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In This Issue

Altered Emotion Perception Linked to Structural Brain Differences in Youth With Congenital Adrenal Hyperplasia

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Abstract

Context: Congenital adrenal hyperplasia (CAH) is a genetic disorder that results in hormonal imbalances and decreased brain volumes in regions important for emotional processing.

Objective: To examine whether emotion perception differs between youth with CAH and control youth, and if these differences relate to brain volumes.

Methods: In this cross-sectional study of 27 youths with CAH (mean age = 12.63 years, 16 female) and 35 age- and sex-matched controls (mean age = 13.03 years, 20 female), each participant rated picture stimuli and completed a 3T structural brain scan. Valence and arousal ratings and reaction times of 61 affective images were assessed. Gray matter volumes were measured by MRI.

Results: Youth with CAH had lower valence ratings for negative ($P = .007$) and neutral ($P = .019$) images. Controls showed differences in reaction times and arousal ratings across stimuli conditions, but youth with CAH did not. Brain volumes of the right amygdala ($P = .025$) and left hippocampus ($P = .002$) were associated with valence ratings. Left rostral middle frontal ($P < .001$) and right medial orbitofrontal cortex ($P = .002$) volumes were negatively related to valence scores only in youth with CAH, whereas left medial orbitofrontal cortex ($P < .001$) volumes were associated with valence scores positively in youth with CAH and negatively in controls.

Conclusion: Findings suggest that youth with CAH perceive emotive stimuli as more unpleasant. Decreased brain volumes in the amygdala, hippocampus, and prefrontal cortex are associated with these measures of altered emotion perception in youth with CAH.

Key Words: congenital adrenal hyperplasia, emotion perception, adrenal insufficiency, magnetic resonance imaging, brain, neuroimaging

Abbreviations: 17-OHP, 17-hydroxyprogesterone; CAH, congenital adrenal hyperplasia; CHLA, Children's Hospital Los Angeles; CMF, caudal middle frontal cortex; fMRI, functional magnetic resonance imaging; IAPS, International Affective Picture System; MOF, medial orbitofrontal cortex; MRI, magnetic resonance imaging; RMF, rostral middle frontal; SAM, Self-Assessment Manikin.

Congenital adrenal hyperplasia (CAH) is a recessive genetic disorder that results in hormonal imbalances due to deficient adrenal steroidogenesis (1). The most common form of CAH is due to 21-hydroxylase deficiency, which leads to a malfunction of cortisol synthesis and excess androgen production (2). This classical form of CAH is present in approximately 1 out of every 15,000 births (3). While CAH may be detected at birth via newborn screening and treated with glucocorticoid therapy shortly thereafter, fetal hormonal imbalances may still result in prenatal virilization, along with postnatal virilization due to varying levels of hormonal control, particularly in females (4).

Given that hormonal imbalances early in development have been linked to a number of brain, cognitive, and emotional outcomes in both animals and humans (5), it is thought that CAH may also affect brain structure and behavior. Support for this notion includes various cognitive, emotional, and gender-typical play preference differences noted in youth with CAH as compared with unaffected children and adolescents (6–10). Moreover, female youth and adults with CAH are at elevated risk for high stress, substance misuse, and psychiatric disorders (11). In line with these behavioral findings, an emerging body of literature has begun to examine structural and functional brain differences in CAH using magnetic resonance imaging (MRI) (12). In a few observational studies, reduced brain volumes have been noted in patients with CAH as compared with unaffected controls, particularly in the amygdala, hippocampus, and prefrontal cortex (13–15). Additionally, microstructural differences have been observed in white matter pathways that connect these brain regions (14, 16). Specifically, the ventral system of emotion perception, which includes the amygdala, is involved in rapid identification of the valence (negative to positive) and arousal (low to high physiological stress response) of an affective stimulus and generation of an appropriate affective response (17, 18). The dorsal system of emotion perception, which includes the hippocampus and prefrontal cortex, is in turn involved in regulating cognitive and behavioral responses to these emotions (17).

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A Message from the Executive Director

Dear Friends,

As we close out 2023, I am grateful for the abundance of support that we have received this year, as it has allowed us to continue to grow and serve the needs of the CAH community.

