Walter Bonfig, Friedhelm Roehl, Stefan Riedl, Jürgen Brämswig, Annette Richter-Unruh, Susanne Fricke-Otto, Angela Hübner, Markus Bettendorf, Eckhard Schönau, Helmut Dörr, Reinhard W. Holl, Klaus Mohnike

Sodium Chloride Supplementation Is Not Routinely Performed in the Majority of German and Austrian Infants with Classic Salt-Wasting Congenital Adrenal Hyperplasia and Has No Effect on Linear Growth and Hydrocortisone or Fludrocortisone Dose

Erstveröffentlichung in / First published in:

Hormone Research in Paediatrics. 2018, 89 (1), S. 7 – 12 [Zugriff am: 19.05.2020]. Karger. ISSN 1663-2826.

DOI: https://doi.org/10.1159/000481775

Original Paper

HORMONE RESEARCH IN PÆDIATRICS

Horm Res Paediatr 2018;89:7–12
DOI: 10.1159/000481775

Received: May 5, 2017
Accepted: September 25, 2017
Published online: October 26, 2017

Sodium Chloride Supplementation Is Not Routinely Performed in the Majority of German and Austrian Infants with Classic Salt-Wasting Congenital Adrenal Hyperplasia and Has No Effect on Linear Growth and Hydrocortisone or Fludrocortisone Dose

Walter Bonfig[a, b] Friedhelm Roehl[c] Stefan Riedl[d] Jürgen Brämswig[e] Annette Richter-Unruh[e] Susanne Fricke-Otto[f] Angela Hübner[g] Markus Bettendorf[h] Eckhard Schönau[i] Helmut Dörr[j] Reinhard W. Holl[k] Klaus Mohnike[l]

[a]Department of Pediatrics, Klinikum Wels-Grieskirchen, Wels-Grieskirchen, Austria; [b]Pediatric Endocrinology, Department of Pediatrics, Technische Universität München, München, Germany; [c]Department of Biometrics, Otto von Guericke Universität Magdeburg, Magdeburg, Germany; [d]Pediatric Endocrinology, St. Anna Kinderspital, University of Vienna, Vienna, Austria; [e]Pediatric Endocrinology, Department of Pediatrics, Universitätsklinikum Münster, Westfälische Wilhelmsuniversität Münster, Münster, Germany; [f]Pediatric Endocrinology, Department of Pediatrics, Helios Klinikum Krefeld, Krefeld, Germany; [g]Pediatric Endocrinology, Department of Pediatrics, Universitätsklinikum Dresden, Technische Universität Dresden, Dresden, Germany; [h]Division of Pediatric Endocrinology and Diabetes, Department of Pediatrics, Universitätsklinikum Heidelberg, Ruprecht-Karls-Universität Heidelberg, Heidelberg, Germany; [i]Pediatric Endocrinology, Department of Pediatrics, Universitätsklinikum Köln, Universität zu Köln, Köln, Germany; [j]Pediatric Endocrinology, Department of Pediatrics, Universitätsklinikum Erlangen, Friedrich Alexander Universität Erlangen, Erlangen, Germany; [k]Institute of Epidemiology and Medical Biometry (ZIBMT), University of Ulm, Ulm, Germany; [l]Pediatric Endocrinology, Department of Pediatrics, Otto von Guericke Universität Magdeburg, Magdeburg, Germany

Keywords

Congenital adrenal hyperplasia · Salt-wasting congenital adrenal hyperplasia · Sodium chloride supplementation · Hydrocortisone · Fludrocortisone

