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Working Memory Performance is Reduced in Children with Congenital Adrenal Hyperplasia

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Abstract

Individuals with classic congenital adrenal hyperplasia (CAH) experience impaired glucocorticoid production and are treated postnatally with glucocorticoids. Prior research with animals and other human populations indicates that glucocorticoids can influence memory, particularly working memory. We tested the hypothesis that children with CAH would show reduced working memory. Children in the United Kingdom, aged 7–11 years, with classical CAH (31 girls, 26 boys) were compared to their unaffected relatives (30 girls, 20 boys) on a test of working memory, the Digit Span test. Vocabulary was also assessed to measure verbal intelligence for control purposes. Children with CAH showed reduced working memory performance compared to controls, on both components of the Digit Span test: $p = .008$ for Digit Span Forward, and $p = .027$ for Digit Span Backward, and on a composite score, $p = .004$. These differences were of moderate size ($d = .53$ to $.70$). Similar differences were also seen in a subset of 23 matched pairs of children with CAH and their relatives ($d = .78$ to $.92$). There were no group differences on Vocabulary. Glucocorticoid abnormality, including treatment effects, could be responsible for the reduced Digit Span performance in children with CAH. Other factors related to CAH, such as salt-wasting crises, could also be involved. Additional research is needed to identify the cause of the memory reduction, which will help to determine if more rapid diagnosis or more precise glucocorticoid treatment would help prevent memory reduction. Educational interventions might also be considered for children with CAH.

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Declaration of interest

The authors have nothing to disclose and there are no conflicts of interest.

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Keywords

Congenital adrenal hyperplasia; glucocorticoid; working memory; androgen

Introduction

Classic congenital adrenal hyperplasia (CAH) is an autosomal recessive condition caused by an enzymatic deficiency. In over 90% of cases, the deficient enzyme is 21-hydroxylase, and this deficiency results in low levels of the glucocorticoid cortisol and in high levels of adrenal androgens, including testosterone, starting at about the seventh week of gestation (Merke and Bornstein, 2005; Speiser and White, 2003; White and Speiser, 2000). Androgen excess during the prenatal period causes genital ambiguity in newborn females with CAH. Management for both male and female patients includes treatment with glucocorticoids postnatally to normalize hormone concentrations (Speiser et al., 2010). Despite this treatment, postnatal glucocorticoid or androgen concentrations may be abnormal, for example, because of delayed diagnosis and treatment, or because of over- or under-treatment with glucocorticoids (Auchus and Arlt, 2013; Debono et al., 2009; Li et al., 2003; White and Speiser, 2000).

Girls and women with classic CAH have been found to show some behavioral masculinization, similar to that seen following experimental manipulations of androgens in other species (Collaer and Hines, 1995; Schwarz and McCarthy, 2008). For example, girls with CAH show increased male-typical childhood play behavior (Berenbaum and Hines, 1992; Hines, 2011; Hines et al., 2004; Pasterski et al., 2005, 2007, 2011), and women with CAH show increased interest in male-typical occupations and reduced heterosexual interests (Beltz et al., 2011; Hines, 2011; Hines et al., 2004; Meyer-Bahlburg et al., 2008; Servin et al., 2003).

The potential impact of glucocorticoid abnormality on behavior in individuals with CAH is relatively unexplored. However, glucocorticoids have been shown to have potent neurobehavioral influences, particularly in relation to learning and memory (Dominique et al., 2000; Kukolja et al., 2011; Lupien and McEwen, 1997; Lupien et al., 2002; Rimele et al., 2013; Tollenaar et al., 2009). Research using rodents and non-human primates shows that the hippocampus, a neural region implicated in memory, is influenced by glucocorticoids during critical periods of early development (Matthews, 2001). In addition, experimentally lowering or elevating glucocorticoid levels in adult rats can cause hippocampal atrophy and memory impairments (Herbert et al., 2006; McEwen and Sapolsky, 1995).

In humans, memory deficits have been found in clinical conditions characterized by prolonged exposure to elevated glucocorticoids, such as Cushing syndrome (for a review, see Sapolsky, 2000) and in individuals receiving glucocorticoid treatment (Lupien et al., 2007; Stuart et al., 2005). In healthy adults, glucocorticoid manipulations have also been found to influence memory, particularly working memory -- the short-term storage and manipulation of information (Baddeley, 1992). For example, men treated with a high dose of hydrocortisone show impaired working memory, assessed using an item-recognition

working memory task (Lupien et al., 1992). Stress-induced increases in cortisol also have been associated with impaired high-load working memory performance (Oei et al., 2006).

