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Glucocorticoid Dose and Type are Associated with Depression Scores in Youth with Classical Congenital Adrenal Hyperplasia

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What is already known on this topic?

Patients with classical congenital adrenal hyperplasia (CAH) exhibit a higher lifetime prevalence of depression, increased prevalence of anxiety in youth, adult-onset mood disorders, personality disorders, alcohol misuse and rates of adult suicidality. Additionally, structural brain alterations have been observed in patients with CAH, with relevance in emotional dysregulation and mood disorders.

What this study adds?

Both glucocorticoid dose and type, specifically dexamethasone, were found to be associated with higher depression scores on the Children's Depression Inventory (CDI) in youth with CAH. In addition, glucocorticoid dose predicts CDI scores (total score and multiple subscales).

ABSTRACT

Objective: Adults with classical congenital adrenal hyperplasia (CAH) exhibit a higher lifetime prevalence of depression, but little is known about onset or etiology of mood disorders in this population. We therefore aimed to assess depression in youth with CAH, compared to controls, using the Children's Depression Inventory (CDI).

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Methods: Youth with classical CAH due to 21-hydroxylase deficiency and age- and sex-matched controls completed the CDI and had analyte and genetic testing.

Results: A total of 31 patients with CAH and 36 controls were included. Youth with CAH exhibited CDI measures that differed significantly by glucocorticoid dose and type. For glucocorticoid dose, significant correlations were found between CDI total T-score ($r=0.42$, $p<0.05$), as well as multiple subscores. Dose also predicted total T-score ($\beta=1.75$), Emotional-Problems ($\beta=1.41$), Negative-Self-Esteem ($\beta=1.91$), Functional-Problems ($\beta=1.90$), Ineffectiveness ($\beta=1.56$), and Interpersonal-Problems ($\beta=2.11$) (all $p<0.01$). For glucocorticoid type [dexamethasone $n=7$, hydrocortisone (HC) $n=24$], scores were higher in patients treated with dexamethasone for total T-score [dexamethasone: 59 (53.5-72), HC: 50 (43.75-55.75)], Emotional-Problems [dexamethasone: 63 (51.0-67.0), HC: 45 (42.0-56.5)], and Negative-Self-Esteem [dexamethasone: 53 (50.0-73.5), HC: 44 (44.0-51.0)] (all $p<0.05$).

Conclusion: Higher HC doses and use of dexamethasone were both found to be associated with higher CDI scores in children and adolescents with classical CAH.

Keywords: Depression, 21-hydroxylase deficiency, congenital adrenal hyperplasia

Introduction

Classical congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency (21-OHD) is characterized by cortisol and aldosterone deficiencies necessitating lifetime glucocorticoid replacement (1). Patients with classical CAH exhibit a higher lifetime prevalence of depression, as well as an increased prevalence of anxiety in youth and adult-onset psychiatric disorders (2,3). In addition, patients with CAH exhibit structural brain alterations, including prefrontal cortex, amygdala, and hippocampal volumes, as well as altered white matter microstructure (4,5,6). Differences in these regions have shown relevance to emotional dysregulation and mood disorders, especially in adolescent populations (7).

Despite these observations, there are few studies on mood disorders in youth with CAH. The timeline for the emergence of mood symptoms in patients with CAH is unclear, with conflicting studies on depression in pediatric patients with CAH (8,9). In addition, cortisol replacement may transition from immediate-release hydrocortisone (HC) to longer-acting glucocorticoids when patients near completion of growth, with little known about the relationship between glucocorticoid type, dose, and mood disorders. Thus, we sought to compare depression survey scores in youth with and without CAH, and to examine relationships with biochemical, genetic, and clinical markers in youth with CAH.

Methods

Participants filled out the Children's Depression Inventory (CDI, 2nd Edition) with higher scores quantifying increased depressive symptomatology (10). We report CDI T-scores which are standardized for age; T-scores above 60 are considered above average. In patients with CAH, medical history was collected from the medical record and genotyping performed as described previously (11). All patients with CAH had 21-OHD as confirmed by biochemical testing and/or genotyping of *CYP21A2*. Age-

and sex-matched controls were recruited via flyers posted at the Children's Hospital Los Angeles and University of Southern California. Written informed consent was obtained from parents/legal guardians of participants <18 years old and participants >14 years old. All minors up to 14 years of age gave assent. Glucocorticoid daily dosing was recorded as HC equivalents ($HCE=dexamethasone\ dose \times 60$) (1).

