Aromatase Inhibitor in conjunction with growth hormone may Improve height in Congenital Adrenal Hyperplasia due to *CYP11B1* deficiency

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Abbreviations:
CAH = Congenital Adrenal Hyperplasia
AI = Aromatase Inhibitor
GH = Growth Hormone
SDS = Standard Deviation Score
DHEAS = Dehydroepiandrosterone Sulphate
ACTH = Adrenocorticotropic hormone
CT = Computed Tomography
DEXA = Dual-energy X-ray absorptiometry
MRI = Magnetic Resonance Imaging
GnRH = Gonadotropin-releasing Hormone

Contributors Statements:
Katherine Hawton: Interpretation of growth data, drafted the initial manuscript, reviewed and revised the manuscript.

Sandra Walton-Betancourth: Collated data for the patient and drafted parts of the initial manuscript, and reviewed and revised the manuscript.

Gill Rumsby: Performed genetic analyses and carried out the initial analyses, and reviewed and revised the manuscript.

Joseph Raine: Suggested writing a case report, provided supervision and reviewed and revised the manuscript.

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Abstract

With an estimated prevalence of 1 in 100,000 births, 11β-hydroxylase deficiency is the second most common form of congenital adrenal hyperplasia (CAH) and is caused by mutations in *CYP11B1*. Clinical features include virilisation, early gonadotropin-independent precocious puberty, hypertension and reduced stature. The current mainstay of management is with glucocorticoids to replace deficient steroids and to minimize adrenal sex hormone over-production, thus preventing virilisation and optimising growth. We report a patient with CAH who had been sub-optimally treated and presented to us at 6 years of age with precocious puberty, hypertension, tall stature, advanced bone age and a predicted final height of 150cm. Hormonal profiles and genetic analysis confirmed a diagnosis of 11β-hydroxylase deficiency. In addition to glucocorticoid replacement, he was commenced on growth hormone (GH) and a third generation aromatase inhibitor (AI), anastrozole, in an attempt to optimise his growth. Following the initiation of this treatment, his growth rate improved significantly and bone age advancement slowed. The patient reached a final height of 177.5cm (+0.81 SDS), 11.5cm above his mid-parental height. This is only the second reported case of the use of an AI in combination with GH to optimise height in 11β-hydroxylase deficient CAH. This novel treatment proved to be highly efficacious with no adverse effects and may therefore provide a promising option to promote growth in exceptional circumstances in individuals with 11β-hydroxylase deficiency presenting late with advanced skeletal maturation and consequent short stature.

Introduction

Growth is a major issue in the management of congenital adrenal hyperplasia (CAH), influenced both by the disease itself and its treatment. Final height in CAH is reduced, and in 21-hydroxylase deficiency is often between -1 and -2 standard deviations of the normal height of a control population (1). Reduced adult height is a consequence of both androgen excess due to the condition itself, potentially leading to early puberty and fusion of the epiphyseal plates, and an undesired side effect of the glucocorticoid treatment required for cortisol replacement and androgen suppression. This reduction in height is more significant the later the condition is diagnosed, or as a result of suboptimal treatment.

We report a novel approach to improve linear growth using recombinant human growth hormone (GH) and anastrozole, an aromatase inhibitor (AI), in combination with glucocorticoids in a patient with late-presenting CYP11B1 deficiency with a markedly advanced bone age. Informed consent was obtained from the patient and his parents to write this case report.

Case report

The patient was born in Turkey to consanguineous parents. He was noted to have a large phallus at birth but no investigations were performed at that stage. He presented at the age of 3 years with pubic hair development and was referred to a paediatric endocrinologist. His blood pressure was 100/70 (53rdcentile for age). Tanner staging revealed Genitalia stage (G) 3, Pubic hair stage (P) 2, Axillary hair stage (A) 1 and testes (T) of 1ml bilaterally, with a height of 114cm (+5.34 SDS) and a significantly advanced bone age of 8 years. Hormonal

profiles revealed elevated 11-deoxycortisol, DHEAS, testosterone and ACTH concentrations with suppressed renin and aldosterone, confirming a diagnosis of 11β-hydroxylase deficiency CAH. CT scan of his abdomen showed bilateral adrenal hyperplasia. He was commenced on hydrocortisone 20mg/m^2/day which was then reduced by 5mg per week until a dose of 10mg/m^2/day was reached within four weeks of commencement of treatment with rapid normalisation of biochemical markers (11-deoxycortisol 4.6 ng/ml and ACTH 25 pg/ml). He subsequently developed hypertension, initially treated with enalapril but following an inadequate response, furosemide was added three times weekly to optimise control.

