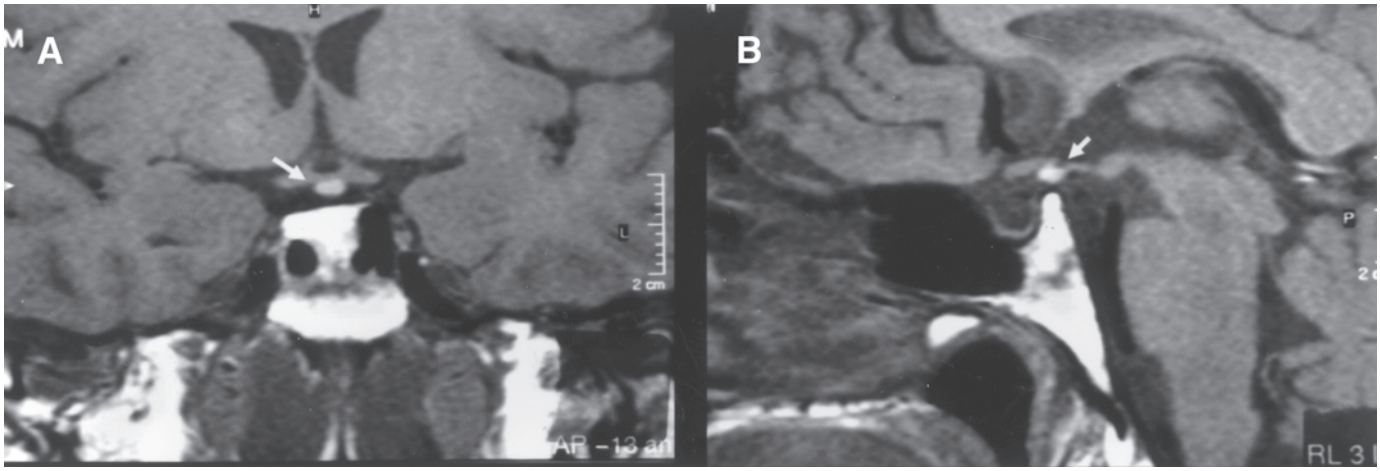

Fig. 2. Coronal **(A)** and saggital **(B)** sections of the hypothalamic–hypophyseal region showing a hypoplastic adenohypophysis, absence of the pituitary stalk and an ectopic neurohypophysis (white arrow) of patient #2.

on the sella floor, no pituitary stalk, and an ectopic neurohypophysis (Fig. 2).

Discussion

Morphological alterations of the hypothalamic–pituitary area on magnetic resonance imaging (MRI), such as pituitary stalk interruption and ectopic posterior lobe, have been associated with congenital MPHD, or, more rarely, with isolated GHD *(18)*. High frequency of perinatal insults, such as breech delivery and/or neonatal hypoxemia, has been demonstrated in these patients indicating a traumatic–ischemic injury of the pituitary stalk or median eminence

as the primary cause of the hormonal deficiencies *(19)*. To our knowledge there was no perinatal insults in the first case however, the documentation of breech delivery in our second patient needs attention. Although loss of function mutations of LHX3 or PROP-1 were not detected in patients with the imaging phenotype described above *(20)*, the possibility of a genetic origin of the MPHD such as a mutation of so far unidentified transcription factor cannot be excluded. The combination of MPHD and retroperitoneal fibrosis in our first patient is of interest. Panhypopituitarism as the first manifestation of retroperitoneal fibrosis due to infiltration of the pituitary gland demonstrated as a tumor mass in MRI has been described *(21)*. However, in that case report, contrary to our patient, the MPHD was of adult onset and was combined with diabetes insipidus. Furthermore, in our patient retroperitoneal fibrosis was diagnosed when he was 44 yr old and at that time his imaging evaluation did not disclose evidence of pituitary involvement of the disease (pituitary enlargement or a tumor mass). Thus, a cause–effect association of MPHD and retroperitoneal fibrosis has to be excluded in our patient.