Although glucocorticoid administration may not affect all working memory-related tasks (Vaz et al., 2011), one working memory task that has been found to be influenced in a number of studies is Digit Span, a task that requires the recall and recitation of strings of numbers both forwards and backwards. Studies of healthy young men have found impaired Digit Span performance following treatment-induced glucocorticoid elevations (Vaz et al., 2011; Wolf et al., 2001), as well as following stress-induced glucocorticoid elevations (Schoofs et al., 2009). Another study found similar impairment following stress-induced glucocorticoid elevations in both men and women who showed strong adrenergic activation following stress (Elzinga and Roelofs, 2005). Thus, research in humans, as well as in non-human animals, suggests that exposure to abnormal glucocorticoid levels, particularly glucocorticoid excess, can have a detrimental impact on working memory.

Given the evidence that glucocorticoids can influence working memory, particularly Digit Span performance, altered performance in the Digit Span test might be hypothesized in individuals with CAH. In the current study, we investigated Digit Span performance in children with CAH and in their unaffected relatives, who served as controls. We tested the hypothesis that Digit Span performance is reduced in children with CAH. Children were also given a test to assess their Vocabulary. This measure has not been related to glucocorticoid exposure, so was used as a control measure and was not anticipated to show group differences.

Methods

Subjects

A total of 107 children were studied, aged 7 to 11 years – 57 with classical CAH (26 boys, 31 girls) and 50 unaffected siblings and cousins (20 boys, 30 girls) who served as controls. Table 1 shows the means (*Ms*) and standard deviations (*SDs*) of the ages for the four groups of children (boys and girls with CAH and control boys and girls). These children were part of a larger study designed to investigate gender-related behavior in 4 – 11 year old children with CAH. The Digit Span test was the only measure that was included with the intent of assessing behavioral effects of glucocorticoids. All other measures were included to assess the possible masculinizing effects of androgens, and results for those measures are being reported separately. Only children from the larger study who were 7 years of age or older completed the Digit Span test, because it is not age-appropriate for younger children.

Most children ($n = 95$) were Caucasian. One was African/Afro-Caribbean, 2 were Asian (Indian/ Pakistani/ Bangladeshi), 2 were Middle Eastern, and 6 were of mixed ethnicity along with Caucasian (African/Afro-Caribbean, Far Eastern, Middle Eastern, or Indo-Caribbean). For 1 child, information on ethnicity was not provided.

Children with CAH were recruited via National Health Service (NHS) Hospitals in the UK (18 boys, 24 girls) or CAH support groups (7 boys, 6 girls). The recruitment of 1 additional boy and 1 additional girl with CAH was achieved through contacts with other subjects (i.e.,

snowball sampling, a recruitment technique particularly useful for rare populations; Kalton and Anderson, 1986). All children with CAH had 21-hydroxylase enzyme deficiency; 50 had salt-wasting CAH (24 boys, 26 girls), and 7 had simple-virilizing CAH (2 boys, 5 girls). None of the children had been treated prenatally with dexamethasone, a glucocorticoid that is sometimes used to treat pregnancies where CAH is suspected. The project was approved by the NHS Health Research Authority, and children and their parents provided written assent and consent, respectively, before taking part.

Measures

Digit Span—The Digit Span test is a subtest taken from the fourth edition of the Wechsler Intelligence Scale for Children (WISC; Wechsler, 2003), a standardized set of subtests with well-established reliability and validity. The Digit Span test includes a forwards phase, Digit Span Forwards (DSF), and a backwards phase, Digit Span Backwards (DSB). Each phase consists of a series of test items, and each test item involves 2 trials, made up of a series of digits of the same length. The length of the series of digits in the first item is 2 digits, and the length increases by one digit for each subsequent item. For DSF, the examiner read out a string of digits, and the child repeated the digits aloud verbatim. For DSB, the child repeated the digits aloud in reverse order. For both forward and backward phases, 1 point was awarded if all digits were repeated correctly. If the child was unable to give a correct response for a specific trial, the child received 0 points and the examiner moved on to the next trial. Once the child was unable to respond correctly to both trials in an item of a particular length, the measure was discontinued. Performance on DSF and DSB was assessed, with a maximum score of 16 points each. The two phases also were combined to form a Digit Span Composite (DSC), with a maximum score of 32 points.

