Impact of Hydrocortisone on Adult Height in Congenital Adrenal Hyperplasia—The Minnesota Cohort

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Objective To estimate the impact of the average daily dose of hydrocortisone (HC) on the amount of growth attained in children with congenital adrenal hyperplasia (CAH). The effect of glucocorticoid therapy on adult height (AH) in children with CAH has yet to be elucidated.

Study design Triple-logistic models estimating components of growth and maturation were fitted to longitudinal records of 104 patients with classic CAH from 3 pediatric medical centers in Minnesota between 1955 and 2012. A total of 3664 clinical encounters were examined. Random-effects longitudinal models with time-related covariates were used to estimate the effect of HC therapy on linear growth.

Results The predicted AH *z*-score (−0.7) was similar between the sexes and among CAH subtypes. The mean growth period HC dose was 18.9 ± 5.6 mg/m^2/day. In the final regression model, HC dose was negatively associated with predicted AH, with each mg/m^2/day increase in average growth period HC dose predicting a 0.37-cm decrease in AH ($P < .004$).

Conclusion This study has quantified the fractional reduction in predicted final AH with an incremental increase in HC dose. These findings have important clinical implications in the decision making balance between HC replacement dose and adrenal androgen suppression in children with CAH. *(J Pediatr 2014;164:1141-6)*.

Congenital adrenal hyperplasia (CAH) is an autosomal recessive disorder of cortisol and aldosterone synthesis. In 90%-95% of cases, CAH is due to 21α-hydroxylase (21α-OHase) deficiency. Adult height (AH) in patients with classic (salt-wasting [SW] or simple-virilizing [SV]) CAH due to 21α-OHase deficiency is affected by both the disease itself and its treatment. Intrinsic to CAH due to 21α-OHase deficiency is the production of excess androgens, which, through aromatization into estrogens, leads to advanced skeletal maturation and early growth plate fusion.[1] Chronic supraphysiological glucocorticoid replacement impairs linear growth by interfering with the pituitary production and secretion of growth hormone, by inhibiting growth hormone production of insulin-like growth factor 1 messenger RNA in liver cells and by creating a state of growth hormone resistance at the growth plate.[2] Previous meta-analyses identified the mean weighted AH SDS in children with CAH as −1.37[3] and −1.38.[4] Whereas those and other previous studies examined the overall impact of CAH on AH, we sought to quantify the degree to which hydrocortisone (HC) dose affects AH. To do this, we applied triple logistic modeling of longitudinal data of children with CAH and used regression models to determine the relationships between treatment variables and AH.

Methods

We performed an ambidirectional cohort study of 104 patients with CAH covering 3664 visits at the 3 largest pediatric medical institutions in Minnesota between 1955 and 2012. The cohort included only cases with available data for height on at least 2 occasions during the following stages of growth: early childhood (0-5 years), mid-childhood (5-10 years), and adolescence (10-15 years). This inclusion criterion was adopted to ensure adequate longitudinal height/age data for these 3 nodal periods of growth for each child. These nodal periods correspond to estimations of the triple logistic model, which summarizes each child's longitudinal height data into infancy, mid-childhood, and adolescent growth periods with respect to time using Bayesian methods. As a result, cases without serial height data clinic visits for these nodal periods were not included.

21α-OHase	21α-hydroxylase
AH	Adult height
βHC	βhydrocortisone
CAH	Congenital adrenal hyperplasia
CDC	Centers for Disease Control and Prevention
HC	Hydrocortisone
OAH	Observed adult height
PAH	Predicted adult height
SV	Simple-virilizing
SW	Salt-wasting

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We selected 104 children with classical CAH (42 males [29 SW; 13 SV] and 62 females [37 SW; 25 SV]) born between May 1955 and January 2000 from the ambidirectional cohort of 209 patients based on availability of sufficient growth data for modeling. A total of 105 patients were excluded, including 55 patients who did not have visits in all 3 growth periods and 50 patients who had nonclassical CAH or received gonadotropin-releasing hormone analog or a growth hormone or aromatase inhibitor. SV and SW subtype classifications were assigned by the treating pediatric endocrinologist based on hormonal criteria and on clinical and biochemical presentation. Glucocorticoid doses were based on prescribed doses. Analysis of the impact of twice-daily and 3-times-daily dosing was not done, because of the variability within patients switching from twice daily to 3 times daily and back again, which would confound such an analysis.

