

## Growth hormone deficiency due to traumatic brain injury in a patient with X-linked congenital adrenal hypoplasia

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**SUMMARY** Engiz Ö, Özön A, Riepe F, Alikashifoğlu A, Gönç N, Kandemir N. Growth hormone deficiency due to traumatic brain injury in a patient with X-linked congenital adrenal hypoplasia. *Turk J Pediatr* 2010; 52; 312-316.

X-linked adrenal hypoplasia congenita (AHC) is characterized by primary adrenal insufficiency and is frequently associated with hypogonadotropic hypogonadism (HH). The production of other pituitary hormones (adrenocorticotropic hormone [ACTH], growth hormone [GH], thyroid-stimulating hormone [TSH], and prolactin [PRL]) is usually normal. Mutations of the DAX-1 gene have been reported in patients with AHC and HH. We present a 13-year-old male patient with AHC caused by a nonsense mutation in the DAX-1 gene who developed GH deficiency following head trauma. He showed signs of adrenal insufficiency at the age of 23 months, and glucocorticoid and mineralocorticoid treatment was started. His parents reported head trauma due to a traffic accident at the age of 21 months. Adrenal computed tomography revealed hypoplasia of the left and agenesis of the right adrenal gland. Decreased growth rate was noted at the age of 12.5 years while receiving hydrocortisone 15 mg/m<sup>2</sup>/day. His height was 139.9 cm (-1.46 SD), body weight was 54.9 kg, pubic hair was Tanner stage 1, and testis size was 3 ml. His bone age was 7 years. His gonadotropin (follicle-stimulating hormone [FSH], luteinizing hormone [LH]) and testosterone levels were prepubertal. The evaluation of GH/insulin-like growth factor-1 (IGF-1) secretion at the age of 13 years revealed GH deficiency. Pituitary magnetic resonance imaging demonstrated a hypoplastic hypophysis (<2.5 mm) and a normal infundibulum. GH treatment (0.73 IU/kg/week) was started. This paper reports a patient with genetically confirmed AHC demonstrating GH deficiency possibly due to a previous head trauma. Complete pituitary evaluation should be performed in any child who has survived severe traumatic brain injury.

**Key words:** X-linked congenital adrenal hypoplasia, growth hormone deficiency, traumatic brain injury.

Adrenal hypoplasia congenita (AHC) is a rare cause of congenital adrenal insufficiency and was first described by Sikl<sup>1</sup>. Affected patients present with salt-wasting and Addisonian crises leading to hyponatremia, hyperkalemia, hypotension, hypoglycemic convulsions, and hyperpigmentation in the first months of life<sup>2,3</sup>. Hypogonadotropic hypogonadism is a frequent feature<sup>4,5</sup>. Other pituitary hormone deficiencies have not been reported previously. The DAX-1 gene (for dosage-sensitive sex reversal, AHC critical region on the X-chromosome, gene 1) has been cloned as the gene responsible

for X-linked AHC<sup>6</sup>. Various mutations have been described in the DAX-1 gene<sup>7-10</sup>. In this paper, we present a patient with combined X-linked AHC and growth hormone (GH) deficiency. A nonsense mutation resulting in a premature stop codon at amino acid position 91 was demonstrated by molecular analysis. GH deficiency in our patient possibly resulted from a traumatic brain injury caused by a traffic accident 11 years before.

### Case Report

The patient, EG, is a 13-year-old male. He was

born by spontaneous vaginal delivery after an uneventful pregnancy with a birthweight of 3500 g. He is the first child of consanguineous parents. He survived a head trauma and an arm fracture due to a traffic accident at the age of 21 months. He was inside a car with his mother, who died during the crash. He was unconscious for several minutes after the accident. He was monitored in the intensive care unit for one day. Cranial computed tomography (CT) demonstrated no hematoma. No intervention was done.

Although there was no evidence of acute adrenal insufficiency during the neonatal period, he manifested vomiting and hyponatremic convulsions at the age of 23 months (measurements at the time were serum Na: 117 mEq/L, serum K: 6.2 mEq/L). He was readmitted to another hospital because of vomiting and convulsions two months later (serum Na: 115 mEq/L, serum K: 4.7 mEq/L).

