Executive functioning in children with congenital adrenal hyperplasia

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ABSTRACT

Congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency is a disorder characterized by impaired cortisol synthesis leading to excessive production of adrenal androgens. Prenatal and postnatal exposure to excess androgens may increase neural vulnerability to insult and affect cognitive functions, particularly dopamine-dependent neural circuits responsible for executive functioning (EF). Our study aimed to investigate relationship between more pronounced androgen exposure and EF-related behaviors in children with CAH, as well as sex differences in these associations. Parents of patients with CAH (n=41, boys=17, girls=24; age: M=8.41, SD=4.43) completed the Behavior Rating Inventory of Executive Function (BRIEF), a measure assessing behavioral manifestations of EF. Assessments of bone age advancement, a proxy of cumulative androgen exposure, were analyzed. Advanced bone age predicted more inhibition difficulties in boys but not in girls, and more difficulties in all other BRIEF domains in the total sample. Excessive androgen production affected EF such that more advanced bone age led to more EF-related difficulties. Sex differences in inhibition may result from estrogen exposure moderating the impact of androgens in girls but not in boys. Future interventions may include targeting EF in patients with CAH to enhance quality of life and reduce cognitive consequences associated with this disease.

Significance of this study

What is already known about this subject?

- Past studies support associations between prenatal testosterone exposure and EF difficulties, although similar associations are not found in girls.
- There are higher rates of attention-deficit hyperactivity disorder in children with CAH in boys compared to girls.
- One study demonstrated impairments in working memory in children with CAH independent of sex.

What are the new findings?

- Boys but not girls with more pronounced androgen effects had greater difficulties in inhibition.
- Higher bone age z-scores were associated with significantly greater EF-related behavioral difficulties in the total sample for all other areas of EF.
- In summary, more pronounced androgen exposure led to more EF-related behavioral difficulties in children with CAH, and sex differences were found such that androgen exposure was related to more inhibitory difficulties in boys with CAH but not in girls with CAH.

How might these results change the focus of research or clinical practice?

- Extends theory and research on effects of androgen production on cognitive functioning.
- Future interventions for cognitive functioning in CAH may include targeting EF difficulties in children with CAH to enhance quality of life and reduce cognitive consequences associated with this disease.
- Considering the effects of prenatal and postnatal glucocorticoid treatment on EF in children with CAH is a logical next step for future studies.

INTRODUCTION

Congenital adrenal hyperplasia (CAH) due to 21-hydroxylase enzyme deficiency is a disorder of adrenal steroid biosynthesis characterized by impaired cortisol synthesis leading to excessive production of adrenal androgens, and through aromatization, increased estrogen production. The forms of CAH, in order of decreasing enzyme severity, include the classic forms, salt wasting (SW) and simple virilizing (SV), and non-classic (NC) form (aka late onset). Classic CAH is the leading cause of ambiguous genitalia in the female newborn. In its most severe form (SW CAH), there is nearly complete obliteration of enzyme activity leading to cortisol and aldosterone deficiency. In SV CAH, patients may have 1–2% enzyme activity which allows for the production of aldosterone. The spectrum of NC CAH ranges from asymptomatic to clinical signs of increased androgen production.

Standard treatment in children with CAH is cortisol (hydrocortisone) replacement therapy. The recommended hydrocortisone dose in growing children is 10–15 mg/m^2/day.[1] Although

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prenatal and postnatal glucocorticoid treatment aims to decrease production of sex hormones, the adverse effects of exposure to elevated adrenal androgens are still evident despite adequate monitoring and patient compliance.[2] Interindividual variability in the cortisol pharmacokinetic parameters, glucocorticoid receptor sensitivity and the limitations of oral hydrocortisone therapy to achieve the circadian rhythm of cortisol secretion result in significant periods of hypocortisolemia and hypercortisolemia and hyperandrogenemia over the course of 24 hours in children with CAH.[3]