The patient was first seen in the UK at the age of 6.49 years, when he presented with tall stature (height 129cm, +2.0 SDS), virilisation (pubertal ratings G3 P3 A1 T 2mls bilaterally), hypertension (146/98mmHg, 99.9th centile for age) and a significantly advanced bone age (13.2 years). Predicted final height was only 150cm (Bailey-Pinneau); considerably less than his mid-parental height (166cm). Genetic analysis revealed a 46,XY karyotype with a homozygous mutation in *CYP11B1*, c.954G>A, a silent change in the last nucleotide of exon 5 predicted to affect splicing (2).

Glucocorticoid replacement was optimised by increasing the hydrocortisone dose from 9mg/m^2/day to 20mg/m^2/day. During his subsequent treatment, the hydrocortisone dose ranged from 20 to 13.7 mg/m^2/day. In order to better control his hypertension, the dose of enalapril was increased to 5mg twice daily, and furosemide was replaced by nifedipine 10mg twice daily.

At the age of 7.38 years, in an attempt to optimise the patient's growth and prevent further bone age acceleration, he was commenced on a third generation AI, anastrozole (1mg/day), in combination with GH (0.87mg/m^2/day). The former was used in an attempt to prevent further bone age acceleration with its inevitable consequence of restricted final adult height. At that point, his height was 131.3cm (+1.43 SDS) and his growth velocity had slowed to 0.8 cm/year (-5.52 SDS).

Following this strategy his growth rate initially decreased but then normalised, and by 10.75 years, his height was 147.8cm (+0.94 SDS) with a growth velocity of 7.5 cm/year (+3.33 SDS). At this stage his pubertal staging was G4P4A1 T 3ml bilaterally and bone age had only slightly progressed to 14 years.

He continued on GH, anastrozole and hydrocortisone with the onset of gonadotropin-dependent puberty at the age of 11.7 years. He had a normal pubertal growth spurt with a maximum growth velocity of 12 cm/year (+2.81 SDS) at 12.93 years of age (Figure 1). Blood pressure remained well controlled. The response to growth hormone was monitored using IGF1/IGFBP3 measurements and growth velocity. The dose of growth hormone was increased from 1mg to 1.2 mg at the age of 10 years, and again to 1.4mg at the age of 13 years. Androgen concentrations were monitored during treatment. Prepubertally, the testosterone concentration was <0.7 nmol/l, at the age of 11 years it was 5.9 nmol/l, at 13 years it was 13.9 nmol/l and by 14 years it had increased to 17.9 nmol/l. Androstenedione was <1.1 nmol/l prepubertally, increasing to 18.1 nmol/l by 11 years, 24.6 nmol/l at 13 years and decreasing to 11.6 nmol/l by 14 years of age.

Anastrozole was stopped at 13 years, and GH treatment at 14 years of age when his height was 172cm (1.13 SDS). No adverse side effects ensued from the anastrozole. Notably, following the cessation of treatment he had a normal DXA scan with L1-L4 bone mineral density 1.00 g/cm^2 (Z-score 1.0) and left hip BMD 1.10 g/cm^2 (Z-score 0.8). Spinal x-ray and MRI spine were also normal. Lipid profile, serum biochemistry including testosterone, and haemoglobin (ranging from 13 – 14.3 g/dl) were within normal physiological concentrations. Currently, at 15.35 years of age, his final height is 177.5cm (+0.81 SDS), with a pubertal staging of G5P5A3 T15ml bilaterally. From the age of 13 years, concordance with treatment was problematic as evidenced by elevated ACTH concentrations (1250ng/L) and he was therefore switched to prednisolone (7.5mg am and 5mg nocte) in order to improve his compliance with glucocorticoid treatment. He continues to grow but his height velocity is now negligible and he has reached his near final adult height, which has exceeded his mid-parental height by 11.5cm.

