The Journal of Clinical Endocrinology & Metabolism, 2023, **00**, 1–6
https://doi.org/10.1210/clinem/dgad307
Advance access publication 31 May 2023
Clinical Research Article

Impact of Newborn Screening on Adult Height in Patients With Congenital Adrenal Hyperplasia (CAH)

Heike Hoyer-Kuhn,[1] Alexander J. Eckert,[2] Gerhard Binder,[3] Walter Bonfig,[4,5] Angelika Dübbers,[6] Stefan Riedl,[7,8] Joachim Woelfle,[9] Helmuth G Dörr,[9] and Reinhard W. Holl[2]

[1]Department of Paediatrics, Faculty of Medicine and University Hospital Cologne, University of Cologne, 50937 Cologne, Germany
[2]Institute of Epidemiology and Medical Biometry, ZIBMT, University of Ulm, 89081 Ulm, Germany
[3]Pediatric Endocrinology, University-Children's Hospital Tübingen, 72076 Tübingen, Germany
[4]Department of Pediatrics, Klinikum Wels-Grieskirchen, 4600 Wels, Austria
[5]Department of Pediatrics, Technical University of Munich, TUM School of Medicine, 80804 Munich, Germany
[6]Department of Pediatrics, University Hospital Münster, 48149 Münster, Germany
[7]Division of Pediatric Pulmology, Allergology and Endocrinology, Department of Pediatrics, Medical University of Vienna, 1090 Wien, Austria
[8]Department of Pediatrics, St. Anna Kinderspital, Medical University of Vienna, 1090 Wien, Austria
[9]Department of Pediatrics and Adolescent Medicine, University Hospital Erlangen, Friedrich-Alexander-University Erlangen-Nuremberg, 91054 Erlangen, Germany

Correspondence: Heike Hoyer-Kuhn, Priv. Doz. Dr. med., Department of Pediatrics, Faculty of Medicine and University Hospital Cologne, University of Cologne, 50937 Cologne, Germany. Email: heike-katharina.hoyer-kuhn@uk-koeln.de.

Abstract

Context: Treatment of children with classical congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency is challenging. Linear growth and adult height are compromised according to recent publications. However, most of these data were obtained in the era before CAH newborn screening.

Design: Body height of patients with classical CAH diagnosed before and after the establishment of newborn screening were analyzed retrospectively.

Patients and Methods: We identified 600 patients with classical CAH (227 male) with data on near-adult height (NAH), target height (TH), and information on newborn screening from the electronic German CAH registry (German Society for Paediatric Endocrinology and Diabetology). Newborn screening was performed in 101 (16.8%) patients. All patients received hydrocortisone with or without fludrocortisone.

To assess the effects of newborn screening, a linear regression model adjusted/stratified for sex and phenotype was used (SAS 9.4).

Results: TH corrected NAH (mean; 95% confidence interval) was closer to 0 in patients with CAH and newborn screening [−0.25 standard deviation score (SDS); −0.44 to −0.06] than in patients without newborn screening (−0.44 SDS; −0.52 to −0.36) ($P = .069$). Screening had no effect on NAH in female patients. In male patients, NAH was significantly better ($P = .033$) with screening than without screening. After stratifying for CAH phenotype, screening did not affect the NAH of patients with salt-wasting CAH. Patients with simple-virilizing CAH had a significantly better cNAH ($P = .034$) with screening (0.15 SDS; −0.28-0.59) than without screening (−0.35 SDS; −0.52 to −0.18).

Conclusions: Our data suggest that newborn screening might be associated with improved NAH in male CAH patients and in patients with simple-virilizing CAH.

Key Words: CYP21A2, congenital adrenal hyperplasia, newborn screening, near adult height

Classical congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency is caused by homozygous or compound heterozygous mutations in the CYP21A2 gene and is characterized by impaired cortisol and increased androgen production. The most severe form of classic CAH is the salt-wasting (SW) form resulting in cortisol and aldosterone deficiency, whereas the form without salt-wasting is called simple-virilizing (SV) CAH (1, 2).