He was referred to Hacettepe University Department of Pediatric Endocrinology at the age of 25 months with suspected adrenal insufficiency. Physical examination showed signs of moderate dehydration and penile hyperpigmentation as well as hyperpigmentation on both knees, elbows, hands and neck. Laboratory evaluation revealed hyponatremia (serum Na: 126 mEq/L) and hyperkalemia (serum K: 6.4 mEq/L). Urine Na was 90 mEq/L. Serum glucose was 73 mg/dl, adrenocorticotropic hormone (ACTH) 1710 pg/ml (N: 10-100), cortisol 11 µg/dl (5-25), and dehydroepiandrosterone sulfate (DHEAS) 17 µg/dl (N: 100-600). Hydrocortisone (30 mg/m<sup>2</sup>/day) and fludrocortisone (0.1 mg/day) therapy as well as oral NaCl were started. Abdominal ultrasonographic examination was normal. Adrenal CT revealed hypoplasia of the left adrenal and agenesis of the right adrenal. The ACTH stimulation test was performed with a bolus injection of 125 µg ACTH (Synacthen, Ciba-Geigy, Wehr, Germany). Blood samples were taken immediately before and 60 minutes after ACTH injection. A grossly impaired cortisol response to ACTH stimulation was obtained (Table I).

He remained on glucocorticoid and mineralocorticoid replacement for 10 years. Clinically, he responded well to these

treatments. He remained at the 50th percentile on the growth curve until 5 years of age. Thereafter, he gradually descended to the 25th percentile and remained there until 9 years of age, after which his growth decelerated to the 3rd percentile. He was evaluated for reduced growth velocity at the age of 12.5 years (Tanner stage 2) while receiving hydrocortisone 15 mg/m<sup>2</sup>/day (Fig. 1). He had elevated ACTH levels during the course of his treatment, possibly due to non-compliance. Therefore, glucocorticoid doses were increased above the recommended replacement doses. His height was 139.9 cm (-1.46 SD), and bone age was 7 years at the time of evaluation. His body weight was 54.9 kg, pubic hair was Tanner stage 1, and testis size was 3 ml. The mid-parental height of the patient was 173 cm. His father did not have a history of delayed puberty.

Laboratory investigations revealed normal thyroid function with free T4: 19.82 pmol/L (normal range: 12-22) and thyroid-stimulating hormone (TSH): 2.42 uIU/mL (normal range: 0.27-4.2). Serum insulin-like growth factor-1 (IGF-1) (161.9 ng/ml, -1.5 SD) and serum IGF binding protein-3 (IGFBP-3) (3494.74 ng/ml,

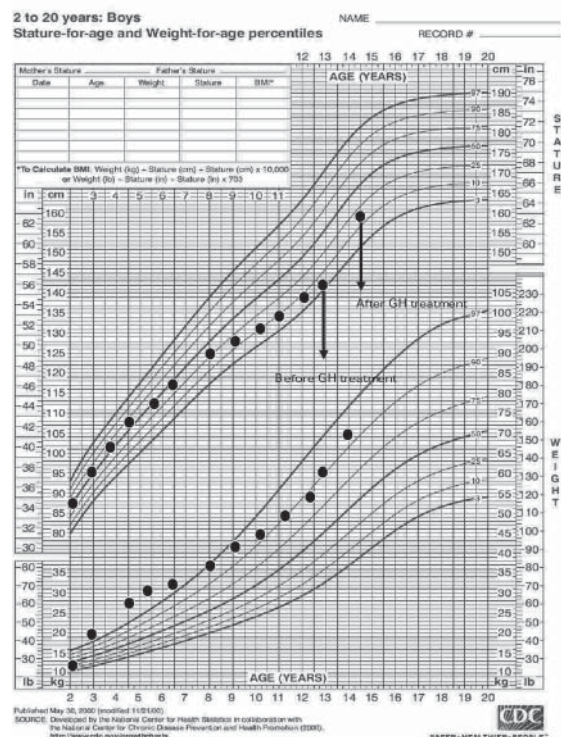


Fig. 1: Growth chart of the patient.

Table I. Standard ACTH Stimulation Test Results of the Patient

	17-OH Progesterone (ng/ml)	Cortisol (µg/dl)	11-Deoxycortisol (ng/ml)
0'	0.136	6.9	4.0
30'	0.38	9.4	
60'	0.19	8.1	4.3
90'	0.39	6.9	6.0

-0.3 SD) were below the mean for age and sex. GH stimulation with L-dopa showed a peak GH of 1.99 ng/ml. Peak GH was 2.96 ng/ml on clonidine stimulation following priming with testosterone. Pituitary magnetic resonance imaging (MRI) revealed a pituitary gland with decreased height (<2.5 mm) (normal pituitary height for his age: 7 mm) and a normal infundibulum. Serum gonadotropins were follicle-stimulating hormone (FSH) 1.67 mIU/mL and luteinizing hormone (LH): <0.07 mIU/mL, while testosterone was <20 ng/dl.