Our two patients with congenital MPHD associated with hypoplastic pituitary, absence of the pituitary stalk, and ectopic posterior lobe described here present some remarkable features: (1) they remained untreated until adulthood, thus providing rare perfect examples of the natural history of congenital MPHD, (2) both patients were able to live without major complaints despite corticotroph deficiency and furthermore our first patient underwent uneventfully abdominal surgery, (3) despite GH deficiency (diagnosed in adult age) and low initial growth velocity, they achieved normal height without any treatment intervention; (4) prolactin levels were within normal range despite the absence of pituitary stalk, perhaps indicating partial lactotroph deficiency. To our knowledge only seven such cases of untreated congenital MPHD, hypoplastic pituitary, absence of the pituitary stalk, and ectopic posterior lobe have been reported so far *(13–16,22–24)*. Four of these patients, similarly to our two cases, reached an adult height of more than 160 cm *(13–16)*.

Accelerated linear growth has been rarely reported in patients with panhypopituitarism following resection of craniopharyngiomas or other supracellar tumors and in association with some intracranial anomalies, such as septo-optic dysplasia and obesity as well *(8–11,27)*. The exact underlying mechanism of growth in the presence of GH deficiency diagnosed according to standard criteria *(26)* is still unclear. Because most of the affected patients showed hyperphagia and excessive weight gain secondary to hypothalamic damage, the hypothesis that hyperinsulinemia could account for the normal height probably partially through the activation of IGF-I receptor has been proposed *(7,12)*. Although insulin levels were not determined in our patients, the abovementioned mechanism is not a probable cause of normal adult height in our patients as predisposing brain surgery, CNS abnormality on MRI, and obesity were lacking. High levels of prolactin *(7)* or other bioavailable GH/IGF-I variants might also promote growth by stimulating bone elongation *(6)*. However, prolactin was not elevated in our patients. Geffner et al. detected a potent growth factor in the serum of a child who grew without GH *(28)* and Murashita et al. found a normal degree of serum growth-promoting activity in a patient who exhibited near-normal growth, without GH *(9)*. Unidentified locally produced growth factors that influence chondrocyte proliferation through mechanisms other than GH *(29)* is also one of the proposed mechanisms leading to the acromegaloid features, previously reported in patients with undetectable GH and IGF-I levels. Hathout et al. reported markedly elevated leptin levels in a boy with panhypopituitarism and normal growth rate *(30)*. In recent in vitro and in vivo studies Maor et al. demonstrated that leptin induced the proliferation and maturation of the chondrocytes and stimulated IGF-I and IGF-I gene expression in the growth centers *(31)*.

The phenotype and the growth pattern of our patients closely resembles the one described by Ouden et al. *(16)*. In this case as in ours, a patient with untreated hypopituitarism due to transection of the pituitary stalk, showed growth retardation in childhood and adolescence, a very low height for age at 18 yr and continuing growth from 18 to 43 yr of age up to a height considerably taller than the target height. Apart from the borderline obesity and concomitant hyperinsulinemia these authors postulated, based on observations that estrogens have a slightly antagonistic effect on the bioactivity of GH *(32,33)*, that in the absence of estrogens a very low GH secretion if present has a greater effect than expected. Also, differences in sex steroids, insulin, and GH sensitivity, especially locally in the chondrocyte environment, could be another contributing factor *(16)*.

It has been demonstrated that although anatomical abnormalities of the pituitary stalk on MRI denote a worse prognosis in patients with MPHD and ectopic neurohypophysis *(18)*, 39% of 18 such patients exhibited normal GH secretory response to dynamic test *(25)* when retested after puberty. Our two patients, however, demonstrated GH deficiency according to the accepted criteria *(26)* when they underwent GH testing in adulthood and thus the possibility that they reached normal growth because of recovery of GH secretion after puberty has to be excluded. Finally, as laboratory data of endocrine evaluation during childhood and puberty are lucking in our patients, an extreme speculation could be that somatotroph and perhaps corticotroph deficiency were gradually developed (as is the case with corticotroph deficiency in some patients with PROP-1 mutation) *(34)*, and full deficiency of these hormones was established in adulthood, after they reached final height. In that case the low growth velocity during puberty can be explained by the luck of growth spurt due to the presence of hypogonadotrophic hypogonadism.

In conclusion we described two cases of untreated idiopathic MPHD reaching normal adult height. The pathophysiology of this phenomenon remains unknown.

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