Statistical Analysis

Data were analyzed using R (v4.0.3, R Foundation for Statistical Computing, Wirtschaftsuniversität Wien, Welthandelsplatz 1 1020, Vienna, Austria). Group comparisons were assessed using chi-square, with Mann-Whitney U tests for CDI scores. Fisher's exact test was used for group comparisons of genetics due to small sample size. Pearson correlations were used to assess associations between continuous variables. CDI scores are reported as median with interquartile ranges unless otherwise noted. Multiple linear regression analysis was used to examine the relationship between glucocorticoid usage and CDI scores, independent of disease severity.

Results

Study Population

The study included 31 youth with CAH and 36 healthy controls (8-18 years; age- and sex-matched) (Table 1). All patients on dexamethasone had been switched from HC due to poor disease control secondary to medication non-compliance, and average duration of dexamethasone therapy prior to the study visit was 29.3 ± 22 months.

Glucocorticoid Dose and Depression in CAH

Group comparisons between CAH and control youth showed no overall differences in CDI (total T-scores or subscores). However, within the CAH group, glucocorticoid dose as HCE was positively correlated with CDI total T-score ($r=0.42$, $p<0.05$) (Figure 1), Negative-Self-Esteem ($r=0.57$, $p<0.001$), Functional-

Problems ($r=0.43$, $p<0.05$), Ineffectiveness ($r=0.36$, $p<0.05$), and Interpersonal-Problems ($r=0.37$, $p<0.05$). Average glucocorticoid dose for patients with CDI total T-score ≥ 60 was 18.1 ± 6.33 mg/m²/day.

When controlling for markers of disease severity [bone age standard deviation (SD), highest 17-hydroxyprogesterone (17-OHP) at diagnosis, waist-to-height ratio (WHR)] by including them in the regression model, glucocorticoid dose at the study visit still predicted total T-score ($\beta=1.75$, $p<0.001$), Emotional-Problems ($\beta=1.41$, $p<0.001$), Negative-Self-Esteem ($\beta=1.91$, $p<0.001$), Functional-Problems ($\beta=1.90$, $p<0.001$), Ineffectiveness ($\beta=1.56$, $p<0.01$), and Interpersonal-Problems ($\beta=2.11$, $p<0.001$).

Table 1. Study participant characteristics			
	CAH (n=31)	Controls (n=36)	p
Sex, female	18 (58.1)	21 (58.3)	1.0
Age, years	12.6±3.2	12.9±2.8	0.5
Range	8.4-18.9	8.7-18.9	
CAH phenotype			
Salt-wasting	29 (93.5)	--	
Simple-virilizing	2 (6.5)	--	
CAH genotype			
Null (0% enzymatic activity)	14 (45.2)	--	
Non-null:	--	--	
A (<2% activity)	11 (35.5)	--	
B (3-7% activity)	5 (16.1)	--	
Treatment			
Dexamethasone	7 (22.6)	--	
Hydrocortisone	24 (77.4)	--	
Glucocorticoid dose, mg/m ² /day	16.3±4.38	--	
Concurrent fludrocortisone	--	--	
Highest 17-OHP at birth, nmol/L	480.3 (622.1)	--	
Highest 17-OHP at birth, ng/dL	15200 (19689)	--	
17-OHP at visit, nmol/L	67.14 (139.7)	--	
17-OHP at visit, ng/dL	2125 (4420.5)	--	
Total testosterone, nmol/L	2.51±2.45	--	
Total testosterone, ng/dL	72.3±70.8	--	
Androstenedione, nmol/L	2.83 (3.94)	--	
Androstenedione, ng/dL	81 (113)	--	
Plasma renin activity, ng/mL/h	3.52±2.89	--	
Bone age, SD	0.87±1.30	0.16±0.62	0.01
Waist-to-height ratio	1.59±0.83	0.82±0.95	0.001
Mean±SD, Median (IQR), or n (%).			
CAH: congenital adrenal hyperplasia, 17-OHP: 17-hydroxyprogesterone, SD: standard deviation, IQR: interquartile range			

A sensitivity analysis of the subset of patients on HC, without any history of dexamethasone usage, showed that glucocorticoid dose still predicted the CDI total T-score ($\beta=1.89$, $p<0.05$). There was no group differences between CDI total T-score or its subscores with patients with ambiguous genitalia ($n=17$) at birth.

