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Near-final height in 82 Chinese patients with congenital adrenal hyperplasia due to classic 21-hydroxylase deficiency: a single-center study from China

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Abstract

Background: The objective of this study was to identify variables that might interfere with reaching the near final height (NFH) in Congenital adrenal hyperplasia (CAH) due to classic 21-hydroxylase deficiency (21-OHD).
Methods: A cross-sectional study of 82 (24 males and 58 females) classic (23 salt-wasting form [SW] and 59 simple-virilizing form [SV]) CAH 21-OHD patients seen in our institution between 1989 and 2015 with 10.6 (0.5~25.5) years of follow-up who reached their NFH was conducted. The variables related to NFH were explored.
Results: NFH (153.35±8.31) cm, (–1.9±1.1) SD was significantly lower than the normal population ($p<0.001$). The treated patients reached a significantly higher NFH (–1.7±1.1) SD than those untreated (–2.6±1.0) SD ($p<0.05$). Both of early treatment and late treatment group were taller than untreated group ($p<0.001$, $p=0.013$, respectively), and early treatment group had a taller height trend than late treatment group ($p=0.089$). A better height outcome was observed in patients with advantage in target height, good compliance, and low hydrocortisone dose by multivariate Cox regression analysis in 62 treatment patients. NFH and hydrocortisone dose was negatively correlated ($r=-0.23$, $p=0.078$) in treated group. Patients complicated by central precocious puberty (CPP) received gonadotropin-releasing hormone analogue (GnRHa) plus letrozole had increased NFH with height SD for bone age and Ht SD improved after treatment compare to no intervention group ($p=0.001$, $p=0.035$).
Conclusions: Patients with classic 21-OHD have blunted final height, as compared with their target height and the population norm, not-treated even worse. Careful treatment adjustments have a favorable influence on growth. Alternative treatments, such as the use of puberty inhibitors GnRHa in addition to anti-estrogen therapy letrozole can somewhat improve NFH in children with 21-OHD complicated by CPP.

Keywords: congenital adrenal hyperplasia; 21-hydroxylase deficiency; near final height; target height.

Introduction

Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive disorders caused by specific enzyme deficiencies in cortisol biosynthesis. 21-Hydroxylase deficiency (21-OHD) is the most common form, comprising 95% of the cases. Seventy-five percent of the classic 21-OHD (salt-wasting form [SW] or simple virilizing form [SV]) have concomitant mineralocorticoid deficiency [1]. Corticosteroids (glucocorticoids and mineralocorticoid) replacement is the primary treatment of 21-OHD. Insufficient or excessive treatments are two common situations observed. Inadequate glucocorticoid (GC) replacement therapy does not suppress excessive secretion of adrenal androgen, causing abnormal growth and developmental patterns, final height is damaged and pseudoprecocious puberty have frequently been observed. Administration of supraphysiological or excessive doses of glucocorticoids has been associated with impaired growth [2]. It has been found that final adult height of children with CAH is shorter than the general population, relating to both, the underlying disease and its treatment [3, 4]. Hence, there is

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a great challenge for pediatric endocrinologists to manage the narrow therapeutic window attempting to substitute cortisol deficiency, inhibit ACTH and androgen excess and optimize growth.

In this paper, we present the results of near final height (NFH) in patients with CAH 21-OHD followed up from 1989 to 2015 in a single institution, and the variables related to this outcome.

Materials and methods

Subjects

The study is based on a retrospective analysis of growth data from registration of patients attended (age range from newborn to 15 years old) at the Children's Growth and Development Center of the First Affiliated Hospital of Sun Yat-Sen University obtained from 1989 to 2015. Eighty two patients (24 males and 58 females, 23 SW type and 59 SV type) of 260 CAH 21-OHD patients seen in our center have reached their NFH.

Clinical assessment

Diagnosis and phenotypic classification of 21-OHD was based on the clinical history, current clinical status, and hormonal criteria. Nine/eighty two were supported by genetical analysis [1]. Ambiguous genitalia presents in all girls, and macrogenitossomia in boys, associated with increased 17-OHP, progesterone and androgens. SW was established according to a report of salt losing crisis, in addition to the need of fludrocortisones acetate to maintain normal electrolyte levels.

