CASE REPORT

Response to Growth Hormone Therapy in Adolescents with Familial Panhypopituitarism

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Familial combined pituitary hormone deficiency is a rare endocrine disorder. We describe growth patterns of four children (3 females and 1 male) from two families with combined pituitary hormone deficiency. These children received growth hormone at ages ranging from 14.5 years to 19 years. While all the female siblings reached their target height, the male sibling was much shorter than mid parental height. The reasons for sexual dimorphism in growth patterns in these children are unclear.

Key words: Familial, Growth hormone, Hypopituitarism.

Familial combined pituitary hormone deficiency is rare(1). Short stature is the most common clinical manifestation of panhypopituitarism(1,2). We describe growth patterns in children from two families with hypopituitarism initiated late on growth hormone (GH) therapy.

CASE REPORTS

Family 1: Two sisters aged 5 and 6 years, presented with complaints of short stature and poor height velocity (2.5 cm/year). At 7 and 8 years, they measured 85 cm and 90 cm. Thyroxine was started for central hypothyroidism. Dynamic GH testing with clonidine revealed GH deficiency. GH therapy could, however, not be started due to financial constraints. They returned at 11.5 and 12.5 years of age when they measured 95 cm and 99 cm (Bone ages- 7.5 years and 8.4 years). Treatment with GH (0.07 IU/kg/day) for one year resulted in height gains of 14 cm and 15.5 cm, respectively. They were lost to follow up thereafter till ages 18 and 19 years when they presented again with short stature and lack of secondary sexual characters. Heights recorded were 137 cm and 141 cm (Bone ages-11.2 and 12 yrs). Hormonal profile at ages 18 and 19 years is given in ***Table* I.** Inspite of low cortisol levels, there was no apparent clinical manifestation of cortisol deficiency. GH therapy given in the dose of 0.1 IU/kg/day for one year and four months resulted in 13 cm and 12.5 cm of height gain, respectively. They were advised regarding intake of steroids during illness and regular telephonic contacts regarding their well being throughout the rest of follow-up were maintained. Estrogens initiated at ages 19.5 and 20.5 years resulted in further height gain. Presently aged 22 and 23 years, they measure 159 cm and 163 cm (0.1 SD and 0.6 SD, respectively), much above the midparental height of 149 cm. Prednisolone therapy has been recently initiated for complaints of excessive sleepiness and lethargy. Two other male siblings are unaffected.

Family 2: This was a family with two children - elder girl and younger boy. The girl presented at 11 years of age with complaints of short stature. Her height was 109 cm at -5.4 standard deviation score and bone age was 8 yrs. Father's height was 165 cm and mother's was 148 cm. Thyroxine was initiated for central hypothyroidism. GH dynamic testing performed two months later revealed GH deficiency. GH therapy however could not be instituted due to financial constraints. She again presented at 18 years of age with complaints of short stature (height 139 cm) and absent secondary sexual characters. GH

TABLE I CLINICAL AND HORMONAL PROFILE OF CASES

Family	Sex	Age*	T4 (nmol/L)	TSH (μIU/mL)	GH Peak (ng/mL)	Prolactin (ng/mL)	Cortisol (5-25 μg/mL)	ACTH stimulated cortisol (mcg/mL)	LH IU/L	FSH IU/L	Height SDS*	Final height SDS
Family 1	F	6	30	0.32	<1	3.8*	2.3*	–	1.2*	2*	–6.4	0.6
	F	5	80	1.2	<1	6.2†	3.1†	–	0.4†	0.4†	–6.6	0.1
Family 2	F	11	Low	0.8	0.79	6	NA	NA	0.2*	0.3*	–5.4	–1.6
	M	7	Low	1.8	0.4	3.5	2.1**	12.6**	0.1†	0.2†	–5.1	–5.4

*Test done at †18 years of age; *19 years of age and **21 years of age; NA: not available; *at presentation*

therapy (0.07 IU/kg/day) given for one year resulted in 5.5 cm height gain. Estrogens were started at 19 years of age. Presently aged 26 years, her height is 152 cm.

The younger brother of the above case presented at 7 years of age with complaints of short stature. His height was 95 cms at -5.1 SDS and bone age of 4 years . Thyroid profile was normal, GH dynamic testing revealed GH deficiency. GH therapy could, however, not be initiated till 14.5 years of age. At this time his height was 121 cm with a prepubertal phenotype. Thyroxine was initiated for central hypothyroidism. GH therapy given for one year (0.1 IU/kg/day) resulted in a poor height gain of 3 cm. Testosterone initiation at 18 years of age caused a further height gain of 6 cm in one year. Cortisol replacement was initiated at 21 years of age for symptomatic hyponatremia causing seizures. Magnetic Resonance Imaging revealed partial empty sella. Presently aged 22 years, he is 137 cm tall at 5.4 SD, much below the midparental height of 163 cm. The genetic analysis of this family revealed homozygous 13 bp deletion in PROP1 gene (112-124Ä) in both these siblings(3).

DISCUSSION

In the present report, affected siblings in the two families had a combination of GH, thyroid stimulating hormone (TSH), gonadotopin and adrenocorticotropin hormone deficiency (characteristically seen in PROP1 gene defects)(1-4). All these hormonal deficiencies, however, did not develop at one time. ACTH deficiency became evident during adulthood in the male sibling; the two female siblings were asymptomatic inspite of low cortisol levels. Such a silent and delayed manifestation of corticotropin deficiency in patients with hypopituitarism has been described earlier(4-6). This late onset hypocortisolism due to Prop 1 gene defects has been attributed to lack of paracrine factors surrounding the corticotrophs and progressive corticotroph apoptosis(4).

The two sisters who were initiated late on sex steroids and corticosteroids were taller than their expected height. Some studies have shown better height outcomes in patients who were initiated on sex steroids at a late age (around 18 years) compared to those exposed earlier(14-15 years)(7,8). It is believed that a greater height at onset of puberty, retarded bone age velocity at pubertal bone age and a protracted pubertal height gain were possibly responsible for better results in patients initiated late on sex steroids. Witz, *et al.*(5) described a cohort of patients with panhypopituitarism who were corticotroph deficent. The subgroup that received hydrocortisone (5-10 mg) had lower growth response to GH compared to those who did not receive steroid supplementation. There are anecdotal reports of poor growth response to GH therapy in boys with hypopituitarism compared to girls. Bosch, *et al.*(9) described two males who showed a poor height gain (2-3.5 cm/yr) with GH therapy initiated at 22 and 24 years. Asteria, *et al.*(4) described two females with Prop 1 deficiency who had height gain of around 9 cm per year with GH therapy and had final height exceeding target height. Lerner, *et al.*(10) described differential growth responses to GH in males and females with hypopituitarism, who

had received craniospinal irradiation therapy. A shorter height in males in this report was attributed to a differential spinal growth in males as compared to the females.

We conclude that patients with combined pituitary hormone deficiencies may benefit with GH therapy even when they present late. Steroid replacement should be minimized to ensure an optimal growth without compromising the need for additional steroids during periods of stress. We observed that females reached their target height, but final height was much less in the only male. Reasons for this sexually dimorphic growth response to GH therapy are unclear and need to be investigated.

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