Final height in congenital adrenal hyperplasia: the dilemma of hypercortisolism *versus* hyperandrogenism

Altura final na hiperplasia suprarrenal congênita: o dilema do hipercortisolismo versus *hiperandrogenismo*

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ABSTRACT

Objective: The purpose of this study was to identify factors that might interfere with reaching the final height in patients with 21-hydroxylase deficiency (21-OHD). **Subjects and methods:** Thirty-one patients with classical 21-OHD who reached their FH in our Institution were evaluated in order to compare the Z score for final height (FHZ) with: (1) the target height, (2) the standard height for the population, and (3) the hydrocortisone treatment schedule. **Results:** The FHZ of -2.13 ± 1.11 had a significant negative correlation with the hydrocortisone doses used throughout the period of study. Patients who reached FH within the normal population range were those who received lower doses of hydrocortisone, as compared to those whose FH remained below -2 SDS. **Conclusion:** We conclude that careful treatment adjustments have a major influence on growth of children with CAH, and that the dose range for hydrocortisone replacement that does not lead to side effects is relatively narrow. The better height outcome was achieved in 21-OHD patients who received lower doses of hydrocortisone. Arq Bras Endocrinol Metab. 2013;57(2):126-31

Keywords
Congenital adrenal hyperplasia; steroid 21-hydroxylase; corticosteroids; hydrocortisone; body height

RESUMO

Objetivo: O objetivo do estudo foi a identificação de fatores que podem interferir na aquisição de altura final de pacientes com a deficiência de 21-hidroxilase (21OHD). **Sujeitos e métodos:** A altura final (escore Z: FHZ) de 31 pacientes com a forma clássica da 21OHD, acompanhados em nossa instituição, foi comparada com: (1) a altura alvo, (2) o padrão de referência para a população, e (3) a dose de hidrocortisona durante o acompanhamento. **Resultados:** Observou-se correlação negativa significativa entre o FHZ de -2,13 ± 1,11 e as doses de hidrocortisona utilizadas durante o período de estudo. Os pacientes que atingiram altura final dentro do padrão de referência para a população usaram doses mais baixas de hidrocortisona quando comparados àqueles que permaneceram abaixo de -2 DP. **Conclusão:** O cuidado nos ajustes das doses durante o tratamento da 21OHD tem grande influência sobre o crescimento das crianças. A faixa de variação da dose de reposição da hidrocortisona que não causa efeitos colaterais é relativamente estreita. O melhor resultado estatural foi observado nos pacientes com 21OHD tratados com doses mais baixas de hidrocortisona. Arq Bras Endocrinol Metab. 2013;57(2):126-31

Descritores
Hiperplasia suprarrenal congênita; esteroide 21-hidroxilase; corticosteroides; hidrocortisona; estatura

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INTRODUCTION

Congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency (21-OHD) is a common autosomal recessive hereditary disorder. Impairment of cortisol synthesis leads to excessive ACTH stimulation of the adrenal cortex, resulting in hyperandrogenism (1).

Treatment of classic 21-OHD consists of replacement doses of gluco- (GC) and mineralocorticoids, aiming to reduce excess androgen, and to allow adequate linear growth. However, several series report that growth in these children is below expectation, as compared with both the reference population and the target height (TH) (2). The reasons for the inadequate growth and impairment of the final height (FH) are not completely understood. A major cause is the difficulty in accomplishing a fine balance between inhibition of excess androgen production – which accelerates bone maturation –, and adequate GC replacement itself – which even at slightly supraphysiologic doses can be deleterious to growth.

In this paper, we present the results of FH in patients with CAH due to 21-OHD followed up for approximately 10 years in a single institution, and the variables related to this outcome.

SUBJECTS AND METHODS

All patients with CAH due to classic 21-OHD followed up at the Pediatric Endocrinology Division of the University Hospital (HC-UFMG) in Belo Horizonte, Brazil, who had achieved the FH by 2005 were evaluated. The study was approved by the Research Ethics Committee of the Institution. After signing the informed consent term, patients and their parents were examined by a single researcher in a pre-scheduled appointment. Data obtained from the beginning of the patient's follow-up at the HC-UFMG were retrieved from the medical records. Patients with other diseases, or those receiving drugs that could affect linear growth were excluded. Twenty-five of the 31 patients (80%) have been regularly followed up from diagnosis to FH.