Detailed information on GC treatment regimens were extracted by chart review. Sixty two patients received hydrocortisol (HC), 16 of them had cortisone acetate (from the age 0 to 11 years), the average time of taking cortisone was 6.3 years. One has been taking prednisone for 4 years (from the age 6 to 10 years). No patient received dexamethasone during the growing years. GC 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]. GC dose equivalents are expressed in milligrams per square meter (mg/m^2). Sodium chloride supplements were given in the newborn period and early infancy. SW CAH and SV CAH patients with elevated plasma rennin level received fludrocortisone treatment at a daily dose of 0.05–0.2 mg since 1995 for the reason of the lack of availability of fludrocortisone in China [1].

All patients underwent physical examination to obtain anthropometric measurements. The auxanological data included height, weight, height standard deviation score (HtSDS), and linear growth velocity (GV). Pubertal maturation (breast and genitalia) was assessed according to the method of Marshall and Tanner.

Follow-up appointments were held every 3–6 months after a definite diagnosis, standard auxological assessment was performed at each visit. Bone age (BA) was determined by the method of Greulich and Pyle [6]. Adult height was predicted according to the Bayley and Pinneau method [7]. NFH was considered to be attained when the growth velocity during the preceding year was <0.5 cm with a BA of over 17 years in boys or 15 years in girls.

All SDS (z-scores) were calculated based upon the Chinese normative growth data, undertaken by the National Surveys on Students Constitution and Health in 2005 in China [8]. BMI (weight/height^2) was calculated. An overweight state was defined as a BMI >85% and ≤95% and obesity as a BMI >95% in childhood using national standards [9].

Definition of short stature: Familial short stature (FSS) is defined as a HtSDS for chronological age below –2 SD. However, –2 SD above mid-parental target height is considered to be within the "normal range" for parental height in a consensus report. Though mid-parental target height (TH) was calculated commonly from the mean height of the parents adjusted for sex, as described by Tanner et al. (average of the father's and mother's height ±6.5 cm) [10]. A more accurate estimate can be achieved using a corrected target height SDS (cTHSDS), which is calculated as 0.72× average of father's and mother's height SDS and the lower limit of the TH range as corrected target height (cTH) –1.6 SDS [11].

Age at diagnosis and treatment: As routine screening for CAH has not been implemented in our state so far, all patients were identified by clinical presentation. Patients diagnosed at an age younger than 1 year were considered to be "early diagnosis", whereas those presenting at an age older than 1 year were considered to be late [12]. "Early treatment" was characterized by anamnestically constant medication intake within age 1–3 years [13]. "Untreated" was considered that the patient received the medication intake when BA was more than 14.75 years in boys or 12.75 years in girls reaching 95% of FH. "Late treatment" means initiation of therapy at the age between "early treatment" and "untreated".

Compliance: A good compliance was considered in children with anamnestically constant medication intake, the number of days to prescribed medication ≥80% of the total number of days of follow-up. Otherwise was considered as a poor compliance [14, 15].

Diagnosis and treatment of central precocious puberty (CPP): Diagnosis is based on observation of clinical signs of puberty (Tanner stage 2) before the chronological age (CA) of 8 in girls and before the CA of 9 in boys, and was confirmed with elevated basal and/or stimulated LH and FSH levels and advancement of BA for CA [16, 17]. Patients complicated with CPP were administrated with gonadotropin-releasing hormone analogue (GnRHa, intramuscular or subcutaneous 28-day depot triptorelin 3.75 mg every 4 weeks), GnRHa combined with oral use of letrozole (1.5 mg/m^2/day, ⩾2.5 mg/day), and none, based on parental choice.

Statistical analysis

The primary end-point variables for this study are the following: near-final height (and SD score) for CA, near-final height (and SD score) for BA, predicted adult height (PAH) (and SD score), and height deficit. Results are expressed as mean±SD where indicated. For statistical

analysis, the Wilcoxon 2-sample test as appropriate for between-group comparisons. We explored the influencing factors determining NFH by using multivariate regression analysis. An analysis of covariance model (one-way ANOVA) was used to correlate the condition of patients complicated with CPP before and after intervention. Pearson correlation was used to calculate the hydrocortisone dose (mean of the whole follow-up) with NFH and BMI. Significance was evaluated at $p<0.05$.

