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Screening for Anxiety and Depression in Children with Congenital Adrenal Hyperplasia

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What is already known on this topic?

Congenital adrenal hyperplasia (CAH) is a chronic genetic condition that has been associated with behavioral mental health changes due to its chronic nature and exposure to elevated androgen levels.

What this study adds?

After undergoing validated mental health screening, children and adolescents with CAH may not present with an increased prevalence of anxiety and depression as prior studies may suggest.

Abstract

Objective: Congenital adrenal hyperplasia (CAH) is an inherited condition in which individuals require multiple daily doses of medication and are at risk for life-threatening adrenal crisis. The chronic nature and severity of CAH place children at risk for psychiatric morbidity. The aim was to assess the degree of anxiety and depressive symptoms in children with CAH.

Methods: A cross-sectional cohort study of children (7-17 years) with CAH and their caregivers were recruited between May and December 2021. Children with hypothyroidism (HT) and their caregivers served as unaffected controls. Validated mental health questionnaires [Children's Depression Inventory 2 Self Report-Short (CDI-2), Screen for Child Anxiety Related Disorders (SCARED), Patient Health Questionnaire modified for Adolescents (PHQ-A); self and proxy] were completed by participants at one clinic visit. Higher scores indicated greater symptoms of anxiety and depression.

Results: A total of 60 children and 56 parents participated. Among the children 34 had CAH (68% female, mean age 11.41 ± 2.5, CAH duration 8.5 ± 4.1) and 26 had HT (73% female, mean age 12.7 ± 2.9 years, HT duration 6.0 ± 4.2 years). There was no increase in anxiety and depression symptoms in children with CAH compared to controls. In sub-analyses, children with CAH and controls reported a greater number of anxiety and depression symptoms than their caregivers on the SCARED and CDI-2, respectively. There was no association between adrenal control and the degree of anxiety or depression symptoms.

Conclusion: Children with CAH do not have more symptoms of anxiety or depression compared to controls. Child and caregiver-proxy responses lack agreement, suggesting that children with CAH may continue to benefit from routine mental health evaluation, regardless of voiced caregiver concern.

Keywords: Anxiety, depression, congenital adrenal hyperplasia

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Introduction

Mental health has become a greater focus in the management of pediatric chronic illness in the last decade, especially as children with chronic conditions are living longer lives and there is an emphasis on improving quality of life (1,2). There has subsequently been a move to integrate mental health assessment and treatment into routine care. Studies thus far have suggested that children with chronic illness present with higher levels of depressive symptoms than healthy peers and that the degree of depressive symptoms can differ between different chronic illnesses (3). Similarly, anxiety is prevalent in those with chronic illness, and children with anxiety and a physical illness may present with more emotional and functional impairment than children with anxiety who do not have a physical illness (4). Research groups have explored the relationship between mental health and pediatric chronic disease in many conditions, such as juvenile idiopathic arthritis and inflammatory bowel disease (5,6). However, there has been limited research into mental health in the pediatric congenital adrenal hyperplasia (CAH) population (7,8,9).

CAH is an inherited, life-long condition that is most commonly caused by a deficiency in the 21-hydroxylase enzyme. This enzyme deficiency disrupts the steroid biosynthesis pathway by decreasing cortisol production and upregulating levels of 17-hydroxyprogesterone (17-OHP). Elevations in 17-OHP shift the pathway towards increased androgen synthesis. Classical and non-classical CAH differ in the degree of enzyme deficiency. Classical CAH presents as either salt-wasting or simple virilizing types. Salt-wasting CAH, accounting for approximately 75% of classical cases, is the most severe form of CAH as it is also due to suboptimal aldosterone production which, without treatment, leads to life-threatening hyponatremia and hyperkalemia (10). Simple virilizing CAH does not present with a significant degree of mineralocorticoid deficiency but does present with considerable elevations in androgen synthesis, leading to genital atypia in biological females. Non-classical CAH is the least severe form because of a milder enzyme deficiency and can present in childhood with premature adrenarche.

CAH often involves the administration of multiple daily medications, in some cases from birth. Since individuals with CAH have glucocorticoid deficiency and a degree of mineralocorticoid deficiency, they remain at risk for life-threatening adrenal crisis if medication is not taken as directed. CAH, more commonly classical CAH, leads to excess androgen production and, therefore, infant girls may present with varying degrees of genital atypia. Moreover, as children with CAH develop, growth acceleration and pubertal advancement may occur at earlier stages, especially if they are not in optimal adrenal control. Given the chronic nature, severity and physical stigmata of CAH, individuals are at risk for psychiatric morbidity.

