ORIGINAL ARTICLE

WILEY

# Assessment of medication adherence in children and adults with congenital adrenal hyperplasia and the impact of knowledge and self-management

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## Abstract

**Background:** Congenital adrenal hyperplasia (CAH) is caused by a deficiency of one of the enzymes required for cortisol biosynthesis. The disease is classified as either classic (severe phenotype), subdivided into simple virilizing (SV) and salt-wasting (SW), or non-classic (NC) CAH. The treatment regime involves life-long glucocorticoid replacement, especially in classic phenotype.

**Objectives:** We aimed to assess medication adherence, endocrine knowledge and self-management in patients with CAH and to compare patients' and physicians' assessments of medication adherence.

**Methods:** A prospective cross-sectional study of 108 patients with CAH (52 children and 56 adults) and 45 parents/caregivers. Two adherence measures were used, a self-reported questionnaire named Adherence Starts with Knowledge (ASK-12) with a cut-off level > 22 defined as poor adherence rate, and an assessment by a physician based on growth rate, 17-hydroxyprogesterone profile, and medical history, ranked using a five-point Likert scale.

Measurements of the patients'/parents' knowledge and self-management were performed using Endocrine Society Clinical Practice Guidelines.

**Results:** Self-reported medication adherence was good with 74% of the participants reported good adherence with higher adherence in patients with the SW form. The highest endocrine knowledge and self-management were found in parents compared with children and adults with classic CAH. There was 30% discordance between the assessments by a physician and the self-reported ASK-12 scores independent of the severity of CAH.

**Conclusion:** Patients and endocrinologists reported high medication adherence, however, discordance was found in 30% of the studied patients. Patients with the more severe form of CAH had higher adherence rates and demonstrated good endocrine knowledge/self-management.

## 1 | INTRODUCTION

Congenital adrenal hyperplasia (CAH) is a rare endocrine disorder caused by a deficiency of one of the enzymes in the cortisol biosynthesis pathway.[1] 21-hydroxylase deficiency (21OHD), accounting for 95%–99% of all CAH cases,[1-3] is characterized by impaired cortisol synthesis and excessive androgen production. The disease is classified as classic (simple virilizing (SV) and salt-wasting (SW)) CAH, and non-classic (NC) CAH.[4] The SW form may lead to lethal salt crises in the neonatal period if untreated, while 10% of individuals with SV risk salt crises during excessive physical stress. Individuals with the NC form develop symptoms of androgen excess, for example, increased growth rate, hirsutism and infertility. The treatment regimen involves life-long glucocorticoid replacement, compulsory in classic and optional in non-classic CAH, as well as mineralocorticoid replacement in most cases of classic CAH.[5]

In growing children, hydrocortisone is the recommended glucocorticoid ($10$–$15$ mg/m$^2$/day divided into 3–4 doses).[6] In adults, either hydrocortisone ($15$-$25$ mg/day divided into 3 doses), or an intermediate long-acting glucocorticoid such as prednisolone ($2.5$–$7.5$ mg/day divided into two doses), or a long-acting dexamethasone ($0.25$–$0.5$ mg once daily) can be used.[5,6]

Patients with CAH receiving supraphysiological glucocorticoid doses have an increased risk of impaired health status such as obesity, insulin resistance, decreased bone mineral density (BMD) and impaired quality of life.[7-10] Even though long-acting glucocorticoids may be preferred from an adherence point of view they seem to have more of the previous mentioned negative health outcomes, especially dexamethasone.[10]

The concept of medication adherence refers to the extent to which patients take their medications as prescribed and is a crucial part of both patient care and reaching clinical goals.[11] In patients with chronic conditions that require long-term drug therapy, poor medication adherence is particularly widespread.[11] Medication adherence can be measured either directly, by measuring the concentration of medications in blood or urine, or indirectly, through self-reports, pill counts, pharmacy refill data or electronic monitoring.[12] Self-reports have been found to overestimate adherence, but they are the most useful method in the clinical setting.[12,13]

Little is known about medication adherence in children and adults with CAH. However, a previously published study showed a lower adherence in adults than in children affected by CAH.[14] Children and adults with CAH may be at particular risk for medication non-adherence during acute situations and illness, which may have fatal consequences.[7,15]

The concordance between patients' and physicians' assessments of medication adherence is critical in the management of CAH to enable the correct identification of non-adherent patients; however, this area is lacking research. To be able to understand the impact on physical, mental, emotional and social functioning in patients with CAH, several factors need to be studied, especially adherence and self-management, including knowledge and stress dosing during illness.[14]

The aims of the current study were to assess medication adherence in patients with CAH, the concordance of their adherence with physicians' assessments, the present state of knowledge and self-management among patients with CAH and the impact of stress dose education. The primary endpoint was to assess medication adherence rate in patients with CAH.

## 2 | PATIENTS AND METHODS

### 2.1 | Study setting

The study was conducted at the Karolinska University Hospital.

### 2.2 | Patient recruitment

We contacted 168 patients with CAH (67 children with parents and 101 adults) and 52 children (78%), 50 parents (75%), and 56 adults (55%) agreed to participate (Figure 1). In total, 59%, 23% and 18% of participants had the SW, SV and NC phenotypes, respectively. All participants were regularly seen by a paediatric endocrinologist, adult endocrinologist or gynaecologist at the Karolinska University Hospital. All participants had the ability to read and understand Swedish and the ability to interpret a ten-point Numeric Rating Scale (NRS).