Results

Anthropometric characteristics of 82 21-OHD patients

Charts from 82 patients (24 males and 58 females, 23 SW and 59 SV type) with 21-OHD were examined. Median follow-up time until the final height was 10.6 years (ranging from 0.5 to 25.5 years). The number of patients with early and late diagnosis, treated and untreated was 19 vs. 63, 62 vs. 20, respectively. The median age at diagnosis was 4.96 (0.17–11.48) (10th–90th) years, with SW patients being diagnosed earlier than SV patients (2.0±3.4 vs. 6.9±3.6 years) ($p<0.001$), 89.5% (17/19) of patients with early diagnosis were SW type.

Stratification analysis of factors affect NFH in all patients

NFH (153.35±8.31) cm, (–1.9±1.1) SD was significantly lower than the population norm ($p<0.001$). There was a significant impairment of NFHSDS compared with the target height SDS ($p<0.001$). No difference of NFHSDS was seen between males and females ($p=0.333$). Similarly, no statistically significant between SW and SV ($p=0.243$). Patients with early diagnosis appeared to be taller than those with late diagnosis ($p=0.019$), and "treatment group" was taller than "untreated group" ($p=0.01$; Table 1). The proportion of the patients who reached NFHSDS within the normal population range (≥–2 SD, >–1 SD) in "treatment group" is higher than that in "untreated group" [64.5% (40/62) vs. 25.0% (5/20), 30.6% (19/62) vs. 5.0% (1/20), respectively, $p<0.01$, $p<0.05$].

The treated patients reached a significantly higher NFHSDS (–1.7±1.1) than those untreated (–2.6±1.0) ($p<0.05$). To further explore the effect of treatment stratification on the NFH, we analyzed the different NFHSDS among early treatment (–1.4±1.1, n=27), late treatment (–1.9±1.0, n=35) and non-treatment groups (–2.6±1.0, n=20) using one-way ANOVA. Both of early treatment and late treatment group were taller than untreated group ($p<0.001$, $p=0.013$, respectively), and early treatment group had a taller height trend than late treatment group ($p=0.089$).

Multivariate Cox regression analysis in 62 treatment patients

We used multivariate regression analysis to explore the factors affect the NFH in treatment group. As shown in Table 2, gender, CAH subtype, age at diagnosis and treatment stratification had no significant influence on NFH in multivariate regression analysis. A slight effect was

Table 1: The clinical and anthropometric characteristics of 82 patients attaining their near final height.

	n (%)	Anthropometric data (cm)		Anthropometric data (SD-score)		p-Value[a]
		cTH	NFH	cTHSDS	NFHSDS	
Total	82	160.18±6.70	153.35±8.31	−1.0±0.9	−1.9±1.1	<0.001[b]
Gender						0.333
Male	24 (29.3)	169.09±3.70	161.42±7.79	−1.0±0.9	−1.8±1.3	
Female	58 (70.7)	156.5±3.32	150.02±5.90	−1.0±0.9	−2.0±1.1	
CAH subtype						0.243
SW	23 (28.0)	164.7±6.3	157.2±8.0	−0.7±0.9	−1.7±1.2	
SV	59 (72.0)	158.4±6.0	151.9±8.0	−1.1±0.8	−2.0±1.1	
Age at diagnosis						0.019
≤1 year	19 (23.2)	164.1±7.3	158.1±6.3	−0.6±1.0	−1.4±0.9	
>1 year	63 (76.8)	159.0±6.1	151.9±8.3	−1.1±0.8	−2.1±1.2	
Treatment or not						0.01
Treatment	62 (75.6)	161.4±7.0	155.3±8.2	−0.8±0.9	−1.7±1.1	
Non-treatment	20 (24.4)	156.3±3.8	147.3±5.2	−1.4±0.8	−2.6±1.0	

[a]p-values estimated using the Wilcoxon 2-sample ([b]p: compare cTHSDS vs. NFHSDS). SW, salt-wasting; SV, simple virilizing; cTH, corrected target height; NFH, near final height; cTHSDS, corrected target height SDS; NFHSDS, near final height SDS.

Table 2: Multivariate regression analysis of different variables affect NFH in treatment groups (n=62).