Exposure to excess adrenal androgens for both sexes, including testosterone during the prenatal and postnatal period, may modulate dopamine systems that shape behavioral manifestations of executive functioning (EF). EF are skills that relate to emotional control, working memory, organization and planning skills, and the ability to be cognitively flexible.[4] Prenatal exposure to excess testosterone may increase vulnerability of dopamine-sensitive areas to subtle insult and prenatal risk factors (eg, low birth weight) through promoting increased cell proliferation and death, slowing prenatal brain development, and increasing lateralization of brain function.[5] Postnatal androgen exposure activates maladaptive neural organizational patterns established prenatally that regulate dopamine synthesis, transport, and metabolism.[6] Animal studies have demonstrated that exposure to elevated androgen levels in postnatal development resulted in reduced dopamine innervation in the frontal cortex and deficits reminiscent of working memory difficulties seen in children with attention-deficit hyperactivity disorder (ADHD).[7]

Past studies support associations between prenatal testosterone exposure and EF difficulties, specifically impulsivity and inattention, in boys during childhood and young adulthood.[8 9] Similar associations were not found in girls,[8] suggesting sex differences in effects of androgen exposure on EF deficits such as inhibition. A further study of children with CAH found higher rates of ADHD (which can include EF difficulties such as inattention and impulsivity) in boys compared to girls.[10] Supporting EF difficulties in CAH, one study demonstrated impairments in working memory in children with CAH independent of sex.[11]

Based on previous research, our study aimed to investigate behavioral manifestations of EF in children with CAH. We hypothesized that children with disease that was poorly controlled with more pronounced androgen effects would have greater EF difficulties. In CAH, elevated adrenal androgens, through aromatization into estrogens, lead to increased growth velocity, rapid bone age maturation, early epiphysial closure, and short stature.[12] Bone age advancement was used as a proxy of disease control and cumulative androgen exposure. A parent rating inventory capturing behavioral manifestations of EF over a significant period (ie, 6 months) was used.

METHOD

Overview of procedures

Parents of patients with CAH (n=41, boys=17, girls=24; mean age at questionnaire: M=8.41, SD=4.43, range: 2.07–17.51 years; SW: n=23, SV: n=8, NC: n=10; mean daily hydrocortisone dose: M=11.51 mg/m^2/day, SD=5.85; 85% Caucasian; 3 Hispanic, 1 African-American, 2 biracial; majority middle-class socioeconomic status; no patients receiving special education at school) were receiving clinical care at the University of Minnesota and were administered measures at a check-up visit. Bone age assessments were collected at the same visit or within a year of the questionnaire visit. In conjunction with monitoring growth, 17-hydroxyprogesterone and androstenedione, change in bone age compared to chronological age is used to assess control of adrenal androgens in response to therapy. For routine care bone age estimation, standardized posterior–anterior radiographs of the left hand and wrist were obtained and the Greulich and Pyle method of comparing the subject's left-hand radiograph to controls was used in our study.[13] The bone age z-scores were then calculated using the bone age and the SD for each patient's sex and chronological age. All data from subjects were obtained in compliance with regulations of the University of Minnesota and the Helsinki Declaration.

Measures

To assess EF, parents completed the Behavior Rating Inventory of Executive Function (BRIEF), a measure assessing behavioral manifestations of EF across multiple domains.[4] The measure included 86 items separated into eight clinical and two validity scales. Five subscales (ie, Inhibit, Shift, Emotional Control, Working Memory, and Plan/Organize) and the Global Executive Composite (GEC, a total across subscales) were selected for this study. These subscales are present across age ranges and spanned across the preschool and school-age BRIEF.[4 14] Each item was rated on a 3-point scale (1=never, 2=sometimes, and 3=often), with higher scores reflecting less effective EF. Subscale scores are computed as t-scores of the mean of items within each subscale, with an average score of 50 and a SD of 15. The majority of our sample was not in the clinical range, although a small percentage demonstrated clinically significant scores on the BRIEF as evidenced by scores higher than 65 on the GEC (n=5, 12% of sample). These five patients were all boys (four SW and one SV) and had ages of ~3, 5 (three patients), and 14. The BRIEF has strong internal consistency and inter-rater and test–retest reliability.[4] This measure also shows strong ecological validity and construct validity,[4] and has been validated in preschool-age children to adults.[15]

Data analytic plan

Bone age advancement was standardized by calculating z-scores of bone age measurements. Profile analyses were conducted to examine difference between subscales on sex and bone age z-score. Analyses examining relationship between bone age z-score and EF were conducted using linear regressions. Sex differences were also investigated using linear regressions. Two-way interactions were decomposed and depicted by solving the regression equations to predict EF from bone age z-score for boys and girls.[16] Decomposition of significant two-way interactions is reported in the text.

