Therapeutic Challenge of Preserving Adult Height in a Patient with Langer Mesomelic Dysplasia and Non-Classic Congenital Adrenal Hyperplasia: A Case Report

Anna S. Nam[1], Judith Ross[2] and Bert Bachrach[1,*]

[1]*University of Missouri Children's Hospital, Columbia, MO;* [2]*Thomas Jefferson University, Philadelphia, PA, USA*

Abstract: Congenital adrenal hyperplasia (CAH), including the non-classic subtype (NCCAH), predisposes patients to adult height (AH) deficit. The effects of glucocorticoid treatment for asymptomatic NCCAH patients on growth remains inconclusive. There is no discussion in the literature on steroid treatment to optimize height in an NCCAH patient predisposed to severe AH deficit due to another condition e.g. Langer mesomelic dysplasia (LMD) caused by the absence of functional SHOX (short stature homeobox) protein. We present a case of an 8 year old female diagnosed with LMD and NCCAH. Hydrocortisone therapy was administered with regular assessments of her height, serum 17OHP, and bone age to optimize adult height. Hydrocortisone dosage ranged from 5-19 mg/m^2/day. Currently, TJ's height is 97.7 cm (-6.5 SD) with a bone age of 10 years and growth velocity of 4.5 cm/year. This represents the first reported case of combined diagnoses of LMD and NCCAH. Treatment dilemmas surrounding glucocorticoid and growth hormone therapies for NCCAH in the context of severe short stature, specifically LMD, are discussed.

Keywords: Corticosteroid therapy, short stature, height deficit.

INTRODUCTION

Langer mesomelic dysplasia (LMD) is a rare condition resulting in severe short stature, mesomelic dysplasias, and Madelung deformity characterized by radial bowing and dorsal dislocation of the ulna. This is caused by homozygous or compound heterozygous mutations of the *SHOX* (short stature homeobox) gene. *SHOX* is located in the pseudoautosomal region 1 (PAR1) of the short arms of the X and Y chromosomes. Haploinsufficiciency of *SHOX* results in Leri-Weill dyschondrostesosis (LWD) with milder phenotypic manifestations of LMD. *SHOX* is also implicated as the cause of growth failure in Turner syndrome (TS) as well as in certain cases of idiopathic short stature [1].

Due to the rarity of LMD, it is addressed most often in the form of individual case reports. It has never been discussed in a patient with another condition of a different etiology that also causes short stature, like congenital adrenal hyperplasia (CAH). Short stature in CAH patients results from premature epiphyseal fusion due to hyperandrogenism. Excess androgen is caused by an enzyme deficiency, most frequently 21-hydroxylase (CYP21A2) that causes impaired cortisol synthesis, lack of negative inhibition of ACTH by cortisol, and shunting of enzymatic pathways toward excess androgen synthesis. Optimization of adult height (AH) is an important challenge in the management of patients with CAH [2, 3].

Here, we present a patient with combined diagnoses of non-classic CAH (NCCAH)—the *least* severe form of 21-hydroxylase deficiency—and LMD—the *most* severe condition of the *SHOX* gene deficiency. We discuss the pathophysiology of growth failure in NCCAH and LMD and the therapeutic dilemmas of CAH management—the challenges of optimal corticosteroid treatment and consideration of growth hormone therapy—in a patient with severe short stature due to LMD.

CASE PRESENTATION

TJ is an 8 year old female diagnosed with LMD as well as NCCAH due to 21-hydroxylase deficiency (21OHD). TJ's prenatal history was unremarkable until 5 months gestation when dwarfism was noted on the ultrasound and a presumptive diagnosis of achondroplasia was made. Family history was negative for a specific diagnosis for height deficit, although her father had been evaluated for short stature as a child. Father's height was 155 cm (-4 standard deviations (SD)), and his limbs showed mesomelic shortening. Mother's height was 156 cm (7th percentile) with mildly increased upper-to-lower segment ratio and span that is less than her height, indicating short limbs. Midparental height was 149 cm. To their knowledge, parents were not in a consanguineous union.

