# A Hypopituitary Patient who Attained Tall Stature without Growth Hormone

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**We describe an unusual patient with hypopituitarism who attained tall stature even without growth hormone (GH). A 37-year-old man was devoid of secondary sexual characteristics, but manifested tall stature with a eunuchoidal feature. Serum levels of GH, insulin-like growth factor-I, gonadotropins and testosterone were all below normal. GH secretion was not enhanced by any provocative stimulus. Adrenocorticotropic hormone increased after administration of corticotropin releasing hormone, but not after insulin-induced hypoglycemia. Thyrotropin increased in response to thyrotropin releasing hormone, but both free T3 and T4 did not rise. Magnetic resonance imaging disclosed a transected pituitary stalk. The present patient had hypopituitarism due to perinatal problems but had grown with the aid of non-GH growth-promoting factors, which suggests that man may be able to achieve statural growth even without GH.**
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***Key words:*** pituitary stalk transection, eunuchoidism, growth hormone (GH), insulin-like growth factor-I, adrenocorticotropic hormone, prolactin

## Introduction

Growth hormone (GH) plays a primary role in stimulating postnatal growth by way of insulin-like growth factor-I (IGF-I), which is produced in the liver in response to GH (1). A deficiency of GH arrests maturation during childhood, and the stature of such subjects is generally much shorter than the average stature (1). However, some cases of GH deficiency attain normal stature as adults. Some patients with craniopharyngioma grow independently of GH secretion (2, 3). As far as we know, there is only one previous case report on growth without GH in hypopituitarism. Ihara et al (4) reported that a panhypopituitary subject who had pituitary stalk transection (PST) on magnetic resonance imaging (MRI) attained normal stature without GH replacement. We herewith report another rare case of GH deficiency who manifested tall stature as adult even without GH. In our patient, it is likely that potent growth-promoting factor(s) other than GH and IGF-I may have played a role in stimulating the growth.

## Case Report

In September 1995, a 37-year-old male was referred to our department for a further evaluation of hypogonadism. He was born with normal presentation, but had a severe jaundice within a month after birth. His first gait occurred at the age of 18 months. Although he was the shortest in his class throughout his school days, he subsequently began to grow slowly but steadily around the age of 18 years old, and had attained the stature of 185 cm by age 30.

On admission to our hospital, his height was 185 cm (mean +2.6 SD) with his upper trunk being 84 cm, lower trunk 101 cm, arm span 182 cm, and body weight 84 kg. He had no goiter. He was devoid of secondary sexual characteristics. The epiphyseal lines in the four limbs were all still unclosed, and his bone age corresponded to that of 15-year-old boys as estimated by X-ray findings according to the Turner's 2nd method. His intelligence (quotient 75) was subnormal according to the Wechsler adult intelligence scale-R test.

His serum GH (<0.3 ng/ml) and IGF-I (21 ng/ml, normal range; 202–433 ng/ml) were undetectable and below normal, respectively. As shown in Table 1, no distinct diurnal rhythm was demonstrated for GH. The patient's GH level did not increase either after the administration of GH-releasing hormone (GRH), or after insulin-induced hypoglycemia. Both serum luteinizing hormone (LH, <0.4 mIU/ml) and follicle-stimulating hormone (FSH, 0.4 mIU/ml) were both below normal. These hormones did not increase after intravenous

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administration of LH-RH. Testosterone levels in the serum (<0.5 ng/dl) and urine (<4.4 μg/day) were both below normal. Plasma adrenocorticotropic hormone (ACTH) increased after human corticotropin releasing hormone (CRH) injection, but not after insulin-induced hypoglycemia [insulin 0.05 U/kg body weight, 0.07 U/kg body weight (not shown in Table)]. Cortisol levels in the serum (2.4 μg/dl) and urine (24.6 μg/day) were both below normal. Serum thyrotropin (TSH) increased in resonse to an intravenous administration of TSH-releasing hormone (TRH), but both free T3 and T4 did not. Urinary osmotic pressure (440 mOsm/kg) and urine volume (about 1,500 ml/day) were within the normal range. MRI of the head revealed a transected pituitary stalk and an ectopic posterior lobe at the proximal stump of the pituitary stalk (Fig. 1). His olfactory sensation was normal, and his sex chromosomal pattern was that of normal males (XY). Under the diagnosis of hypopituitarism due to PST, we started a replacement therapy of hydrocortisone (10 mg per day) orally, levothyroxine sodium (25 μg per day) orally, and testosterone enanthate (250 mg once per two weeks) intramuscularly. After one year of such treatment, his voice began to drop in pitch, although pubic hair did not grow. His height did not further increase.