Vocabulary—The Vocabulary subtest of the WISC served as a measure of verbal intelligence. Children were required to provide a definition of a word read aloud to them by the examiner. In terms of scoring, a good synonym for a word item, for example, would be awarded 2 points. A lack of content in the child's response or a vague knowledge of the word item is awarded 1 point only. An obviously incorrect response or one with no real understanding is given 0 points. The Vocabulary measure is discontinued if the child receives a score of 0 after 5 consecutive attempts.

Statistical Analyses

Two-way analyses of variance (ANOVAs) were used to investigate the influence of diagnosis (CAH, control) and of sex (male, female) on working memory performance. Sex was included as a factor, as well as diagnosis, because much of the prior research showing glucocorticoid effects on memory has involved only males, and so effects might be limited to males. When age or Vocabulary correlated with a specific task component, a two-way analysis of covariance (ANCOVA) was used, with age or Vocabulary entered as a covariate, instead of an ANOVA. Children with CAH who had one or more sibling and/or cousin in the control sample were included in a pair-wise matched analysis to establish whether findings for these pairs of related children would resemble those for the full sample. All analyses were two-tailed, with alpha set at .05. In addition, effect sizes (*d*; Cohen, 1988) were calculated to provide an indication of the size of any group differences. In regard to

behavior, an effect size of 0.8 or greater is generally considered to be large, one of 0.5 moderate, and one of 0.2 small. Effect sizes below 0.2 are viewed as negligible. To put these in context, a large effect ($d = 0.8$) would resemble a difference between groups in IQ of about 12 points, a moderate effect ($d = 0.5$) would resemble a difference in IQ scores of about 8 points, and a small effect ($d = 0.2$) would resemble a difference in IQ scores of about 3 points (Cohen, 1988).

Results

Initial Analyses

Data for age, Vocabulary and Digit Span for the full sample are shown in Table 1. Two-way (diagnosis $\times$ sex) ANOVAs on age and Vocabulary scores showed no significant main effects or interactions, indicating no significant group differences in age or Vocabulary (Table 1). Correlations of age and Vocabulary with each of the task components showed that age did not correlate significantly with DSF, $r = .15$, $p = .120$, but age did correlate significantly and positively with DSB, $r = .19$, $p = .046$, and DSC, $r = .21$, $p = .032$. Vocabulary did not correlate significantly with DSF, $r = .04$, $p = .683$, DSB, $r = .13$, $p = .189$, or DSC, $r = .09$, $p = .341$. Therefore, an ANOVA was used to analyze data for DSF, whereas an ANCOVA, with age entered as the covariate, was used for DSB and DSC.

Digit Span

For DSF, the two-way ANOVA revealed a significant main effect of diagnosis, $F(1,103)=7.20$, $p=.008$, but no significant main effect of sex, $F(1,103)=0.88$, $p=.350$, and no significant diagnosis $\times$ sex interaction, $F(1, 103)=2.22$, $p=.140$.

For DSB, the two-way ANCOVA similarly revealed a significant main effect of diagnosis, $F(1, 102)=5.01$, $p=.027$, but no significant main effect of sex, $F(1,102)=0.89$, $p=.348$, and no significant diagnosis $\times$ sex interaction, $F(1, 102)=0.60$, $p=.439$. The covariate, age, also was not significant, $F(1, 102)=3.03$, $p=.085$.

For DSC, the two-way ANCOVA again revealed a significant main effect of diagnosis, $F(1,102)=8.94$, $p=.004$, but no significant main effect of sex, $F(1,102)=1.51$, $p=.221$, and no significant diagnosis $\times$ sex interaction, $F(1, 102)=2.66$, $p=.106$. The covariate, age, also was not significant, $F(1, 102)=3.69$, $p=.058$.

