The Relation of Peripubertal and Pubertal Growth to Final Adult Height in Children with Classic Congenital Adrenal Hyperplasia

Eric M. Bomberg, MD[1], O. Yaw Addo, PhD[2], Jennifer Kyllo, MD[3], Maria T. Gonzalez-Bolanos, MD[1], Aida M. Ltief, MD[4], Siobhan Pittock, MD[4], John H. Himes, PhD[5], Bradley S. Miller, MD, PhD[1], and Kyriakie Sarafoglou, MD[1]

Objectives To determine the relationships between peripubertal and pubertal timing and growth, along with glucocorticoid exposure, to the reduced final adult height seen in patients with congenital adrenal hyperplasia (CAH).

Study design Chart review of 104 children with classic CAH (41 males: 28 salt-wasting, 13 simple-virilizing; 63 females: 38 salt-wasting, 25 simple-virilizing) were selected from a cohort from 3 medical institutions in Minnesota. Triple logistic modeling of longitudinal data was performed to determine patterns of peripubertal and pubertal growth.

Results Hydrocortisone dose was similar between subtypes and during all growth periods. Simple-virilizing boys ($P < .01$) and girls ($P < .01$) were diagnosed later than their salt-wasting counterparts. Height at take-off SDS was reduced for patients with salt-wasting (boys: $P < .01$; girls: $P < .01$), and bone age at take-off SDS was more advanced for patients with simple-virilizing (boys: $P < .01$; girls: $P = .05$). Bone age at pubertal onset SDS was advanced for all patients, but more so for boys and girls with simple-virilizing. Although all patients had reduced final adult height SDS, this was more pronounced in patients with salt-wasting.

Conclusion Reduced final adult height SDS in patients with salt-wasting vs simple-virilizing may be attributable in part to a later age of diagnosis and resultant less prolonged exposure to hydrocortisone. This finding suggests that duration of hydrocortisone treatment in the peripubertal period, independent of the hydrocortisone dose, may affect final adult height in patients with CAH. *(J Pediatr 2015;166:743-50)*.

Congenital adrenal hyperplasia (CAH) attributable to 21-hydroxylase deficiency is an autosomal-recessive disorder that blocks cortisol synthesis and impairs cortisol-mediated negative-feedback control of pituitary adrenal corticotropic hormone secretion. Consequently, adrenal corticotropic hormone is oversecreted, stimulating excessive 17-hydroxyprogesterone and adrenal androgen synthesis, including androstenedione. Excess production of androgens, through aromatization into estrogens, leads to advanced bone maturation and early growth plate fusion,[1] ultimately contributing to a diminished final adult height in comparison with healthy norms.[2-4]

Glucocorticoid replacement is the mainstay of treatment in classic CAH.[5] The goal of this therapy is to maintain normal prepubertal and pubertal development to help children reach their genetic growth potential. The typical oral cortisol replacement with hydrocortisone in children with CAH is 10-15 mg/m^2/day.[5] The estimated daily cortisol production in healthy children, in contrast, is 6-8 mg/m^2/day.[6] Exposure to greater than physiologic doses of glucocorticoids negatively affects growth by interfering with the pituitary production and secretion of growth hormone, inhibiting growth hormone production of insulin-like growth factor-1 messenger RNA in liver cells and creating a state of growth hormone resistance at the growth plate.[7]

Reports on the timing of onset and course of puberty in children with CAH have been mixed, and there is still controversy over certain factors related to critical periods of growth in this population. To address these issues, we applied triple logistic modeling of longitudinal data, a technique novel to CAH studies, to determine patterns of peripubertal and pubertal growth and development and the effect of hydrocortisone during these growth periods in 104 children with CAH. We also sought to determine whether the shorter final adult height seen in glucocorticoid-treated patients with CAH was attributable to reduced pubertal height gain or changes in the peripubertal timeframe.

Methods

We performed medical chart review of 104 children with classic CAH (male [n = 41]: 28 salt-wasting, 13 simple-virilizing; female [n = 63]: 38 salt-wasting, 25 simple-virilizing) seen between the years 1955 and 2012 at 3 medical institutions in Minnesota. Patients were selected from the cohort on the basis

CAH	Congenital adrenal hyperplasia
PAH	Predicted adult height

From the [1]Department of Pediatrics, University of Minnesota Children's Hospital, Minneapolis, MN; [2]Global Health, Rollins School of Public Health of Emory University, Atlanta, GA; [3]Pediatrics, Children's Hospitals of Minnesota, Minneapolis, MN; [4]The Mayo Clinic College of Medicine, Rochester, MN; and [5]Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, Minneapolis, MN

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of availability of sufficient growth data for modeling. Only cases with available data for height on at least 2 occasions during the following stages of growth were included: early childhood (0-4.99 years), mid-childhood (5-9.99 years), and adolescence (10-15 years). These inclusion criteria were adopted to ensure that there were longitudinal data on heights and age for these 3 periods that typify a child's growth. Subtype classification (salt-wasting vs simple-virilizing) was assigned by a pediatric endocrinologist at each participating institution and was based on clinical, hormonal, biochemical, and in some cases, molecular testing. Children with nonclassic CAH and those who received growth hormone, gonadotropin-releasing hormone analogues, or aromatase inhibitors were not included in the analysis.