Therapy is based on a lifelong substitution with glucocorticoids and, additionally, with mineralocorticoids in the SW form of CAH. Treatment of CAH has been characterized as a tightrope act balancing the effects of hyperandrogenism and hypercortisolemia (3). One of the most important therapeutic goals is normal growth, but both undertreatment and overtreatment with glucocorticoids can affect growth. There are numerous reports in the literature demonstrating that the linear growth of individuals with CAH is impaired and adult height is compromised in relation to the general population and to the individual target height. Two large meta-analyses have shown that CAH patients lose about 1 SD in final height corrected for parental height (4, 5). There were many different factors reported affecting height outcomes such as the age at diagnosis, type of CAH, sex, age at the start of puberty, dose and preparation of glucocorticoids, use of mineralocorticoids, and patient adherence (1, 6, 7). However,

Received: 16 March 2023. **Editorial Decision:** 24 May 2023. **Corrected and Typeset:** 12 June 2023

nearly all long-term studies are on children diagnosed in the pre-newborn CAH screening era.

It was speculated that early diagnosis by newborn screening would help to normalize growth and achieve better final height outcomes. The objective of this retrospective analysis was to assess the height outcomes of children with classical CAH who were diagnosed by newborn screening in comparison to children born before screening was established.

Materials and Methods

We identified 600 children with classical CAH due to 21-hydroxylase deficiency with data on near-adult height (NAH), target height (TH), and the information on whether newborn screening was conducted. Among the cohort, 101 children were diagnosed by newborn screening for CAH. For this analysis, we used only data with clearly documented information on newborn screening between 1998 and 2003. After 2004, general newborn screening was implemented. The data was derived from 37 pediatric endocrinology centers (3 from Austria) that enter their data in the electronic registry of the German Society for Paediatric Endocrinology and Diabetology, which is hosted at the Zentralinstitut für Biomedizinische Technik, Institute of Epidemiology and Medical Biometry of the University of Ulm, Germany. Pseudonymized data are transferred for central analysis, including a validation step and a benchmarking report, twice yearly. The data set includes data on phenotype, genotype, auxology, laboratory results, Tanner stages, medication, and surgical interventions. All data were collected during routine care. Each participating center was initiated into the use of the documentation software after approval by local review boards was obtained. Consent has been obtained from each patient or parent after a full explanation of the purpose and nature of data documentation and anonymized analysis.

For the analysis, we used auxological data, phenotype data (SW, SV), data on Tanner's stages of puberty, data on medication, and the parameters NAH and parental TH. Standard deviation scores (SDS) for height were calculated according to German references (8). NAH was defined if height velocity was <2 cm/year if bone age was ≥14 years (females) or ≥16 years (males) or if chronological age was >16 years (females) or >17 years (males) (9). Parental TH was calculated according to Tanner (10). Corrected NAH was calculated as the difference between NAH and TH, and corrected NAH (cNAH) height SDS was calculated as the difference between NAH SDS and TH SDS. Total pubertal growth was defined as growth from the onset of puberty (girls: Tanner stage B2; boys: testicular sizes>3 mL) to NAH (11). Bone age at the onset of puberty was determined using radiographs of the left hand and the method of Greulich and Pyle (12).

Statistical Analysis

All statistical analyses were performed with SAS-version 9.4 build TS1M7 in batch mode (Statistical Analysis Systems, SAS Institute Inc., Cary, NC, USA) on a Windows-Server 2019 mainframe computer. For descriptive analysis, data are shown as median values with lower and upper quartiles. Categorical data were assessed as percentages.

Multivariable linear regression models were used to analyze cNAH by screening status adjusted or stratified for sex and phenotype. The data of the regression models are shown as adjusted mean with lower and upper 95% confidence intervals.

Results

Until September 2021, 600 patients with classical CAH (373 female, 227 male) and complete data sets regarding the information on newborn screening, phenotype, NAH, and parental height to calculate TH were identified in the registry (Table 1). Newborn screening was performed in 101 (16.8%) patients. All patients were treated with hydrocortisone alone or in combination with fludrocortisone. The median age (lower and upper quartile) of the patients at NAH was 15.9 years (14.8-17.0). The SW form of CAH was documented in 410 (68.3%) patients, and 190 (31.7%) patients were classified as SV-CAH.