As shown in Table 1, children with CAH achieved lower M s for DSF, DSB, and DSC compared to unaffected controls (Figure 1). Table 2 shows the M s and SD s for children with the different forms of CAH as well as for unaffected controls. The pattern of M s suggests a greater reduction in Digit Span performance in the children with salt-wasting CAH compared to simple-virilizing CAH. However, the sample size for children with simple-virilizing CAH is small. Nonetheless, the effect sizes for the difference between controls and children with salt-wasting CAH were larger for DSF, DSB and DSC when compared to the effect sizes for controls and children with simple-virilizing CAH (see Table 3).

Matched Pair Analysis

There were a total of 23 CAH-relative pairs. Where there were cases of more than one relative per child with CAH, or more than one child with CAH per relative control, data were averaged for the relative controls or children with CAH, respectively. For Vocabulary, there were no significant differences between the CAH versus relative pairs, $t(22) = -.69$, $p = 0.50$, $d = 0.14$. However, children with CAH showed significantly reduced performance compared to controls on DSF, $t(22) = -4.01$, $p = 0.001$, $d = 0.78$; DSB, $t(22) = -2.93$, $p = 0.008$, $d = 0.84$; and DSC, $t(22) = -4.01$, $p = 0.000$, $d = 0.92$. See Table 4 for information on the relationships between the children in the matched pair analysis.

Discussion

Children with CAH, regardless of sex, showed significantly reduced performance compared to controls on DSF, DSB and DSC, with effect sizes of 0.57, 0.53 and 0.70, respectively. No group differences were seen in performance on the control measure of verbal intelligence, Vocabulary. Prior research also has found that verbal intelligence, and intelligence in general, is not altered in individuals with CAH as compared to their unaffected relatives (Berenbaum and Bryk, 2010). Thus, our sample seems typical of samples of individuals with CAH in this respect. In addition, the normal Vocabulary performance in the children with CAH indicates that the observed reduced Digit Span performance does not reflect a global reduction in cognitive performance. Data from the pair-wise matched analysis supported the findings in the main analyses, where children with CAH did not differ from controls on Vocabulary, but did show reduced Digit Span performance. The effect sizes for DSF, DSB and DSC in the matched analysis were large ($d = 0.78$, 0.84 and 0.92 , respectively).

We predicted reduced Digit Span performance in children with CAH based on their postnatal treatment with glucocorticoids. Working memory performance does not show a sex difference in typically developing children (Alloway et al., 2006), and there was no sex difference in working memory performance in our study. It is therefore unlikely that the CAH-related differences we observed in working memory performance were caused by androgen exposure. In contrast, as noted earlier, evidence from both rodents and humans suggests that glucocorticoid elevation can impair memory performance. In addition, in humans, this impairment has been seen with particular consistency for working memory as assessed with the Digit Span test (Elzinga and Roelofs, 2005; Schoofs et al., 2009; Vaz et al., 2011; Wolf et al., 2001). Thus, it is possible that postnatal glucocorticoid treatment of children with CAH may compromise their working memory ability. This might occur, in particular, because postnatal treatment sometimes produces elevated glucocorticoid levels (Auchus and Arlt, 2013; Debono et al., 2009; White and Speiser, 2000). Indeed, supraphysiological doses of glucocorticoids are sometimes necessary to normalize the high levels of adrenal androgens in patients with CAH (Speiser et al., 2010). Thus, elevated concentrations of glucocorticoids could be responsible for the reduced Digit Span performance found in our sample of children with CAH.

Although glucocorticoid excess is the most obvious explanation of reduced working memory in children with CAH, other factors might also have contributed. Research in adult rats sometimes has found memory-related impairment not only after experimentally

elevating glucocorticoid levels, but also after lowering them (McEwen and Sapolsky, 1995). Just as glucocorticoid treatment in individuals with CAH can sometimes be excessive; it also can sometimes be insufficient (Reisch et al., 2011). There has been less research exploring a potential relationship in humans between low glucocorticoid levels and memory functioning, although a possible inverted U-shaped relationship between glucocorticoids and human memory has been suggested (Belanoff et al., 2001). Thus, we cannot rule out the possibility that our results could relate to insufficient, as well as to excessive, postnatal glucocorticoid treatment. Quantification of exposures for individual patients might appear to be a way to determine if over-treatment or under-treatment predicts memory-related impairment. Reliable quantification is difficult, however, for example, because of changes in treatment dosages or patient compliance over time. In addition, some periods of development might be particularly important for glucocorticoid effects, but knowledge as to when these periods might occur is lacking. Individual differences in sensitivity to glucocorticoids also would complicate the interpretation of information on dosage.