### 2.3 | Procedure

Eligible patients were invited to participate by an invitational letter that was either sent home or administrated in connection with a routine visit at the hospital. Informed written consent was obtained from all participants and assent was obtained from children older than 7 years. The study was approved by the Regional Ethics Committee of Stockholm (Dnr 2018/1666-31).

### 2.4 | Measurement for worries and concerns

All children, parents and adults were asked to grade their experiences of worries and concerns about CAH using a NRS ranging from 0 to 10.
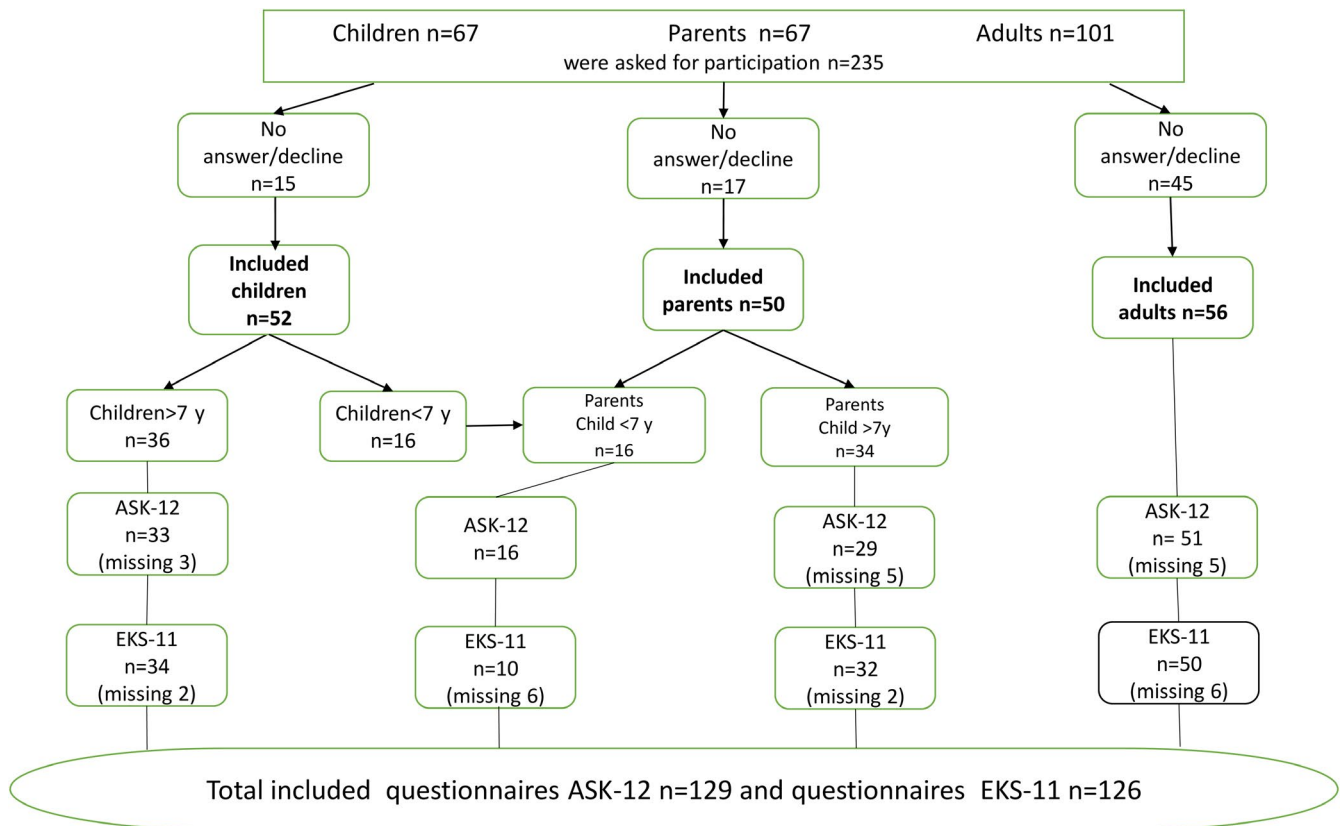
**FIGURE 1** Flowchart showing patient recruitment and questionnaires: Self-Reported Medication Adherence (ASK-12) and Endocrine knowledge and self-management (EKS-11) in children with CAH, their parents and adults with CAH [Colour figure can be viewed at wileyonlinelibrary.com]

## 2.5 | Questionnaires

The two instruments Adherence Starts with Knowledge (ASK-12) and Endocrine Society's Physician and Care Team Assessment of Patients Skill Set (Endocrine Knowledge and Self-management; EKS-11) were translated into Swedish with parallel forward translations, which were harmonized and translated back into English and compared to the original version. Two questionnaires, one for children and one for parents, were designed to be easily comprehensible by the two groups of participants. ASK-12 is based on ASK-20 and have been validated to have a good internal consistency reliability and test-retest reliability.[16] Endocrine Knowledge and Self-management (EKS 11) is a tool for paediatricians, teenagers and young adults to assess endocrine knowledge and skills. Our patients were classified as having good CAH knowledge if the right answer-rate was ≥80% as defined in previous reports.[17]