Prior studies have largely been limited to the adult CAH population. Men with CAH have been found to have increased rates of psychiatric disorders and suicidality, especially in those who experienced a delayed diagnosis of CAH (11). Women have been noted to have increased anxiety, and women with classical CAH (particularly, simple virilizing CAH) have double the risk of having a psychiatric diagnosis compared to age-matched controls (7). Review of the literature has found few dedicated pediatric studies evaluating mental health in children with CAH and conclusions have been variable (7,8,9). As such, there remains a need to further characterize mental health concerns in the pediatric CAH population.

The aim of this study was to assess the degree of anxiety and depression symptoms in children and adolescents with CAH using validated mental health questionnaires during a routine follow-up visit.

Methods

Participants

Children diagnosed with CAH or hypothyroidism (HT) and who were between the ages of 7-17 years and their respective caregivers were eligible for this single-center, prospective, observational cohort study. All the prospective participants with CAH had 21-hydroxylase deficiency. Sex of children was specified by karyotype analysis in those found to have atypical genitalia only. To the best of our knowledge, all children were raised in accordance with their chromosomal sex. A non-CAH control group was deemed necessary given the baseline mental health concerns stemming from the Coronavirus disease-2019 (COVID-19) pandemic, which was concurrent with the study period.

Children with HT (congenital or autoimmune) were chosen as the control group as they also have a chronic illness, require daily administration of medication, and have frequent medical visits and laboratory assessments, similar to children with CAH. In addition, children with HT have a bimodal age of presentation similar to CAH; congenital HT and classical CAH are often diagnosed in the newborn period and autoimmune HT and non-classical CAH are diagnosed in later childhood. However, unlike the CAH population, children with HT do not share the added stressors associated with physical stigmata (from hyperandrogenism or precocious puberty) and adrenal crisis

(requiring glucocorticoid stress-dosing and hospitalization). All children with HT were biochemically euthyroid at the time of questionnaire administration.

Participants were recruited from the pediatric endocrinology and urology clinics at NewYork-Presbyterian Hospital/Weill Cornell Medical Center (NYPH/WCMC). NYPH/WCMC is one of eight CAH Comprehensive Care Centers in the United States. Study assessments were completed over seven months from May 2021 to December 2021. Child and caregiver participants were excluded if unable to read English and if child participants had another chronic illness (diabetes or nephropathy) or malignancy.

A total of 116 participants (60 children and 56 caregivers) completed questionnaires on anxiety and depression symptoms. Two caregivers completed separate proxy forms as they had two children with CAH. One caregiver did not complete proxy forms for their two children with CAH.

Data Collection

Written consent was obtained from caregivers and written assent from child participants. All caregivers completed a demographic questionnaire. One-time questionnaires were completed at a single routine clinic visit. Children completed questionnaires privately, and all children ages 7-11 years were offered help in reading and clarifying questions. Intelligence levels were not separately measured in child participants but all children, to the best of our knowledge, were in his or her appropriate grade level, on discussion with the caregivers. Children were told that if there were concerns of harm to self or others, confidentiality would be broken and parents and appropriate individuals would be notified.

Upon completion, child questionnaires were scored immediately. Higher scores indicated a greater number of symptoms of anxiety or depression. A risk assessment flowsheet, including need for emergency room assessment, was used if acute safety risk (acute suicidality) was a concern. Appropriate community resources were given to children and caregivers for further mental health evaluation. All child participants received a $10 electronic gift card. This study was approved by the Weill Cornell Medicine Institutional Review Board, approval #20-04021748, date: 22.02.2022.

Measures

Children completed age-appropriate questionnaires on anxiety and depression. All caregivers completed an associated proxy questionnaire.

Children's Depression Inventory 2 Self Report-Short (CDI-2) (12): A 12-item self-report assessing signs of depression and validated for ages 7-17 years and takes approximately five minutes to complete. A modified T-score of ≥60 ("at-risk") may indicate the presence of a depressive disorder.

Screen for Child Anxiety Related Disorders (SCARED) (13): A 41-item self-report screening for anxiety disorders and validated for ages 8-18 years, which takes approximately 10 minutes to complete. It includes five subscales: *panic disorder or significant somatic symptoms, generalized anxiety disorder, separate anxiety disorder, social anxiety disorder* and *significant school avoidance*. A total score of ≥25 ("at-risk") may indicate the presence of an anxiety disorder.