CAH diagnosis was based on the presence of ambiguous genitalia, which occurred in all girls, and macrogenitossomia (in boys), associated with increased 17OHP and androgens. Salt wasting (SW) was established according to a report of salt losing crisis, in addition to the need of fludrocortisone acetate to maintain normal electrolyte levels. Male patients with the simple virilizing form (SV) presented incomplete precocious puberty before four years of chronological age (CA) with acceleration of bone age (BA).

FH was characterized by growth velocity less than 0.5 cm per year, and bone age greater than 15 for girls and 17 years for boys (3). All bone ages were interpreted by an experienced radiologist by means of X-rays of the left hand and wrist, using the Greulich and Pyle method (4).

Twenty-six patients received three doses of hydrocortisone daily (half in the morning). The doses were not uniform since the study included patients who initiated treatment before or after 1995, when the recommended treatment schedule was modified after the study of Silva and cols. (5), switching from 15-25 mg/m² BSA/day to 10-15 mg/m² BSA/day. In an attempt to improve compliance with the treatment, five patients received long-acting GC (four received prednisone and one, dexamethasone). In order to have a uniform analysis, long-acting GCs were transformed into equivalent doses of hydrocortisone, as follows: hydrocortisone 30 mg = prednisone 6 mg = dexamethasone 0.375 mg (6), according to body surface area. Fludrocortisone acetate at 0.05 to 0.2 mg per day was used as replacement mineralocorticoid therapy. None of the patients underwent puberty block.

Due to the wide fluctuation of 17OHP and androstenedione plasma concentrations, patients were subdivided into two groups for laboratory evaluation: those presenting less than 50% of the results greater than six-fold the maximum reference value, considered as satisfactory controls (group 1), and those presenting more than 50% above these values, considered as inadequate controls (group 2). Complete normalization of lab results was not considered a primary therapeutic target during patient follow-up. The adequacy of mineralocorticoid replacement was assessed by absence of clinical signs and maintenance of normal electrolyte levels.

Poor treatment compliance was considered whenever this information was specified in the medical records.

Statistical analysis

Z scores for height were calculated at baseline, at two years of CA, and at the FH (FHZ), using the National Center for Height Statistics (NCHS) reference (7); Z scores for bone age were also calculated at the same moments, and for the TH. All FH values were adjusted for sex, the CAH form, and hormonal parameters. FH of patients who used higher and lower than 15 mg/m²

BSA/day mean hydrocortisone dose were compared, as well as the GC doses of those who did or did not reach the FH within the normal range for the overall population (> -2 SD scores). Comparisons within the same group were performed by the Student's *t* test for paired samples, whereas comparisons between different groups were done by analysis of variance or by the Kruskal-Wallis non-parametric test, when indicated. Simple regression analysis was used to correlate the hydrocortisone dose (median of the whole follow-up) with FH. Epinfo software version 6.0 was used for all the statistical analysis, whereas the Epinutri program was used for anthropometric evaluation. Rejection of the null hypothesis was set at 5% ($p < 0.05$).

RESULTS

Table 1 shows the clinical characteristics of the 31 patients with 21-OHD studied: 26 (84%) were female and 17 (54.8%) were salt-wasters. Median age at the beginning of follow-up was 2 yrs. and 3 mo. (ranging from newborn to 8 yrs. and 3 mo.). Mean follow-up until the final height was 10.3 ± 4.2 yrs. Mean FHZ of the whole group was -2.13 ± 1.11. There were no significant differences between the final heights and sex, compliance with treatment, the clinical form of CAH, and hormone control. The mean FHZ of 20 patients with known TH was -1.97 ± 1.15. There was a significant impairment of FHZ compared with the target height Z ($p = 0.022$), demonstrating that these children did not reach their genetic potential.

The median dose of hydrocortisone used was 13.7 mg/m² BSA/day (ranging from 10.9 to 40 mg/m² BSA/day). A moderately significant negative correlation ($r = -0.48$, $r2 = 0.23$, $p < 0.05$) was observed between the doses of hydrocortisone and FH. Group 1 used a significantly higher mean hydrocortisone dose (22.6 ± 8.2 mg/m²/day) than group 2 (13.1 ± 1.1 mg/m²/day). Patients who used doses lower than 15 mg/m² BSA/day reached a significantly higher mean FHZ (-1.83 ± 1.00) than those who used doses higher than 15 mg/m² BSA/day (FHZ: -2.68 ± 1.14; $p = 0.038$). On the other hand, patients who reached normal FH (n = 10), defined as > -2SD of the mean height for the overall population, used a significant ($p = 0.035$) lower median dose of hydrocortisone (13.05 mg/m² BSA/day) than those (n = 18) who remained shorter (median HC dose: 14.85 mg/m² BSA/day) (Table 2).