Abstract

Introduction: Sodium chloride supplementation in salt-wasting congenital adrenal hyperplasia (CAH) is generally recommended in infants, but its implementation in routine care is very heterogeneous. ***Objective:*** To evaluate oral sodium chloride supplementation, growth, and hydrocortisone and fludrocortisone dose in infants with salt-wasting CAH due to 21-hydroxylase in 311 infants from the AQUAPE CAH database. ***Results:*** Of 358 patients with classic CAH born between 1999 and 2015, 311 patients had salt-wasting CAH (133 females, 178 males). Of these, 86 patients (27.7%) received oral sodium chloride supplementation in a mean dose of 0.9 ± 1.4 mmol/kg/day (excluding nutritional sodium content) during the first year of life. 225 patients (72.3%) were not treated with sodium chloride. The percentage of sodium chloride-supplemented patients rose from 15.2% in children born 1999–2004 to 37.5% in children born 2011–2015. Sodium chloride-supplemented and -unsupplemented infants did not significantly differ in hydrocortisone and fludrocortisone dose, target height-corrected height-SDS,

E-Mail karger@karger.com
www.karger.com/hrp

Walter Bonfig, MD
Department of Pediatrics
Klinikum Wels-Grieskirchen
AT-4600 Wels
E-Mail walter.bonfig@mri.tum.de

and BMI-SDS during the first 2 years of life. ***Conclusion:*** In the AQUAPE CAH database, approximately one-third of infants with salt-wasting CAH receive sodium chloride supplementation. Sodium chloride supplementation is performed more frequently in recent years. However, salt supplementation had no influence on growth, daily fludrocortisone and hydrocortisone dose, and frequency of adrenal crisis.

Introduction

Congenital adrenal hyperplasia (CAH) is an autosomal-recessive disorder of adrenal steroidogenesis, in which cortisol metabolism is impaired. 90–95% of cases are caused by 21-hydroxylase deficiency due to *CYP21A2* mutations [1].

Mineralocorticoid deficiency occurs in approximately 75% of cases of 21-hydroxylase deficiency (salt-wasting CAH). Conventional treatment of CAH due to 21-hydroxylase deficiency consists of glucocorticoid and mineralocorticoid replacement [1–3]. It is generally recommended that infants with salt-wasting CAH are additionally treated with sodium chloride supplementation [3]. This recommendation is based on a study on sodium balance in 8 infants with salt-wasting CAH [4].

Clinical experience shows, that not all pediatric endocrinologists follow this recommendation. The aim of our study was to evaluate the frequency of sodium chloride supplementation in a large CAH cohort and to analyze its effect on growth and on fludrocortisone and hydrocortisone dose.

Patients and Methods

The AQUAPE CAH initiative (AQUAPE: Arbeitsgemeinschaft für Qualitätssicherung in der pädiatrischen Endokrinologie) is based on a software for prospective documentation of clinical follow-up data in patients with CAH. It also serves as a quality control procedure and contributes to a cumulative CAH research database. Thirty-seven pediatric endocrine centers in Germany and Austria participate in AQUAPE CAH. Anonymized data are transferred annually. The data are verified and corrected at the coordinating center, if necessary. Each center complied with local ethical and data management guidelines. All data were collected during routine care and the AQUAPE CAH initiative was approved by the local ethics committee.

Patients with classic CAH due to 21-hydroxylase deficiency born after 1999 were included for analysis. 358 patients with classic CAH (5,022 patient visits) were identified. The majority (76.0%) of patients was diagnosed by newborn screening (in some German federal states newborn screening started later than 1999). In most patients the diagnosis of 21-hydroxylase deficiency was confirmed by mutation analysis of the *CYP21A2* gene and classification of salt-wasting CAH was supported by "severe" *CYP21A2* mutations, homozygous gene deletions, or conversions consistent with ≤1% 21-hydroxylase activity. Only patients with salt-wasting CAH received sodium chloride supplementation and were included in the analysis. Sodium chloride dose was calculated as mmol/kg/day, fludrocortisone dose was calculated as $\mu g/m^2$/day and hydrocortisone dose was calculated as mg/m^2/day. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. BMI standard deviation score (BMI-SDS) was derived from national contemporary reference data by Kromeyer-Hauschild et al. [5]. Height data was corrected for target height and is expressed as corrected height-SDS using national contemporary reference data [6].