Patient Health Questionnaire modified for Adolescents (PHQ-A) (14): A 9-item measure assessing for symptoms of depressive disorders, validated for ages 11-17, which takes approximately two minutes to complete. A total score of ≥10 ("at-risk") has good sensitivity for major depressive disorder. Suicide risk is screened with Yes/No questions.

Caregivers were given proxy forms of all the child questionnaires.

Pre-pandemic General Population Normative Data: The data was used and available for the SCARED (13) and CDI-2 (12).

SCARED Normative Data: Participants included 635 healthy young people (7 to 18 years old) and parent dyads and questionnaires were completed before 2019.

CDI-2 Normative Data: Participants included up to 1,100 healthy young people (7 to 17 years old) and parent dyads. Data based on participant age and gender were available.

PHQ-A normative data was also available but our study's sample size was insufficient to draw meaningful conclusions.

Adrenal Control

Adrenal control was based on 17-OHP values obtained over the prior 12-month period. Levels were drawn 1-2 hours after a morning hydrocortisone dose (normal practice at this center). Adrenal control was determined if participants had at least four 17-OHP levels in the prior twelve-month period. "Good" control was defined as 17-OHP < 1.000 ng/dL greater than or equal to 75% of the time, "moderate" if 17-OHP < 1.000 ng/dL more than 25% and less than 75% of the time, and "poor" if 17-OHP < 1.000 ng/dL less than or equal to 25% of the time."

Statistical Analysis

Descriptive statistics were used to describe the cohort of patients using n (%) and mean, standard deviation, median, interquartile range for categorical and continuous factors. Chi-square test or Fisher's exact test was used to compare the proportion of "at-risk" individuals between CAH and HT children. Wilcoxon rank sum test was used to compare raw scores from each questionnaire (SCARED, CDI-2, and PHQ-A) between children with CAH and HT, as well as their caregivers. Kruskal-Wallis test was used to compare raw scores of each questionnaire across different disease classifications (CAH: salt-wasting, simple virilizing, non-classical) or adrenal control (poor, fair, good). When comparing the general population to our cohort of CAH and HT children, a t-test was used. Linear mixed modelling was used to determine difference in scores on the questionnaires between children and caregivers.

All p-values were two-sided with statistical significance evaluated at the 0.05 alpha level. Ninety-five percent confidence intervals for all parameter estimates of interest were calculated to assess the precision of the obtained estimates. All analyses were performed in R version 4.0.5 (R Foundation for Statistical Computing, Vienna, Austria).

For analyses pertaining to adrenal control, patients included had four 17-OHP completed at NYPH/WCMC. Patients who completed 17-OHP levels at a different hospital were removed.

Results

Baseline Characteristics

Baseline characteristics are summarized in Table 1. Sixty children, ages 7-17 years, completed an anxiety and/or depression questionnaire based on age eligibility. Fifty-eight parent participants completed an anxiety and/or depression proxy questionnaire (Table 2).

Participant Anxiety

Of the children who completed the SCARED (CAH n = 30, HT n = 25), there was no difference in total scores between the CAH and HT groups (p = 0.2). Similarly, there was no difference in at-risk scores between the CAH and HT groups (p = 0.4), scoring "at risk" in 33% and 44%, respectively.

Seven children in each group had a history of anxiety based on caregiver report, and the difference in social anxiety scores was not significant (p = 0.6). There was no difference in scores among the other subscale categories.

Table 1. Child participant characteristics

Child characteristic	CAH (n = 34)	Hypothyroidism (n = 26)
Disease classification, n (%)	Classical: 23 (68) Non-classical: 11 (32)	Congenital: 7 (27) Autoimmune: 19 (73)
Sex, %		
Male	32	27
Female	68	73
Mean ± SD age at assessment, years (SD)	11.41 ± 2.54	12.68 ± 2.91)
Median age at diagnosis, years (IQR)	0.04 (0.00, 7.16)	6.9 (0.4, 11.9)
Mean ± SD duration of condition, years	8.48 ± 4.12	5.99 ± 4.21
Race/ethnicity, %		
Non-hispanic white	67.6	53.8
Hispanic	14.7	23.1
Asian	8.8	15.4
Multiracial	2.9	3.8
Other	5.9	3.8
Insurance type, %		
Private	79	96
Public	21	4
Family income, %		
< $100,000	26.5	19
≥$100,000	58.8	73
Declined	8.8	8
Unknown	5.9	0
Reported prior history of anxiety or depression, n (%)	7 (22)	5 (19)

SD: standard deviation, IQR: interquartile range, CAH: congenital adrenal hyperplasia

Participant Depression

Sixty children completed the CDI-2 (CAH n = 36, HT n = 26) and there was no difference in total T-scores (p = 0.4) or at-risk scores (p = 0.5). Caregivers identified three children with CAH and two children with HT as having a history of depression; there was no difference in total T-scores in this subset (p > 0.9).