## 2.6 | Measurements of adherence

Two different methods for measuring adherence were used. The first was a self-reported indirect method, ASK-12,[18] that measures barriers to treatment adherence. ASK-12 includes a 12-item scale with three adherence-related subscales; *Behavior* (5 items), *Health*

*beliefs* (4 items) and *Inconvenience/forgetfulness* (3 items). The *Health belief* and *Inconvenience* items were rated with the following 5 response options: strongly agree, agree, neutral, disagree and strongly disagree. For *Behavior*, 5 different response options were used: in the last week, in the last month, in the last 3 months, more than 3 months ago and never. The total score has a range of 12–60. Higher scores indicate more barriers to adherence or greater problems with adherence behaviour. We determined a cut-off level for non-adherence to be 22.[19] Less than 22 was categorized as good adherence.

The second method for measuring adherence was a direct method comprising an analysis of 17-hydroxyprogesterone (17OHP) levels based on 24 hour profiles from dried blood spots that were collected at home by the patient or with the help of a caregiver and then sent in to the laboratory by mail.[20] After analysis, an assessment of the patient's medication adherence by a paediatric and/or adult endocrinologist was registered. Patients with NC CAH and no glucocorticoid treatment were excluded from this direct method of measuring adherence.

## 2.7 | Measurements of present state of knowledge and self-management

Measurements of the patients'/parents' knowledge and self-management were performed using the Questionnaire EKS-11 (Supplemental

data). As defined in previous reports, patients were classified as having acceptable/good knowledge and self-management if the EKS score was 11–14, whereas an EKS score over 14 indicated poor knowledge and self-management.[19]

Baseline data assessing age, sex, and anthropometric and an-amnestic details including assessment of worrying about CAH were documented. Body mass index (BMI) was calculated ($kg/m^2$), and then the BMI-SDS was calculated.[21]

## 2.8 | Assessment of adherence by an endocrinologist

Adherence was assessed by one paediatric and one adult endo-crinologist using a five-point Likert scale,[22] where 1–2 indicated poor adherence, 3 adequate adherence and 4–5 good adherence. The assessment for children was based on growth rate, diurnal 17OHP profiles and medical history while the assessment for adults was based only on diurnal 17OHP profiles and medical history.

## 2.9 | Evaluation of practical CAH training course

A subset of families (8 children and 13 parents), randomly selected from the children and parents included in the study, took part in a 2.5-hour practical training course covering CAH, adrenal crisis, stress-related glucocorticoid dosing during illness, and how to administer or self-administer an intramuscular injection of hydrocortisone. The impact of the course was measured by comparing ASK-12 and EKS-11 scores in those who had completed the CAH course with those who had not.

## 2.10 | Statistics

Descriptive statistics were expressed as mean ± SD, median (ranges), or numbers and percentages as adequate. ANOVA was used to evaluate the difference in the mean of ASK-12 and physicians' assessments of medication adherence. The power calculation was based on previously results with regard to ASK-scores. To ensure 80% power to identify a difference of 3 unit between groups using α =0.05, 44 patients were needed in each group. Mann–Whitney U test was used to evaluate the differences in the median of EKS-11. Chi-square and Fisher's exact test were used to test the degree of association between categorical variables. A general linear model was performed to examine the associations between ASK-12 and phenotype groups while controlling for potential covariates. Correlations were assessed using Spearman's rank order test. $p$-values < .05 were regarded significant. Statistical analyses were performed using SPSS for Windows version 22 (SPSS, IL, USA).

## 3 | RESULTS

The cohort consisted of 108 patients (55% males) including 52 children (61% males) and 56 adults (50% males). All had 21OHD (59% SW, 23% SV and 18% NC) (Table 1). Five adults with NC did not answer ASK-12 because they had no glucocorticoid treatment at the time of the study and two adults with SW failed to answer ASK-12 but completed the EKS-11 (Figure 1).

### 3.1 | Glucocorticoid therapy

Among children with CAH, 50 (96%) received hydrocortisone (all classic), one (2%) received prednisolone (classic) and one (2%) received no treatment (NC). Adults with classic CAH had treatment with prednisolone in 32 cases (78%), seven (17%) had hydrocortisone and two (4%) had modified-release hydrocortisone (Chronocort®). Of the 15 patients with NC CAH (26%), nine (60%) had prednisolone, one (6%) received hydrocortisone and five (33%) had no treatment.

### 3.2 | Worries and concerns

Self-reported worries and concerns were measured using a numeric rating scale that showed that parents of children with CAH were more worried than both children and adults with CAH (3.6 (0–9), 1.3 (0–5) and 1.7 (0–9), $p$ = .001 and $p$ = .001, respectively), with no differences found between the phenotypes.

### 3.3 | ASK-12, self-reported medication adherence

Self-reported medication adherence measured using ASK-12 was classified as good in 26 (79%) children aged seven years and older and 33 (65%) adults with CAH. Poorer adherence scores were found in adults than in children aged seven years and older (19.9 (5.2) vs. 18.8 (3.7), $p$ = .04; Table 2).