Glucocorticoid Type and Depression in CAH

When patients with CAH were stratified by glucocorticoid type [dexamethasone ($n=7$), HC ($n=24$)], those on dexamethasone exhibited higher scores on the CDI (Figure 2) compared to those on HC. There was no relationship between duration of

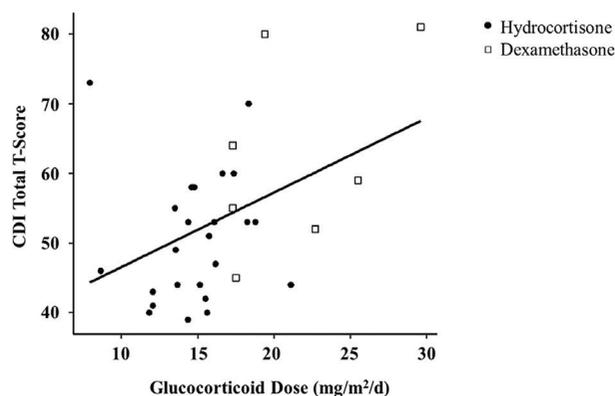


Figure 1. Depression associated with GC dose and type. Glucocorticoid dose (mg/m²/day; dexamethasone converted to hydrocortisone equivalents) was positively associated with CDI Total t-scores for youth with classical CAH ($r=0.42$, $p<0.05$)
 CDI: Children's Depression Inventory, GC: glucocorticoid, CAH: congenital adrenal hyperplasia

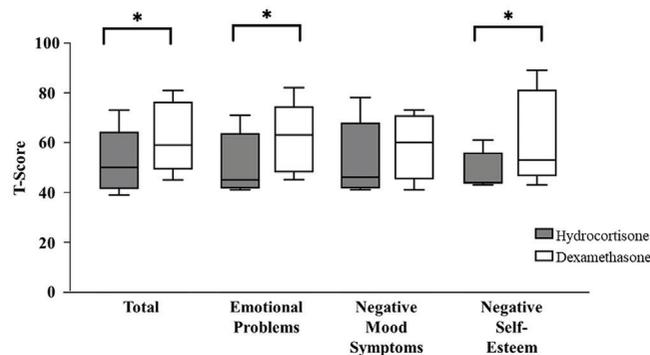


Figure 2. CDI T-scores by GC type. Youth with classical CAH on dexamethasone treatment (white) exhibit higher CDI total T-scores, as well as subset scores for Emotional Problems and Negative Self-Esteem, compared to youth with CAH on hydrocortisone (gray). * $p<0.05$
 CDI: Children's Depression Inventory, GC: glucocorticoid, CAH: congenital adrenal hyperplasia

dexamethasone treatment and CDI scores. Statistical differences between dexamethasone- and HC-treated groups were reported for total T-score [dexamethasone: 59 (53.5-72.0), HC: 50 (43.8-55.8), $p<0.05$], Emotional-Problems [dexamethasone: 63 (51.0-67.0), HC: 45 (42.0-56.5), $p<0.02$], and Negative-Self-Esteem [dexamethasone: 53 (50.0-73.5), HC: 44 (44.0-51.0), $p<0.05$].

When controlling for markers of disease severity [bone age SD, highest 17-OHP at diagnosis, WHtR], patients on dexamethasone had higher total T-scores ($\beta=18.5$, $p<0.001$) compared to those taking HC.

Genetics and Depression in CAH

Null and non-null patients did not exhibit differences in CDI total score ($p=0.9$), subscores, GC dosage ($p=0.34$) or the GC treatment type that they were receiving ($p=0.4$).

Discussion

The main findings of our study show that both glucocorticoid dose and type were associated with higher depression scores on the CDI in youth with classical CAH. Our findings support prior observations that increased glucocorticoid doses are associated with higher CDI scores in CAH adolescents (12). Notably, we found the use of dexamethasone for glucocorticoid replacement to be associated with higher depression scores in youth with classical CAH.