Twenty-nine children completed the PHQ-A (CAH n = 13, HT n = 16). Children in the CAH group were found to have lower mean total scores than the HT group (p = 0.038) but had no difference in at-risk scores (p = 0.4). Of note, 87.5% (14 of 16) children in the HT group had a history of autoimmune HT. One child was found to have suicidal ideation in the HT group.

Child Versus Caregiver Proxy Scores

As seen in Figure 1, differences were noted between child and caregiver scores on all questionnaires. After evaluating SCARED mean total scores, both the CAH (p < 0.001) and HT (p < 0.001) groups showed that children reported a greater number of anxiety symptoms than reported by their respective caregivers. Similarly, children in both groups reported a greater number of depression symptoms than reported by their respective caregivers (CAH p = 0.002 and HT p < 0.001). With PHQ-A scores, there was no significant

Table 2. Parent participant characteristics

Parent characteristic	CAH (n = 32)	Hypothyroidism (n = 26)
Sex, %		
Male	19	23
Female	81	77
Mean age at assessment, years (SD)	45 (6)	47 (6)
Highest level of education, n (%)		
High school or less	5 (16)	1 (3)
Associate or bachelor	16 (50)	10 (39)
Master/professional	11 (34)	15 (58)
Marital status, n (%)		
Divorced/separated/widowed	4 (13)	1 (4)
Married	27 (84)	21 (81)
Single	1 (3)	4 (15)
Reported prior history of anxiety or depression, n (%)	15 (47)	9 (35)

SD: standard deviation, CAH: congenital adrenal hyperplasia

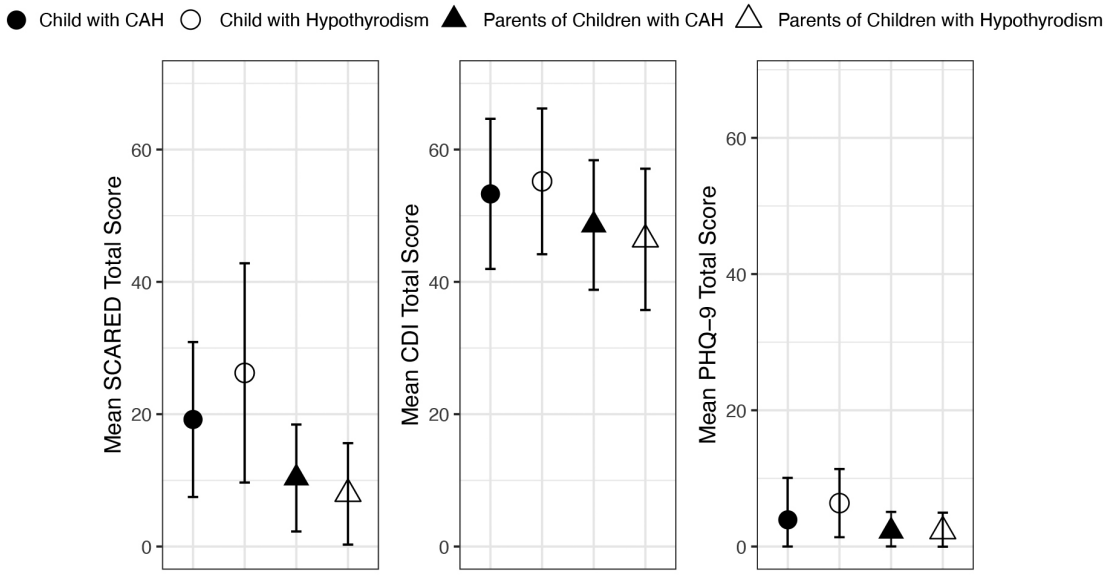

Figure 1. Child and parent scores on the CDI-2, SCARED, and PHQ-A

CAH: congenital adrenal hyperplasia, CDI-2: Children's Depression Inventory 2 Self Report-Short, SCARED: Screen for Child Anxiety Related Disorders, PHQ-A:

Patient Health Questionnaire modified for Adolescents

difference in scores between children with CAH and their caregivers (p = 0.300). However, children with HT reported a greater number of depression symptoms than their caregivers reported (p = 0.005). After controlling for age, a difference remained between children and caregivers in both their SCARED and CDI-2 scores (p < 0.001).