Our community has been afforded more opportunities to connect with one another during support group meetings, awareness walks, webinars, conferences, and more! This year, our Patient Education Conference was held in Seattle, WA to better serve patients and families on the west coast. However, participants still came from far and wide while hailing from 15 different states across the country. We have also added new support groups to further connect our community.

The Patient Education Conference is always a powerful event as patients and families have an opportunity to meet each other, often for the first time. Our Patient Advisory Summit brought together patients, caregivers, and industry partners to help to better understand the patient journey as they work to develop new treatments for CAH. These conversations are always enlightening and empowering, and we are grateful for the participants who shared their experiences.

We are also very excited about bringing CAH stories directly to you through our new podcast, CAH Pulse. Every month we will bring you the voices of patients, parents, other caregivers, as well as medical professionals and other researchers who have dedicated their lives to the CAH community. Be sure to subscribe and listen! If you would like to be a guest, please reach out to let us know.

We want to hear directly from you about how we can better serve you. We look forward to another great year ahead!

Wishing you a happy, healthy, and fruitful 2024!

Warmly,

Dina M. Matos
Executive Director

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Despite consistent evidence of structural brain differences in regions important for emotion processing and differences in behaviors linked to emotion, only 2 studies have examined emotion perception in patients with CAH as compared with controls (19, 20). Both studies implemented emotional tasks in conjunction with functional magnetic resonance imaging (fMRI). The first study found that adolescents with CAH showed significantly higher brain activation in the amygdala, fusiform gyrus, and occipital cortex compared with control children when looking at angry and fearful faces as compared to happy and neutral faces (19). Moreover, youth with CAH rated angry and fearful faces as significantly more negative than controls did (19). The second study, which included the same sample of youth but implemented a different fMRI task, found that youth with CAH had significantly poorer memory encoding of fearful faces as opposed to neutral faces as well as different activation patterns in the amygdala and hippocampus compared to control youth (20). Taken together, these initial studies provide evidence that youth with CAH may perceive emotions differently, particularly in response to negative stimuli. However, it remains unclear whether these findings are limited to facial expressions or if they may generalize to other affective stimuli, and whether these differences in emotion perception relate to the aforementioned structural differences in youth with CAH (13–15).

Therefore, the present study implemented a set of standardized, emotionally-evocative photographs from the International Affective Picture System (IAPS) and valence and arousal rating scales of the Self-Assessment Manikin (SAM) to examine emotion perception in a sample of youth with and without CAH (21–24). The IAPS allows for a nuanced understanding of emotion perception by incorporating dimensions of both valence (negative, neutral, positive subjective experience) and arousal (low, moderate, high physiological stress) brought on by an affective stimulus (18, 21, 22). We hypothesized that youth affected with CAH would show differences in both valence and arousal ratings of IAPS images. We additionally hypothesized that brain volumes of regions implicated in emotion processing, including the amygdala, hippocampus, and prefrontal cortex, would relate to IAPS ratings. Lastly, reaction times were also measured to test two competing hypotheses of whether CAH may affect only affective content, with no impact on emotional processing speed, or whether processing speed may be impacted as well.