RESULTS

There were no significant differences across sex for age: t=−1.47, p=0.15; bone age z-score: t=1.63, p=0.11; total daily hydrocortisone mg/m^2: t=−0.07, p=0.95; or

Table 1 Means, t-tests (sex) in children with congenital adrenal hyperplasia

	Total (n=41)		Boys (n=17)		Girls (n=24)		Sex difference	
	M	SD	M	SD	M	SD	t-Test (df)	p Value
Inhibit	49.93	13.00	52.53	16.06	48.08	10.30	1.08 (39)	0.29
Shift	46.90	9.73	49.71	12.88	44.92	6.28	1.58 (39)	0.12
Emotional	50.22	14.04	55.29	18.34	46.63	8.74	2.02 (39)	0.05
Working Memory	49.00	11.82	53.29	16.47	45.96	5.58	2.03 (39)	0.05
Plan/Organize	47.85	12.28	51.35	16.51	45.38	7.55	1.56 (39)	0.13
Global Executive Composite (GEC)	48.37	14.39	53.00	19.39	45.08	8.45	1.78 (39)	0.08

diagnosis: $\chi^2(2)=5.92$, p=0.052. There were no significant differences across diagnosis for sex: F=3.21, p=0.052; bone age z-score: F=0.54, p=0.59; or total daily hydrocortisone mg/m^2: F=0.03, p=0.973; GEC: F=0.92, p=0.41. There was a significant difference in diagnosis for age (F=4.74, p=0.015) such that patients with NC CAH (M=11.66, SD=4.62) were significantly older than classic CAH (SW: M=7.81, SD=4.25, d=0.87, r=0.40; SV: M=6.09, SD=2.40, d=1.51, r=0.60). The mean GEC of CAH children and each of the subscale scores were slightly lower but comparable to the sample of children on which norm-adjusted BRIEF scores were based (t=50.00), with lower scores indicating lower ratings for EF-related behavioral difficulties (t=48.37 vs t=50.00) (t=0.69, p=0.49). There were no significant differences in mean scores between sex across subscales (table 1).

Profile analyses (threshold: p=0.05) revealed no significant differences between sex (p=0.066) and bone age z-score (p=0.162) across the five subscales used. A two-way significant interaction with sex was found for inhibitory behaviors after controlling for the false discovery rate (FDR) (m=5) (Inhibit: B=−0.47, t=−2.77, ΔR^2=0.14, p=0.009, FDR α=0.010; Shifting: B=−0.07, t=−0.35, ΔR^2=0.003, p=0.725, FDR α=0.050; Emotional Control: B=−0.34, t=−2.07, ΔR^2=0.07, p=0.046, FDR α=0.020; Working Memory: B=−0.36, t=−2.01, ΔR^2=0.08, p=0.052, FDR α=0.030; Planning/Organization: B=−0.32, t=−1.74, ΔR^2=0.06, p=0.090, FDR α=0.040; GEC (analyzed separately): B=−0.32, t=−1.87, ΔR^2=0.06, p=0.070).[17] Decomposition of the interaction with inhibit revealed that higher bone age z-score was associated with significantly greater inhibitory difficulties in boys but not in girls (Inhibit: B=3.18, t=3.84, p<0.001 vs B=−0.95, t=−0.75, p=0.46) (figure 1).

To examine all other subscales, as well as the GEC, the sample was collapsed across sex. Higher bone age z-score was associated with significantly greater EF-related behavioral difficulties in the total sample in all other subscales after controlling for the FDR (m=4) (Shifting: B=0.43, t=2.95, ΔR^2=0.18, p=0.005, FDR α=0.025; Emotional Control: B=0.52, t=3.84, ΔR^2=0.27, p<0.01, FDR α=0.013; Working Memory: B=0.35, t=2.32, ΔR^2=0.12, p=0.026, FDR α=0.050; Planning/Organization: B=0.38, t=2.52, ΔR^2=0.14, p=0.016, FDR α=0.038), as well as the GEC (B=0.49, t=3.49, ΔR^2=0.24, p=0.0012).