Twenty-eight cases (28%) identified themselves as non-adherent; 12 (43%) of these reported barriers in the item 'I forget to take my medicines some of the time' and in the item 'Taking medicines more than once a day is inconvenient'. Forty-five participants (42%) answered yes to 'Have you not had medicine with you when it was time to take it?'. A comparison of different ASK-12 items showed differences in *Inconvenience /Forgetfulness* and *Behavior score* between the different phenotypes with a better adherence-score for patients with the SW than NC form ($p$ < .001 and $p$ = .005, respectively). There was no difference in the *Health Beliefs* score between phenotype groups.

We found a significant difference in ASK-12 scores when comparing patients with SW, SV and NC CAH (18.2 (4.3), 19 (3.4) and 23.1 (5.8), respectively, $p$ = .001), with lower scores (indicating

**TABLE 1** Demographic and clinical characteristics of children and adults with congenital adrenal hyperplasia divided into three phenotypes—salt-wasting (SW), simple virilizing (SV) and non-classic (NC)

| Characteristics | All | | | | | Children | | | | | Adults | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Total | SW | SV | NC | p SW/SV/NC | Total | SW | SV | NC | p SW/SV/NC | Total | SW | SV | NC | p SW/SV/NC |
| | n = 108 | n = 64 | n = 25 | n = 19 | | n = 52 | n = 38 | n = 10 | n = 4 | | n = 56 | n = 26 | n = 15 | n = 15 | |
| Age, median (range), years | 22 (1–75) | 16 (1–66) | 30 (4–75) | 35 (8–69) | .01 | 10 (1–18) | 10 (1–18) | 10 (4–16) | 15 (8–18) | .1 | 43 (20–75) | 41 (21–66) | 47 (20–75) | 42 (23–69) | .3 |
| Male, n (%) | 60 (56) | 38 (59) | 18 (72) | 4 (21) | | 32 (62) | 24 (63) | 7 (70) | 1 (25) | | 28 (50) | 14 (54) | 11 (73) | 3 (20) | |
| Female, n (%) | 48 (44) | 26 (41) | 7 (28) | 15 (79) | | 20 (38) | 14 (37) | 3 (30) | 3 (75) | | 28 (50) | 12 (46) | 4 (27) | 12 (80) | |
| BMI SDS, mean (SD) | | | | | | 0.48 (1.2) | 0.54 (1.3) | 0.35 (0.9) | 0.21 (0.8) | | | | | | |
| BMI, mean (SD) | | | | | | | | | | | 26.5 (3.9) | 25.6 (3) | 28.4 (5) | 25.8 (3.5) | |
| Worries and concerns, (0–10), median (range) | 0 (0–9) | 0 (0–9) | 0 (0–9) | 2 (0–8) | .2 | 1 (0–9) | 1 (0–5) | 1 (0–9) | 1 (0–4) | .7 | 0 (0–9) | 0 (0–9) | 0 (0–8) | 2 (0–8) | .1 |
| No. of answers | 87 | 45 | 23 | 19 | | 36 | 24 | 8 | | | 51 | | | | |
| Missing/answer by parent child < 7 years (n) | 21 | 19 | 2 | | | 16 | 14 | 2 | | | 5 | 5 | | | |
| Wear a MediAlert identification, n (%) | 46 (48) | 26 (46) | 14 (70) | 6 (33) | .2 | 13 (28) | 9 (24) | 3 (50) | 1 (25) | .4 | 33 (66) | 17 (77) | 11 (79) | 5 (36) | .04 |
| Missing | 11 | 5 | 5 | 1 | | 5 | 1 | 4 | | | 6 | 4 | 1 | 1 | |
| Administered Hydrocortisone injection, n (%) | 11 (11) | 8 (13) | 3 (13) | | | 5 (10) | 5 (13) | | | | 6 (12) | 3 (14) | 3 (21) | | |
| Missing | 9 | 5 | 3 | 1 | | 3 | 1 | 2 | | | 6 | 4 | 1 | 1 | |

**TABLE 2** Comparing ASK-12 scores in children, their parents and adults with congenital adrenal hyperplasia divided into three phenotypes—salt-wasting (SW), simple virilizing (SV) and non-classic (NC)