After six months, he was reevaluated. His height velocity in the last year was 4.7 cm/year. The mean hydrocortisone dose was 16.6 mg/m<sup>2</sup>/day during his follow-up period. Serum FSH was 3.49 mIU/mL, LH: 0.14 mIU/mL, prolactin: 6.6 ng/ml (N: 2.5-18.1), and DHEAS: <15 µg/dl (N: 100-600). A repeat clonidine stimulation test following priming with testosterone revealed a peak GH level of 7.2 ng/ml. Recombinant human growth hormone (rhGH) treatment was started. A total height gain of 17 cm was achieved after 1.5 years of GH treatment. Moreover, molecular analysis of the *DAX-1* gene was performed as described before<sup>11</sup>. Exons 1 and 2 of the *DAX-1* gene were amplified by polymerase chain reaction (PCR), and the PCR products were directly sequenced. Hemizygoty for c.273C>A (Y91X) was identified. This nonsense mutation results in a premature stop codon at amino acid position 91 which produces a truncated *DAX-1* protein with predicted complete loss of function<sup>7</sup>.

## Discussion

This report presents GH deficiency possibly due to traumatic brain injury in a patient with genetically confirmed AHC. GH deficiency following traumatic brain injury has been previously reported in children<sup>12,13</sup>. Recently,

a study by Poomthavorn et al.<sup>14</sup> reported evidence of pituitary dysfunction in 9 of 117 pediatric survivors of severe traumatic brain injury. Four of these patients had multiple pituitary hormone deficiencies, including GH deficiency. Two patients with GH deficiency received GH treatment and achieved a final height in the appropriate target height range. Einaudi et al.<sup>15</sup> studied pituitary function in 48 survivors of childhood traumatic brain injury, and reported hypothalamo-pituitary dysfunction in 10% of the cases. GH deficiency was the most frequent disorder in the study group. Two patients with normal pituitary function immediately after traumatic brain injury subsequently developed hypopituitarism after 12 months. Adrenal insufficiency was diagnosed in one patient while GH deficiency was observed in the other.

Delay in the diagnosis of hypopituitarism after traumatic brain injury appears to be a common problem. Benvenga et al.<sup>16</sup> reported post-traumatic GH deficiency in a patient 42 years after the accident. Mariani et al.<sup>17</sup> also reported a similar patient following an interval of five years. The presented patient with AHC had suffered a head trauma at the age of 21 months. GH deficiency, probably as a result of the head injury, was discovered at the age of 13 years. Thus, growth disorders may become manifest many years after the trauma.

The reason why GH deficiency is observed as the most common pituitary defect after traumatic brain injury is unclear. Necrotic, ischemic changes in the pituitary represent damage of the somatotroph cells, while the same changes in the hypothalamus represent damage of the neurons secreting growth hormone releasing hormone (GHRH)<sup>18</sup>. Apoptosis of the neurons due to ischemia and inflammation can also be observed after traumatic brain injury<sup>19</sup>.

The presented patient received oral glucocorticoid replacement therapy for 10 years. He was evaluated for reduced growth velocity at the age of 12.5 years. GH deficiency was diagnosed. Long-term replacement treatment with high doses of steroids in adrenal disorders such as congenital adrenal hyperplasia (CAH) is known to have a negative influence on growth. A study performed about the use of hydrocortisone in CAH showed that a daily dose greater than 25 mg/m<sup>2</sup>/day started early in the course of the disease caused a transient deceleration of height velocity<sup>20</sup>. Another study by Bonfig et al.<sup>21</sup> reported that pubertal growth was significantly reduced in patients with CAH when hydrocortisone doses greater than 17 mg/m<sup>2</sup>/day were used. The daily total glucocorticoid dose used in patients with AHC is less than that used in patients with CAH. Therefore, glucocorticoid replacement treatment used in this patient is not expected to have a negative effect on his growth velocity.

Growth hormone deficiency is not a feature of X-linked AHC. There is only a single report by Seminara et al.<sup>10</sup> of a patient with height well below the 5th percentile throughout infancy and childhood. The child underwent dynamic anterior pituitary testing at the age of 9.1 years, which revealed normal GH response. Other tests showed normal TSH and prolactin levels. His gonadotropin levels (FSH, LH) failed to rise in response to gonadotropin-releasing hormone (GnRH) at all time points. Direct sequencing of the *DAX-1* gene of that patient revealed a hemizygous 501delA mutation.

In conclusion, this is a report of coincidental X-linked AHC and post-traumatic brain injury-induced GH deficiency. Molecular diagnosis of AHC was confirmed by *DAX-1* gene mutation. GH deficiency was demonstrated by GH stimulation tests, and pituitary hypoplasia on pituitary MRI. GH treatment was started. The previous head trauma possibly contributed to the GH deficiency noted in our patient. Hypopituitarism following trauma in the pediatric age group is an important endocrinological complication. Examination of pituitary hormones may be necessary in patients with growth disorders following traumatic brain injury.

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