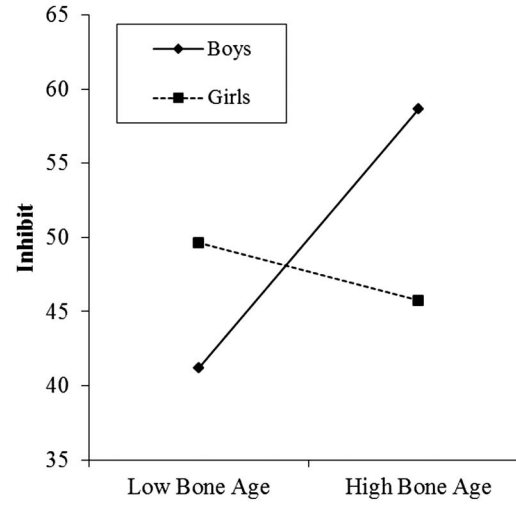

Figure 1 Bone age predicting inhibition in boys and girls.

DISCUSSION

We found that boys but not girls with more pronounced androgen effects (indicated by greater bone age z-scores) had greater difficulties in inhibition. Higher bone age z-scores were associated with significantly greater EF-related behavioral difficulties in the total sample for all other areas of EF. Our results were consistent with one study finding working memory difficulties in children with CAH.[11] Reorganizational effects of prenatal exposure to testosterone on dopamine-dependent neural circuits responsible for EF,[5] as well as postnatal activating effects,[6] may lead to greater EF difficulties, as manifested in the behavior of children with CAH. Moreover, prenatal exposure to testosterone may lead to prolonged development of the dopaminergic system, leading to greater vulnerability to environmental insults (eg, toxins) and structural abnormalities.[5] There was no difference in bone age z-scores across diagnoses, which may be explained by the fact that all NC CAH participants in this study were diagnosed at a later age due to advanced bone age and required hydrocortisone treatment.

Our findings are in line with a previous study finding higher rates of ADHD (which includes EF difficulties such as inattention and impulsivity) in boys with CAH compared to girls with CAH.[10] Our results are also consistent with previous studies supporting associations between prenatal

testosterone exposure and difficulties inhibiting impulses in boys but not in girls during childhood.[8] For certain types of EF difficulties, such as inhibition, prenatal and postnatal effects of other hormones, such as estrogen, may play a role in shaping behavioral manifestations of EF. Estrogen has been found to counteract the effects of testosterone during prenatal development,[18] and inhibition may be particularly affected by estrogen compared to other EF domains, such as working memory or shifting.[19] Estrogen has been found to modulate inhibitory control in women compared to men,[19] suggesting postnatal effects of estrogen on maintaining inhibitory control in girls but not in boys despite higher androgen exposure in both sexes.

Considering the effects of prenatal and postnatal glucocorticoid treatment on EF in children with CAH is a logical next step for future studies. All participants were on glucocorticoid therapy and the majority were receiving hydrocortisone therapy during our study, which itself may lead to impairments in EF (eg, working memory, inhibition, and planning in one study).[20] Interindividual variability in cortisol pharmacokinetic parameters, glucocorticoid receptor sensitivity, and limitations of oral hydrocortisone therapy in matching circadian rhythms of cortisol secretion may complicate the investigation of the impact of hydrocortisone on EF in children with CAH.

Although literature is strongly supportive of the causative link between increased androgen exposure and negative neuropsychological outcomes, this was a cross-sectional study and alternative explanations should be explored in future studies. For example, it may be proposed that advanced skeletal age could be the result, rather than the cause, of decreased EF. For example, greater EF difficulties may lead to decreased adherence to a strict medication regimen intended to delay advanced bone age, which may then lead to greater advancement of bone age. Another example could be a poorly organized family structure that negatively influences development of effective EF in the child and compliance with medication. Exploring causal directions for the link between decreased EF and advanced bone age may help clarify these relations.

This study extends theory and research on effects of androgen production on cognitive functioning. Our study also used parental rating scales to capture behavioral manifestations of EF over a period of time, avoiding potential confounding effects of fluctuating hormone levels on EF. More pronounced androgen exposure led to more EF-related behavioral difficulties in children with CAH, and sex differences were found such that androgen exposure was related to more inhibitory difficulties in boys but not in girls with CAH. Future interventions for cognitive functioning in CAH may include targeting EF difficulties in children with CAH to enhance quality of life and reduce cognitive consequences associated with this disease.

Competing interests None declared.

Ethics approval This study has been approved by the University of Minnesota IRB prior to data collection.

Provenance and peer review Not commissioned; externally peer reviewed.

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