Blood pressure values were compared with reference values for systolic and diastolic blood pressure from Flynn [7] (0–12 months of age). A blood pressure above the 95th centile was considered hypertensive.

Statistical analysis was performed with the software package SAS version 9.2 (Statistical Analysis Systems, SAS Inc., Cary, NC, USA). A p value <0.05 was considered significant (2-sided). Between-group comparisons were performed with the nonparametric Mann-Whitney U test.

Results

In total, 358 patients (153 female, 205 male) with classic CAH born after 1999 were identified in the database. Of these, 311 (86.9%) patients (133 female, 178 male) were classified as salt-wasting CAH and 47 (13.1%) patients were classified as simple virilizing CAH (20 female, 27 male). The female-to-male ratio is unusual and might be explained by the combination of the neonatal screening program and a bias in patient inclusion, since not all German and Austrian pediatric endocrine centers participate in AQUAPE CAH. Of 311 patients with salt-wasting CAH, 86 (27.7%) patients were additionally treated with sodium chloride. In salt-wasting patients born between 1999 and 2004, only 15.2% of patients received salt supplementation, whereas 34.4% of salt-wasting patients born between 2005 and 2010 were additionally treated with sodium chloride. In salt-wasting patients born between 2011 and 2016 the fraction of salt-supplemented patients was 37.5%.

Mean additional sodium chloride supplementation (without feeding/nutrition) during the first year of life was 0.9 ± 1.4 mmol/kg/day. After the first year of life, sodium chloride supplementation was discontinued in the vast majority of patients.

In Tables 1 and 2, the data for fludrocortisone and hydrocortisone dose, target height-corrected height-SDS, and BMI-SDS during the first 2 years of life are compared

Table 1. Comparison of fludrocortisone and hydrocortisone dose, body mass index (BMI)-SDS and target height (TH)-corrected height-SDS between sodium chloride-supplemented and -unsupplemented patients with salt-wasting congenital adrenal hyperplasia (mean ± SD)

	Salt supplementation group (n = 86)	No salt supplementation group (n = 225)	p value
Start of treatment			
Fludrocortisone, μg/m^2/day	442±201	376±237	0.1469
Hydrocortisone, mg/m^2/day	17.7±5.2	22.0±10.3	0.1633
BMI-SDS	0.1±1.4	0.2±1.2	0.8727
TH-corrected height-SDS	0.7±1.2	0.7±1.5	0.9645
3 months			
Fludrocortisone, μg/m^2/day	434±213	428±230	0.8979
Hydrocortisone, mg/m^2/day	18.1±4.6	18.9±8.3	0.5027
BMI-SDS	–0.1±1.3	–0.2±1.6	0.6552
TH-corrected height-SDS	0.3±1.2	0.0±1.6	0.2434
1 year			
Fludrocortisone, μg/m^2/day	208±92	188±77	0.2093
Hydrocortisone, mg/m^2/day	12.8±2.9	12.7±5.2	0.9276
BMI-SDS	0.0±1.1	0.2±1.3	0.2988
TH-corrected height-SDS	–0.3±1.1	–0.5±1.2	0.4793
2 years			
Fludrocortisone, μg/m^2/day	130±56	116±54	0.1048
Hydrocortisone, mg/m^2/day	12.1±3.1	12.0±2.9	0.8287
BMI-SDS	0.2±1.1	0.3±1.0	0.4727
TH-corrected height-SDS	–0.2±1.0	–0.2±1.1	0.6152

between patients with and without sodium chloride supplementation: patients with and without sodium chloride supplementation do not differ in their mean daily fludrocortisone or hydrocortisone dose. There was also no influence of salt supplementation on growth and BMI-SDS during the first 2 years of life.

