RESEARCH

Hydrocortisone dosing in children with classic congenital adrenal hyperplasia: results of the German/Austrian registry

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Abstract

Objective: Treatment of classic congenital adrenal hyperplasia (CAH) is necessary to compensate for glucocorticoid/mineralocorticoid deficiencies and to suppress androgen excess. Hydrocortisone (HC) is preferred in growing children with classic CAH but recommendations regarding dosage/administration are inconsistent. The aim of this study was to evaluate HC dosing in children with CAH in relation to chronological age, sex, and phenotype based on a multicenter CAH registry.

Design: The CAH registry was initiated in 1997 by the AQUAPE in Germany. On December 31st 2018, data from 1571 patients were included.

Methods: A custom-made electronic health record software is used at the participating centers. Pseudonymized data are transferred for central analysis. Parameters were selected based on current guidelines. Descriptive analyses and linear regression models were implemented with SAS 9.4.

Results: We identified 1288 patients on exclusive treatment with hydrocortisone three times daily (604 boys; median age 7.2 years; 817 salt-wasting phenotype, 471 simple-virilizing phenotype). The mean (lower-upper quartiles) daily HC dose (mg/m² body surface area) was 19.4 (18.9–19.8) for patients <3 months (*n* = 329), 15.0 (14.6–15.3) for age ≥3–12 months (*n* = 463), 14.0 (13.7–14.3) for age 1–5.9 years (*n* = 745), 14.2 (14.0–14.5) for age 6 years to puberty entry (*n* = 669), and 14.9 (14.6–15.2) during puberty to 18 years (*n* = 801).

Fludrocortisone was administered in 74.1% of patients with a median daily dosage of 88.8 µg.

Conclusion: Our analyses showed that still a high proportion of children are treated with HC doses higher than recommended. This evaluation provides comprehensive information on nationwide hydrocortisone substitution dosages in children with CAH underlining the benefit of systematic data within a registry to assess daily practice.

Key Words

- CYP21A2
- glucocorticoids
- fludrocortisone
- treatment

Endocrine Connections
(2021) **10**, 561–569

Introduction

Classic congenital adrenal hyperplasia (CAH) is a hereditary autosomal recessive condition affecting adrenal steroidogenesis. Most of the cases (90–95%) are caused by mutations in the 21-hydroxylase gene (*CYP21A2*) leading to altered cortisol synthesis with reduced cortisol levels in affected persons (1, 2). Additionally, aldosterone synthesis is impaired in about 75% of cases resulting in salt-wasting CAH. The CAH form with salt-wasting is characterized as classic CAH (SW) whereas the form without salt-wasting is called simple-virilizing CAH (SV) (3). *CYP21A2* gene mutations are associated with a variety of clinical phenotypes depending on the residual 21-hydroxylase activity. Recently, genotype–phenotype associations were described in a large cohort of children with CAH from the AQUAPE CAH registry (4).

Treatment in classic CAH is necessary to compensate for glucocorticoid and mineralocorticoid deficiencies and also to blunt the ACTH secretion, the major driver of adrenal androgen production (5).

Oral glucocorticoid regimens aim to roughly mimic the physiological diurnal pattern but allow the ACTH suppression to escape in-between doses (6).

There are numerous reviews and guidelines available for the treatment of children with CAH (7, 8). Recently, it was stated in a Cochrane review that the evidence levels of the presented data were not strong enough to draw firm conclusions about the most effective glucocorticoid replacement scheme in CAH (8).

The current guideline from the Endocrine Society recommends, in growing individuals with classic CAH, maintenance therapy with hydrocortisone (10–15 mg/m² body surface area) (7). A questionnaire among ESPE members performed in 2000/2001 showed that most of the children with CAH were treated with hydrocortisone in higher doses (median dose between 13.75 and 17.5 mg/m² BSA depending on age) than currently recommended (9).

