CASE REPORT

Combined treatment with GH and anastrozole in a pubertal boy with Cushing's disease and postsurgical GH deficiency

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Abstract

Growth failure is a characteristic manifestation of pediatric Cushing's disease. Catch-up growth is usually incomplete after cure of the disease, and final height is often compromised. Possible mechanisms for this phenomenon include postoperative persistence of GH hyposecretion and absence of retardation of bone maturation in spite of GH deficiency. This report describes the outcome in the case of a boy with Cushing's disease for whom GH replacement therapy was combined with anastrozole, an aromatase inhibitor, in order to delay skeletal maturation and extend the available time for linear growth. The case of a 14 years 4-months-old pubertal male (Tanner stage III) with GH deficiency after successful surgical treatment of Cushing's disease is presented. His height was 147.2 cm (−2.34 SDS), and his midparental target height 171.2 cm (−0.95 SDS). Bone age was 13.5 years and predicted adult height 163.2 cm (−2.2 SDS). Combined treatment was administered for 2.5 years. GH was maintained up to age 18 years. Anastrozole induced a substantial deceleration of bone age. Near-final height at 18 years was 169.5 cm (−1.07 SDS). Puberty progressed normally. Compared with population reference data, bone mineral density before GH plus anastrozole treatment was −4.07 SDS in the lumbar spine and −1.85 SDS in the femoral neck. These measures increased to −1.95 and −0.89 SDSs respectively, at 18 years, when GH was discontinued. Combined treatment with GH and aromatase inhibitors could be a therapeutic alternative to improve the stature of pubertal boys with Cushing's disease and postsurgical GH deficiency.

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Introduction

Growth delay and short stature are typical manifestations of Cushing's syndrome in children (1, 2). The mechanism for this impairment of longitudinal growth is probably multifactorial. Experimental studies have shown that glucocorticoids act locally by inhibiting the proliferation of chondrocytes within the growth plate (3). On the other hand, several alterations of the somatotrophic axis have been demonstrated in the hypercortisolemic state, including reduced biological activity of insulin-like growth factor 1 (IGF1) and inhibition of GH release (4). Importantly, suppression of GH secretion may continue several years after the resolution of Cushing's syndrome (4, 5). In this regard, insufficient post-cure catch-up growth and significantly compromised final height have been observed among children with surgically cured Cushing's disease (6, 7). Therefore, additional therapeutic strategies directed to improve the final stature of these patients are needed.

A recently introduced approach to increase the height potential in pubertal boys with short stature relies on the retardation of bone delay maturation by means of the use of aromatase inhibitors. These compounds have yielded promising results for patients with idiopathic short stature, GH deficiency, and gonadotropin-independent precocious puberty. To date, they have not been assayed in patients with Cushing's syndrome. Here, we report the results of combined treatment with GH and anastrozole, a potent aromatase inhibitor, on near-final height in a boy with Cushing's disease and deficiency of GH after transphenoidal surgery.

Materials and methods

Height SDSs were calculated using 2008 sex-specific Spanish population reference growth charts (8). Midparental target height was calculated as the average of parents' heights + 6.55, and expressed as height SDS

using normative data for adults. Bone ages were determined by the method of Greulich & Pyle (9). Adult-height prediction was estimated by the Bailey–Pineau method (10).

Areal bone mineral densities at the lumbar spine (L2–L4) and the neck of the right femur were measured by dual energy X-ray absorptiometry (DXA) using the Hologic Delphi W (S/N 70558, QDR System Software version 12.6, Waltham, MA, USA). For comparison with data from a Spanish reference population, which were determined by Lunar-DXA (11, 12), the results of bone mineral density were transformed by applying the formula described by Genant *et al.* (13), and expressed as SDSs.

Results

A 14 years 1-month-old boy was referred to our Endocrinology Department for evaluation of short stature. He had presented a normal growth until age 10 years, when his height velocity started to decrease. The patient was a student with high academic performance, and his parents had not noticed other changes in his physical appearance. Personal and family medical history was otherwise unremarkable. Physical examination showed a rounded and slightly reddish face, but other classical stigmata of Cushing’s syndrome were absent. However, screening laboratory investigations showed an elevated excretion of urinary free cortisol. A more exhaustive in-patient hormonal assessment led to a diagnosis of Cushing’s disease (Table 1). Pituitary magnetic resonance imaging showed a 5-mm microadenoma in the left half of the

gland. The patient underwent a selective surgical resection of the lesion by the transsphenoidal approach, without complications. His morning cortisol and ACTH levels were undetectable on the sixth postoperative day, and he was discharged on oral hydrocortisone replacement, which was maintained for up to 18 months, when morning plasma cortisol was 10.5 µg/dl and ACTH 37 pg/ml.