Clinical Data

Patient characteristics are shown in Table 1. In the CAH cohort with newborn screening (n = 101), the distribution between females and males was almost equal, whereas in the cohort diagnosed clinically without screening (n = 499), there were 1.8 times more females than males (322 f; 177 m).

CAH children with newborn screening were treated significantly earlier ($P < .001$) at a median age of 0.03 years (lower and upper quartiles: 0.01-0.21) than children without screening at 0.5 years (0.04-6.80). By splitting the group of CAH children without newborn screening according to the phenotype, our data show that children with CAH-SW (n = 156; 91 f, 65 m) were treated significantly earlier ($P < .001$) at 0.05 years (0.03-0.41) than children with CAH-SV (n = 94; 65 f, 29 m) at 6.85 years (4.77-8.99). By further splitting the SV group without screening according to sex, the median CA at the start of therapy was not different between girls (7.47 years; 5.76-9.965) and boys (6.78 years; 4.17-8.467).

At the onset of puberty, chronological age, and bone age was not different between children with and without newborn screening. The results of bone age were not available for all children. The median hydrocortisone (HC) dosage at the end of the first year of life was not significantly different between both groups, The median HC dosages (mg/m^2) at the beginning of puberty [13.0 (11.1-15.0)] and at near adult height [14.3 (12.0-16.6)] of children diagnosed by newborn screening were significantly lower than of children diagnosed clinically with 15.1 (12.1-18.2) and 16.0 (12.8-18.7), respectively (Table 1). However, data on HC dosages were not available for all children.

Auxological Data

Across all 600 CAH patients, the median NAH-SDS was −0.90 SDS (−1.66 to −0.10), and cNAH-SDS was −0.38 SDS (−1.04-0.26). Sex had no effect on the height at the onset of puberty and on total pubertal growth (Table 2). The median NAH of the girls with CAH was 161.5 cm (156.5-166.5); −0.81 SDS (−1.55 to −0.04), and the boys with CAH had a median height of 172.4 cm (166.6-177.3); −1.05 SDS (−1.86 to −0.37). The median cNAH-SDS was slightly better (not significant) in female CAH patients with −0.22 SDS (−0.90-0.31) than in male patients with −0.59 SDS (−1.24-0.01). The phenotype had statistically significant effects on the height-SDS at the onset of puberty and on cNAH-SDS (Table 2). At the start of puberty, children with

Table 1. Characteristics of CAH children (n = 600) in relation to newborn screening; data are shown as median (lower and upper quartiles)

Clinical data	With screening n = 101	Without screening n = 499	*P*
Sex: n female (%); n male (%)	51 f (50.5); 50 m (49.5)	322 f (64.5); 177 m (35.5)	NA
Phenotype: n SW (%); n SV (%)	76 SW (75.2); 25 SV (24.8)	257 SW (42.8); 242 SV (40.3)	NA
Chronological age (years)			
At the start of HC therapy	0.03 (0.01-0.21)	0.50 (0.04-6.80)	$P < .001$
At the onset of puberty	11.04 (9.83-12.18)	11.17 (9.56-12.64)	NS
Bone age (years)			
At the onset of puberty	12.3 (11.0-13.0); n = 41	12.0 (11.0-13.0); n = 154	NS
HC dosage (mg/m^2)			
At the end of the 1. Year	15.9 (11.3-18.8); n = 43	17.5 (13.9-22.2); n = 84	NS
At the beginning of puberty	13.0 (11.1-15.0); n = 75	15.1 (12.1-18.2); n = 297	$P < .001$
At the near adult height	14.3 (12.0-16.6); n = 95	16.0 (12.8-18.7); n = 422	$P = .044$

Abbreviations: CAH, congenital adrenal hyperplasia; f, female; HC, hydrocortisone; m, male; NA, not available; NS, not significant for $P < .05$; *P*, level of statistical significance; SV, simple virilizing; SW, salt wasting.

the SV-form of CAH were significantly taller ($P < .01$) than children with CAH-SW [0.40 SDS (−0.62-1.39) vs −0.06 SDS (−0.83-0.77)]. The median cNAH-SDS of children with the SV form was significantly better ($P < 0.02$) with −0.14 SDS (−0.77-0.46) than that of the patients with the SW form [−0.51 SDS (−1.09-0.15)].