Adequate dosing is impeded by the lack of a suitable low-dose HC preparation until recently, short half-life, fractional distribution of doses, differences in HC absorption and half-life, and increased cortisol clearance during puberty also influenced HC dosing.

The objective of this analysis was an evaluation of the administered hydrocortisone dosages in children from birth up to 18 years of age with classic CAH in Germany and Austria based on a nationwide registry (assessed period 1997–2018).

Additionally, age- and sex-related aspects were evaluated. HC dosages between children with or without

salt-wasting were compared. Fludrocortisone dosages were also assessed in the whole cohort and according to the salt-wasting status and sex. Furthermore, aspects of overtreatment in case of a HC dosage above the recommended amount of 15 mg/m² BSA were assessed (height, weight, BMI, and blood pressure). Participating centers were defined as big and small centers to assess the influence of the center size to treatment regimens.

Periods of treatment (before or after 2005 (introduction of neonatal screening in most regions)) were compared to assess the influence of the nationwide neonatal CAH screening and ensuing treatment recommendations.

Patients and methods

The AQUAPE (Arbeitsgemeinschaft für Qualitätssicherung in der pädiatrischen Endokrinologie/Working Group on Quality management in Pediatric Endocrinology) was started in 1997 in Magdeburg, Germany. The study (registry) was approved by the ethical committee of Saxony-Anhalt, Germany. Prospective follow-up data of patients with CAH were collected in a standardized database. Later, the German Society for Paediatric Endocrinology and Diabetology (DGKED) took responsibility for the registry (DGKED-QS)). Until now 49 centers have participated in the DGKED-QS registry. Centers were defined as big center if they cared for more than 19 patients; small centers were defined as centers caring for 19 or less patients. This definition was chosen based on the fact that with 19 patients as border nearly 50% of the patients have been treated in a big/small center. A custom-made electronic health record software is used at the participating centers for standardized documentation. Pseudonymized data are transferred for central analysis, including a validation step and a benchmarking report, twice yearly. The parameters were selected based on current treatment guidelines and are used for quality management and research. The data set includes data on phenotype, genotype, repetitive laboratory results, medication, anthropometric details, and surgical interventions.

All data were collected during routine care. Each participating center was initiated into the use of the documentation software after local ethic committee approval was obtained. Written consent has been obtained from each patient or subject after full explanation of the purpose and nature of all procedures used.

On December 31st 2018, the database included data from 1571 patients (705 male; 44.9%). Patients receiving

HC treatment only were selected, excluding patients on prednisolone or dexamethasone. Additionally, patients receiving HC in less than three dosages per day were excluded ($n = 23$). Finally, data of 1288 patients (simple-virilizing CAH $n = 471$; salt-wasting CAH $n = 817$; type of CAH was entered in the database by the local treating physician based on clinical aspects) with an age ≤ 18 years, who received three doses of hydrocortisone per day, and with complete anthropometric details were included in the analysis.

Age, sex, weight, length/height, BMI, hydrocortisone dosage, body surface area, daily split of dosage, phenotype, blood pressure, and information on additional fludrocortisone treatment were included in the assessment. Body surface area was calculated according to the formula by Dubois and Dubois (10). Overall, 45 centers from Germany and 4 centres from Austria contributed longitudinal data to this analysis. Age groups were defined as follows: children from birth (first day of treatment) to 3 months of age, ≥ 3 months to 12 months, 1 year to 5.9 years, 6 years up to onset of puberty (Tanner stage B2 in girls; testicular volume $> 3\text{mL}$ in boys), and pubertal children up to 18 years of age. In this longitudinal analysis, individual patients could contribute to several age groups, with appropriate statistical modeling of dependencies.

HC dosages were also evaluated in relation to two time periods, before January 1st 2005 and afterwards). The 2005 cut-off was chosen, as it was assumed that in 2005 most areas in Germany had implemented the neonatal CAH screening.