Variables	β-coefficient	95% confidence interval		p-Value
		Lower limit	Upper limit	
Gender (male vs. female)	−0.150	−0.682	0.383	0.575
CAH subtype (SW vs. SV)	0.405	−0.219	1.028	0.199
Age at diagnosis (<1 year vs. ≥1 year)	0.091	−0.641	0.823	0.805
Treatment stratification ("early treatment" vs. "late treatment")	−0.310	−1.000	0.380	0.371
Compliance ("good" vs. "poor")	−0.473	−1.009	0.063	0.083
cTHSDS	0.522	0.254	0.791	<0.001
HC dose, mg/m²/day	−0.068	−0.114	−0.023	0.004
Used multivariate regression analysis				

observed in patients rated as having "good" compliance as compared with those rated as having "poor" compliance (p=0.083). There are significant effects of cTHSDS and HC dose on NFH in the 62 treatment patients. CTHSDS had a positive correlation with NFH (p<0.001), while HC dose negatively related to NFH (p<0.004).

Patients with short status

To further explore the factor of cTHSDS in determining 21-OHD patients NFH, we also emphasized the patients with genetic short status. When we compared the NFH of our cases to the Chinese standards, 37 of the 82 patients (45.1%) had a NFHSDS <−2 (<3rd percentile). Seven patients (7/82) had a family history of short stature. The distribution of 37 patients' (NFHSDS <−2) target range (NFHSDS-cTHSDS) is shown in Figure 1. The distribution is skewed to the left with 21 persons (21/37=56.8%) below the target range (NFHSDS-cTHSDS <−1.6), who belong to the "true short status", while 16 of them in the range of genetic height.

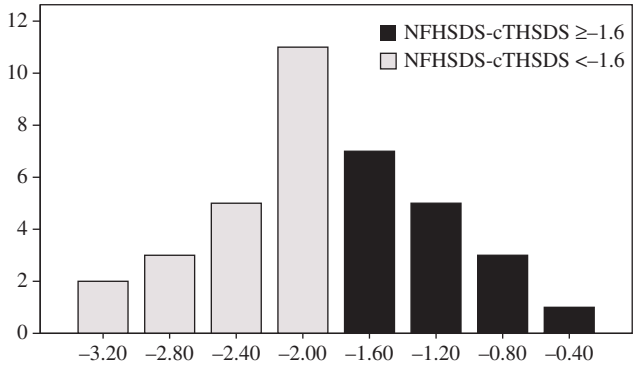

Figure 1: Distribution of 37 patients' (NFHSDS <−2 SD) target height range (NFHSDS-cTHSDS).
Patients labeled with grey is NFHSDS-cTHSDS <−1.6, while black is NFHSDS-cTHSDS ≥−1.6.

HC dose in relation to BMI and NFH

The average hydrocortisone dose (cortisone and prednisone dose converted to an equivalent dose of hydrocortisone) in our center before 2010 was 18.91 mg/m²/day (12.1–35.5 mg/m²/day). After 2010 the average dose of hydrocortisone was 13.78 mg/m²/day. NFH and hydrocortisone dose was negatively correlated (r=−0.23, p=0.078) in treated group.

Six of 82 patients (6/82, 7.32%) were obese (2/6, SW male) or overweight (4/6). There was no correlation between the hydrocortisone dosage and the BMI in 62 treatment patients (r=0.007, p=0.098).

Complicated with CPP

Thirty-two of the 62 treatment patients (20 females and 12 males) were confirmed to be complicated with CPP. Twenty-two of them received alternative treatments, of whom 11 received GnRHa treatment, 11 received combined treatment of GnRHa and anti-estrogen therapy letrozole. The left 10 patients had no GnRHa or letrozole treatment.

The mean baseline characteristics of the following three groups were similar. The majority of the patients were female (7 of 11), and the mean age at enrollment was 7.4 years (age range from 4.8 to 10 years). BA was markedly advanced compared with CA by 4.2 years in three groups. The treatment during time of the three group was (2.5±1.8) years. NFHSDS of GnRHa plus letrozole group (−1.3±0.8) had significance taller than no intervention group (−2.5±1.0, p=0.005). $HtSDS_{BA}$ and Ht SD improved after intervention with GnRHa plus letrozole compare

with no intervention group (p=0.001, p=0.045, respectively). While NFHSDS of GnRHa group (–1.8±0.9) had no significant improved compare to the no intervention group (p=0.062; Table 3).