Newborn Screening and Adult Height

To assess the effects of newborn screening, we used linear regression models adjusted/stratified for sex and phenotype. The auxological results are also plotted in Fig. 1.

The cNAH-SDS (mean; 95% confidence interval) was slightly but nonsignificantly better in patients with newborn screening (−0.25; −0.44 to − 0.06) than in patients without newborn screening (−0.44; −0.52 to −0.36). Evaluation of the data in relation to sex showed that newborn screening had no effect on cNAH-SDS in female CAH patients: with screening −0.24 SDS (−0.50-0.02), without screening −0.30 SDS (−0.40 to −0.20) ($P = .66$). Male CAH patients had a significantly better cNAH-SDS ($P = .033$) with newborn screening (−0.35, −0.62 to −0.07) than without screening (−0.69, −0.83 to −0.54). After stratifying for CAH phenotype, the adjusted mean cNAH-SDS of patients with SW-CAH was −0.40 SDS (−0.61-0.20) for patients with screening and −0.49 (−0.58-0.39) for patients without screening ($P = .46$). In contrast, the adjusted mean cNAH-SDS of patients with SV-CAH was significantly lower ($P = .034$) in nonscreened patients (−0.35 SDS; −0.52 to −0.18) than in patients with newborn screening (0.15 SDS; −0.28-0.59).

Discussion

By assessing the effects of newborn screening using linear regression models adjusted/stratified for sex and phenotype, we could show an increase in TH cNAH in patients with SV-CAH and in male CAH patients who were treated with hydrocortisone alone or in combination with fludrocortisone.

It has been shown in the past that patients with classical CAH do not often achieve their growth potential and therefore experience reduced adult height compared to the general population and to target height (adjusted parental height). There are some limitations in evaluating the published adult height data. First, different references for growth data have been used to calculate the SDS. For example, in the 2 meta-analyses from 2001 and 2010 that have been published as yet, Eugster et al used the references of Tanner and Davies (13), whereas Muthusamy et al estimated the SDS from the calculations made in reference to the national databases used by each of the included studies (4, 5). Second, final height data were often not considered in relation to the target height, and third, final height data was reported in cohorts that were diagnosed clinically and not by newborn screening.

We report NAH data in relation to the genetic height potential by calculating cNAH as the difference of NAH-SDS minus target height-SDS of 600 patients with classical CAH. The cNAH (SDS) of our patient cohort (mean: −0.41 SDS) was comparable to recently published results for patients with classical CAH born between 1990 and 2012 in Switzerland (mean cNAH: −0.6 SDS) (14). The data show that the corrected NAH in patients with classical CAH is still compromised but is less than reported earlier in both published meta-analyses (mean: −1.2 SDS and −1.03 SDS) (4, 5). Female patients with CAH had slightly better NAH-SDS and cNAH-SDS values than male patients. Thus our results confirm data in the literature where it has been shown that cNAH of men with classic CAH was more reduced than that females (4, 15, 16). Height SDS at puberty and total pubertal growth were not affected by sex (5). Pubertal growth was similar in comparison to healthy children as found by Troger et al (14).

Our data show that phenotype had an effect on height SDS at the onset of puberty. Children with the SV form of CAH were significantly taller than children with CAH-SW. It was speculated that this might be due to the fact that children with SV-CAH were diagnosed later than patients with SW-CAH (17). The evaluation of the impact of the clinical CAH form on NAH revealed contradictory results in the literature: Our results confirm the data of Blomberg et al who found that patients with SW-CAH were shorter than patients with SV-CAH (18). However, it has also been shown that the

Table 2. Descriptive auxological data [median (lower and upper quartiles)] of patients with classical CAH and complete auxological data according to sex and phenotype; level of significance