Table 1. Participant demographics, stratified by group

Variable	Control (n = 35)	CAH (n = 27)	Group difference	P
Age (years)	13.03 ± 2.79	12.63 ± 3.35	t(50.3) = −0.50	.62
Sex				
Male	15 (42.9%)	11 (40.7%)	$\chi^2(1) = 0.00$	1.00
Female	20 (57.1%)	16 (59.3%)		
Wechsler IQ	103.03 ± 15.30	100.22 ± 16.67	t(53.5) = −0.68	.50
Family income				
<$49k	15 (42.9%)	11 (40.7%)	$\chi^2(1) = 0.00$	1.00
>$49k	19 (54.3%)	14 (51.9%)		
Not reported	1 (2.8%)	2 (7.4%)		
Ethnicity				
Hispanic	20 (57.1%)	11 (40.7%)	$\chi^2(2) = 2.53$	.28
Non-Hispanic	15 (42.9%)	16 (59.3%)		
Race				
White	17 (48.6%)	12 (44.4%)	$\chi^2(4) = 2.09$	.72
Black	4 (11.4%)	2 (7.4%)		
Asian	2 (5.7%)	1 (3.7%)		
Mixed	2 (5.7%)	4 (14.8%)		
Not reported	10 (28.6%)	8 (29.6%)		
Maternal education (years)	4.85 ± 3.47	13.85 ± 3.32	t (55.1) = 1.14	.26
Handedness				
Right	30 (85.7%)	25 (92.6%)	$\chi^2(1) = 1.97$	.66
Left	5 (14.3%)	2 (7.4%)		
Tanner pubertal stage	3.31 ± 1.62	2.81 ± 1.64	t(55.7) = −1.19	.24
CAH form				
Salt-wasting	—	25 (92.6%)	—	—
Simple-virilizing		2 (7.4%)		
CAH newborn screen				
Yes	—	12 (44.4%)	—	—
No		15 (55.6%)		
Bone age standard deviation (BA SD)	—	1.44 ± 3.10	—	—
Fludrocortisone total daily dose (mg)	—	0.11 ± 0.04	—	—
Glucocorticoid total daily dose (mg/m^2)	—	16.5 ± 4.7	—	—
17-hydroxyprogesterone (ng/dL) [nmol/L]	—	3656 ± 4694.8 [110.8 ± 142.3]	—	—
Plasma renin activity (ng/mL/h)	—	3.5 ± 2.9	—	—
Androstenedione (ng/dL) [nmol/L]	—	150.5 ± 227.8 [5.2 ± 8]	—	—
Testosterone (ng/dL) [nmol/L]	—	76.5 ± 155.3 [2.7 ± 5.4]	—	—

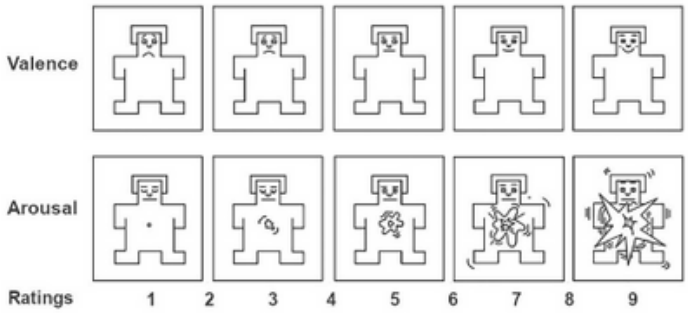

Figure 1. Self-Assessment Manikin (SAM) of valence and arousal (23). Following standard protocol for administering the IAPS to children. SAM endpoints for positive valence (Rating of 9) included "happy" or "pleased," whereas negative valence (Rating of 1) included "angry" or "sad." SAM endpoints for high arousal (Rating of 9) included "excited" or "nervous" for high arousal, whereas for low arousal (Rating of 1) included "calm" or "sleepy."

Table 2. IAPS valence ratings and reaction times

	Valence ratings			Valence reaction times		
	df	F-statistic	P	df	F-statistic	P
Valence condition	2, 3983	1023.65	<.001	2, 3983	2.64	.07
Arousal condition	2, 3983	15.25	<.001	2, 3983	0.06	.94
Group (CAH vs controls)	1, 63	6.92	.012	1, 63	0.91	.34
Sex	1, 63	2.34	.13	1, 63	1.08	.30
Age	1, 63	0.31	.58	1, 63	3.67	.06
Valence-by-group interaction	2, 3983	10.90	<.001	2, 3983	4.70	.009

Results reflect ANOVA of linear mixed effect models, including valence conditions (negative, neutral, positive), arousal conditions (low, moderate, and high), group (CAH vs controls) and covariates; degrees of freedom (df) are presented (numerator, denominator) as well as F-statistic and associated P value. Significant P values (P < 0.05) are bolded.