Pregnancy was carried to term without any complications. At birth, TJ's weight was 3.8 kg (82nd

*Address correspondence to this author at the University of Missouri Children's Hospital, DC058.00, 400 N Keene St, Ste 118, Columbia, MO 65201, USA; Tel: 573-884-4772; Fax: 573-884-8823;
E-mail: bachrachb@health.missouri.edu

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percentile), length 46 cm (-2.6 SD), head circumference 39.5 cm (98th percentile). Upper-to-lower segment ratio was 1.4:1, and the extremities were noted to have rhizomelic and mesomelic shortening with wrist deformities consistent with LMD. Other signs of the SHOX gene insufficiency included micrognathia, abnormal auricular development (length <3rd percentile), and short metacarpals indicated by palmar and hand lengths (both <3rd percentile). Full body X-ray and CT images were concordant with physical exam findings: the long bones were shortened with curving of the radius and tibia, bilaterally. The diagnosis of LMD was confirmed with mutation analysis by PCR and sequencing which revealed homozygous whole gene deletions at the *SHOX* locus (Esoterix, a specialized laboratory service). It is presumed that the parents were each heterozygous for the *SHOX* gene mutation based on their phenotype; however, genetic testing of the parents was cost prohibitive for this family.

Concurrently, TJ was evaluated for 21OHD, due to an elevated 17-hydroxyprogesterone (17OHP) on newborn screening. Physical exam demonstrated normal external female genitalia, and lab evaluation showed normal renin and aldosterone levels with a mildly elevated 17OHP (807 ng/dL). Genetic testing by PCR and multi-plex mini-sequencing revealed compound heterozygosity in *CYP21A2* with a V281L mutation in one allele and a large gene conversion in the other with a 30 kb deletion between CYP21A1P pseudo-gene and CYP21A2 gene (Esoterix), which can be classified as mild and severe mutations, respectively. This was consistent with the diagnosis of NCCAH. Given the skeletal abnormalities and elevated 17OHP, cytochrome P450 oxidoreductase deficiency (Antler-Bixley syndrome) may have been considered. Nonetheless, the genetic studies clearly revealed combined diagnoses of LMD and NCCAH.

Hydrocortisone treatment was initiated with regular assessments of her height (Figure **1**), serum 17OHP (Table **1**), and bone age. The dose of hydrocortisone ranged from 5-19 mg/m^2/day, currently at 5 mg/m^2/day. Adequacy of treatment and adjustments to dosage were determined based on maintaining appropriate growth without advancing bone age significantly as well as 17OHP levels without necessarily normalizing or suppressing it. 17OHP levels started to rise starting age 5 yr 9 mo; however, hydrocortisone dose was not increased. This was due to the patient's steady growth and sporadic and infrequent visits in the recent years. Administration of human recombinant growth hormone (hrGH) as a therapeutic option for improving height potential was discussed with the parents. They have thus far declined therapy due to potential side effects.

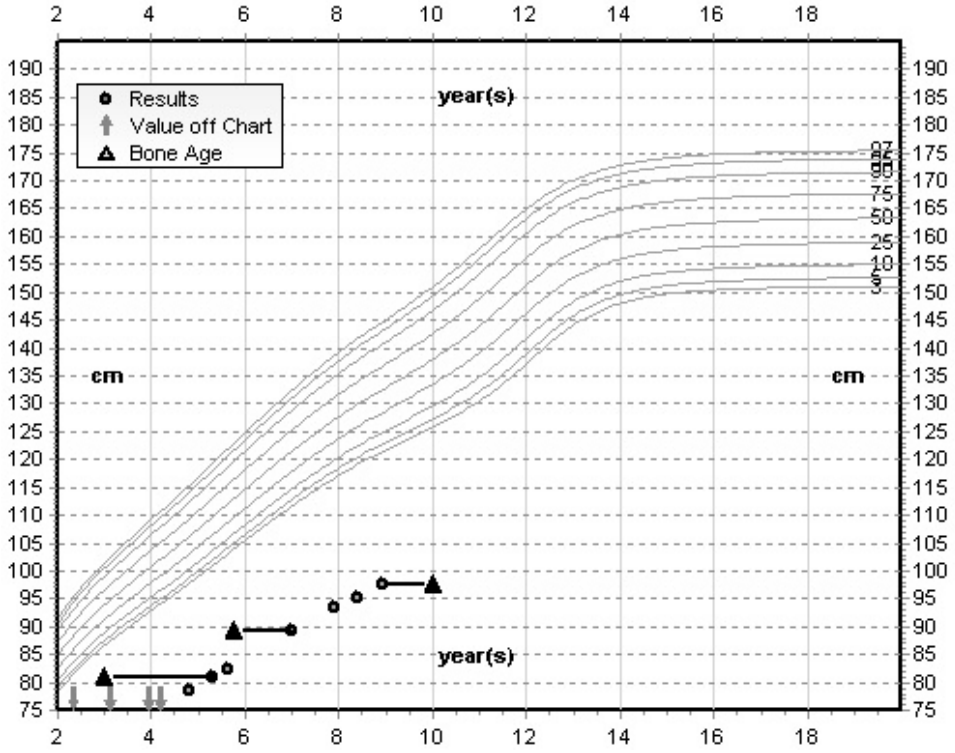

Figure 1: Growth chart of stature-for-age, 2-20 years, for girls. Bone age is shown as triangles in comparison to chronological age (circles) with connecting lines.