Detailed information on glucocorticoid treatment regimens were extracted by chart review. The majority of the patients (n = 86) were receiving HC; 6 of those 86 patients were initially on cortisone acetate, and 2 patients switched to prednisone in a later growth period. Owing to how far back our cohort goes, 17 patients were on cortisone acetate; 3 of those 17 switched to prednisone in a later growth period. One patient was treated with prednisone. None of the patients in our cohort received dexamethasone during the growing years. Glucocorticoid dose equivalents were calculated based on growth-suppressing effects compared with HC, as follows: 30 mg of HC = 37.5 mg of cortisone acetate = 6 mg of prednisone.[5,6] Glucocorticoid dose equivalents are expressed in milligrams per square meter (mg/m^2). All 66 patients with SW CAH and 15 of the 38 patients with SV CAH received fludrocortisone at some point during the growth period. Bone ages were extracted from the clinical records based on endocrinologist or radiologist reports using standard clinical methodologies.

Triple Logistic Models

We calculated predicted growth trajectories, height, growth velocities, and adult stature in children using triple logistic techniques for linear growth from early childhood through adulthood.[7,8] This technique uses Bayesian estimations for robust computation of growth measurements in the presence of irregular or fragmented data, and uses locally weighted curve fitting methods to model data for all nodal points of growth.[9] AUXAL version 3.1 (Scientific Software International, Lincolnwood, Illinois) was used to estimate all growth measurements.[7] We used the root mean squared error to diagnose the fit of all triple logistic models. All modeled growth velocity and attained height curves were independently inspected by 2 pediatric endocrinologists relative to the raw data to further ascertain appropriate fit.

Normative Control Groups

Owing to the longitudinal nature of the growth data in our cohort, we reviewed other longitudinal growth studies for availablity of similar auxologic and timing variables. We chose data from the Fels Research Institute longitudinal study (1929 to date) because the statistical modeling technique used (double logistic regression) is closest to our growth modeling techniques.[10] Comparative estimates for predicted AH (PAH) from the general population were obtained from the Fels study.[10-12] We calculated *z*-scores for the therapeutic and reference groups based on Centers for Disease Control and Prevention (CDC) 2000 normative growth data (for 1963-1994).

Statistical Analyses

We used mixed-regression models to study longitudinal associations among the main exposure, growth period HC treatment, and PAH. We modeled clinic visits with HC dosages within subjects specified as a random effect. This allowed us to accommodate variable timing of clinic visits and to take into account the visit-to-visit correlations and effects in the estimation of associations. In addition to the main exposure of interest, we included the following potential confounders as covariates in the model: age (as a time-varying covariate), CAH subtype (SV; SW), fludrocortisone dosing, sex, clinic visited, and relative bone age (calculated as bone age − chronological age). In addition, we included decade of therapy to control for changes in treatment regimens and secular trends in growth over the 5 decades.

We assessed effect modification by conducting stratified analysis by sex, and found that associations did not vary by sex; as a result, we performed pooled analyses with adjustment for sex. We also adjusted for departure from linearity (curvilinearity) of associations using a quadratic term as fixed effect, and found it to be statistically significant (βhydrocortisone $[\beta_{HC}]^2 = 0.003$; $P = .029$).

We developed a suppression score variable to account for clinical management. This suppression score, with nominal values for adequately suppressed, undersuppressed, and oversuppressed, was determined from a composite of 5 historical control measurements in the clinical database based on normative ranges.[13-15] 17α-hydroxyprogesterone was considered adequately suppressed if <1000 ng/dL, undersuppressed if >1000 ng/dL, and oversuppressed if <200 ng/dL. Androstenedione, urinary 17-ketosteroids, and pregnanetriol were categorized similarly based on the respective age and sex-specific normal ranges. Standard regression diagnostics were followed to ensure that estimates were not unduly affected by influential data points. The differences between triple logistic model–estimated AH and clinically observed AH (OAH) were examined by paired *t* tests in subjects who were followed into adulthood.

We also assessed differences in mid-parental height and OAH of a subset of the cohort and their offspring. Finally, we examined how the height of the parents of the CAH cohort differed from the US national mid-AH using 1-sample median tests. Mid-parental target height was estimated as the mean height of both parents adjusted for sex, whereas the average parental height was calculated as the mean of the median height for males (176.19) and females (163.13) in the CDC 2000 height-for-age tables at age 18 years.