Materials and Methods

Study Participants

This study was cross-sectional and approved by the Institutional Review Board of the University of Southern California (USC) and Children's Hospital Los Angeles (CHLA). Written consent was obtained from all parents or legal guardians, and/or participants, and all minors up to 14 years of age gave assent, in accordance with The Code of Ethics of the World Medical Association. Participants included 62 children and adolescents aged 8 to 18 years old. For the purposes of our study, "youth" refers to participants from our sample including both children and adolescents. Twenty-seven youths with CAH (16 female; 12.6 ± 3.4 years) were recruited from the Children's Hospital Los Angeles (CHLA) CAH Comprehensive Care Center. Thirty-five age- and sex-matched control participants (20 female; 13.0 ± 2.8 years) were recruited from

Table 3. Valence ratings and reaction times post hoc comparisons

		Control		CAH		Group difference	
IAPS Valence		Estimate (SE)	P	Estimate (SE)	P	Estimate (SE)	P
Negative Valence	Ratings	3.20 (0.16)	—	2.43 (0.17)	—	−0.77 (0.22)	.007
	RT [log (s)]	0.36 (0.09)	—	0.11 (0.09)	—	−0.23 (0.12)	.38
Neutral Valence	Ratings	5.38 (0.16)	—	4.69 (0.17)	—	−0.69 (0.21)	.019
	RT [log (s)]	0.31 (0.09)	—	0.18 (0.09)	—	−0.13 (0.12)	.85
Positive Valence	Ratings	6.56 (0.15)	—	6.47 (0.16)	—	−0.09 (0.21)	1.00
	RT [log (s)]	0.20 (0.09)	—	0.17 (0.09)	—	−0.02 (0.12)	1.00
Negative vs Neutral Valence	Ratings	−2.18 (0.17)	<.001	−2.26 (0.17)	<.001	—	—
	RT [log (s)]	0.03 (0.07)	1.00	−0.07 (0.07)	.91	—	—
Negative vs Positive Valence	Ratings	−3.35 (0.11)	<.001	−4.04 (0.12)	<.001	—	—
	RT [log (s)]	0.14 (0.05)	.014	−0.06 (0.05)	.78	—	—
Neutral vs Positive Valence	Ratings	−1.18 (0.16)	<.001	−1.78 (0.16)	<.001	—	—
	RT [log (s)]	0.11 (0.06)	.41	0.01 (0.07)	1.00	—	—

Results reflect "emmeans" post hoc tests contrasting CAH and control valence ratings and reaction times across negative, neutral, and positive IAPS image conditions. Estimates represent estimated mean valence scores (ranging from 1 to 9, negative to positive) and reaction times (log-transformed, in seconds) for each image condition, while contrast estimates represent mean changes in valence scores and reaction times for each change in image condition. Group differences represent mean estimates of CAH − control ratings and reaction times across each image condition and contrast. Significant contrasts (P < .05) are bolded. Abbreviations: CAH, congenital adrenal hyperplasia; IAPS, International Affective Picture System; RT, reaction time; SE, standard error.

Table 4. IAPS arousal ratings and reaction times

	Arousal ratings			Arousal reaction times		
	df	F-statistic	P	df	F-statistic	P
Valence condition	2, 3987	45.96	<.001	2, 3987	10.29	<.001
Arousal condition	2, 3987	241.54	<.001	2, 3987	15.88	<.001
Group (CAH vs controls)	1, 63	0.02	.89	1, 63	0.66	.42
Sex	1, 63	3.00	.09	1, 63	1.76	.19
Age	1, 63	6.99	.010	1, 63	3.00	.09
Group-by-Arousal Interaction	2, 3987	3.93	.020	2, 3987	3.48	.031

Results reflect ANOVA of linear mixed effect models, including valence conditions (negative, neutral, and positive), arousal conditions (low, moderate, and high), Group (CAH vs controls) and covariates; degrees of freedom (df) shown (numerator, denominator) as well as F-statistic and associated P value. Significant P values (P < .05) are bolded.

flyers posted at CHLA and the University of Southern California, and from the General Pediatric clinic at CHLA. Health-related exclusionary criteria for all participants included prenatal drug or alcohol exposure, premature birth, serious medical illness (other than CAH), eating disorders, or psychotropic medication. Participants were screened for any significant neurological conditions (e.g., epilepsy and traumatic head injury) and psychiatric/developmental disorders (e.g., autism, attention-deficit/hyperactivity disorder, schizophrenia, and self-harm tendencies) which, if present, barred participation. Participants were also screened for any factors that would prevent proper and safe usage of MRI, such as irremovable ferrous materials (e.g., braces), uncorrectable vision impairments (e.g., blind spots and colorblindness), need for hearing aids, or claustrophobia.