Statistical analysis

Continuous variables were aggregated as median, upper and lower quartiles. Categorical data were assessed as percentages. General linear regression models were used to compare hydrocortisone requirement by age-group, by age and sex, and for patients with or without fludrocortisone therapy. To analyze hydrocortisone requirement for patients treated before and after 2005, a general linear regression model adjusted for age-group and interaction was used. Repeated measurements per subject were taken into account using first-order autoregressive covariance structure. This model was used to accommodate the fixed effects of treatment and time and the covariation between repeated measures data on the same subject at different times (11). To adjust for multiple comparisons, Tukey–Kramer test was used. Data were not additionally adjusted for BMI as length/height and weight are the basis for the body surface area calculation, which then would have

been included in the model twice. In clinical routine, HC dosing according to m^2 body surface area is recommended, why this parameter was chosen? Estimated means and 95% CI were calculated. A P -value < 0.05 was defined as statistically significant. Statistical analysis was performed with SAS-version 9.4 build TS1M5 in batch mode (Statistical Analysis Systems, SAS Institute Inc., Cary, NC, USA) on a Windows-Server 2016 mainframe computer.

Results

Until December 2018, 1288 patients treated three times daily exclusively with HC were included in the registry. A salt-wasting form of CAH was documented in 817 patients, whereas 471 were classified as simple-virilizing CAH. Out of 49 participating centers, 42 were defined as small centers (86%, number of patients, $n = 724$), and 7 as big centers (14%, number of patients, $n = 564$).

The median age of the cohort was 7.2 years (3.7–10.7), the median age of start of puberty in girls was 10.18 years, in boys 10.99 years. The whole cohort presented with a median height of -0.02 SDS (-0.81 – 0.72) and a median weight of 0.51 SDS (-0.28 – 1.32). Forty-seven percent of the patients were male. Additional characteristics of the patients are shown in Table 1.

The median daily hydrocortisone dosage per m^2 body surface area (BSA) was 14.4 mg (12.3 – 16.7) for patients between birth (age at first documented dose was the day of birth) and 18 years. The absolute median HC dosage depending of the time of day was 6.9 mg (5.6 – 8.3) in the morning, 3.5 mg (2.8 – 4.4) at midday, and 3.8 mg (3.0 – 4.70) in the evening.

The estimated mean dosages differed significantly between the different age groups: after adjustment for sex differences, the highest estimated dose was given in the youngest age group (0–3 months): 19.4 (18.9 – 19.8) mg ($n = 329$) in comparison with all other groups ($P < 0.0001$), whereas the HC dosages in the other groups were not statistically different: 15.0 (14.6 – 15.3) (≥ 3 –12 months; $n = 463$), 14.0 (13.7 – 14.3) (1–5.9 years; $n = 745$), 14.2 (14.0 – 14.5) (6 years–onset of puberty; $n = 669$) and 14.9 (14.6 – 15.2) (puberty–18 years; $n = 801$). Comparing the estimated mean HC doses/ m^2 BSA between the prepubertal group and the pubertal group reveals a slight but significant increase from 14.2^2 to 14.9 mg/ m^2 ($P < 0.0001$). The median age of start of puberty in girls was 10.18 years, in boys 10.99 years.

Additionally, the mean HC doses according to age and time of day are presented in Figs 1 and 2.

Table 1 Patient characteristics with classic CAH and hydrocortisone treatment.

Characteristic	Value
Total number of included patients (<i>n</i>)	1288
Male <i>n</i> (%); Female <i>n</i> (%)	604 (46.9); 684 (53.1)
Salt-wasting CAH <i>n</i> (%)	817 (63.4)
Simple-virilizing CAH <i>n</i> (%)	471 (36.6)
BSA m ² (median (lower-upper quartile))	1.0 (0.7–1.4)
Age 0–3 months (<i>n</i>)	329
Age ≥ 3–12 months (<i>n</i>)	463
Age 1–5.9 years (<i>n</i>)	745
Age 6–entry puberty years (<i>n</i>)	669
Age pubertal–18 years (<i>n</i>)	801
Hydrocortisone: <i>n</i> (%)	1288 (100)
Fludrocortisone: <i>n</i> (%)	955 (74.1)

BSA, body surface area.