**Table 1. Endocrinological Examinations**

(a) Diurnal variation

| Time | 04:00 | 08:00 | 12:00 | 16:00 | 20:00 | 24:00 (h) |
|---|---|---|---|---|---|---|
| GH (ng/ml) | <0.3 | <0.3 | <0.3 | <0.3 | <0.3 | <0.3 |
| ACTH (pg/ml) | 15.6 | 11.1 | <5.0 | <5.0 | 7.7 | 11.2 |

(b) Loading test (GRH 100 μg, Human CRH 100 μg, TRH 500 μg, and LH-RH 100 μg, iv bolus)

| Time | 0 | 15 | 30 | 60 | 90 | 120 (min) |
|---|---|---|---|---|---|---|
| GH (ng/ml) | <0.3 | <0.3 | <0.3 | 0.9 | 1.0 | 0.5 |
| ACTH (pg/ml) | 14.5 | 108.3 | 83.4 | 42.6 | 30.4 | |
| TSH (μU/ml) | 8.37 | 38.4 | 51.9 | 62.1 | 52.1 | 40.0 |
| PRL (ng/ml) | 7.2 | 15.2 | 16.1 | 13.0 | 10.9 | 9.8 |
| LH (mIU/ml) | <0.4 | <0.4 | <0.4 | <0.4 | <0.4 | <0.4 |
| FSH (mIU/ml) | 0.4 | 0.6 | 0.7 | 0.8 | 0.9 | 0.9 |
| Cortisol (μg/dl) | 2.4 | 6.4 | 9.9 | 8.5 | 6.6 | |
| Free $T_3$ (pg/ml) | 5.5 | | | | | 4.2 |
| Free $T_4$ (ng/dl) | 0.5 | | | | | 0.4 |

(c) Insulin-induced hypoglycemia test (insulin 0.05 U/Kg BW, iv bolus)

| Time | 0 | 15 | 30 | 60 | 90 | 120 (min) |
|---|---|---|---|---|---|---|
| Glucose (mg/dl) | 85 | 65 | 52 | 75 | 80 | 82 |
| GH (ng/ml) | <0.3 | <0.3 | <0.3 | <0.3 | <0.3 | <0.3 |
| ACTH (pg/ml) | 15.9 | 10.9 | 17.1 | 19.5 | 17.0 | 16.5 |
| Cortisol (μg/dl) | 2.7 | 2.3 | 1.9 | 2.1 | 2.6 | 3.1 |

(d) LH-RH test (100 μg, iv bolus) after administration of LH-RH (100 μg, im) for 6 days

| Time | 0 | 15 | 30 | 60 | 120 (min) |
|---|---|---|---|---|---|
| LH (mIU/ml) | <0.4 | 0.9 | 0.7 | 0.6 | 0.4 |
| FSH (mIU/ml) | 1.1 | 2.7 | 3.1 | 3.1 | 3.0 |

iv: intravenous, im: intramuscular. Normal basal ranges: serum GH: <3.1 ng/ml, plasma ACTH: 9–52 pg/ml, serum TSH: 0.60–3.66 μIU/dl, serum PRL: 1.5–9.7 ng/ml, serum LH, 1.8–5.2 mIU/ml, serum FSH: 2.9–8.2 mIU/ml, serum cortisol: 4.0–18.3 μg/dl, serum free $T_3$: 2.47–4.34 pg/ml, serum free $T_4$: 4.5–12.0 μg/dl.