Discussion

Currently, final adult height in classic CAH 21-OHD in China is only reported in a small sample of the limited coverage. Since 1989, hundreds of CAH 21-OHD patients were diagnosed and treated in our center. Here we present the NFH distribution in 82 patients with classic CAH 21-OHD. Although there are many studies on the final height of CAH patients, our study is the first study with large sample data of 82 CAH patients in a single center from China, even from Asia.

The near adult height SDS of Chinese children with classic CAH 21-OHD was (–1.9±1.1) in this study, while the cHSDS was (–1.0±0.9). There was a significant impairment of NFHSDS (–1.9 SD) compared with the cTHSDS (–1.0 SD), demonstrating that these patients did not reach their genetic potential. Either treatment or not, the NFH of classic 21-OHD children is shorter than the normal population, non-treatment even worse, as reported by other authors [13, 18, 19]. Previous meta-analyses identified the mean weighted FHSDS in patients with 21-OHD as –1.37 [12] and –1.38 [18]. Median follow-up time until the final height was 10.6 years (0.5~25 years). As some of untreated patients had reach NFH when they saw a doctor, the follow-up time in their growing was short.

As the result showed, the NFH of 21-OHD patients is associated with treatment or not and the age at diagnosis in our center. The treatment group of NFHSDS was taller than the non-treatment group of NFHSDS. NFHSDS of treatment group had more patients reached the normal population range (≥–2 SD) and above –1 SD than the non-treatment group, which is consistent with the report of Manoli et al. [20]. Besides, patients with early diagnosis were significance taller than those with late diagnosis and good compliance plays a positive effect on NFH of treatment patients in our study. Previous studies demonstrate that late diagnosis was an important factor that associated with a poor height outcome [21, 22]. Diagnosis up to one year of CA and good treatment compliance had a positive influence in FH [18, 22]. Poor compliance, as noted by Eugster et al. [12], may be an important factor

Table 3: Auxological characteristics for 32 21-OHD patients complicated with CPP before and after intervention.

Variables n (Male/Female)	GnRHa+letrozole 11 (4/7)	GnRHa 11 (4/7)	No intervention 10 (4/6)
Age, year			
Baseline	7.3±1.6	7.4±1.6	7.3±0.8
After intervention	9.7±1.3	9.5±2.2	9.4±1.7
Bone age, year			
Baseline	11.7±1.8	11.6±1.2	11.8±1.8
After intervention	13.0±1.4[a]	13.0±1.0[b]	14.3±0.8
Baseline Ht, cm			
Baseline	133.4±10.8	132.2±9.7	133.3±9.0
After intervention	147.4±10.9	146.1±9.5	145.2±8.0
$HtSDS_{CA}$			
Baseline	1.6±2.2	1.4±1.1	1.7±1.6
After intervention	1.7±2.9	1.1±1.9	1.2±1.3
$HtSDS_{BA}$			
Baseline	–2.6±0.7	–2.5±1.3	–2.5±1.4
After intervention	–1.6±0.8[a]	–2.1±0.8[b]	–3.0±1.0
NFH, cm	157.6±8.9	153.8±8.9	154.2±7.1
NFHSDS	–1.3±0.8[a]	–1.8±0.9	–2.5±1.0
TH, cm	162.2±7.3	161.5±6.7	161.0±8.3
THSDS	–0.5±0.7	–0.6±0.6	–0.9±0.6
Ht SD improved after intervention	1.1±1.0[a]	0.4±0.7	0.3±1.0

Values are expressed as the mean±SD, median. CA, chronological age; BA, bone age; $HtSDS_{CA}$, height SD for chronological age; $HtSDS_{BA}$, height SD for bone age; Ht SD improved after intervention=NFHSDS-PHVSDS. [a]"GnRHa+letrozole" compared with "no intervention" p<0.05; [b]"GnRHa" compared with "no intervention" p<0.05. An analysis of covariance model (One-way ANOVA) was used to correlate the condition of patients complicated with CPP before and after intervention.

in height outcome with unsuppressed androgen secretion causing premature fusion of the epiphyseal growth centers.