| | Total | p m/f | SW | SV | NC | p SW/SV/NC | post hoc SW vs NC | post hoc SV vs NC | p C/A | p C/P/A | post hoc p vs A |
|---|---|---|---|---|---|---|---|---|---|---|---|
| No. of answers, n (male/female) | 129 (74/55) | | 82 (52/30) | 29 (20/9) | 18 (2/16) | | | | | | |
| ASK-12 score, mean (SD) | 18.7 (5.6) | .1 | 17.7 (4.2) | 19.2 (3.4) | 22.4 (6.1) | <.001 | <0.001 | 0.045 | | .019 | .015 |
| Male | 18.1 (3.9) | | 17.4 (3.9) | 19.4 (3.2) | 23 (2.8) | | | | | | |
| Female | 19.5 (5.4) | .09 | 18.3 (4.7) | 18.8 (4) | 22.3 (6.4) | | | | | | |
| Good adherence rate ASK-12 score < 22, n (%) | 95 (74) | .2 | 66 (81) | 20 (69) | 9 (50) | .02 | | | | | |
| Included patients, n | 108 | | 64 | 25 | 19 | | | | | | |
| Missing /answer by parent child < 7 years, n | 24 | | 15 | 5 | 4 | | | | | | |
| No. of answers in children > 7 years and adults, n (male/female) | 84 (47/37) | | 49 (31/18) | 20 (14/6) | 15 (2/13) | | | | | | |
| ASK-12 score, mean (SD) | 19.5 (4.7) | | 18.5 (4.2) | 19.1 (3.5) | 23.1 (5.9) | .003 | 0.002 | 0.03 | | | |
| Male | 19 (3.9) | | 18.3 (4.1) | 17.7 (2.7) | 23 (2.8) | | | | | | |
| Female | 20 (5.5) | .3 | 17.4 (4.9) | 22.3 (2.1) | 23.1 (6,2) | | | | | | |
| Good adherence rate ASK-12 score < 22, n (%) | 59 (70) | | 38 (78) | 14 (70) | 7 (47) | .07 | | | | | |
| Children (C), n | 52 | | 38 | 10 | 4 | | | | | | |
| missing/answer by parent | 3/16 | | 13 | 5 | 1 | | | | | | |
| No. of answers, n (male/female) | 33 (21/12) | | 25 (18/7) | 5 (3/2) | 3 (0/3) | | | | | | |
| ASK-12 score, mean (SD) | 18.8 (3.7) | | 18 (3.6) | 20.8 (2.6) | 22.7 (2.9) | .045 | | | | | |
| Male | 18.7 (3.8) | | 18.3 (3.9) | 21 (2.6) | 23 (2.8) | | | | | | |
| Female | 19.0 (3.7) | .8 | 17 (2.9) | 20 (3.5) | 22.7 (2.9) | | | | | | |
| Good adherence rate ASK-12 score < 22, n (%) | 26 (79) | .6 | 21 (84) | 3 (60) | 2 (67) | .4 | | | | | |
| Parents (P), n | 50 | | 36 | 10 | 4 | | | | | | |
| Missing | 5 | | 3 | 1 | 1 | | | | | | |
| No. of answers, n (male/female) | 45 (27/18) | | 33 (21/12) | 9 (6/3) | 3 (0/3) | | | | | | |
| ASK-12 score, mean (SD) | 17.3 (4.1) | | 16.6 (3.9) | 19.2 (3.3) | 19 (7) | .17 | | | | | |
| Male | 16.4 (3.1) | | 16.1 (3.2) | 17.7 (2.7) | 0 | | | | | | |
| Female | 18.5 (5.1) | .1 | 17.4 (5) | 22.3 (2.1) | 19 (7) | | | | | | |
| Good adherence rate ASK-12 score < 22, n (%) | 36 (80) | .07 | 28 (85) | 6 (67) | 2 (67) | .4 | | | | | |
| Adults (A), n | 56 | | 26 | 15 | 15 | | | | | | |
| Missing | 5 | | 2 | 3 | 3 | | | | | | |

(Continues)

a good adherence rate) in patients with SW CAH (Table 2). Self-reported adherence was similar in children and adults when parental adherence assessments were included. A good self-reported adherence rate was seen in 95 cases (74%) when all ASK-12 assessments were analysed together (Table 4).

When comparing ASK-12 scores for the entire cohort, we could see that parents estimated their children to have better adherence than adults with CAH ($p$ = .015). When comparing different phenotypes, a higher adherence rate was found in patients with SW than in those with SV and NC CAH ($p$ = .02) (Table 2). When comparing phenotypes and adherence scores in children, parents and adults separately, a better adherence-score was found in children and adults with SW than in those with SV and NC CAH ($p$ = .045 and $p$ = .04, respectively), and no difference was found in parents.

When comparing children's and parents' ASK-12 scores, a tendency for an association was found ($r$ = .4, $p$ = .06) as well as an association between ASK-12 scores and self-reported assessment of worries and concerns ($r$ = .2, $p$ < .05).

## 3.4 | Medication adherence assessed by physicians

When adherence was measured using the direct method and evaluated by endocrinologists, the medication adherence was rated as good in 46 (45%) patients, 32 (31%) adequate adherence and 24 (24%) poor adherence (Figure 2). No difference was found between the phenotype groups. In children, 24 (46%) were rated to have good adherence, 11 (22%) adequate adherence and 16 (31%) poor adherence with no difference found between the phenotype groups. Of the children assessed to have poor adherence, 12 (75%) responded that they had barriers in *Inconvenience/Forgetfulness* items. In adults, a good medication adherence was found in 22 patients (43%), adequate in 21 (41%) and poor in eight (16%). Associations between self-reported (SR) medication adherence and physicians' assessments of medication adherence are shown in Table 3. The discordance rate was 31%. Seventeen patients rated their adherence as poor in contrast to the doctors' assessments that was good / adequate and 14 patients had a self-rating as good regarding their adherence that was disparate to the doctors' assessments.

## 3.5 | EKS-11, self-reported knowledge and self-management

Self-reported knowledge and self-management were classified as good for 30 patients (37%). Of the 52 patients (63%) identified as having poor knowledge and management, all studied patients reported poorer scores in EKS Basic and EKS Acute scores. When comparing genders, a higher proportion of good EKS-11 scores was reported in males (Table 4).