Anthropometric measures, bone age determination, and a complete assessment of the pituitary function were performed three months after surgery. A clonidine stimulation test showed decreased response of GH (peak value 1.21 µg/l) and serum levels of IGF1 were 186 µg/l. The rest of the pituitary function was normal. Bone density was 0.575 g/cm² in the lumbar spine and 0.576 g/cm² in the right femoral neck (−4.07 and −1.85 SDS respectively, for reference population data).

At age 14 years 4 months, replacement GH therapy (0.035 mg/kg per day) was initiated. Because of the poor height prognosis, adjuvant treatment with aromatase inhibitors was offered, and the patient began on anastrozole 1 mg/day. Assent for combined use of GH and anastrozole was previously provided by the patient, and his parents signed a written informed permission, approved by the Ethics Committee of the Hospital Universitario Insular of Las Palmas.

Growth rate increased significantly. After 2.5 years of combined treatment, when the patient was aged 17 years 0 month, he had gained 21.5 cm in height but his bone age had advanced only 1 year. Adult-height prediction had improved to 171.9 cm. Anastrozole was then stopped. In the subsequent year, while still under GH therapy, bone age advanced to 15 years 9 months and the patient had grown by only 1 cm. GH therapy was withdrawn at 18 years 0 month. Last (near-final) height measure was then 169.5 cm (−1.07 SDS, i.e. −0.12 SDS below his projected midparental height). Testosterone increased to normal adult male values and estradiol (E₂), determined by an automated immunoassay method (Beckman Coulter, Brea, CA, USA), was undetectable during anastrozole treatment. No more sensitive assays for plasma E₂ were available at our center. Normal values for both testosterone and E₂ were observed after the removal of anastrozole. Hormonal changes did not induce apparent physical or psychological side effects, and puberty progressed adequately after initiation of treatment. Auxological data and the results of radiological and hormonal investigations are summarized in Tables 1 and 2 and Fig. 1. A new bone densitometry performed at 18 years 0 month showed a bone mineral density of 0.875 g/cm² at the lumbar spine and 0.743 at the right femoral neck (−1.95 and −0.89 SDS respectively). Thoracic and lumbosacral X-ray studies were performed when the patient was 18 years 6 months and failed to show fractures or vertebral deformities (Table 2).

Table 1 Baseline (age 14 years 1 month) characteristics of the study subject.

Height (cm; SDS)	147 (−2.18)
BMI (kg/m ² ; SDS)	27.5 (+1.62)
Blood pressure (mmHg)	120/70
Tanner stage	III
Growth rate (cm/year; SDS)	2.5 (−5.72)
Bone age (years/months)	13/6
Predicted adult height (cm; SDS)	163.2 (−2.2)
Target height (cm; SDS)	171.2 (−0.95)
Plasma cortisol (µg/dl)	
Basal (0800 h) ^a	12.3, 17.1
Basal (2400 h) ^a	17.1, 14.5
Urinary free cortisol (µg/day)	
Basal ^a	> 450, > 450
Low-dose dexamethasone suppression test ^b	20.5
High-dose dexamethasone suppression test ^c	18.7
Basal plasma ACTH (0800 h; pg/ml)	41
Desmopressin stimulation test (10 µg i.v.)	
Plasma cortisol (µg/dl; basal/peak)	17.9/29.6
Plasma ACTH (pg/ml; basal/peak)	44/99

^aTwo samples obtained on two consecutive days.
^bDexamethasone 0.3 mg/m² (0.35 mg) every 6 h for 48 h.
^cDexamethasone 1.2 mg/m² (1.8 mg) every 6 h for 48 h.

Figure 1 Growth chart representing the height (squares) and height for the bone age (circles) of the patient through the follow-up period. Arrows: 1) start of GH and anastrozole treatment; 2) end of anastrozole treatment; 3) end of GH treatment.

Discussion

Growth failure is a characteristic manifestation of Cushing's disease during childhood and adolescence. In addition, although surgical correction of hypercortisolism leads to an improvement of growth rate, post-cure catch-up growth is frequently incomplete and final adult height is significantly compromised (6, 7). One of the possible reasons for the poor catch-up growth could be that hyposecretion of GH associated with glucocorticoid excess persists long after cure of the disease. Additionally, bone age of patients with Cushing's disease is often concordant with their chronological age (2, 6, 7). This absence of bone age delay in spite of GH deficiency is probably related to the increased secretion

of adrenal androgens (14), and might contribute to reduce the growth potential by shortening the available time until epiphyseal plate closure.