Blood pressure was only measured or documented in the database in one-third of patients (33.3%) during the first year of life. Blood pressure data are shown in Table 3. Blood pressure above the 95th centile was measured in 13.6% of patients treated with hydrocortisone and fludrocortisone only and in 21.0% of patients who were additionally supplemented with sodium chloride. This difference was statistically not significant (p = 0.228). Also, no significant correlation between hypertension and sodium chloride supplementation was found. Unfortunately, data on renin or plasma renin activity and serum sodium concentrations were insufficient for a more detailed analysis. After the start of gluco- and mineralocorticoid therapy, no adrenal or salt-wasting crises were reported in both groups during the evaluation period.

Mean target height-corrected height-SDS dropped from +0.7 SDS to –0.2 SDS over the study period, whereas BMI-SDS remained relatively stable.

Discussion

In the German-Austrian AQUAPE CAH database, approximately one-third of salt-wasting CAH infants are supplemented with sodium chloride. A trend towards salt supplementation in salt-wasting CAH infants can be observed in recent years, although the majority of infants with salt-wasting CAH are still not salt supplemented. Reasons for supplementing sodium chloride are the low nutritional content in breast milk or formula and the higher demand in the state of salt waste [4, 8]. Of course, normal plasma sodium concentrations are essential for regular thriving, but the question is if this can only be achieved in children with salt-wasting CAH by additional salt supplementation during infancy or also with administration of sufficient but not harmful doses of fludrocortisone. Frequently reported reasons for omitting sodium chloride substitution are feeding problems and gastrointestinal symptoms associated with salt supplementation and the belief or experience that sufficient fludrocortisone doses are equally effective in stabilizing sodium concentrations and avoiding salt-wasting crises. Interestingly, sodium chloride supplementation had no significant effect on fludrocortisone dose in our cohort.

Table 2. Comparison of fludrocortisone and hydrocortisone dose, body mass index (BMI)-SDS and target height (TH)-corrected height-SDS between sodium chloride-supplemented and -unsupplemented patients with salt-wasting congenital adrenal hyperplasia

	Salt supplementation group (n = 86)			No salt supplementation group (n = 225)		
	P10	median	P90	P10	median	P90
Start of treatment						
Fludrocortisone, μg/m^2/day	217.2	420.6	850.9	176.2	400.6	877.1
Fludrocortisone, μg/day	50.0	100	200	40.0	100.0	200.0
Hydrocortisone, mg/m^2/day	12.9	17.6	23.8	11.8	17.6	35.1
BMI-SDS	–1.6	–0.1	1.9	–2.8	–0.4	1.1
TH-corrected height-SDS	–1.2	0.1	1.9	–2.2	0.2	2.3
3 months						
Fludrocortisone, μg/m^2/day	223.7	336.2	629.8	169.8	320.2	509.4
Fludrocortisone, μg/day	75.0	100.0	200.0	50	100	150
Hydrocortisone, mg/m^2/day	8.9	13.7	18.5	9.7	14.4	19.1
BMI-SDS	–0.7	0.3	2.1	–1.1	0.3	2.0
TH-corrected height-SDS	–0.7	0.6	1.8	–1.3	0.5	1.7
1 year						
Fludrocortisone, μg/m^2/day	109.9	204.1	315.6	110.1	180.5	263.9
Fludrocortisone, μg/day	50.0	100.0	150.0	50.0	75.0	125.0
Hydrocortisone, mg/m^2/day	9.0	12.2	16.6	8.5	11.6	16.2
BMI-SDS	–1.5	0.1	1.5	–1.5	0.1	1.8
TH-corrected height-SDS	–2.2	–0.3	1.1	–2.0	–0.35	0.9
2 years						
Fludrocortisone, μg/m^2/day	79.8	112.2	202.0	48.1	100.6	179.2
Fludrocortisone, μg/day	50.0	50.0	100.0	25.0	50.0	100.0
Hydrocortisone, mg/m^2/day	9.0	11.2	18.1	8.5	11.8	15.5
BMI-SDS	–1.3	0.2	1.6	–1.0	0.1	1.7
TH-corrected height-SDS	–1.4	–0.3	1.1	–1.4	–0.3	1.2

P10, 10th centile; P90, 90th centile.