When comparing children, parents and adults, we found that parents had a better EKS score than their children and adults with CAH, but no difference between genders was found. When we
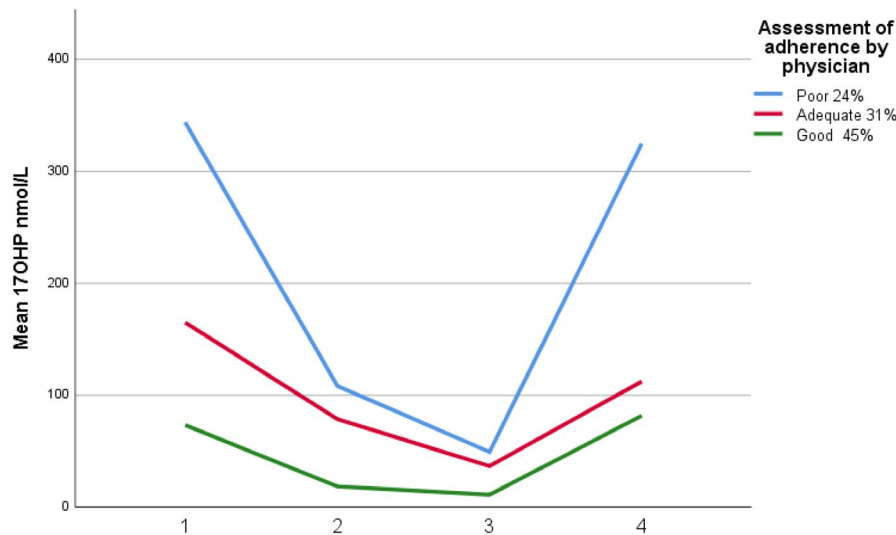
TABLE 2  (Continued)

| | Total | p m/f | SW | SV | NC | p SW/SV/NC | post hoc SW vs NC | post hoc SV vs NC | p C/A | p C/P/A | post hoc p vs A |
|---|---|---|---|---|---|---|---|---|---|---|---|
| No. of answers, n (male/female) | 51 (26/25) | | 24 (13/11) | 15 (11/4) | 12 (2/10) | | | | | | |
| ASK-12 score, mean (SD) | 19.9 (5.2) | | 19 (4.8) | 18.6 (3.7) | 23.2 (6.5) | .04 | 0.06 | 0.07 | 0.04 | | |
| Male | 19.3 (4.1) | | 18.2 (4.6) | 19.8 (3.4) | 23 (2.8) | | | | | | |
| Female | 20.5 (6.2) | .4 | 20 (5.1) | 15.2 (2.1) | 23.2 (5.1) | | | | | | |
| Good adherence rate ASK-12 score < 22, n (%) | 33 (65) | .5 | 17 (71) | 11 (73) | 5 (42) | .2 | | | | | |

Abbreviations: C, Children. P, Parents. A, Adults.

**FIGURE 2** Endocrinologists' assessments of adherence. Evaluations of 17-hydroxyprogesterone (17OHP) 24-hour profiles at 4 time points; 1 (morning), 2 (lunch), 3 (evening) and 4 (following morning), graded as poor/adequate/good

**TABLE 3** Association between self-reported (SR) medication adherence and physicians' assessments (PA) of medication adherence

|  | SR Good | SR Poor | No. of patients |
|---|---|---|---|
| PA Good | 35 (35%) | 11 (11%) | 46 |
| PA Adequate | 24 (24%) | 6 (6%) | 30 |
| PA Poor | 14 (14%) | 9 (9%) | 23 |
| No. of patients | 73 | 26 | |

*Note:* Self-reported adherence measured in children (n = 34) and parents when child < 7 years (n = 18). ASK-12: Missing 3, Excluded NC CAH with no treatment n = 6.

analysed the entire study group and compared phenotypes, a difference in EKS-11 scores was found; patients with SW/SV had better knowledge and self-management than those with NC CAH.

Parents with a child with SW CAH had better EKS Acute scores than parents with a child with SV or NC CAH (p = .02).

We found correlations between children's and parents' ESK-11 scores (r = .5, p = .003), ASK-12 and EKS-11 scores (r = .2, p = .03), but not between physicians' assessments and self-reported ASK-12 or EKS-11 with no differences found between phenotypes.

The eight children and 13 parents who completed a 2.5-hour CAH practical training course had better EKS-11 scores than the children and parents who had not completed the course (12.7 (11–18) vs. 14.8 (12–22), p = .01). No differences in the ASK-12 score were found between participants who had or had not completed the training course (data not shown).

Medical-alert IDs were frequently used by 13 children (27%) and 33 adults (66%) (p < .001). Eleven (10%) of all included participants,

including five SW children/parents as well as four SW and two SV adults, responded that they had had/or had given an acute intramuscular injection of hydrocortisone at home or in hospital.

## 4 | DISCUSSION

This is the first study investigating self-reported medication adherence in patients with CAH and comparing these to assessments of medication adherence performed by endocrinologists. It pinpoints specific difficulties in clinical follow-up. Overall, a good level of medical adherence was found. Both the medication adherence reported by the patients/parents and the endocrinologists was good/adequate, 74% and 76%, respectively, but discordance occurred in one third. Our result of a poor adherence rate about 20% is a concern and may put patients at serious risk of adrenal crisis and subsequent death. Non-adherent prevention remains a permanent challenge for healthcare providers caring for patients with CAH.