Classical CAH	Whole group n = 600	Female n = 373	Male n = 227	SV n = 190	SW n = 410
Height at the start of puberty	148.9 cm (140.6-155.9) 0.07 SDS (−0.73-0.92)	144.9 cm (137.6-152.1) 0.02 SDS (−0,73-0.81)	152.8 cm (145.0-160.7) 0.16 SDS (−0,72-1.19)	148.0 cm (139.7-159.5) 0.40 SDS[b] (−0.62-1.39)	148.3 cm (141.4-154.8) −0.06 SDS[b] (−0.83-0.77)
TPG	18.3 cm (11.2-23.9)	17.9 cm (10.0-23.1)	19.9 cm (12.0-25.3) −1.14 SDS	18.0 cm (8.5-23.5) −1.15 SDS	18.3 cm (11.9-23.9)
	−0.88 SDS (−1.79-−0.25)	−0.71 SDS (−1.56-−0.21)	(−2.10-−0.45)	(−2.01-−0.42)	−0.73 SDS (−1.73-−0.12)
TH	169.0 cm (162.5-176.9)	164.5 (161.0-168.5)	178.0 cm (174.0-181.5)	168.2 cm (162.0-174.5)	169.1 cm (163.0-177.5)
	−0.50 SDS (−1.05-0.09)	−0.53 (−1.05-0.09)	−0.43 (−1.03-0.09)	−0.56 SDS (−1.13-0.15)	−0.49 SDS (−1.03-0.03)
NAH	165.4 cm (159.7-171.5)	161.5 cm (156.5-166.5)	172.6 cm (166.4-177.3)	164.9 cm (158.9-172.0)	165.4 cm (160.0-171.4)
	−0.90 SDS (−1.66-−0.10)	−0.81 SDS (−1.54-−0.03)	−1.04 SDS (−1.86-−0.37)	−0.79 SDS (−1.54-0.04)	−0.98 SDS (−1.69-−0.26)
cNAH (NAH-TH)	−0.38 SDS (−1.04-0.26)	−0.22 SDS (−0.90-0.31)	−0.59 SDS (−1.24-0.01)	−0.14 SDS[a] (−0.77-0.46)	−0.51 SDS[a] (−1.09-0.15)

Abbreviations: CAH, congenital adrenal hyperplasia; cNAH, corrected near adult height; NAH, near adult height; SV, simple virilizing; SDS, standard deviation score; SW, salt wasting; TH, parental target height; TPG, total pubertal growth.
[a]$P < .05$.
[b]$P < .01$

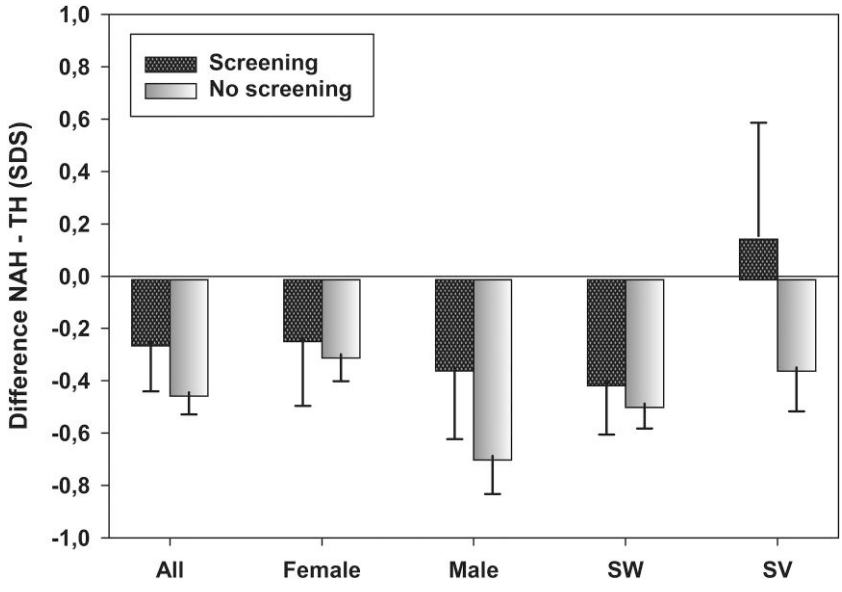

Figure 1. Corrected NAH SDS values of CAH children (n = 600) treated with hydrocortisone alone or in combination with fludrocortisone. Corrected NAH (SDS) was calculated as the difference between NAH and TH (SDS). Depicted are the adjusted mean values and the lower or upper confidence limit of the whole cohort and the data according to sex and CAH phenotype. Black columns: with CAH newborn screening; grey columns: without screening.