Youths with CAH had either the salt-wasting (n = 25) or simple-virilizing form (n = 2), as diagnosed by positive newborn screen and confirmatory serum analytes (n = 12), biochemically ± genotype (n = 15). At the time of the study visit, patients with CAH were on daily glucocorticoid dosing (16.5 ± 4.7 mg/m2 / day) with glucocorticoid dose equivalencies calculated based on growth-suppressing effects of longer-acting glucocorticoids compared with hydrocortisone (prednisone dose was multiplied by 5 and dexamethasone dose was multiplied by 80) (25). Almost all patients with CAH were also treated with fludrocortisone (0.11 ± 0.04 mg/day). Pubertal (Tanner) staging was assessed by a pediatric endocrinologist. Bone age (BA) advancement can be a marker of prolonged and/or excess exposure to postnatal androgens, and the individual's standard deviation for bone age (BA SD) can serve as an index of BA advancement as an average (mean)

Table 5. Arousal ratings and reaction time post hoc comparisons

		Control		CAH		Group difference	
IAPS Arousal		Estimate (SE)	P	Estimate (SE)	P	Estimate (SE)	P
Low arousal	Ratings	2.64 (0.23)	—	2.77 (0.25)	—	0.13 (0.31)	.10
	RT [log (s)]	−0.04 (0.12)	—	−0.03 (0.13)	—	0.01 (0.16)	1.00
Moderate arousal	Ratings	4.16 (0.21)	—	4.13 (0.23)	—	−0.03 (0.30)	1.00
	RT [log (s)]	0.07 (0.11)	—	−0.11 (0.12)	—	−0.18 (0.16)	.82
High arousal	Ratings	4.90 (0.22)	—	4.51 (0.23)	—	−0.39 (0.31)	.74
	RT [log (s)]	−0.03 (0.11)	—	−0.18 (0.12)	—	−0.15 (0.16)	.92
Low vs moderate arousal	Ratings	**−1.12 (0.18)**	**<.001**	**−1.36 (0.19)**	**<.001**	—	—
	RT [log (s)]	−0.11 (0.08)	.62	0.08 (0.08)	.85	—	—
Low vs high arousal	Ratings	**−2.26 (0.20)**	**<.001**	**−1.74 (0.21)**	**<.001**	—	—
	RT [log (s)]	−0.01 (0.08)	1.00	0.15 (0.09)	.42	—	—
Moderate vs high arousal	Ratings	**−0.74 (0.13)**	**<.001**	−0.38 (0.14)	.05	—	—
	RT [log (s)]	0.10 (0.05)	.36	0.07 (0.06)	.81	—	—

Results reflect "emmeans" post hoc tests contrasting CAH and control arousal ratings and reaction times across low, moderate, and high arousal IAPS image conditions. Estimates represent estimated mean arousal scores (ranging from 1 to 9, low to high) and reaction times (log-transformed, in seconds) for each image condition, while contrast estimates represent mean changes in arousal scores and reaction times for each change in image condition. Group differences represent mean estimates of CAH-Control ratings and reaction times across each image condition and contrast. Significant contrasts (P < 0.05) are bolded. Abbreviations: CAH, congenital adrenal hyperplasia; IAPS, International Affective Picture System; RT, reaction time; SE, standard error.

for their age and sex (26). To determine BA, a radiograph of the left hand was read by a single blinded pediatric endocrinologist (M.S.K.) using the Greulich-Pyle method (27). BA SD was determined utilizing digital software (28). BA was obtained at the time of the study visit or within 5 months of the visit if taken for clinical purposes. Individuals who had the time of the study visit had their prior BA X-rays reviewed to confirm early full maturity.

Youth with CAH and control participants did not differ significantly in age, sex, IQ [as measured by 2 subtests of the Wechsler Adult Intelligence Scale (WASI) IV test] (29), socioeconomic status, race and ethnicity, maternal education, handedness, or Tanner pubertal stage (Table 1).