Children with CAH generally receive glucocorticoid replacement as hydrocortisone in a dose of 12-15 mg/m²/day plus 0.1-0.15 mg/day of fludrocortisone for patients with salt-wasting CAH (Hughes, 2009). Analysis of dose differences within this narrow range was not possible as a marker of cumulative glucocorticoid exposure over time. Furthermore, formal statistical comparison between children with salt-wasting and simple-virilizing CAH was not possible in our study due to small numbers in the latter group. However, we did examine means and effect sizes for the two forms of the disorder (see Tables 2 and 3), which suggested greater Digit Span reduction in children with salt-wasting compared to simple-virilizing CAH. However, as mentioned, due to the small sample of children with simple-virilizing CAH, we are unable to reach firm conclusions.

Salt-wasting crises represent another possible contributor to reduced working memory performance in children with CAH. Children with the more severe, salt-wasting form of CAH are at risk of adrenal crises, the repercussions of which can include brain damage and cognitive impairment (White and Speiser, 2000). It is possible that the reduced Digit Span performance observed in our sample of children with CAH, particularly in those with the salt-wasting form of CAH, may have partly resulted from salt-wasting crises and the associated symptoms, such as hypoglycemia. Research has not directly addressed the cognitive consequences of salt-wasting crises and hypoglycemia in CAH. However, research on individuals with Type 1 Diabetes Mellitus has found that memory, particularly working memory, including as assessed with the Digit Span test, is vulnerable to negative effects of hypoglycemia (Bade-White and Obrzut, 2009). Thus, it is possible that hypoglycemia may have contributed to reduced working memory in children with CAH. The pattern of means and effect sizes in our sample suggests that the effects found in Digit Span performance might be greater in individuals with salt-wasting CAH than in those with simple-virilizing CAH. This evidence is consistent with a role of hypoglycemic episodes, since these would apply in particular to individuals with salt-wasting CAH, who are more cortisol deficient than individuals with simple-virilizing CAH, and so would be more at risk of experiencing hypoglycemia. However, our sample of children with simple-virilizing CAH was small ($n = 7$). Studies of larger samples of individuals with simple-virilizing CAH would be useful to

rigorously evaluate differences in memory performance related to different forms of the CAH disorder.

Although the precise causes of the reduction in Digit Span performance in children with CAH have yet to be determined, the reduction has potentially important implications. Working memory is necessary to acquire and perform a variety of other tasks, and working memory at age 5 has been found to be a better predictor of academic attainment at age 10, including both literacy and numeracy, than IQ (Alloway and Alloway, 2010). Working memory ability also predicts other higher order cognitive abilities, including mathematical skills (Alloway and Passolunghi, 2011) and prior studies have reported reduced mathematical-related performance in individuals with CAH (Baker and Ehrhardt, 1974; Perlman, 1973; Sinforiani et al., 1994). Interventions to improve working memory in healthy children have been found to improve mathematical reasoning (Holmes et al., 2009), attention (Thorell et al., 2009) and reading performance (Loosli et al., 2012). Thus, given the importance of working memory to cognitive and academic performance, and its amenity to training, educational interventions to improve working memory might be considered for children with CAH.

Summary and Conclusions

Our research suggests that children with CAH show reduced working memory as assessed with the Digit Span test. Future research could assess other aspects of working memory, in addition to Digit Span, as well as other cognitive abilities that relate to working memory, to assess the extent and implications of the current findings. Postnatal glucocorticoid excess appears to be the most likely explanation for the reduced working memory performance, although glucocorticoid insufficiency or the consequences of salt-wasting crises, such as hypoglycemia, also could be involved. Future research in individuals with CAH could investigate these possible causes too. Universal screening for CAH at birth and timely and carefully calibrated treatment might help guard against reduced working memory performance in individuals with CAH. In addition, prior evidence that individuals with CAH show reduced performance on quantitative tasks, and that training can improve working memory and associated aspects of cognitive performance, suggest that training to improve working memory performance might be useful for children with CAH.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- We found reduced short term memory assessed using Digit Span in children with CAH.
- General intelligence as assessed with vocabulary was not affected.
- The reduced memory scores could relate to glucocorticoid abnormality or treatment.
- Digit Span problems may relate to reported reduction of numeracy in children with CAH.