To demonstrate differences between boys and girls, the cohort was divided according to sex. Included were 604 boys with a median age of 6.8 years (3.1–10.5) and 684 girls with a median age of 7.7 (4.4–11.0) years. Adjusting for age, estimated mean HC dosages did not differ significantly between boys and girls in the whole cohort (boys: 15.5 mg (15.1–1587) vs girls 15.5 mg (15.3–15.8); $P=0.6571$). Further results of the mean HC dosages according to sex and age groups are presented in Table 2.

Additionally, mean HC doses adapted to age groups and phenotype of CAH are presented in Table 2.

Out of all patients on HC, 74.1% ($n=955$) received additional fludrocortisone (FC) with a median dosage of 88.8 (71.9–116.7) µg per day. Patients with FC treatment ($n=955$) displayed a median age of 6.1 years (2.8–9.7) (50.2% male) vs 10.3 years (7.6–12.3) in the group without

FC treatment ($n=333$; 37.5% male). Out of 604 boys, 479 (79.3%) were treated additionally with FC in a median dosage of 87.5 (72.0–119.8) µg per day, whereas 69.6% (476 out of 684) of the girls received FC in a median dosage of 90.0 (71.9–115.2) µg daily.

In the FC treated group, 789 patients were classified as patients with SW-CAH and 166 patients classified as SV-CAH. In the group without FC treatment, 28 were classified as SW-CAH patients, and 305 as SV-CAH patients.

Further results on HC requirement according to FC use and clinical phenotype are presented in Figs 3 and 4.

The percentage of overtreated patients defined by an applied HC dosage of >15 mg/m² BSA was in the age group 0–3 months 73.3%, in the age group ≥ 3–12 months 37.6%, 1–5.9 years 33.6%, 6 years–onset of puberty 38.3%, and puberty–18 years 50.6%. Taking into account the whole cohort, 44.1% of the patients received an overtreatment, and still 41% an overtreatment excluding the age group of 0–3 months.

Comparing patients in the different age groups according to overtreatment on different clinical parameters were presented in the following: BMI SDS was significantly different in the age group 0–3 months ($P=0.0116$), ≥ 3–12 months ($P<0.0010$), 1–5.9 years ($P=0.0060$), 6 years–onset of puberty ($P<0.0037$), and puberty–18 years ($P=0.0198$).

No significant differences in height SDS according to dosage and age were detected: in the age group 0–3 months $P=0.9436$, age group ≥ 3–12 months $P=0.1316$, 1–5.9 years $P=0.5950$, 6 years–onset of puberty $P=0.9774$, and puberty–18 years $P=0.0966$.

Figure 1

Hydrocortisone dosages in children with congenital adrenal hyperplasia according to age.

Figure 2

Hydrocortisone dosages in children with congenital adrenal hyperplasia according to time of day.

Table 2 Differences in Hydrocortisone dosages (mg/m² BSA) according to age between boys and girls and salt-wasting/simple-virilizing type of CAH; data given as estimated mean and 95% CI.

Age group	Boys	Girls	p value	Salt-wasting	Simple-virilizing	p value
0–<3 months	18.52 (17.91–19.13)	20.22 (19.61–20.83)	0.0046	19.70 (19.22–20.18)	17.36 (16.34–18.38)	0.0018
≥3–12 months	14.49 (13.98–14.99)	15.47 (14.96–15.98)	0.1733	15.06 (14.66–15.46)	14.44 (13.63–15.25)	0.8940
1–5.9 years	13.95 (13.53–14.36)	14.00 (13.59–14.42)	1.000	13.90 (13.56–14.26)	14.27 (13.74–14.81)	0.9937
6–start of puberty	14.44 (14.01–14.87)	14.08 (13.68–14.49)	0.9757	14.31 (13.94–14.68)	14.29 (13.81–14.77)	1.000
Puberty–18 years	15.23 (14.79–15.68)	14.72 (14.34–15.10)	0.7816	15.42 (15.04–15.81)	14.24 (13.81–14.67)	0.0070

The levels for systolic and diastolic blood pressure according to hydrocortisone dosage were not significantly different in the five age groups. Comparison of the prescribed HC dosages in small vs big centers revealed a statistical significant higher mean HC dosage in small centers with 15.7 mg/m² BSA (15.4–16.0) vs 15.3 mg/m² BSA (14.9–15.6) in big centers.