Abbreviations: CAH, congenital adrenal hyperplasia; NAH, near adult height; SDS, standard deviation score; SV, simple virilizing CAH; SW, salt wasting CAH; TH, target height.

final height outcome was either not different (15) or even better in patients with SW-CAH (19, 20).

So far, many different factors have been identified as having an impact on the adult height of CAH patients such as age at diagnosis, glucocorticoid therapy, clinical phenotype, adequacy of treatment, and patient compliance. See reviews (1, 3, 6, 7, 21). We could not consider additional factors such as patient compliance or hydrocortisone dosage in our statistical model since the data were either not reported or reported incompletely in the registry. We speculate that patient compliance was not different between CAH children with and without screening. However, this assumption is based only on results of almost identical chronological ages and bone ages at the onset of puberty (Table 1). The data might be biased

since the number of patients with reported chronological age at start of therapy was not identical to the number of all patients studied. The same conclusion is valid for the hydrocortisone dosages, which we calculated for 3 different time points. Our data show that children diagnosed by newborn screening had significantly lower HC dosages at the beginning of puberty and at NAH. By using regression models, it has been shown in the literature that the hydrocortisone dose was negatively associated with predicted adult height (17, 22). Thus, with regard to our results, HC dosages might affect final height in children with CAH diagnosed by newborn screening.

It has also been shown that early CAH diagnosis, often defined as the start of treatment before 1 year of age, improves the outcome (4, 19, 23). The age at diagnosis of the CAH-SW patients was younger than those with CAH-SV with no difference by sex. Thus, children with the SW form of CAH might be of advantage in relation to final height because they are diagnosed and treated earlier than children with the SV form. In our cohort, children with CAH-SV, diagnosed clinically, were treated as early as children diagnosed by newborn screening, whereas children with CAH-SW without screening were treated significantly later.

The impact of neonatal screening for CAH on height outcomes was not yet evaluated systematically. In 2003, Balsamo et al reported that 4 of the 7 patients with CAH diagnosed via neonatal screening achieved a final height equal to or above the TH (19). To the best of our knowledge, there is only 1 study from Taiwan that compared the adult height data of 60 nonscreened patients with data of 18 patients diagnosed by newborn screening (23). All patients were treated with glucocorticoids at diagnosis, and mineralocorticoid was added for patients with the SW form. The adult height SDS of the nonscreened patients was significantly lower than that of the screened group. There was no significant group difference in adult height SDS corrected for target height SDS since the TH-SDS was lower in the nonscreened group.

Our data confirm and extend these results on a larger basis. The corrected NAH-SDS across all CAH patients was slightly but nonsignificantly better in patients diagnosed by newborn screening. However, it was significantly better in male CAH patients diagnosed by screening. After stratifying for CAH phenotype, the adjusted mean corrected NAH-SDS was significantly higher in screened patients with the SV form, whereas screening did not affect the cNAH of CAH-SW patients (Fig. 1).

Our study has some limitations. While data collection was prospectively designed, the analysis of the data was retrospective. The data was derived from a registry. Since some data with an impact on growth outcomes were reported incompletely, we could not adjust our statistical model for these factors. Not all patients have actually achieved final adult height. The data is not completely comprehensive for Germany since not all German pediatric endocrinology centers participated. However, the CAH Registry is one of the largest cross-border CAH registries. Our findings across all patients are comparable with those of other investigators and with the results of available meta-analyses.

In summary, our data suggest that CAH newborn screening might be associated with improved height outcomes of children with classical CAH. In particular, adult height was significantly better in CAH-SV and in male CAH newborns identified by screening.

Acknowledgments

We highly appreciate the long and outstanding work of Professor Klaus Mohnike who was responsible for the registry for nearly two decades. His valuable and continuous input formed the basis of this registry.