The majority of patients were taking hydrocortisone (86 of 104). Seventeen patients were on cortisone acetate, one patient was treated with prednisone, and no patients received dexamethasone during the growth years. Glucocorticoid dose equivalencies were calculated on the basis of their growth-suppressing effects in comparison with hydrocortisone, as follows: 30 mg of hydrocortisone = 37.5 mg of cortisone acetate = 6 mg of prednisone.[8,9] Glucocorticoid dose equivalents were expressed in milligrams per square meter (mg/m^2). All patients with salt-wasting and CAH and 15 of the 38 patients with simple-virilizing and CAH received fludrocortisone at some point during the growth period.

Triple Logistic Models

We calculated predicted growth trajectories, height velocities, and predicted adult height (PAH) in children by using triple logistic techniques for linear growth spanning early-childhood, mid-childhood, and adolescent periods of growth.[10] The triple logistic model uses Bayesian model estimations to fit 3 logistic curves to serial height data for individuals (**Figure**) using AUXAL 3.1 software (Scientific Software International, Inc, Skokie, Illinois).[10] Adequacy of the triple logistic model fit was adjudged with the root mean squared errors. All modeled growth velocity and attained height curves were independently inspected by 2 pediatric endocrinologists relative to the raw data to further ascertain fit as previously described.[4] Growth variables estimated by this technique included PAH, age at take-off, height at take-off, velocity at take-off, adolescent height increment (growth between take-off and final adult height), and velocity at peak height velocity.

Pubertal and Peripubertal Timing Measurements

As mentioned previously, age at take-off was determined from triple logistics modeling and reflects the onset of the

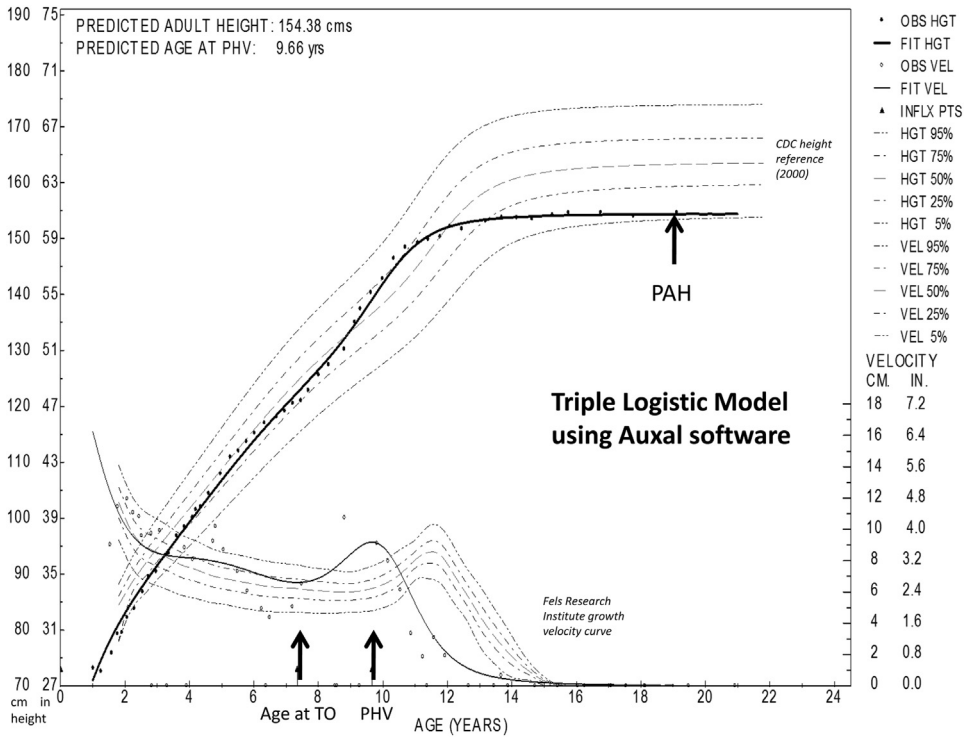

Figure. Serial height (*closed circles*) and growth velocity (*open circles*) data from a representative patient from the Minnesota CAH cohort are plotted against Centers for Disease Control and Prevention height reference curve and Fels Research Institute growth velocity curve. The *solid lines* represent the growth curve calculated by AUXAL software using triple logistic modeling for this patient based upon the available growth data. The triple logistic model is used to calculate auxologic variables including the age at take-off, age at peak height velocity, and PAH (*arrows*). *PHV*, predicted height velocity; *TO*, take-off.