We found a statistically significant difference between the administered HC dosages in relation to the period before or after introduction of general screening for CAH (calendar year 2005). Before 2005, the adjusted mean dosage was 16.4 (16.1–16.7) mg HC per m² BSA and after 2005 the dosage was 14.6 (14.3–14.9) mg HC per m² BSA ($P < 0.0001$).

Discussion

We present hydrocortisone dosages in children with classic CAH according to age, sex, daytime, phenotype, and additional fludrocortisone treatment. Our real-world data reveal a preponderance of the salt-wasting phenotype as expected based on previous case-series.

There are different glucocorticoid preparations used in order to normalize androgen secretion and to achieve sufficient glucocorticoid levels in affected patients (12, 13, 14). Depending on the preparation used, different effects on growth pattern and final height have been detected and published previously (12, 13, 14). As HC therapy is the standard of care for pediatric patients (12, 15, 16), we selected 1311 patients exclusively on HC among 1571 patients in the registry. Out of these 1288 received HC three times daily and therefore have been included in our analyses. Furthermore, 260 children (16.5%) treated with other preparations such as prednisolone or dexamethasone were excluded.

The median daily HC dosage, including all age groups, of 14.4 mg/m² BSA is within the current recommended range of substitution between 10–15 mg/m² BSA (7). The median dosage also implies that 44% of all patients (41% of the patients older than 3 months) received a dosage higher than 15 mg/m² BSA, which represents overdosage according to guidelines. Division of HC into three daily doses is generally recommended. In our cohort this regimen seems to be implemented in most cases as 1288 out of 1311 patients received three HC dosages per day.

Figure 3 Hydrocortisone dosages in children with congenital adrenal hyperplasia according to additional fludrocortisone treatment and time of day.

Figure 4 Hydrocortisone dosages in children with congenital adrenal hyperplasia according to additional fludrocortisone treatment and salt-wasting status.

The morning dosage is the highest dosage in the whole cohort as well as in all different age groups.

A significant decrease in the calculated mean HC dose after the first three months of age could be found. To the best of our knowledge, there is no evidence that higher dosages in the neonatal period reduce life-threatening events (17). Furthermore, there are different trials available showing an association between high dose glucocorticoid treatment and short stature in adulthood (15, 18, 19, 20). On the one hand one might speculate that there is a rationale behind higher neonatal HC dosages based on the fast increase in body weight and BSA in the first months of life with the need for continuous follow-up and frequent dosage adjustments to reduce the risk of insufficient glucocorticoid substitution. On the other side one could argue that the higher dosages are not prescribed deliberately but there is just an inadequate dose adjustment in the youngest children due to absent adequate weight adjusted preparations in the past. Therefore one could assume that a high hydrocortisone dosage in newborns and young children is accepted due to fast growing during that age. These remarks are not proven but try to explain the higher dosages which are not tolerable in the future due to the known side effects of an overtreatment mentioned also in this discussion.

Additionally, up until May 2015 the only approved HC tablets available in Germany were 10 mg HC tablets, these were inadequate for precise dosing especially in newborns with a BSA $\sim 0.2 \text{ m}^2$.