Furthermore we thank the following ceners for contributing data to the CAH-Registry: Aue Kinderklinik, Berlin Charité Unikinderklinik, Berlin Lichtenberg, Bielefeld Evangelisches Krankenhaus, Bochum Endokrinologikum Ruhr, Bonn Unikinderklinik, Bremen-Nord Kinderklinik, Chemnitz Kinderk linik, Cottbus Kinderarztpraxis, Dornbirn Kinderklinik, Dresden Gemeinschaftspraxis, Dresden Universitäts-Kinderklinik, Erlangen Universitäts-Kinderklinik, Essen Universitätskinderk linik, Frankfurt Universitätskinderklinik, Freiburg Univer sitätskinderklinik, Greifswald Universitäts-kinderklinik, Halle/ Saale, Kinderklinik, Hamburg Kinder-MVZ am Wilhelmstift, Hamburg MVZ Dr. Commentz, Hannover Medizinische Hochschule, Heidelberg Praxis, Heidelberg Universitäts-Kinderklinik, Hildesheim St. Bernward Kinderklinik, Homburg Universitäts-Kinderklinik, Innsbruck Universitäts-Kinderklinik, Jena Universitäts-Kinderklinik, Kiel Universitäts-Kinderklinik, Krefeld Kinderklinik, Köln Praxis Dr. Korsch, Köln Unikinderklinik, Leipzig Universitäts-Kinderklinik, Lübeck Universitäts-Kinderklinik, Magdeburg Universitäts-Kinderklinik, Magdeburg städtische Kinderklinik, München Haunersche Kinderklinik der LMU, München-Gauting Kinderarztpraxis, München-Schwabing, Münster Universitätskinderklinik, Nürnberg Cnopfsche Kinderklinik, Oldenburg Endokrinol ogisches MVZ Pädiatrie, Paderborn Kinderklinik, Rotenburg Kinderklinik, Stade Elbekliniken Kinderklinik, Tübingen Universitäts-Kinderklinik, Ulm Endokrinologikum, Ulm Universitäts-Kinderklinik, Wels Kinderklinik, Wien Univer sitätskinderklinik

Author Contributions

H.H.-K., H.G.D., and R.W.H. carried out study design and project management. Data analysis was done by A.J.E. and R.W.H. Scientific discussion of study results was done by H.H.-K., H.G.D., A.J.E., W.B., and R.W.H. Preparation of the manuscript was done by H.H.-K. and H.G.D. Editing and final approval of the manuscript were done by all authors.

Disclosures

The authors have nothing to disclose.

Data Availability

Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

References

1. Claahsen-van der Grinten HL, Speiser PW, Ahmed SF, *et al*. Congenital adrenal hyperplasia-current insights in pathophysiology, diagnostics, and management. *Endocr Rev*. 2022;43(1): 91-159. doi: 10.1210/endrev/bnab016
2. El-Maouche D, Arlt W, Merke DP. Congenital adrenal hyperplasia. *Lancet*. 2017;390(10108):2194-2210. doi: 10.1016/S0140-6736(17)31431-9