Table 1: 17-Hydroxyprogesterone (17OHP) Levels throughout Treatment. 17OHP was measured by liquid chromatography-tandem mass spectrometry (LC/MS/MS) either by ARUP Laboratories or Quest Diagnostics. (mo = months, yr = years)

Age	17OHP (ng/dL)
4 mo	1141
7 mo	83
11 mo	26
1 yr 3 mo	468
1 yr 6 mo	19
1 yr 10 mo	20
1 yr 4 mo	16
2 yr 2 mo	27
2 yr 5 mo	<15
3 yr 11 mo	42
5 yr 9 mo	1321
7 yr	3499
8 yr	1315

TJ's developmental course has been marked with normal milestones. Now 8 years old, her height is 97.7 cm (6.5 SD below the mean) with a body mass index of 33.4 kg/m^2, a bone age of 10 years (2.6 SD above the mean), and growth velocity of 4.5 cm/year. She is at Tanner Stage 1 for breast and pubic hair.

DISCUSSION

Pathophysiology of Adult Height Deficit in NCCAH and LMD

Adult height in NCCAH patients, while on average greater than that of classic CAH patients, is still below the general population mean and expected height based on midparental height [4]. In CAH patients, androgen excess results from shunting of cortisol precursors to sex hormone biosynthesis. Hyperandrogenism, in turn, leads to accelerated linear growth velocity and advanced bone age with premature epiphyseal fusion, resulting in cessation of growth and AH deficit. This occurs primarily by the action of excess estrogens that are peripherally aromatized from androgens [2]. Moreover, excess adrenal androgen causes central precocious puberty by prematurely activating the hypothalamic-pituitary-gonadal axis, which further exacerbates accelerated bone maturation and epiphysial fusion [5]. Thus failure to treat or inadequate suppression of androgen synthesis with exogenous corticosteroid leads to adult short stature.

Short stature due to *SHOX* insufficiency in LMD is much more devastating with a mean height deficit of -6.18 SDS [6]. *SHOX* is expressed in the middle portion of the developing long bones which correlates with the bowing and shortening of the forearms and lower legs; its expression in the distal portions accounts for the Madelung deformity and shortened metacarpals [7]. Furthermore, Munns *et al.* found that SHOX is expressed in fetal and childhood human epiphyseal plate up to the time of growth plate fusion implicating its role in chondrogenesis [8]. Even though the precise role of the SHOX protein has not yet been elucidated, histological features of LMD suggest that SHOX may be involved in the regulation of chondrocyte differentiation, prevention of skeletal maturation and growth plate fusion [1]. Specifically, it may counteract the skeletal maturing effects of estrogen. Although this remains controversial, it is supported by the clinical finding that SHOX insufficiency affects females more severely than males [1]. Moreover, Fukami *et al.* showed that height deficit SDS worsened from childhood to adulthood in female patients with *SHOX* haploinsufficiency implying that gonadal estrogen plays a role in pubertal growth restriction in this disorder [9].

In our patient, not only is short stature compounded by the two disease processes but also the mechanisms underlying growth failure in these disorders appear to have a synergistic effect: both the excess of the *promoter* of acceleration of linear bone maturation and premature epiphyseal plate fusion i.e. androgen and estrogen from CAH, and the absence of the *regulator* of bone growth at the epiphyseal plate i.e. SHOX from LMD, contribute to decreased height potential. Estrogen appears to be a player in the pathophysiology of growth failure in both disease processes. Thus it is reasonable to infer that the consequences of estrogen excess in a patient deficient in SHOX—to counteract the actions of estrogen-induced bone maturation—would be much more severe than in those with CAH alone, or vise versa, the absence of SHOX in the context of hyperestrogenism may result in a more severe short stature than in a patient with only LMD. Consequently, LMD and CAH could have a compounding effect on our patient's height if androgen and estrogen production are not suppressed with corticosteroid.