Emotion Perception

Each participant was shown 61 images from the International Affective Picture System (IAPS) on a computer screen using PsychoPy software (21, 30). Each image was classified as either negative, neutral, or positive valence (e.g., injured people, books, or puppies, respectively) and low, moderate, or high arousal (e.g., people reading, eating, or screaming, respectively) based on IAPS reference data (22). Participants rated each image on a scale of 1 to 9 for valence (negative to positive) and arousal (low to high) using the SAM depicted in Fig. 1 (23, 24). SAM endpoints were described using words like "happy" and "pleased" for positive valence, "angry" and "sad" for negative valence, "excited" and "nervous" for high arousal, and "calm" and "sleepy" for low arousal, following standard protocol for administering the IAPS to children (31). Each image rating trial began with a 5-second preparation slide stating, "Get ready to rate the next slide." Each image was then shown for 6 seconds. Immediately after the image left the screen, participants rated each image for valence and arousal. Reaction times were also measured for each rating. Participants went through 3 practice trials prior to data collection, and a total of 61 experimental trials for which data were collected.

Structural MRI

We have reported full MRI details on this sample and their main findings previously (15). Briefly, structural brain images were acquired at the University of Southern California's Center for Image Acquisition using a Siemens Magnetom Prisma 3 Tesla MRI scanner with a 32-channel head coil. Total intracranial volume, bilateral hippocampus and amygdala volumes, and bilateral volumes of the superior, rostral middle, caudal middle, lateral orbitofrontal, and medial orbitofrontal prefrontal cortices were obtained and segmented using the Desikan-Killiany Atlas (32)

Data Analysis

Prior to analysis, all variables were examined for outliers and outcome variables were examined for normality. No significant outliers were observed. All outcome variables except valence and arousal reaction times were approximately normally distributed. Thus, reaction times were rescaled to seconds and log-transformed to achieve normality. Post analysis, residual diagnostics were performed, and all assumptions of normality, linearity, and homoscedasticity were met.

Data were analyzed using RStudio v1.4 packages "lme4" and "lmerTest" for linear mixed-effects modeling (33–35). Initial mixed-effects models were conducted for each valence, arousal, and corresponding reaction times as outcome variables, with random intercepts for subject ID accounting for the repeated-measures design. Group-by-valence or group-by-arousal condition interaction effects were tested for based on the outcome variable (i.e., group-by-valence condition interaction for valence outcomes, group-by-arousal condition interaction for arousal outcomes) while controlling for age and sex. For ease of interpretability, age was mean-centered. Controls were selected as the reference group, with CAH representing the main effect group. Male was coded as the reference sex, with main effects for sex representing females. Neutral valence and moderate arousal were coded as the reference image conditions for valence and arousal, respectively, with main effects for low or high arousal and negative or positive valence. The model was formatted as follows:

$$\begin{aligned} Outcome \sim\ & Valence\ Condition + Arousal\ Condition \\ & + Group + Sex + Age_{MC} \\ & + Group^{*}Image\ Condition + (1|Subject\ ID). \end{aligned}$$

A total of 4 models were constructed, where "Outcome" refers to each of the following 4 outcome variables: valence rating, arousal rating, valence reaction time, and arousal reaction time. "Image Condition" refers to the