Table 1. Clinical characteristics of 31 patients with CAH due to classic 21-OHD who reached their final height

	n (%)
Gender	
Male	5 (16)
Female	26 (84)
Clinical presentation	
Salt-wasting	17 (54.8)
Virilizing form	14 (45.2)
Age at diagnosis (yrs.)	
Median	2.3
Range	1 mo. – 8 yrs.
Hydrocortisone dose (mg/m²/d)	
Median	13.7
Range	10.9 – 40
Anthropometric data (Z-score)	
Final height	-2.13 ± 1.11
Target height (n = 20)	-1.25 ± 0.75

Table 2. Hydrocortisone doses and final heights of 31 patients with CAH due to classic 21-OHD who reached their final height

Hydrocortisone dose (mg/m²/d)	Final height (Z-score)	*p*
Median (n = 31)		
13.7 (10.9-40)	-2.13 ± 1.11	< 0.05*
13.05 (n = 10)	> -2SD	0.035
14.85 (n = 18)	< -2SD	
Mean		
Group 1 (n = 11)		
22.6 ± 8.2	-2.68 ± 1.14	
Group 2 (n = 20)		0.038
13.1 ± 1.1	-1.83 ± 1.00	

* Simple linear regression.

Seventeen children were up to 2 years and 4 months when treatment was initiated; mean follow-up until FH was 12.5 ± 1.76 years, and the median daily HC dose during follow-up was 15.49 mg/m² BSA. Mean FHZ was -2.05 ± 0.98 and pretreatment height Z score was -0.60 ± 2.35, disclosing a statistically significant ($p = 0.014$) height loss during the growth period, although no difference was observed when the FH scores were compared with height scores at two years of CA age (-1.37 ± 2.3; $p = 0.21$). Twelve patients with known target heights presented mean FHZ of -1.73 ± 0.98, which was not significantly different from their target height of -1.24 ± 0.81 ($p = 0.096$), demonstrating that they reached their genetic potential.

DISCUSSION

Despite recent developments in CAH, several issues related to patient growth and final height remain unsolved. Most recent series have shown that affected patients have blunted final height, as compared with their targets. In a meta-analysis involving 561 patients, Eugster and cols. found mean FH (-1.37 SD) higher than previously reported (-2.0 SD), but still lower than the values found in the overall population (8). Another meta-analysis including 35 eligible studies showed that the final height of CAH patients (-1.38 SD) is lower than the population norm, and is lower than expected given parental height (9). Diagnosis up to one year of CA and good treatment compliance had a positive influence in FH (8-10); however, the reasons for this shortfall are not fully known. It is believed that treatment interference is a major cause, in addition to the influence of excessive androgen production that occurs despite the best possible control. Recent data point out to the harmful impact of glucocorticoid treatment in FH outcomes (11), and other reports suggest better outcomes after the use of lower HC doses (12-13). Alternative treatments, such as the use of growth hormone associated to puberty inhibitors, in addition to anti-estrogen therapy, were used in an attempt to improve height prognosis in these patients (14-17). However, the high cost, greater likelihood of non-compliance with multi-drug regimens, and the associated side effects, render these alternatives little attractive. Nonetheless, an ideal corticosteroid replacement schedule has not yet been devised. Baseline cortisol secretion is estimated at 5.7 to 10 mg/m² BSA/24h in normal individuals (18), but physiological doses of GC are apparently insufficient to normalize ACTH in the setting of 21OH deficiency. Even if ACTH normalization is attained, androgen secretion not necessarily normalizes, since the shunt induced by the enzymatic block increases the proportion of intermediate steroids in the androgen pathway, even with reduced cortical activity. As a result, patients with 21OHD would present, during treatment, either normal to low androgen concentrations with hypercortisolism, or adequate cortisol concentrations but increased androgen levels, or still, mild hypercortisolism and mild hyperandrogenism (16). This would be the core of discussions regarding conventional treatment in which all three situations may have a negative effect on growth. Therefore, the key issue regarding treatment and growth in 21-OHD is keeping a fine balance between exogenous hypercortisolism and endogenous hyperandrogenism, both playing a reciprocal negative influence on final height.