Adrenal Control and Mental Health

Adrenal control was determined in a subset of 23 children as only 23 children had at least four 17-OHP levels in the prior 12-month period. Table 3 includes the number of participants deemed to be in good, fair or poor adrenal control. There was no difference in adrenal control between the salt-wasting, simple virilizing and non-classical CAH groups (p = 0.11). Moreover, there was no difference in adrenal control when comparing classical (salt-wasting and simple virilizing) and non-classical CAH groups (p = 0.2). Seventy-eight percent of participants were considered to have fair or good control (22% poor, 43% fair, 35% good).

For children with CAH who scored as at-risk on the SCARED and CDI-2, there was no difference in adrenal control (p > 0.999). Of children who scored at-risk on the SCARED (n = 10) and had available 17-OHP levels (n = 7), 86% (6 of 7) had 17-OHP levels that were considered fair or good. Similarly, 86% (6 of 7) of those who scored at risk on the CDI-2 had 17-OHP levels that were considered fair or good. Adequate analysis for the PHQ-A would have been unreliable due to small sample size so was not performed.

Our results, albeit in a small sample, suggest that children with CAH have no difference in the number of anxiety symptom scores comparing those aged 7-11 years with 12-17 years (p = 0.500), illustrated in Table 4. Interestingly, there was a difference in the depression symptom scores comparing the same age groupings, with the 7-11 year group having higher CDI-2 scores (p = 0.016). The HT group showed no difference in scores with regards to anxiety and depression symptoms between the two age groups (p = 0.300).

COVID-19 Pandemic Comparisons

Anxiety

As seen in Table 5, when the CAH and HT groups were separately compared to the pre-pandemic general population, both the CAH and HT groups had significantly higher anxiety symptom scores (p = 0.0051 and p = 0.0004, respectively).

Depression-Gender

With regards to depression based on the CDI-2, CAH boys were found to have lower depression scores compared to both HT boys and pre-pandemic population boys (p = 0.026 and p = 0.031, respectively). There was no difference in

Table 3. Adrenal control among CAH child participants

	Adrenal control		
	Poor (25% or less), n = 5[1]	Fair (25 to 74.99%), n = 9[1]	Good (75% or more), n = 8[1]
CAH diagnosis			
Simple-wasting	2 (40)	7 (78)	4 (50)
Simple virilizing	2 (40)	1 (11)	0 (0)
Non-classical	1 (20)	1 (11)	4 (50)
Prior genitoplasty			
No	0 (0)	2 (33)	1 (33)
Yes	1 (50)	4 (67)	2 (67)
Pending	1 (50)	0 (0)	0 (0)
Unknown	3	3	5

[1]n (%).
CAH: congenital adrenal hyperplasia

Table 4. Median scores in CDI-2 and SCARED comparing younger and older age groups

Characteristic	7-11 years, n = 21[1]	12-17 years, n = 13[1]	p value[2]
CDI-2 total score			
CAH	52 (48, 60)	44 (43, 50)	**0.016**
HT	48 (45, 59)	55 (48, 65)	0.400
SCARED total score			
CAH	22 (15, 29)	11 (7, 28)	0.500
HT	17 (14, 29)	25 (15, 40)	0.300

[1]Median (IQR).
[2]Wilcoxon rank sum test.
CAH: congenital adrenal hyperplasia, HT: hypothyroidism, CDI-2: Children's Depression Inventory 2 Self Report-Short, SCARED: Screen for Child Anxiety Related Disorders

Table 5. General child population vs. child participant scores

Mean total calculated scores (SD)	CAH	HT	General	p
SCARED[1]	19.2 (11.71)	26.24 (16.57)	12.65 (9.37)	CAH vs. HT p = 0.2 CAH vs. Gen **p = 0.0051** HT vs. Gen **p = 0.0004**
CDI-2				
Age[2]				
7-12 years	3.8 (3)	4.17 (3.33)	2.7 (2.82)	CAH vs. HT p = 0.8 CAH vs. Gen p = 0.0977 HT vs. Gen p = 0.1567
13-17 years	3.44 (3.97)	5.71 (4.48)	3.48 (3.42)	CAH vs. HT p = 0.14 CAH vs. Gen p = 0.976 HT vs. Gen p = 0.0866
Gender[3]				
Female	4.78 (3.18)	5.32 (4.36)	3.09 (3.36)	CAH vs. HT p > 0.900 CAH vs. Gen **p = 0.02** HT vs. Gen **p = 0.04**
Male	1.45 (1.97)	4.14 (2.85)	2.95 (2.99)	CAH vs. HT **p = 0.035** CAH vs. Gen **p = 0.0313** HT vs. Gen p = 0.3137