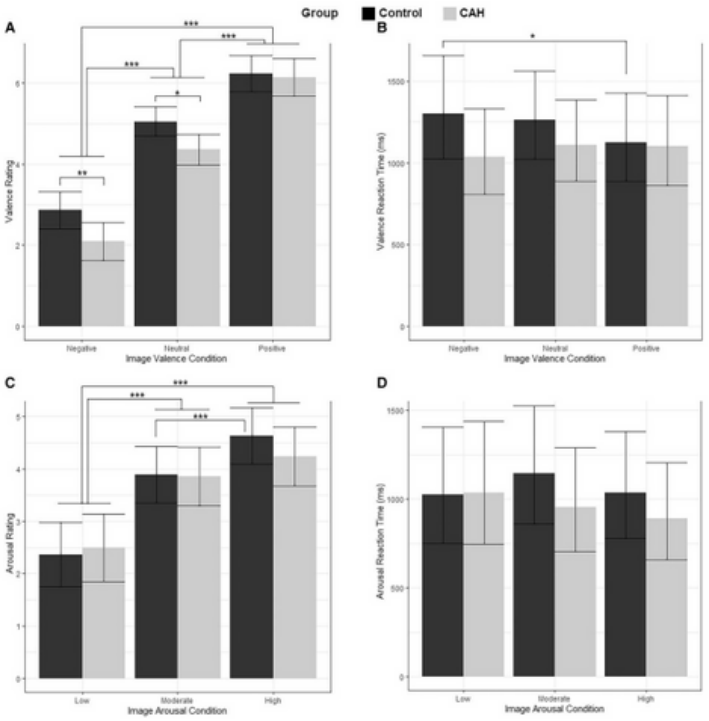

Figure 2. IAPS valence and arousal ratings and reaction times. Means and standard errors stratified by group (youth with CAH vs controls) for A) valence ratings, B) valence reaction times, C) arousal ratings, and D) arousal reaction times. CAH youth in gray and control youth in black. Significant post hoc comparisons denoted by *<.05; **<.01; ***<.001.

affective marker corresponding to the model outcome (i.e., valence condition for valence ratings and reaction times, arousal condition for arousal ratings and reaction times). ANOVA was then performed for each linear mixed effect model to assess the significance between valence or arousal conditions of IAPS, as well as group-by-valence or group-by-arousal condition, depending on the model of interest. For significant interactions, exploratory post hoc tests comparing model-predicted outcomes between image condition types and significant group-by condition interactions were conducted using the R package "emmeans" (36). This served as a test for equality of means of each outcome variable, after controlling for all covariates and model assumptions.

Following detection of group differences in valence ratings, backward stepwise selection was used to select a model examining the explanatory power of structural brain differences in predicting group differences in valence ratings. Stepwise selection was used due to the exploratory

Table 7. Associations of valence ratings with brain volumes

	df (numerator, denominator)		F-statistic		P	
Valence condition	2, 3689.1		961.47		<.001	
Arousal condition	2, 3689		18.19		<.001	
Group (CAH vs controls)	1, 62.4		10.10		.002	
Sex	1, 62.1		14.04		<.001	
Age	1, 61.7		17.82		<.001	
ICV	1, 62.1		.03		.85	
Group-by-valence interaction	2, 3689.1		13.26		<.001	
Group-by-arousal interaction	2, 3689		4.27		.014	
Group-by-sex interaction	1, 61.8		12.24		.001	
Brain volume effects by hemisphere	Left	Right	Left	Right	Left	Right
Amygdala	—	1, 62.1	—	5.30	—	.025
Hippocampus	1, 62.5	—	10.65	—	.002	—
CMF	—	1, 61.6	—	.03	—	.85
RMF	1, 61.8	1, 61.8	9.76	4.07	.003	.048
MOF	1, 61.7	1, 61.9	1.79	12.73	.19	.001
Group-by-CMF interaction	—	1, 62	—	4.73	—	.033
Group-by-RMF interaction	1, 61.7	1, 61.8	18.83	3.95	<.001	.051
Group-by-MOF interaction	1, 61.7	1, 61.8	22.77	14.06	<.001	<.001

(negative, neutral, positive), arousal conditions (low, moderate, and high), group (CAH vs controls), identified brain regions of interest and covariates. Significant P values (P < .05) are bolded. Abbreviations: CMF, caudal middle frontal; ICV, total intracranial volume; MOF, medial orbitofrontal; RMF, rostral middle frontal.

nature of our analyses, to eliminate nonsignificant predictor variables and prevent overfitting. The initial model considered all brain regions of interest, which were all mean-centered and scaled for ease of interpretability. Brain volumes in cubic millimeters were scaled by 1,000 for each subregion, and by 10,000 for total intracranial volume. Valence and arousal image conditions, mean-centered age, and total intracranial volume were adjusted for as fixed effects in the model, alongside subject ID as the random intercept. Interaction effects between group and all brain regions of interest were also considered. The P value for exclusion in backward stepwise selection was set at .05. Again, we ran an ANOVA to assess significance across IAPS valence and arousal conditions, and follow-up post hoc tests were completed using the R package "emmeans" (36).

