

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 = Adrenocorticotrophic 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.

Mehul Dattani: Suggested the novel treatment for the patient, and reviewed and revised the manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

1 **Abstract**

2

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

1 **Introduction**

2 Growth is a major issue in the management of congenital adrenal hyperplasia (CAH),
3 influenced both by the disease itself and its treatment. Final height in CAH is reduced, and in
4 21-hydroxylase deficiency is often between -1 and -2 standard deviations of the normal height
5 of a control population (1). Reduced adult height is a consequence of both androgen excess due
6 to the condition itself, potentially leading to early puberty and fusion of the epiphyseal plates,
7 and an undesired side effect of the glucocorticoid treatment required for cortisol replacement
8 and androgen suppression. This reduction in height is more significant the later the condition
9 is diagnosed, or as a result of suboptimal treatment.

10

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

16

17

18 **Case report**

19 The patient was born in Turkey to consanguineous parents. He was noted to have a large
20 phallus at birth but no investigations were performed at that stage. He presented at the age of
21 3 years with pubic hair development and was referred to a paediatric endocrinologist. His
22 blood pressure was 100/70 (53rdcentile for age). Tanner staging revealed Genitalia stage (G)
23 3, Pubic hair stage (P) 2, Axillary hair stage (A) 1 and testes (T) of 1ml bilaterally, with a
24 height of 114cm (+5.34 SDS) and a significantly advanced bone age of 8 years. Hormonal

1 profiles revealed elevated 11-deoxycortisol, DHEAS, testosterone and ACTH concentrations
2 with suppressed renin and aldosterone, confirming a diagnosis of 11 β -hydroxylase
3 deficiency CAH. CT scan of his abdomen showed bilateral adrenal hyperplasia. He was
4 commenced on hydrocortisone 20mg/m²/day which was then reduced by 5mg per week until
5 a dose of 10mg/m²/day was reached within four weeks of commencement of treatment with
6 rapid normalisation of biochemical markers (11-deoxycortisol 4.6 ng/ml and ACTH 25
7 pg/ml). He subsequently developed hypertension, initially treated with enalapril but
8 following an inadequate response, furosemide was added three times weekly to optimise
9 control.

10

11 The patient was first seen in the UK at the age of 6.49 years, when he presented with tall
12 stature (height 129cm, +2.0 SDS), virilisation (pubertal ratings G3 P3 A1 T 2mls bilaterally),
13 hypertension (146/98mmHg, 99.9th centile for age) and a significantly advanced bone age
14 (13.2 years). Predicted final height was only 150cm (Bailey-Pinneau); considerably less than
15 his mid-parental height (166cm). Genetic analysis revealed a 46,XY karyotype with a
16 homozygous mutation in *CYP11B1*, c.954G>A, a silent change in the last nucleotide of exon
17 5 predicted to affect splicing (2).

18

19 Glucocorticoid replacement was optimised by increasing the hydrocortisone dose from
20 9mg/m²/day to 20mg/m²/day. During his subsequent treatment, the hydrocortisone dose
21 ranged from 20 to 13.7 mg/m²/day. In order to better control his hypertension, the dose of
22 enalapril was increased to 5mg twice daily, and furosemide was replaced by nifedipine 10mg
23 twice daily.

24

1 At the age of 7.38 years, in an attempt to optimise the patient's growth and prevent further
2 bone age acceleration, he was commenced on a third generation AI, anastrozole (1mg/day), in
3 combination with GH (0.87mg/m²/day). The former was used in an attempt to prevent further
4 bone age acceleration with its inevitable consequence of restricted final adult height. At that
5 point, his height was 131.3cm (+1.43 SDS) and his growth velocity had slowed to 0.8
6 cm/year (-5.52 SDS).

7

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

12

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

24

1 Anastrozole was stopped at 13 years, and GH treatment at 14 years of age when his height
2 was 172cm (1.13 SDS). No adverse side effects ensued from the anastrozole. Notably,
3 following the cessation of treatment he had a normal DXA scan with L1-L4 bone mineral
4 density 1.00 g/cm² (Z-score 1.0) and left hip BMD 1.10 g/cm² (Z-score 0.8). Spinal x-ray and
5 MRI spine were also normal. Lipid profile, serum biochemistry including testosterone, and
6 haemoglobin (ranging from 13 – 14.3 g/dl) were within normal physiological concentrations.
7 Currently, at 15.35 years of age, his final height is 177.5cm (+0.81 SDS), with a pubertal
8 staging of G5P5A3 T15ml bilaterally. From the age of 13 years, concordance with treatment
9 was problematic as evidenced by elevated ACTH concentrations (1250ng/L) and he was
10 therefore switched to prednisolone (7.5mg am and 5mg nocte) in order to improve his
11 compliance with glucocorticoid treatment. He continues to grow but his height velocity is
12 now negligible and he has reached his near final adult height, which has exceeded his mid-
13 parental height by 11.5cm.

14

15 **Discussion**

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

23

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

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

9

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

23

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

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

7

8 Although combination treatment with GH and AIs appeared to be efficacious in these two
9 individuals with no adverse effects, these data need to be reproduced by conducting
10 randomized controlled trials in a larger number of patients. Given the rarity of this condition,
11 such studies are likely to be difficult, although they may be possible if other forms of CAH (eg
12 21-hydroxylase deficiency due to *CYP21A2* mutations) presenting with virilisation and
13 advanced skeletal maturation are included. Further work is needed to elucidate the optimal
14 timing for the introduction and duration of treatment with AI and GH to optimise linear growth
15 and to identify those patients who may benefit most from this treatment. Current data involving
16 the use of AIs in growth disorders have been generally promising with respect to safety profiles
17 (7, 9, 11, 12). However, additional studies are required to establish the long-term side effects
18 of treatment with AIs in this patient group, including the evaluation of their impact on later
19 fertility, lipid profiles and bone mineral density.

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