As we all know, the age of diagnosis differs in diverse CAH forms. Median age of diagnosis of SW patients was 3.0 months, while SV was 6.83 years. SW patients usually have a symptom of salt losing crisis and the need of fludrocortisones acetate to maintain normal electrolyte levels which easy to be diagnosed early. Therefore, regardless of sex, age at diagnosis of the SW patients was younger than the SV patients, in early diagnosis group the SW patients account for 89.5% (17/19). The NFHSDS between the SW and SV were no significant different in our data, which in accordance with an analysis of 125 children adult height data with CAH by Bonfig et al. [23]. The neonatal screening programs for CAH was not implemented in China so far, the diagnosis of almost all patients was late in our study, particularly for the SV CAH, and patients usually present later with clinical findings of hyperandrogenemia and advanced skeletal maturation.

For adult height estimation of 21-OHD CAH patients, considering the influence of FSS, a more accurate estimate can be achieved using a cTHSDS [24]. In our study, NFHs of 37 (45.1%) patients were below than –2 SD. When we use the cTH limit, only 25.6% (21/82) of patients belong to the "true short status". We found that cTHSDS was an important factor that affected the NFH treatment 21-OHD patients. Children in an advantage of cTHSDS had taller height than the population references. Genetics have an important impact on the child's height. Therefore, the judgment for CAH 21 OHD patients' adult height may be too low at present, larger patient samples are needed to evaluate.

For the relationship between glucocorticoids dose and 21-OHD adult height, the mean dose of hydrocortisone used in our study was 18.91 mg/m^2/day (ranged from 12.1 to 35.5 mg/m^2/day). NFH was negatively related to the dosage of hydrocortisone in treatment group, which was the same as those reported previously [1, 25]. Kyriakie Sarafoglou et al. [26] reported a retrospective study from 1955 to 2012 of 104 patients with CAH the mean growth period HC dose was 18.9±5.6 mg/m^2/day. And they also founded that the growth period average HC dose ranged from 9.4 to 39.2 mg/m^2/day had an inherent impact on PAH (–3.5 cm) even at the lowest dose (9.4 mg/m^2/day) in cohort.

The pediatric consensus statement in 2010 demonstrated that when doses exceed 20 mg/m^2/day in infants and 15–17 mg/m^2/day in adolescents, there is a loss of height SD score and shorter adult height [27, 28], and recommended GC replacement for children is with 10–15 mg/m^2/day of hydrocortisone divided into three daily doses [1].

CPP often develops in patients with CAH due to androgen activation of the hypothalamic-pituitary-gonadal axis, thus exacerbating premature epiphyseal fusion. GnRHa is classic medication for precocious puberty. Letrozole is a selective third-generation aromatase inhibitor (AI), reducing the conversion of androgen to estrogen hormone by inhibiting the synthesis of aromatase, thus reduces the level of estrogen in the body, slow down growth-plate maturation. Although it has been predicted that letrozole administration would improve the PAH in CAH patients [29], this is the first report of the use of letrozole in combination with GnRHa in CAH patients resulting in an improvement of NFH. NFHSDS of GnRHa plus letrozole group had significance taller than no intervention group in our cohort. A possible explanation for the excellent response to GnRHa combined with letrozole treatment in CAH patients may be that the GnRHa are capable of suppressing the hypothalamic-pituitary-gonadal axis, acts synergistically with letrozole by reducing the conversion of androgen to estrogen hormone to collaborate delay BA mature and prolong growth space. The results of GnRHa intervention did not reach statistical significance in NFHSDS compared with no intervention group. This could be explained by their extremely advanced BA for CA before initiating GnRHa therapy, results in a deceleration of BA advancement with a parallel decrease in growth velocity which was similar to the previous studies [30, 31]. Further research and larger patient samples are needed to evaluate the efficiency of GnRHa plus letrozole in the treatment of children with CAH and CPP.

Another aspect of the adverse effects of gulcocorticoid is their relation to obesity, frequently reported for CAH patients of all variants [30, 32]. In 62 treatment patients, we could not find any correlation of BMI with GC.

We found that either treatment or not, the classic 21-OHD children NFH is shorter than the normal population, and most of them are not capable of reaching their genetic height potential, non-treatment even worse. Early diagnosis and improvements of compliance with medical substitute therapy, should ultimately lead to superior outcomes in all aspects of 21-OHD, including adult stature. An average daily hydrocortisone dose of 18.91 mg/m^2/day ended up with an adult height below the TH lead us to believe that we should use the lowest possible dose for treatment. In addition, the associated adjuvant therapy schedule can somewhat improve the NFH.

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