The mechanism by which glucocorticoid therapy interferes with growth is complex and multifactorial. Relatively slight supraphysiologic levels may be enough to blunt growth velocity. In a previous study, we have already reported in a group of CAH children that a short period of daily hydrocortisone doses of 15 mg/m² was associated to better growth velocity when compared to another short period using 25 mg/m² BSA, despite the limited inhibition of androgen production. At that time, we were concerned whether the high concentrations of androgens would cause advanced bone age, thus offsetting the benefit of the lower doses of GC upon FH (5). Others also observed a negative effect of a hydrocortisone dose of 17.64 ± 3.60 mg/m² BSA/day on growth, preventing children from achieving their genetic potential (19). In the present study, an improvement in FH was observed in patients receiving the median hydrocortisone dose of 13.05, as compared with the 14.85 mg/m² BSA/day dose, suggesting that the margin for dose adjustments without producing side effects is relatively narrow.

In addition, the negative effect of the hydrocortisone dose seems to be greater according to the period of life in which this dose is administered. Studies evaluating GC effect during childhood evidenced a negative influence of the daily dose of GC upon growth velocity and FH in children up to one or two years of CA and in prepubertal children (11,20-23). Similar to Manoli and cols. who showed a positive correlation of FHZ and height at 2 years of age in salt-losing patients (21), the present study corroborates that height loss occurs mainly within the first two years of life. In addition, some reports showed that FH was greater in patients with early treatment, up to 20 months (24) and before 3 years of CA (20), although these data are controversial among the authors (3,23). In this study, a group of patients who initiated treatment early reached their TH. There is now some evidence that, with appropriate clinical management, children can achieve their genetic potential (2,13,21).

An increased risk of developing obesity (2) is another possible consequence of hypercortisolism in children with CAH. In a recent study, the presence of increased fat mass with abdominal and truncal fat distribution suggests the possibility of hypercortisolism in the patients (25). It was also stated that body fatness is a problem starting in early childhood in CAH patients, despite

"physiological" corticosteroid doses; thus, further refinement of the glucocorticoid replacement regimens, as well as measures to change lifestyle are needed (26).

Conversely, minimizing hyperandrogenism is not an easy task. Our study showed that the use of hydrocortisone doses closer to the physiological requirements could lead to more appropriate growth, regardless of hormonal control, as also found by others. Excessive androgen exposure seems to affect the growth periods in different ways (19). The report of untreated SV patients who did not undergo growth acceleration up to 18 months of age (27) is in line with the report of relative resistance to androgens in growth at this age (28), and with the finding of an alternative backdoor pathway existing in the androgen biosynthesis of 21-OHD patients, which explains divergences between virilization and androgen levels seen in clinical practice (29); likewise the same happens during puberty, a period with physiological increase of androgens (6). Therefore, it seems desirable to avoid higher hydrocortisone doses, mainly in these periods. The use of long-acting glucocorticoids that could efficiently suppress adrenal androgen production presents great potential for overtreatment, and should be considered with extreme caution (30).

Besides the influence of androgens in growth of children with CAH, recent data have alerted practitioners to other possible consequences of hyperandrogenism in these patients. It has been suggested that CAH patients develop an unfavorable cardiovascular risk profile either because of the existence of hyperandrogenism in undertreated patients, or because of the iatrogenic hypercortisolism consequent to excess glucocorticoid (31,32). Hyperandrogenism, an independent risk factor for hyperinsulinism, and iatrogenic hypercortisolism could both contribute to hyperinsulinism and insulin resistance in these patients (33-35). Therefore, there are still several unresolved questions in respect to the persistent hyperandrogenism in these patients.

In conclusion, our results confirm that the use of hydrocortisone doses closer to physiological requirements is able to lead adequate linear growth and final heights within expected ranges. Patients receiving early treatment reached the target height regardless of achieving an optimal control of hyperandrogenism. Lower doses of hydrocortisone and early initiation of treatment were associated to better FH. In view of these results, we believe that, in patients treated for CAH, hypercortisolism is more harmful to growth than hyperandrogenism. However, additional studies are necessary to fully appreciate the possible consequences of long-term poor androgen control.

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