Davies *et al.* (15) reported the results of replacement hormonal therapy with human GH in 12 patients with Cushing's disease and post-cure deficiency of GH. To block skeletal maturation and extend the available time for linear growth, GNRH analog therapy was additionally given to four patients who were in puberty. Although the authors claimed that most of these patients attained normal height, the mean difference between the final or latest height SDS and the midparental height SDS still was -1.2 , a result similar to that observed by other authors in patients who did not receive GH therapy (6, 7). The outcome in the case of the four subjects who were treated with GH and GNRH analogs was slightly better. The difference between the mean final (or latest) height and the mean midparental target height of these cases was -0.9 SDS. This suggests a possible benefit of postponing normal puberty for improving the final height in subjects with Cushing's disease. However, apart from its modest effects on height gain, controlled studies performed in subjects with short stature due to other etiologies have shown that treatment with GNRH agonists provokes a significant reduction of bone mineral density (16, 17). Because glucocorticoid excess decreases bone accretion, the effects of GNRH on bone mineral density would be of particular concern in patients with Cushing's disease.

Another more recently introduced therapeutic approach to delay bone maturation and increase adult height consists of restraining the effects of estrogens on the growth plate with the use of aromatase inhibitors. These drugs inhibit the biosynthesis of estrogens by blocking aromatase, the rate-limiting enzyme in the conversion of androgens to estrogens. The most compelling evidence supporting the use of aromatase inhibitors as growth-promoting agents comes from four randomized, double-blinded, placebo-controlled trials conducted in male subjects with GH deficiency,

Table 2 Clinical, radiological, and biochemical outcome in the case of the patient through the follow-up period.

Age (years/months)	14/3	14/10	15/4	15/10	16/4	16/11	17/4	18/0
Height (cm)	147.2	154.2	159.5	164	166	168.5	169.3	169.5
Height (SDS)	-2.34	-1.9	-1.52	-1.06	-0.95	-0.85	-0.88	-1.07
BMI (SDS)	1.88	1.69	1.56	1.52	1.48	2.29	2.45	2.73
Tanner stage	III	IV	V	V	V	V	V	V
Bone age (years/months)	13/6	13/6		13/9	14/0	14/6	15/3	16/0
Predicted adult height (cm)	163.2	165.1		170.5	171.2	171.9	171.7	
Predicted adult height (SDS)	-2.2	-1.9		-1.06	-0.95	-0.85	-0.88	
Testosterone (ng/ml)	1.65	5.84	5.35	5.14	6.3	4.91	3.21	2.58
Estradiol (pg/ml)		<20	<20	<20	<20	<20	33	36
IGF1 (μ g/l)	186	935	890	842	740	383	519	550
GH therapy (0.035 mg/kg per day)	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Anastrozole (1 mg/day)	No	Yes	Yes	Yes	Yes	Yes	No	No
Hydrocortisone (12 mg/m ² per day)	Yes	Yes	Yes	No	No	No	No	No

idiopathic short stature, or constitutional delay of growth and puberty (18, 19, 20, 21). All these studies showed that treatment with aromatase inhibitors effectively delays bone maturation and increases predicted adult height. Long-term follow-up data from the first of them (22), in which boys with constitutional delay of growth and puberty were treated with letrozole for one year during adolescence, support the view that the achieved increase in predicted adult height also results in taller final adult height.

Although only short-term follow-up is still available, these controlled clinical trials have provided a good safety profile for treatment with aromatase inhibitors. No adverse effects have been demonstrated on glucose, plasma lipid concentrations, and insulin sensitivity (20, 23), spermatogenesis (24), and cognitive function (25). Additionally, aromatase inhibitors did not induce detrimental effects on bone mineral density (19, 20, 26). A more recent report suggested that boys with idiopathic short stature treated with letrozole might be predisposed to asymptomatic vertebral wedge deformities (27), although the relevance of these findings is unknown.

On the whole, available evidence makes aromatase inhibitors an appealing therapeutic option for pubertal boys with Cushing's syndrome and poor height prognosis. In the herein-reported case, combined treatment with GH and anastrozole was administered during 2.5 years. Bone maturation was substantially delayed and the difference between the near-final height and the projected height before starting therapy was 6.2 cm (net gain of height SDS of +1.12). Final stature was close to the expected midparental height (169.5 cm (−1.07 SDS) vs 171.2 cm (−0.95 SDS)). Pubertal changes were attained at normal age and no side effects of treatment were observed. In particular, anastrozole did not seem to negatively affect bone mineralization. As expected after the resolution of Cushing's syndrome, areal bone mineral densities in the femoral neck and the lumbar spine, which were severely diminished immediately after transsphenoidal surgery, had improved significantly when assessed 3.6 years later. On the other hand, biochemical assessment of estrogen suppression was probably obscured in our case by the use of a direct immunoassay for the measuring of serum E_2 . Immunoassays lack the sensitivity and specificity necessary for the accurate detection of E_2 in pubertal children. Other more sensitive methods, such as mass spectrophotometry, can be more appropriate to monitor patients using this class of drugs.

This case suggests that the combination of GH and aromatase inhibitors could be a valid therapeutic option for selected cases of pediatric Cushing's disease. However, for the present, this new therapeutic modality must be considered experimental. Further investigations should be addressed to determinate the efficacy and safety of this therapy.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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