Corticosteroid Treatment in NCCAH and LMD

Although most patients with NCCAH present in childhood or later with clinical features including hirsutism, premature pubarche, oligomenorrhea, and

infertility, some patients are identified during infancy through the new-born screening program [10] as in our case. Treatment of asymptomatic patients as those discovered upon newborn screening remains inconclusive due to the lack of evidence. Current recommendations according to the Endocrine Society Clinical Practice Guidelines on CAH advise against treatment of asymptomatic NCCAH patients [11]. A major adverse effect of corticosteroid administration is acute adrenal insufficiency due to iatrogenic adrenal suppression, and high dose treatment can result in iatrogenic Cushing syndrome [12].

Nonetheless, there exists no substantial evidence against prophylactic treatment of asymptomatic NCCAH, especially in situations where appropriate linear growth is the primary therapeutic goal. Most studies on glucocorticoid therapy—in the dosing, type of exogenous steroid, timing of initiation of therapy, duration of treatment—and its effect on the growth of CAH patients have examined the outcomes in *classic* CAH patients or CAH patient populations without distinguishing subtypes [13-21]. Though not unanimous, several reports demonstrate that early diagnosis and treatment (i.e. <1 or <3 years old) are correlated with more favorable height outcomes compared to those who were not treated, treated later or inadequately treated [13, 16, 19-21]. Notably, two studies that examined growth outcomes in *non-classic* CAH patients suggest that early treatment confers improved height potential [4, 22]. NCCAH patients who received treatment showed decreased reduction in growth potential compared to those who were not treated [4]. In the other study, patients who received corticosteroid therapy one year before the onset of pubertal signs resulted in attainment of expected height based on midparental height whereas patients who were treated after the onset of puberty did not [22].

Glucocorticoid therapy would help prevent advanced bone age and accelerated growth velocity. However, they frequently occur and go unnoticed before the onset of signs of hyperandrogenism [3, 4]. Given the data discussed above, early initiation of treatment in asymptomatic NCCAH patients may be considered especially if the optimization of adult height is the main goal. The decision to begin corticosteroid administration in NCCAH patients should be made on an individual basis. In our case, our main goal was to optimize height in a patient predisposed to a severe height deficit due to LMD. Therefore, we began treatment in TJ during infancy taking care not to overtreat. Given that there was no discussion in the literature of corticosteroid therapy for NCCAH in patients with severe short stature, this decision was supported by clinical evidence showing favorable growth outcomes of early corticosteroid treatment in NCCAH patients, granted the evidence was for older children, not infants. TJ has maintained a growth velocity of about 4.5 cm/year for the past two years with a current height SD of -6.5. Given the rarity and heterogeneity of LMD and the compounding diagnosis of NCCAH, it is impossible to assess the adequacy of treatment based on height and growth pattern, further contributing to the challenge of sustaining appropriate therapy in this patient. Moreover, the patient has become obese with a BMI of 33.4 kg/m^2 which may have been contributed by steroid therapy, adding another challenge to optimizing therapy. Dietary counseling has been provided for the parents.

Growth Hormone Treatment in NCCAD and LMD

rhGH is administered to minimize height deficit in numerous conditions with or without a primary GH deficiency. Clinical trials of rhGH with or without leuprolide in patients with CAH, including those with the non-classic subtype, have shown to improve linear growth velocity, height prediction, and height deficit for bone age [23] as well as AH [5].

rhGH therapy has also been implemented in patients with SHOX haploinsufficiency. The effectiveness of GH therapy for improving AH is well established in patients with TS [24], and studies show that patients with SHOX haplodeficiency had improved height outcomes [25, 26]. With respect to patients with homozygous deficiency of the *SHOX* gene, Shah *et al.* report rhGH therapy administered to a patient with dual diagnoses of TS and LMD for four years starting at age eleven; this did not show improvement in growth velocity [24].

For our patient, rhGH administration was considered and discussed with TJ's parents. Given the lack of evidence for rhGH treatment of patients with homozygous deficiency of SHOX, it would have been an experimental therapeutic option. Regardless, parents have thus far declined treatment due to potential side effects.

CONCLUSION

In conclusion, this represents the first reported case of combined diagnoses of LMD and NCCAH. This illustrates the treatment challenges and dilemmas surrounding corticosteroid and rhGH therapies for

NCCAH for the attainment of optimal adult height in a patient with severe short stature due to LMD. The decision to treat an asymptomatic NCCAH patient with corticosteroid should be made on an individual basis and may be considered in a patient predisposed to severe short stature.

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