Our results differ in that we found self-reported adherence just as good as physicians' reports of adherence, and this can be compared to a recently published study of patients with persistent asthma demonstrating a discordance in half of the cases.[23] The results show that adherence classified as medium by physicians was associated with a higher risk of discordance, both for over- and underestimations of adherence. Several studies in adults have demonstrated that physicians consistently underestimate patients' non-adherence.[24-26]

The data presented here on self-reported adherence rates were good, but this may be due to participants overestimating their adherence. Previous studies have reported rates of self-reported adherence to long-term pharmacological treatments for chronic illnesses to be only about 50%.[27] Difficulties in measuring adherence in clinical settings are well-known[28] and subjective measures of adherence are potentially inaccurate because they depend on the patient's

**TABLE 4** Comparing EKS-11 score in children, their parents and adults with congenital adrenal hyperplasia divided into three phenotypes—Salt-Wasting(SW), Simple Virilizing(SV) and Non-Classic(NC)

| | Total | p M/F | SW | SV | NC | p SW/SV/NC | p C/P/A |
|---|---|---|---|---|---|---|---|
| All participants | | | | | | | |
| No. of answers, n (male/female) | 126 (73/53) | | 80 (51/29) | 25 (19/6) | 21 (3/18) | | |
| Total score, median (range) | 15 (11–22) | | 15 (11–22) | 14 (11–19) | 16 (11–22) | .037 | |
| Male, median (range) | 14 (11–22) | | 13 (11–22) | 14 (11–19) | 19 (18–21) | | |
| Female, median (range) | 15 (11–22) | .2 | 15 (11–22) | 12.5 (11–18) | 15.5 (11–22) | | |
| Good knowledge/self-management EKS-11 score < 15, n (%) | 67 (53) | .06 | 46 (57) | 15 (60) | 6 (28) | .05 | |
| Included patients , n | 108 | | 64 | 25 | 19 | | |
| Missing/answer by parent child < 7 years, n | 26 | | 17 | 5 | 4 | | |
| No. of answers in children > 7 years and adults, n (male/female) | 82 (46/36) | | 47 (30/17) | 18 (14/4) | 17 (2/15) | | |
| EKS-11 score, median(range) | 15 (11–22) | | 15 (11–22) | 15 (11–19) | 16 (11–22) | .5 | |
| Male | 15 (11–22) | | 15 (11–22) | 15 (12–19) | 20 (19–21) | | |
| Female | 16 (11–22) | .6 | 16 (11–20) | 13.5 (11–18) | 16 (11–22) | | |
| Good knowledge/self-management EKS-11 score < 15, n (%) | 30 (37) | .02 | 18 (38) | 8 (44) | 4 (23) | .015 | |
| Children ('C), n | 52 | | 38 | 10 | 4 | | |
| Missing/answer by parent | 2/16 | | 12 | 5 | 1 | | |
| No. of answers, n (male/female) | 34 (22/12) | | 26 (18/8) | 4 (3/1) | 4 (1/3) | | |
| Total score, median (range) | 16 (11–22) | | 16 (11–22) | 15 (14–18) | 17.5 (16–22) | .3 | |
| Male, median (range) | 15 (11–21) | | 15 (11–21) | 14 (14–16) | 19 (19) | | |
| Female, median (range) | 16.5 (15–22) | .02 | 16.5 (15–22) | 18 (18) | 18 (16–22) | | |
| Good knowledge/self-management EKS-11 score < 15, n (%) | 9 (27) | .5 | 7 (27) | 2 (50) | 0 (0) | .3 | |
| Parents (P), n | 50 | | 36 | 10 | 4 | | |
| Missing | 8 | | 4 | 3 | 1 | | |
| No. of answers, (male/female) | 42 (26/16) | | 31 (20/11) | 7 (5/2) | 4 (1/3) | | |
| Total score, median (range) | 12 (11–18) | | 12 (11–18) | 13 (11–14) | 16 (11–21) | .1 | |
| Male, median (range) | 12 (11–18) | | 11.5 (11–16) | 13 (11–14) | 18 (18) | | |
| Female, median (range) | 12.5 (11–21) | .15 | 12 (11–18) | 12.5 (12–13) | 14 (11–21) | | |
| Good knowledge/self-management EKS-11 score < 15, n (%) | 37 (88) | .6 | 28 (90) | 7 (100) | 2 (50) | .9 | |
| Adults (A), n | 56 | | 26 | 15 | 15 | | |
| Missing | 6 | | 3 | 1 | 2 | | |
| No. of answers, (male/female) | 50 (25/25) | | 23 (13/10) | 14 (11/3) | 13 (1/12) | | |
| Total score, median (range) | 15 (11–22) | | 15 (11–22) | 15 (11–19) | 15 (11–21) | .7 | <.001 |
| Male, median (range) | 15 (11–22) | | 14 (11–22) | 15 (12–19) | 21 (21) | | |
| Female, median (range) | 15 (11–20) | .4 | 15 (11–18) | 11 (11–19) | 15 (11–20) | | |
| Good knowledge/self-management EKS-11 score < 15, n (%) | 21 (42) | .5 | 11 (48) | 6 (43) | 4 (31) | .7 | |