[1]CAH n = 30, HT n = 25, General population n = 635.
[2]7-12 years: CAH n = 25, HT n = 12, General population n = 600; 13-17 years: CAH n = 9, HT n = 14, General population n = 500.
[3]Female: CAH n = 23, HT n = 19, General population n = 524; Male: CAH n = 11, HT n = 7, General population n = 522.
SD: standard deviation, CAH: congenital adrenal hyperplasia, HT: hypothyroidism, CDI-2: Children's Depression Inventory 2 Self Report-Short, SCARED: Screen for Child Anxiety Related Disorders

scores between HT boys and pre-pandemic population boys (p = 0.31). CAH and HT girls had higher depression scores compared to pre-pandemic population girls (p = 0.02 and p = 0.04, respectively). There was no difference in scores between CAH and HT girls (p = 0.5).

Depression-Age

There was no significant difference in depression scores with regards to age (7-12 years and 13-17 years groups) between the CAH and HT groups (7-12y p > 0.9 and 13-17y p = 0.140). There was no difference in scores with regards to the same age groups between the CAH and pre-pandemic general population (7-12y p = 0.1 and 13-17y p = 0.98) and between the HT and pre-pandemic general population (7-12y p = 0.16 and 13-17y p = 0.09).

Discussion

Current standard of care guidelines for CAH management recommend that individuals undergo mental health evaluations given the psychological and physical stressors that may surround a diagnosis of CAH (10). Contributing factors towards this recommendation include CAH being a chronic disease, risk of severe electrolyte imbalance, presence of genital atypia, signs of hyperandrogenism and caregiver distress. Our findings demonstrate that children and adolescents with CAH do not have a greater degree of anxiety or depression symptoms as compared to controls unaffected by CAH. These results challenge the notion that individuals with CAH, especially children and adolescents, may be at higher risk for having mental health concerns, specifically anxiety and depression. Findings from earlier CAH studies that included children with CAH have reported varying conclusions with regards to mental health.

A large, Swedish retrospective cohort study of women and girls with CAH (7) identified girls less than 12 years of age as having an increased risk of a psychotic disorder (p < 0.05) but this conclusion was limited by low statistical power. Risk of any psychiatric disorder, including anxiety, increased in those greater than or equal to 18 years of age. The authors note that the odds of having a psychiatric disorder was higher in those born before 1986, which was the year in which newborn screening for CAH was just introduced. Children who participated in our study were diagnosed with CAH after the advent of CAH newborn screening in the United States, which may have allowed for more prompt recognition of classical CAH and initiation of hormone treatment, lessening the continued exposure to elevated androgens that has been associated with increased rates of psychopathology (8).

Mueller et al. (8) conducted a prospective cohort study from 2002-2009 to characterize psychiatric morbidity in children (ages 8-18 years) with genetic etiologies of hyperandrogenism, including classical CAH. Their results revealed that 19% of females and 21% of males with classical CAH had anxiety disorders. Major depression was within the category of "mood disorder" and was evident in 0% of CAH females and 3% of CAH males. A limitation of this study was its lack of a control group, as the authors argued a healthy control group could not control for both the experiences of a chronic medical condition and genetic contributions to a psychiatric disorder. Our study selected children with HT as control participants. HT is a chronic condition that has a similar bi-modal age of diagnosis distribution as CAH. Pediatric HT management involves chronic medical therapy but neither has the additional concerns for serious illness and hospitalization nor the physical stigmata related to hyperandrogenism. Our data suggest there was no difference in at-risk anxiety and depression symptom scores between children with CAH and HT. Among those with classical CAH, at-risk scores for anxiety and depression symptoms were 26% (5 of 19) and 22% (5 of 23), respectively. Additionally, parents of children were asked to self-report their own history of anxiety and depression. In children with CAH who scored at-risk for anxiety, 38% (3 of 8) of parent participants also had a history of anxiety and 57% (4 of 7) of depression. Similarly, of children with HT who scored at-risk for anxiety, 45% (5 of 11) of parents also had a history of anxiety and 12% (1 of 8) of depression. We therefore did not find a statistical difference between the parents of children with CAH and HT. Previous studies have suggested that carriers of CAH may have psychological vulnerability to stress (15,16). None of our parent participants were carriers of CAH. If there were parent participants found to be carriers, it would be difficult to determine whether it is the carrier status itself or the responsibility of caring for a child with CAH that may cause the vulnerability to stress.