3. Sharma R. Congenital adrenal hyperplasia and growth outcomes. *Indian J Pediatr*. 2019;86(2):111-112. doi: 10.1007/s12098-018-2841-7
4. Eugster EA, Dimeglio LA, Wright JC, Freidenberg GR, Seshadri R, Pescovitz OH. Height outcome in congenital adrenal hyperplasia caused by 21-hydroxylase deficiency: a meta-analysis. *J Pediatr*. 2001;138(1):26-32. doi: 10.1067/mpd.2001.110527
5. Muthusamy K, Elamin MB, Smushkin G, *et al*. Adult height in patients with congenital adrenal hyperplasia: a systematic review and metaanalysis. *J Clin Endocrinol Metab*. 2010;95(9):4161-4172. doi: 10.1210/jc.2009-2616
6. Mallappa A, Merke DP. Management challenges and therapeutic advances in congenital adrenal hyperplasia. *Nat Rev Endocrinol*. 2022;18(6):337-352. doi: 10.1038/s41574-022-00655-w
7. Mooij CF, Webb EA, van der Grinten HL C, Krone N. Cardiovascular health, growth and gonadal function in children and adolescents with congenital adrenal hyperplasia. *Arch Dis Child*. 2017;102(6):578-584. doi: 10.1136/archdischild-2016-311910
8. Kromeyer-Hauschild K, Moss A, Wabitsch M. Referenzwerte für den body-mass-Index für kinder, jugendliche und erwachsene in deutschland. *Anpassung der AGA-BMI-Referenz im Altersbereich von 15 bis 18 Jahren*. 2015;9(3):123-127.
9. Ranke MB, Lindberg A, Price DA, *et al*. Age at growth hormone therapy start and first-year responsiveness to growth hormone are major determinants of height outcome in idiopathic short stature. *Horm Res*. 2007;68(2):53-62. doi: 10.1159/000098707
10. Tanner JM. A correction to the TW2 RUS-based tables for predicting adult height. *Ann HumBiol*. 1978;5(5):491-492. doi: 10.1080/03014467800003151
11. Ranke MB, Lindberg A. Observed and predicted total pubertal growth during treatment with growth hormone in adolescents with idiopathic growth hormone deficiency, Turner syndrome, short stature, born small for gestational age and idiopathic short stature: KIGS analysis and review. *Horm Res Paediatr*. 2011;75(6):423-432. doi: 10.1159/000324117
12. Greulich WW, Pyle SI. *Radiographic Atlas of Skeletal Development of the Hand and Wrist*. Stanford University Press; 1959.
13. Tanner JM, Davies PW. Clinical longitudinal standards for height and height velocity for North American children. *J Pediatr*. 1985;107(3):317-329. doi: 10.1016/s0022-3476(85)80501-1
14. Troger T, Sommer G, Lang-Muritano M, *et al*. Characteristics of growth in children with classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency during adrenarche and beyond. *J Clin Endocrinol Metab*. 2022;107(2):e487-e499. doi: 10.1210/clinem/dgab701
15. Bonfig W, Bechtold S, Schmidt H, Knorr D, Schwarz HP. Reduced final height outcome in congenital adrenal hyperplasia under prednisone treatment: deceleration of growth velocity during puberty. *J Clin Endocrinol Metab*. 2007;92(5):1635-1639. doi: 10.1210/jc.2006-2109
16. Nermoen I, Bronstad I, Fougner KJ, *et al*. Genetic, anthropometric and metabolic features of adult Norwegian patients with 21-hydroxylase deficiency. *Eur J Endocrinol*. 2012;167(4):507-516. doi: 10.1530/EJE-12-0196
17. Sarafoglou K, Addo OY, Turcotte L, *et al*. Impact of hydrocortisone on adult height in congenital adrenal hyperplasia—the Minnesota cohort. *J Pediatr*. 2014;164(5):1141-1146.e1. doi: 10.1016/j.jpeds.2014.01.011
18. Bomberg EM, Addo OY, Kyllo J, *et al*. The relation of peripubertal and pubertal growth to final adult height in children with classic congenital adrenal hyperplasia. *J Pediatr*. 2015;166(3):743-750. doi: 10.1016/j.jpeds.2014.11.027
19. Balsamo A, Cicognani A, Baldazzi L, *et al*. CYP21 genotype, adult height, and pubertal development in 55 patients treated for 21-hydroxylase deficiency. *J Clin Endocrinol Metab*. 2003;88(12):5680-5688. doi: 10.1210/jc.2003-030123
20. Pinto G, Tardy V, Trivin C, *et al*. Follow-up of 68 children with congenital adrenal hyperplasia due to 21-hydroxylase deficiency: relevance of genotype for management. *J Clin Endocrinol Metab*. 2003;88(6):2624-2633. doi: 10.1210/jc.2002-021433
21. Nordenström A, Lajic S, Falhammar H. Long-term outcomes of congenital adrenal hyperplasia. *Endocrinol Metab (Seoul)*. 2022;37(4):587-598. doi: 10.3803/EnM.2022.1528
22. Bonfig W, Pozza SB, Schmidt H, Pagel P, Knorr D, Schwarz HP. Hydrocortisone dosing during puberty in patients with classical congenital adrenal hyperplasia: an evidence-based recommendation. *J Clin Endocrinol Metab*. 2009;94(10):3882-3888. doi: 10.1210/jc.2009-0942
23. Tsai MM, Tsai WY, Lee CT, Liu SY, Chien YH, Tung YC. Adult height of children with congenital adrenal hyperplasia due to 21-hydroxylase deficiency. *J Formos Med Assoc*. 2023;122(2):106-112. doi: 10.1016/j.jfma.2022.09.007