Table 3. Blood pressure data

	Salt supplementation group			No salt supplementation group		
	P10	median	P90	P10	median	P90
Systolic blood pressure, mm Hg	80	105	128	80	100	125
Diastolic blood pressure, mm Hg	49	64	82	45	63	84

n = 294 blood pressure measurements in children with salt supplementation, n = 570 blood pressure measurements in children without salt supplementation during the first year of life. P10, 10th centile; P90, 90th centile.

In both groups, fludrocortisone dose was rather high during the first year of life, which can partially be explained by the relative mineralocorticoid resistance in infancy [8, 9]. Nevertheless, fludrocortisone doses might have been too high especially in children with salt supplementation, so that no difference in true fludrocortisone needs could be detected.

The challenge in infants and toddlers with CAH persists in finding the appropriate fludrocortisone dose in order to avoid life-threatening salt-wasting crises often

triggered by minor illness and, at the same time, avoid fludrocortisone overdosage to prevent arterial hypertension. In a single center study, 45.5% of infants had systolic hypertension during the first year of life and 57.6% of 1- to 1.5-year-old infants had systolic hypertension when higher fludrocortisone doses were given and when plasma renin activity was at the lower normal range or suppressed [10]. In that study, both systolic and diastolic blood pressure correlated with fludrocortisone dose, but not with BMI. These infants were not supplemented with sodium chloride. Unfortunately, data on blood pressure and renin or plasma renin activity were incomplete in the AQUAPE CAH database for children younger than 3 years of age. The presented data on sodium supplementation in CAH infants has been extracted from a quality control database and therefore cannot completely answer complex scientific questions. But it is still interesting to note that the majority of German and Austrian pediatric endocrinologists are hesitant to treat CAH infants with salt and prefer higher fludrocortisone doses. It would be of great interest to compare the implementation rate of sodium replacement with other countries, but such data have not been published so far.

In the original study [4], on which the recommendation of salt supplementation in salt-wasting CAH is based, an increase in fludrocortisone dose resulted in a slight increase in systolic blood pressure (5–10 mm Hg) and had no effect on renal sodium excretion, whereas a decrease in plasma potassium concentration was observed. The calculated mean negative sodium balance on constant hydrocortisone (20–25 mg/m^2/day) and fludrocortisone (150–200 μg/m^2/day) replacement was 2.2 mmol/kg/day and ranged from 0.5 to 4.9 mmol/kg/day. With sodium chloride supplementation in that range, the authors were able to normalize plasma sodium concentrations. The authors also reported that salt supplementation can be stopped after a few months, when precursor hormones such as progesterone and 17-hydroxyprogesterone with anti-mineralocorticoid effects have been lowered by glucocorticoid replacement therapy or when more salty foods are given.

The reported loss in height-SDS during the first year of life in infants with and without salt supplementation in the AQUAPE CAH cohort has also been reported previously in other CAH cohorts [11, 12]. High birth length of CAH children might be the result of hyperandrogenism in utero, and glucocorticoid treatment after birth leads to normalization of hyperandrogenism and a decline in growth velocity.

In a longitudinal analysis of growth and puberty in 21-hydroxylase-deficient patients, Van der Kamp et al. [13] compared growth and final height of 17 salt-supplemented salt-wasting CAH patients to 17 salt-wasting CAH patients without salt supplementation. Salt supplementation was given between 0.19 and 0.9 years in a mean dose of 2.5 mmol/kg/day. The fludrocortisone dose between the two groups was comparable, but the hydrocortisone dose was significantly higher in the salt supplementation group. Mean length-SDS at 2 years was higher in the salt-supplemented group (–1.0 SDS vs. –1.56 SDS) and final height corrected for target height was also higher in the salt-supplemented group (–0.83 SDS vs. –1.69 SDS). In a multiple regression analysis, final height-SDS showed a positive correlation with salt supplementation during the first year of life in patients with salt-wasting CAH. In that study, also, no data on blood pressure, renin, or plasma renin activity was analyzed.