Figure 1.
Ms and SDs (+/-1) for DSF, DSB and DSC performance in children (boys and girls combined) with CAH and in controls

Table 1

Ms (and SDs) for Digit Span, age and Vocabulary in boys and girls with CAH and in unaffected controls

	CAH		Controls	
	Male (<i>n</i> =26)	Female (<i>n</i> =31)	Male (<i>n</i> =20)	Female (<i>n</i> =30)
Age	8.48 (1.25)	8.69 (1.37)	9.29 (1.56)	8.90 (1.70)
Vocab	10.50 (2.94)	9.35 (3.39)	10.65 (2.50)	10.70 (3.03)
DSF^a	7.81 (2.00)	7.58 (1.91)	8.30 (1.81)	9.30 (2.51)
DSB^a	5.50 (1.48)	5.58 (1.29)	6.05 (1.43)	6.47 (1.55)
DSC^a	13.31 (2.53)	13.16 (2.42)	14.35 (2.83)	15.77 (3.31)

Vocab, Vocabulary.

^aChildren with CAH performed significantly poorer compared to unaffected controls

Table 2

Ms (and *SDs*) for Digit Span in children with salt-wasting CAH, simple-virilizing CAH and controls (boy and girls combined)

		Salt-wasting CAH (<i>n</i> = 50)	Simple-virilizing CAH (<i>n</i> = 7)	Controls (<i>n</i> = 50)
DSF	<i>M (SD)</i>	7.60 (1.88) ^a	8.29 (2.36)	8.90 (2.28)
DSB	<i>M (SD)</i>	5.52 (1.40) ^a	5.71 (1.11)	6.30 (1.50)
DSC	<i>M (SD)</i>	13.12 (2.43) ^a	14.00 (2.65)	15.20 (3.18)

^aChildren with salt-wasting CAH performed significantly poorer compared to unaffected controls

Table 3

Effect sizes (d) for Digit Span performance when comparing control children to children with CAH and the salt-wasting and simple-virilizing forms of CAH

	CAH v Controls ($n = 57$ v 50)	Salt-wasting CAH v Controls ($n = 50$ v 50)	Simple-virilizing CAH v Controls ($n = 7$ v 50)
DSF	0.57	0.62	0.26
DSB	0.53	0.54	0.44
DSC	0.70	0.74	0.41

Table 4

CAH-relative pairs (including sex of child with CAH, their specific diagnosis and the sex and relationship status of their matched relative)

CAH-relative pair number	Child with CAH (sex, diagnosis)	Participating relative(s) (sex, relationship)
1	Male, salt-wasting CAH	Female, sibling Female, cousin
2	Female, salt-wasting CAH	Female, sibling Female, cousin
3	Female, salt-wasting CAH	Female, sibling
4	Female, simple-virilizing CAH Male, simple-virilizing CAH	Female, sibling
5	Male, salt-wasting CAH	Male, cousin
6	Female, simple-virilizing CAH	Male, sibling
7	Male, salt-wasting CAH	Female, sibling
8	Female, salt-wasting CAH	Female, adopted sibling
9	Male, salt-wasting CAH	Female, sibling
10	Male, salt-wasting CAH	Female, sibling Male, sibling
11	Female, salt-wasting CAH	Male, sibling
12	Female, salt-wasting CAH	Female, sibling Male, cousin
13	Female, salt-wasting CAH	Female, sibling
14	Male, salt-wasting CAH	Female, sibling Female, cousin Female, cousin
15	Male, salt-wasting CAH	Male, sibling
16	Female, salt-wasting CAH	Male, sibling
17	Female, salt-wasting CAH	Female, cousin
18	Female, salt-wasting CAH	Female, sibling
19	Male, salt-wasting CAH	Female, cousin Male, cousin Male, cousin

CAH-relative pair number	Child with CAH (sex, diagnosis)	Participating relative(s) (sex, relationship)
20	Male, salt-wasting CAH	Female, cousin
21	Male, salt-wasting CAH	Female, sibling Female, sibling
22	Female, salt-wasting CAH	Female, sibling
23	Male, salt-wasting CAH	Male, sibling