Abbreviations: A, Adults; C, Children; P, Parents.

willingness and/or memory to report poor adherence, which could be perceived to compromise their patient-provider relationship.[29] However, most of our participants had been treated continuously by the same physician, which may be a reason for the good results as continuity may improve quality of care and adherence.[30] It is also possible that adherence is better among individuals with a congenital chronic disorder than those with a disorder contracted later in life. Taking medication all your life may obviate the element of getting used to a new situation or the need to accept a disorder. Despite our results of good adherence rates, discordance was found

in 30% of participants when compared to the endocrinologists' assessments. This illustrates the clinical problem and the difficulty in distinguishing between treatment effects and adherence in addition to influencing and motivating the group of non-adherent patients.

Different barriers for adherence were identified with inconvenience and forgetfulness being the most common barriers for children and their parents, while behaviour issues were most common among adults. This highlights the importance of healthcare providers continuously discussing different barriers with their patients.

Traditionally, medication adherence has been evaluated from the patient perspective, although more recent studies have focused more on healthcare providers.[31] This is in accordance with a previous study that demonstrates the benefit of utilizing a multimethod approach (ie using both indirect and direct methods) to identify non-adherence in patients with a chronic disease as a first step to reduce non-adherence.

We found that parent-reported adherence was better than self-reported adherence in adults with CAH, which is in line with a qualitative study investigating the caregivers' view.[27] This may be explained by the fact that parents have a solid knowledge of the disorder and the responsibility parents feel when their child suffers from an acute illness.[32]

It is already known that reasons for poor medication adherence include disease characteristics and severity as well as treatment factors.[33] This may explain our results showing that children with SW had better adherence than children with SV and NC CAH.

There were fewer children in our cohort who carried an emergency disease-specific ID card than adults. One explanation may be that children do not want to wear an ID necklace displaying their disorder, making them different from their peers, while adults keep their card in their wallet/mobile phone. It may also be related to the fact that children normally do not carry an ID card, and that parents may think that their children are cared for by adults during school hours and organized activities. However, in our opinion, there is a need for improvement.

The successful management of CAH requires good parental and patient knowledge and an understanding of the disorder; physicians have to be able to identify gaps in their patients' knowledge. Our results showed that 53% of children, parents and adults had good knowledge of CAH and good self-management skills. In addition, better rates of endocrine knowledge and self-management were found among the families who had attended the CAH training course, which is in accordance with other studies.[33] We found a correlation between ASK-12 and ESK-11 scores, adherence and knowledge. There is a general agreement that patient education is essential for adherence.[16] However, no better self-reported adherence rate was found in our sub-study, but this could be explained by a lack of power. Different self-reported assessments of endocrine knowledge may be helpful for healthcare providers before practical CAH training for parents and patients in order to tailor information and to promote a positive outcome for patients with CAH.[34]

A necessary step towards improving the patients' use of medication and self-management in the event of an acute illness is to identify non-adherence. One method is to include standardized assessments of knowledge but also adherence in each out-patient visit. When physicians acknowledge the common barriers to medication adherence, children, parents and adults may be more likely to disclose adherence difficulties and as a result, receive the support they need.[29,35]

There are several limitations to our study. The sample size was relatively small, even though it is one of the larger CAH studies, and the study was geographically restricted to one major tertiary centre. Therefore, our findings may not be representative. Providers were asked to estimate patients' adherence, and their perception of adherence was based on the diurnal 17OHP profiles and medical history (plus growth patterns in children) at the time of inclusion. There may be a marginal risk that the physicians' perception of adherence could reflect a broader time frame. Patients' and physicians' estimates were assessed at one time-point, and there was no standard way to define discordance. We used one approach to define discordance based on a previously used accepted cut-off. This level may be discussed, but has been used in patients with chronical illness before.[36] Endocrine Knowledge and Self-management (EKS-11) is not a validated questioner but is a tool for paediatricians, teenagers and young adults to assess endocrine knowledge and skills. The ASK-12 demonstrated adequate reliability and validity and has been developed to easily identify factors that influence medication adherence and used across a spectrum of chronic diseasesy,[18,37] however, it has not been previously used in patients with CAH.

## 5 | CONCLUSION

Self-reported medication adherence levels were good in most patients with CAH. Patients with classic CAH had higher adherence scores with good endocrine knowledge and self-management. However, discordance was found between self-reported adherence and physicians' assessments in 30%. There is a clinical problem with difficulties to identify and reach out to non-adherent patients. To improve the patient's and physician's agreements, adherence barriers and behavioural patterns should be assessed routinely and monitored and discussed regularly.

### AUTHOR CONTRIBUTIONS
KE conceived the study, applied for research funding, performed the study, conducted statistical analyses, interpreted the results and wrote the paper. AS conceived the study, oversaw the study

and critically revised the paper. SL oversaw the study and critically revised the paper. AHL oversaw the study and critically revised the paper. HF conceived the study, interpreted the results, oversaw the study and critically revised the paper. AN conceived the study, applied for research funding, conducted statistical analyses, interpreted the results, oversaw the study and co-wrote the paper.

## DATA AVAILABILITY STATEMENT

Data available on request from the authors.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.