In summary, in the AQUAPE CAH database, approximately only one-third of infants with salt-wasting CAH receive sodium chloride supplementation. Sodium chloride supplementation is performed more frequently in recent years. However, salt supplementation had no influence on growth and daily fludrocortisone and hydrocortisone dose in a cohort that received relatively high fludrocortisone doses during the first year of life.

Disclosure Statement

The authors have nothing to disclose. No funding has been received.

References

1 Speiser PW, White PC: Congenital adrenal hyperplasia. N Engl J Med 2003;349:776–788.
2 Hughes IA: Congenital adrenal hyperplasia – a continuum of disorders. Lancet 1998;352:752–754.
3 Speiser PW, Azziz R, Baskin LS, Ghizzoni L, Hensle TW, Merke DP, Meyer-Bahlburg HF, Miller WL, Montori VM, Oberfield SE, Ritzen M, White PC, Endocrine Society: Congenital adrenal hyperplasia due to steroid 21-hydroxylase deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2010;95:4133–4160.
4 Mullis PE, Hindmarsh PC, Brook CG: Sodium chloride supplement at diagnosis and during infancy in children with salt-losing 21-hydroxylase deficiency. Eur J Pediatr 1990;150:22–25.

5 Kromeyer-Hauschild K, Wabitsch M, Kunze D, Geller F, Geiß HC, Hesse V, von Hippel A, Jaeger U, Johnson D, Korte W, Menner K, Müller G, Müller JM, Niemann-Pilatus A, Remer T, Schaefer F, Wittchen HU, Zabransky S, Zellner K, Ziegler A, Hebebrand J: Percentiles of body mass index in children and adolescents evaluated from different regional German studies (in German). Monatsschr Kinderheilkd 2001;149:807–818.
6 Neuhauser H, Schienkiewitz A, Schaffrath Rosario A, Dortschy R, Kurth BM: Referenzperzentile für anthropometrische Maßzahlen und Blutdruck aus der Studie zur Gesundheit von Kindern und Jugendlichen in Deutschland (KiGGS). 2013, Robert Koch-Institut, Berlin, RKI-Hausdruckerei, Berlin (ISBN 978-3-89606-218-5).
7 Flynn JT: Neonatal hypertension: diagnosis and management. Pediatr Nephrol 2000;14:332–341.
8 Bizzarri C, Pedicelli S, Cappa M, Cianfarani S: Water balance and "salt wasting" in the first year of life: the role of aldosterone-signaling defects. Horm Res Paediatr 2016;86:143–153.
9 Martinerie L, Pussard E, Foix-L'Hélias L, Petit F, Cosson C, Boileau P, et al: Physiological partial aldosterone resistance in human newborns. Pediatric Research 2009;66:323–328.
10 Bonfig W, Schwarz HP: Blood pressure, fludrocortisone dose and plasma renin activity in children with classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency followed from birth to 4 years of age. Clin Endocrinol 2014;81:871–875.
11 Bonfig W, Schmidt H, Schwarz HP: Growth patterns in the first three years of life in children with classical congenital adrenal hyperplasia diagnosed by newborn screening and treated with low doses of hydrocortisone. Horm Res Paediatr 2011;75:32–37.
12 Kawano A, Kohno H, Miyako K: A retrospective analysis of the growth pattern in patients with salt-wasting 21-hydroxylase deficiency. Clin Pediatr Endocrinol 2014;23:27–34.
13 Van der Kamp HJ, Otten BJ, Buitenweg N, De Muinck Keizer-Schrama SMPF, Oostdijk W, Jansen M, Delemarre-de Waal HA, Vulsma T, Wit JM: Longitudinal analysis of growth and puberty in 21-hydroxylase deficiency patients. Arch Dis Child 2002;87:139–144.