Our findings agree with a recent retrospective review of behavioral health diagnoses from a large pediatric database (PEDSnet) that abstracted at least one outpatient visit from 2009-2019 (CAH n = 1647, controls n = 6588). Their results found that children with CAH, when compared to controls, did not have a statistically significant increase in anxiety or depressive disorder diagnoses (9). The authors argue that there may be a higher risk of developing and diagnosing mental health disorders during adolescence. Our results, although from a small sample, suggest that children with CAH have no difference in the number of anxiety symptoms between 7-11 years and 12-17 years. However, there was a difference with regards to depression symptoms with the 7-11 year-old group having higher CDI-2 scores. The HT group showed no difference in anxiety and depression symptom scores between the two age groups. Younger age at CAH diagnosis and a diagnosis of classical CAH may have contributed to the younger age group having higher CDI-2 scores. In our cohort, the median age at CAH diagnosis was 0.00 years versus 2.25 years between the 7-11 and 12-17 year old age groups, respectively. A larger percentage of the younger age group compared to the older age group had classical CAH (71% vs. 61.5%). Children with classical CAH, as compared to non-classical CAH, have a younger age at diagnosis, higher rate of genital atypia and may have a more significant concern for adrenal crisis given the greater degree of enzyme deficiency. Larger studies could help investigate and further delineate these possible contributing factors. Of note, prior studies have shown that individuals with classical CAH may also have decreased adrenomedullary function that can potentially affect their ability to cope with psychological stressors (17,18). Our data did not assess adrenomedullary function in our patients to challenge this conclusion.

In adult men with CAH, Falhammar et al. (11) found that the risk of psychiatric morbidity increased in men born before the introduction of CAH newborn screening, possibly due to prolonged androgen exposure. Elevated androgens are thought to play a role in behavior in children with CAH (8,19). However, associations with anxiety and depression have not been as clear. Our study is one of the first to examine whether a child's degree of adrenal control correlates with anxiety or depression. Eighty percent were found to be in fair or good control. Though we acknowledge that the sample size for this sub-analysis was very small, there was no significant increase in anxiety or depression symptom scores in those with poor control.

In March 2020, the COVID-19 pandemic was at its peak. Our study recruitment began approximately one year after this time, in May 2021, and continued until December 2021. During this recruitment period, several studies reported increased rates of anxiety and depression in the pediatric population (20,21,22). Given the influence of the pandemic on mental health, it was important for our study to include a control group of children since they, too, similarly experienced the potential mental health consequences of the pandemic. Our study participants, both CAH and HT controls, had overall higher anxiety symptom scores compared to the pre-pandemic pediatric population. With regards to depression, girls from both the CAH and control groups, had higher depression symptom scores when compared to the pre-pandemic population; this finding is similar to what has been found in recent studies (21,22).

Interestingly, boys with CAH were found to have lower depression symptoms scores compared to both HT controls and the pre-pandemic population, although as our sample size was small, it is difficult to deduce reasons for this.

It is important to note that child scores for anxiety and depression (CDI-2) were higher than reported by parents in both CAH and HT groups. Internalizing symptoms include feelings of anxiety, loneliness and sadness (23). Angold et al. (24) found that by late adolescence, at least 20% of females and 7% of males exhibit internalizing symptoms. Children also often report internalizing symptoms at higher rates than their parents consider (25). Our results suggest that children with CAH may benefit from routine mental health evaluations, regardless of voiced caregiver concern, given the lack of agreement between child and parent proxy responses.

A few theories emerged as to why our cohort of children with CAH were not found to have an increased predominance of anxiety or depression symptoms when compared to HT controls. Our institution is considered a Center for Excellence in CAH, the first of eight designated centers by CARES Foundation. It was our experience after engaging with children and their families during visits that parents expressed a confidence in the care provided to their children. Patients are seen by a pediatric endocrinologist with extensive experience with CAH treatment and management. They are expected to follow up every three months in order to allow for careful dose adjustments that help optimize growth and development. As previously mentioned, nearly half of our CAH participants were found to be in good adrenal control. Androgens play a role in human behavior (26) and elevated androgens have been associated with an increase in severe behavioral symptoms in girls with CAH (27). In our cohort of females with classical CAH, 69% (n = 11) underwent genitoplasty and 6% (n = 1) were planning to undergo later in the year. Prior studies have suggested that adults with an XX karyotype and classical CAH supported genitoplasty within the first year of life (28). Whether completion and timing of genitoplasty is truly correlated with mental health outcomes is not clear, as no long-term observational studies have been completed. Our results show that 67% (6 out of 9) of children with a history of genitoplasty did not score at-risk for anxiety and 73% (8 out of 11) did not score at-risk for depression.