A common treatment approach was the substitution with $3 \times 2.5 \text{ mg}$ per day (a quarter tablet) in newborns which resulted in a dosage of $\sim 37.5 \text{ mg/m}^2$ assuming a BSA of 0.2 m^2 . Alternatively, custom-made preparations are used. An international web-based survey about the types of medication in children with adrenal insufficiency (AI) revealed that the majority of children received a compounded medication with a high variability of contained HC (21). In May 2015 a new commercially available HC preparation was approved for HC substitution in newborns and children up to 18 years (Alkindi® with 1, 2 or 5 mg HC as granules in capsules for opening, Diurnal Company, UK) (22). Hydrocortisone granules were commercially available since February 2018. In 2020 results of a prospective pediatric trial from Neumann *et al.* were published presenting that this pediatric licensed drug formulation in form of granula allowing a weight adapted dosing results in a lower daily dose in children age 0–8 years compared to our data (23).

The HC dosage was significantly higher in pubertal children which might depend on an altered endocrine

milieu in pubertal children. Different studies have described alterations of the cortisol clearance, half-life of free cortisol, and insulin resistance leading to a reduction of the treatment efficacy due to an increased androgen secretion in pubertal children (24, 25, 26).

The analyses comparing the percentage of patients treated with an overdosage and patients receiving a dosage in the recommended range of $10\text{--}15 \text{ mg HC/m}^2 \text{ BSA}$ demonstrated no clear pattern in our cohort regarding BMI/height SDS/weight SDS and blood pressure. At the moment no data about the final height in association to the absolute amount of HC of the individual patient received over the childhood are available out of our registry. However, one has to keep in mind that it was shown by other groups that a HC dosage exceeding $17 \text{ mg/m}^2 \text{ BSA}$ during puberty could reduce final height in children with CAH (18). Therefore the presented data on overdosing should initiate a (re-)debate on dosing and weight adjusted HC preparations in the participating centers.

Comparing HC dosages between boys and girls revealed no significant difference. Interestingly, girls receive a higher dose in the first year of life whereas this trend reverses subsequently. For that phenomenon no clear explanation is available to the best of our knowledge. No recommendations for different dosages in boys vs girls are available. Therefore it might also be an incidental finding. Changing practices on salt supplementation in SW-CAH have recently been published based from this registry (27). Evaluation of sodium chloride supplementation revealed an increasing use of sodium chloride supplementation in the period from 1999 to 2015, but sodium chloride supplementation had no influence on the dosages of HC and FC (27). Because mineralocorticoids also have a glucocorticoid effect, one could assume that children with SW-CAH receiving FC need lower HC dosages. However, our results showed a significant difference of HC dosages with even a higher HC dosage in the group with additional FC treatment compared to the group treated with HC only.

In our cohort 28 children with a documented salt-wasting type of CAH have not been treated with additional FC, which would be expected in SW-CAH. However, the diagnosis of salt-wasting is still challenging and might be based on clinical (vomiting), laboratory (low serum sodium) or genetic data, however the genotype–phenotype correlation in CAH is not consistent in 100% of the cases as it could be shown previously in our registry (4). It should be kept in mind that in the registry the type of CAH was entered by the treating physician based on clinical aspects. This might explain the results

showing children defined as patients with SW-CAH but without FC treatment which is implausible in the view of the authors. The evaluation of patients treated before 2005 or after 2005 revealed a significant downward trend in the total daily dose of HC, which goes along with the updated recommendations from the Endocrine Society to treat with the lowest effective dosage (7). Additionally, the neonatal CAH screening causes an early diagnosis of the affected patients and the adaptation of adequate treatment concepts and prescribed dosages of HC (15).

Limitations

Our results are limited by different aspects discussed here: The centres involved in the registry differ in the number of CAH patients they care for. Therefore the structure of care and the experience in treating children with CAH might be quite different leading to heterogeneous treatment approaches.

The data are entered by each center in the database without financial compensation which might have led to delayed and incomplete data entry.

The information available in the registry is predefined and necessarily limited. For example, there is no information about the precise time of day the HC dosages were administered (only the information morning–midday–evening is available), this information would have been interesting for discussion of dosages according to age.