Discussion

We report a relatively novel approach for the treatment of predicted adult short stature in 11β-hydroxylase deficient CAH. Despite presenting late with a bone age that was advanced by 7 years, linear growth surpassed expectations following treatment with GH and anastrozole. Predicted final height upon his initial presentation in the UK was exceeded by 27.5cm and mid-parental height by 11.5cm. To our knowledge, this is only the second documented case (3) of combination therapy with GH and an AI to optimise growth in a patient with 11β-hydroxylase deficiency.

Efforts to improve final height in children with CAH have led clinicians to investigate alternative and adjunctive therapies, such as GH, gonadotropin-releasing hormone (GnRH)

agonists, AIs, androgen blockers, or a combination of these medications. Much of the evidence relating to treatment to improve height potential in CAH has focused on the more common 21-hydroxylase deficiency. One study of 34 individuals with 21-hydroxylase deficiency showed that GH, either alone or in combination with a GnRH analogue, improves final adult height, with an average 9cm height gain in males (4). Evidence for adjunctive treatments to improve growth in 11β-hydroxylase deficiency is more limited (5). There are some case reports that suggest that GH in combination with GnRH agonists may be useful in improving height outcomes in children with 11β-hydroxylase deficiency (5, 6).

AIs block the action of P450 aromatase, which converts androgens into oestrogens, and can be used to decelerate growth plate fusion by minimising oestrogen action. Evidence is accumulating regarding their use to increase final height in a range of conditions affecting stature. In one study of 52 patients with GH deficiency, anastrazole in combination with GH therapy was shown to increase predicted adult height (by 6.7cm vs 1.0cm with GH alone) while maintaining normal pubertal progression (7). A randomized controlled trial of boys with constitutional pubertal delay treated with the AI letrozole plus testosterone (n=9) for 1 year during adolescence significantly improved near-final adult heights compared to testosterone with placebo (8). In one study involving 28 children with 21-hydroxylase deficiency, the combination of a reduced dose of hydrocortisone with an anti-androgen (flutamide) and an AI (testolactone) slowed bone maturation whilst maintaining growth velocity compared to a conventional high dose glucocorticoid regimen (9); this study is still ongoing and the patients have now been switched to letrozole (10).

The only other reported case using this approach in 11β-hydroxylase deficiency was a patient with a 46,XX karyotype, who was raised as male and had had an oophorectomy following

presentation at the age of 3 years in Pakistan with virilisation and cryptorchidism (3), and similarly had received suboptimal initial corticosteroid treatment. After presenting in Canada at the age of 7 years with an advanced bone age and hypertension, corticosteroids were optimised before commencing GH and letrozole at 8 and 9 years of age respectively. As in our case, adult height prediction was exceeded and no adverse effects were found in terms of vertebral malformation, bone fragility or dyslipidaemia.

Although combination treatment with GH and AIs appeared to be efficacious in these two individuals with no adverse effects, these data need to be reproduced by conducting randomized controlled trials in a larger number of patients. Given the rarity of this condition, such studies are likely to be difficult, although they may be possible if other forms of CAH (eg 21-hydroxylase deficiency due to *CYP21A2* mutations) presenting with virilisation and advanced skeletal maturation are included. Further work is needed to elucidate the optimal timing for the introduction and duration of treatment with AI and GH to optimise linear growth and to identify those patients who may benefit most from this treatment. Current data involving the use of AIs in growth disorders have been generally promising with respect to safety profiles (7, 9, 11, 12). However, additional studies are required to establish the long-term side effects of treatment with AIs in this patient group, including the evaluation of their impact on later fertility, lipid profiles and bone mineral density.

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