Study Limitations

There were several limitations with our study. Our study recruitment was at a single institution and completed over a seven-month period. As CAH is a rare condition with an incidence of approximately 1:14,000 to 1:18,000 births (10), the sample size of a single institution obtained during this time period was fairly significant. However, expanding the study to include multiple institutions over a longer study interval would potentially change or strengthen our findings. Moreover, our study highlights the pediatric CAH population at a center of excellence in which children are given specific expert care, and we recognize that the study results may not be generalizable. Therefore, it would be valuable to expand the study to patients who are both at centers of excellence and not at centers of excellence. Our study used validated mental health questionnaires that were free (SCARED, PHQ-A) or low-cost (CDI-2), and of a short time-commitment. The main limitation of these questionnaires was that these are self-report measures, which may introduce bias compared to an independent evaluator. However, these questionnaires are the most commonly used research self-report measures for youth depression and anxiety, as well as the most frequently used screening tools in pediatric clinical practice. Though the questionnaires used were reliable general screeners for anxiety and depression, they were not specific to CAH-related concerns. A questionnaire including topics on gender identity, genital surgery and body image may provide a more comprehensive view and insight into anxiety and depression symptoms in the CAH population. This study included parent participants with a history of anxiety and/or depression. As children may have a genetic predisposition to anxiety and depression (29), our study is limited by the absence of exclusion of these few parent participants who reported such history. Our study included participants with both classical and non-classical CAH. There have been reports regarding anxiety in adults with non-classical CAH that has suggested that having non-classical CAH may contribute to anxiety (30) and that females with non-classic CAH can have higher anxiety scores as compared to age and sex-matched controls (31). However, we acknowledge that those with non-classical CAH versus classical CAH may have different degrees of mental health concerns. Additionally, elevated 17-OHP levels were used as a biochemical marker for anxiety in our study but elevated dehydroepiandrosterone sulfate and pregnenolone sulfate levels may also have an effect on anxiety (30). With regards to our control group, the majority of HT participants did not have congenital HT so comparisons between those with classical CAH were affected by sample size. We recognize there was a female predominance in our sample. Therefore, our results cannot necessarily be extrapolated to males. Lastly, this study was completed one year after the start of the COVID-19 pandemic, a time during which there was evidence of increasing rates of anxiety and depression among youth. We attempted to control for the overall increase in mental health concerns by the inclusion

of the HT control group. Although our findings on anxiety and depression were similar to what had been found in the general youth population during this time, it would be important to replicate this study several years removed from the pandemic to ascertain whether the increased mental health concerns were related to the pandemic or are inherent to the HT population.

Conclusion

Our study suggests that children with CAH do not have a greater degree of anxiety or depression symptoms compared to controls with HT, despite having more unique risk factors for increased psychiatric morbidity. Expertise in care, frequent patient follow-up and good adrenal control may have played a role in alleviating anxiety and depression symptoms. Our study also illustrates the ease and benefit of mental health questionnaire administration at routine visits, especially as mental health evaluations by trained providers are currently difficult to obtain due to resource availability, scheduling difficulties and insurance barriers. Moreover, such screenings at routine visits can highlight any differences in patient-caregiver perspective with regards to internalizing symptoms of anxiety and depression. Future multicenter studies that are several years removed from the COVID-19 pandemic will better aid in the understanding of mental health in children with CAH and whether further measures should be considered in optimizing CAH care.

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Ethics

Ethics Committee Approval: This study was approved by the Weill Cornell Medicine Institutional Review Board, approval #20-04021748, date: 22.02.2022.

Informed Consent: Written consent was obtained from caregivers and written assent from child participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Corinne Catarozoli, Karen Lin-Su, Marianne Jacob, Oksana Lekarev, Design: Karen Lin-Su, Marianne Jacob, Oksana Lekarev, Data Collection or Processing: Charlene Thomas, Karen Lin-Su, Marianne Jacob, Oksana Lekarev, Analysis or Interpretation: Charlene Thomas, Karen Lin-Su, Marianne Jacob, Oksana Lekarev, Dix Poppas, Literature Search: Karen Lin-Su, Marianne Jacob, Oksana Lekarev, Dix Poppas, Writing: Corinne Catarozoli, Charlene Thomas, Karen Lin-Su, Marianne Jacob, Oksana Lekarev.

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