Furthermore the results of dosage and overdosage should trigger a discussion about the best HC formulation for children with CAH. Additionally, the monitoring concept for children with CAH might be included in these discussions (e.g. frequency of visits based on age, saliva sampling for all patients). No information about the type of administered HC formulations is available yet. The database should offer new entry options to analyze for example, the influence of the applied HC formulation in the future. At present benchmarking reports are sent to all participating centers twice a year. These reports might be a useful tool for treatment improvement and standardization.

CAH is one of approximately 5000–8000 known rare diseases that affect about 6% of the population. Standardized medical care is still not accessible for all patients and research activities in the field of rare diseases are challenging. To the best of our knowledge, there are only a few national and cross-border/international registries and from these only a few systematic publications in the field of CAH (28, 29, 30, 31). The German CAH registry was started more than twenty years ago and

contains therefore data from >1500 patients representing one of the largest cross-border CAH registries. This fact strengthens the value of our analysis.

In summary this large, multicentre evaluation provides comprehensive information on real life – doses for hydrocortisone substitution in children with CAH. Though different theoretical considerations are published regarding HC dosages according to e.g. age, sex, type of CAH or concomitant FC treatment, our results present the real-world practice in a cohort of >1500 children and adolescents with CAH. Future long-term data could evaluate the effect of newly approved HC formulations for pediatric patients with respect to final height, prescribed dosages, and numbers of adrenal crises. Intermittent evaluation of the documented data in a registry gives the chance to critically assess current care and treatment outcome. Adaptation and continuation of a registry such as the German CAH registry seems to be worthwhile as it contains systematic data of children with a rare disease and provides insights into the daily practice of a large cohort. In the future, the German/Austrian registry plans to cooperate closely with international registries, for example the European ERN I-DSD/I-CAH registries (29).

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding

This analysis was supported by a grant to the German Society for Pediatric Endocrinology and Diabetology (DGKED) by Diurnal Limited (Cardiff; United Kingdom).

Author contribution statement

F-W Röhl, K Mohnike, K Fink, R W Holl carried out study design and project management. Scientific discussion of study results was done by M Bettendorf, H-G Dörr, A Huebner, K Kapelari, A Richter-Unruh, S Riedl, T Rohrer, and J Woelfle. Data analysis was done by K Fink, R W Holl, and H Hoyer-Kuhn. Preparation of the manuscript was done by H Hoyer-Kuhn. Editing and final approval of the manuscript were done by all authors.

Acknowledgements

We thank the following centers for contributing data to the DGKED-CAH-registry: Aue Kinderklinik, Berlin Charité Unikinderklinik, Berlin Lichtenberg, Bielefeld Evangelisches Krankenhaus, Bochum Endokrinologikum Ruhr, Bonn Unikinderklinik, Bremen-Nord Kinderklinik, Chemnitz Kinderklinik, Cottbus Kinderarztpraxis, Dornbirn Kinderklinik, Dresden Gemeinschaftspraxis, Dresden Universitäts-Kinderklinik, Erlangen Universitäts-Kinderklinik, Essen Universitätskinderklinik, Frankfurt Universitätskinderklinik, Freiburg Universitätskinderklinik, Greifswald Universitätskinderklinik, Halle/Saale, Kinderklinik, Hamburg Kinder-MVZ am Wilhelmstift, Hamburg MVZ Dr Commenz, 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 Klinik, München-Gauting Kinderarztpraxis, München-Schwabing, Münster Universitätskinderklinik, Nürnberg Cnopfsche Kinderklinik, Oldenburg Endokrinologisches MVZ Pädiatrie, Paderborn Kinderklinik, Rotenburg Kinderklinik, Stade Elbekliniken Kinderklinik, Tübingen Universitäts-Kinderklinik, Ulm Endokrinologikum, Ulm Universitäts-Kinderklinik, Wels Kinderklinik, Wien Universitätskinderklinik.

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Received in final form 21 April 2021

Accepted 28 April 2021

Accepted Manuscript published online 28 April 2021