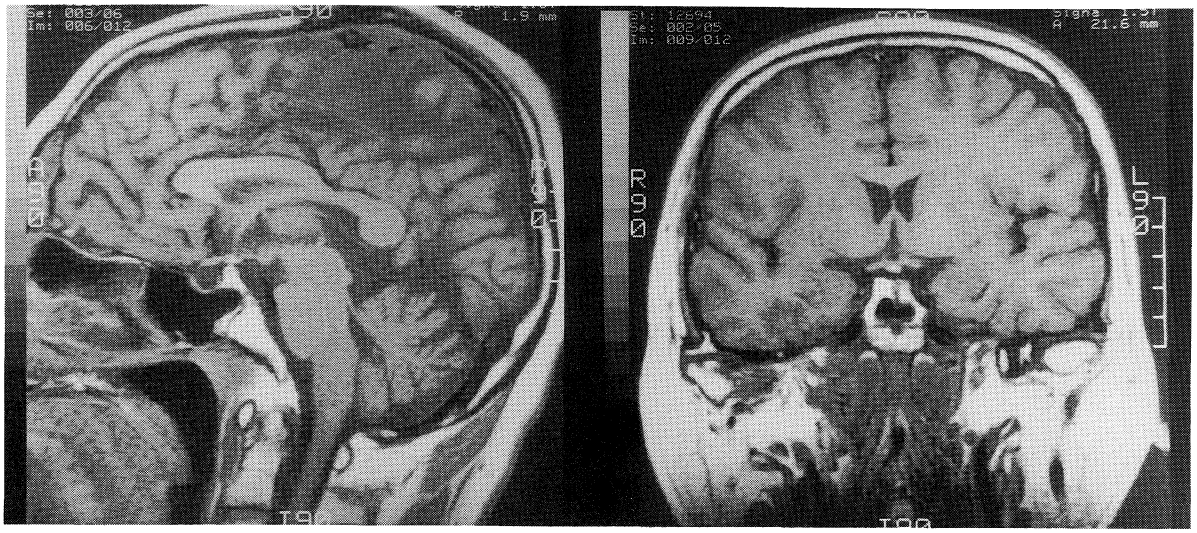

**Figure 1. Magnetic resonance imaging of the head. Sagittal and coronal T1-weighted images demonstrate the presence of a transected pituitary stalk and an ectopic posterior pituitary lobe at the proximal stump of the pituitary stalk.**

## Discussion

The growth in the present patient may probably have been independent of GH secretion, because both GH and IGF-I levels were low, and GH secretion was not stimulated by insulin-induced hypoglycemia. He had a severe jaundice of unknown cause after birth. Although he had no head trauma thereafter, MRI of the pituitary gland on admission demonstrated a transected pituitary stalk and an ectopic posterior lobe (5, 6). Moreover, he did not grow taller throughout his school days, and did not develop secondary sexual characteristics. These findings strongly suggest that this patient has had hypopituitarism (at least the lack of GH and gonadotropins) due to perinatal problems, and that he had grown independently of GH and IGF-I secretion during adolescence.

Growth independent of GH has been reported in some cases of craniopharyngioma, but in only one case of hypopituitarism due to PST (4). It is known that there exist some growth-promoting factors other than GH and IGF-I, and thyroid hormone, insulin, prolactin (PRL) and IGF-II play significant roles in postnatal somatic growth even without GH (1, 2, 7, 8). In most cases with thyroid hormone deficiency a severe growth failure occurs, and these patients have nearly absolute growth arrest (1, 9). Thyroid hormone stimulates growth not only by secreting pituitary GH but also by directly accelerating cartilaginous maturation. In our present patient, TSH increased after TRH, but thyroid hormones did not. This may suggest the presence of TSH with a low bioactivity, as in some cases of hypophysial damage (4). Insulin is known to bind to the IGF-I receptor, increase chondrogenesis, and stimulate growth without GH (1, 10). Actually, some patients with hyperinsulinemia have been reported to finally achieve tall stature (11). PRL also seems to have a growth-promoting effect, although its detailed mechanism of action remains to be elucidated (1). IGF-II, which is similar in structure to IGF-I (8), acts as one of somatomedins and is less GH-dependent than IGF-I. In our patient, it is possible that these several growth factors independent of the GH-IGF-I axis promoted his statural growth. In addition to this, the delayed epiphyseal closure due to his probably long-lasting hypogonadism may have also helped maintain the sustained growth.

In summary, we report an unusual case of GH deficiency who achieved tall stature. The growth of our patient may probably have been mediated by non-GH growth-promoting factors. This case interestingly suggests that man may be able to grow even without GH.

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