Dexamethasone use could select for patients with a high degree of disease severity, poor control of disease, and/or non-adherence to medication use. A major question is whether high GC dose and/or type directly leads to depression symptoms in CAH, or reflects disease severity that can increase the propensity for psychiatric morbidity. As was seen in our cohort of patients, dexamethasone is often given to older adolescents and adults with CAH who struggle with hormonal control as an effective, potent, long-acting glucocorticoid for suppressing the excess production of adrenal androgens. However, dexamethasone has major physical side effects, with long-term use potentially leading to modification of the hypothalamic–pituitary–adrenal axis in psychiatric etiology, a direct effect on emotion regulatory networks, and/or the potential to lead to higher psychiatric morbidity and decreased quality of life (1,13). Confounders of disease severity in youth with CAH on dexamethasone may also include altered brain structural volumes with white matter changes that could put them at risk of increased psychiatric disorders (5,7).

To further study disease severity, we examined genotype and showed no significant relationship with depression or glucocorticoid dose/type. We and others have also found that 17-OHP values, another indicator of disease severity, are a poor marker for anxiety or depression symptoms in CAH. Impaired

mental health could inherently impact hormonal control and thereby the intensity of glucocorticoid treatment needed in the patient. In our cross-sectional study, however, our findings suggest that disease severity is less likely to be a main contributor to the differences seen in depression scores in CAH youth (8).

There may be inherent differences in CAH youth that make them susceptible to depression, and it is also possible that depression and stress lead to increased ACTH levels, thereby leading to increase in androgens and sub-optimal disease control, necessitating higher HC doses or switching to dexamethasone, as seen in our patient population. These changes likely occur over the lifetime, and the adolescent population studied may be too young to significantly see these effects compared to controls. Brain structural changes in CAH patients start as early as *in utero* due to displaced hormonal pathways. Such structural changes, nevertheless, likely do not translate to differences in psychiatric disorders until late adolescence, which would be an older cohort than our patients studied (7). To assess inherent susceptibility to depression versus effects of medication on mood in this patient population, future longitudinal research is merited to examine patients with CAH as their own controls, thereby monitoring CDI values throughout adolescence and young adulthood with a focus on changes in glucocorticoid dosing.

Study Limitations

Our study had some other limitations, including a relatively small sample size, and two patients slightly older than 17 years, the upper limit of validity for the CDI survey. It would be useful to study a larger number of patients with CAH treated with dexamethasone, including a broader age range and longitudinal measures of glucocorticoid dosing and neuroimaging. The majority of studies examining glucocorticoid and CDI-based evaluations of depression are related to anti-inflammatory treatments in other conditions, with dexamethasone attributed to depression scores in conditions such as pediatric inflammatory bowel disease (14). As studies continue to emerge in patients with primary adrenal insufficiency, where glucocorticoid treatment is used for replacement of cortisol deficiency, our understanding of the relationship between lifelong cortisol replacement and depression will improve.

Conclusion

In conclusion, our findings suggest that both the dose and type of glucocorticoid the patient is taking are associated with higher scores for depression in youth with classical CAH. Further studies are merited to assess the frequency and natural history of clinical depression in adolescents and young adults with CAH, especially in patients utilizing dexamethasone for glucocorticoid replacement therapy. Regardless of etiology, the utilization of dexamethasone should be reconsidered as novel therapeutics

emerge, for example modified-release HC, and corticotropin-releasing hormone receptor antagonists, for the optimal replacement of cortisol and control of excess adrenal androgens.

Ethics

Informed Consent: Informed consent for publication was obtained from the patient's parents.

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Footnotes

Authorship Contributions

Concept: Mark Chih-Wei Liang, Megan M. Herting, Mitchell E. Geffner, Mimi S. Kim, Design: Mark Chih-Wei Liang, Megan M. Herting, Mitchell E. Geffner, Mimi S. Kim, Data Collection or Processing: Mark Chih-Wei Liang, Nicole Fraga, Nare Minaeian, Megan M. Herting, Tania A. S. S. Bachega, Analysis or Interpretation: Mark Chih-Wei Liang, Nicole Fraga, Nare Minaeian, Megan M. Herting, Tania A. S. S. Bachega, Literature Search: Mark Chih-Wei Liang, Writing: Mark Chih-Wei Liang, Nicole Fraga, Nare Minaeian, Megan M. Herting, Mitchell E. Geffner, Mimi S. Kim.

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