Finally, following any significant group differences between youth with CAH and controls, we ran supplemental analyses on our subsample of youth with CAH, examining the effects of variables clinically relevant to CAH. These included CAH form (salt-wasting vs simple-virilizing), lab analytes (serum 17-hydroxyprogesterone [17-OHP], testosterone and androstenedione, and plasma renin activity levels [liquid chromatography tandem mass spectrometry, LC/MS-MS, for all; Quest Diagnostics, San Juan Capistrano]; inter-assay and intra-assay coefficients of variation were less than 5%), and fludrocortisone and glucocorticoid dosages (full list of variables reported in Table 6). We tested for univariate effects of each clinical variable in its own model, with valence and arousal condition, sex, and age as covariates, formatted as:

$$Outcome \sim Valence\ Condition + Arousal\ Condition + Sex + Age_{MC} + Clinical\ Variable + (1|Subject\ ID).$$

Table 6. Associations between IAPS valence ratings and clinical features among youth with CAH

	Initial model		CAH form (SW vs SV)		Diagnosed at birth (yes vs no)		Bone age SD		Fludrocortisone total daily dose (mg)		Glucocorticoid total daily dose (mg/m^2)		17-OHP (ng/dL)		Plasma renin activity (ng/mL/h)		Androstenedione (ng/dL)		Testosterone (ng/dL)	
	Std. B (95% CI)	P	Std. B (95% CI)	P	Std. B (95% CI)	P	Std. B (95% CI)	P	Std. B (95% CI)	P	Std. B (95% CI)	P	Std. B (95% CI)	P	Std. B (95% CI)	P	Std. B (95% CI)	P	Std. B (95% CI)	P
Intercept	0.41 (0.17, 0.64)	<.001	0.41 (0.17, 0.64)	<.001	0.41 (0.17, 0.65)	<.001	0.28 (0.12, 0.44)	<.001	0.41 (0.17, 0.64)	<.001	0.42 (0.21, 0.64)	<.001	0.26 (0.10, 0.42)	<.001	0.41 (0.17, 0.64)	<.001	0.28 (−0.11, 0.67)	<.001	0.27 (0.09, 0.44)	<.001
Negative valence	−0.94 (−1.10, −0.78)	<.001	−0.94 (−1.10, −0.78)	<.001	−0.94 (−1.10, −0.78)	<.001	−0.84 (−0.96, −0.73)	<.001	−0.96 (−1.12, −0.80)	<.001	−0.94 (−1.10, −0.78)	<.001	−0.84 (−0.95, −0.73)	<.001	−0.94 (−1.10, −0.78)	<.001	−0.82 (−1.20, −0.45)	<.001	−0.84 (−0.95, −0.73)	<.001
Positive valence	0.49 (0.34, 0.65)	<.001	0.49 (0.34, 0.65)	<.001	0.49 (0.34, 0.65)	<.001	0.54 (0.43, 0.65)	<.001	0.50 (0.34, 0.65)	<.001	0.49 (0.34, 0.65)	<.001	0.55 (0.44, 0.66)	<.001	0.49 (0.34, 0.65)	<.001	0.38 (0.02, 0.73)	.039	0.55 (0.44, 0.66)	<.001
Low arousal	−0.43 (−0.59, −0.28)	<.001	−0.43 (−0.59, −0.28)	<.001	−0.43 (−0.59, −0.28)	<.001	−0.31 (−0.42, −0.20)	<.001	−0.46 (−0.61, −0.30)	<.001	−0.43 (−0.59, −0.28)	<.001	−0.30 (−0.40, −0.19)	<.001	−0.43 (−0.59, −0.28)	<.001	−0.51 (−0.86, −0.16)	.004	−0.30 (−0.40, −0.19)	<.001
High arousal	−0.04 (−0.13, 0.05)	.44	−0.04 (−0.13, 0.05)	.44	−0.04 (−0.13, 0.05)	.44	−0.02 (−0.08, 0.04)	.55	−0.03 (−0.12, 0.06)	.53	−0.04 (−0.13, 0.05)	.44	−0.01 (−0.08, 0.05)	.70	−0.04 (−0.13, 0.05)	.44	−0.06 (−0.27, 0.15)	.60	−0.01 (−0.08, 0.05)	.70
Female	−0.21 (−0.47, 0.05)	.12	−0.20 (−0.47, 0.06)	.13	−0.20 (−0.47, 0.07)	.13	−0.15 (−0.32, 0.03)	.10	−0.19 (−0.46, 0.07)	.14	−0.23 (−0.46, −0.00)	.050	−0.12 (−0.29, 0.04)	.13	−0.21 (−0.47, 0.05)	.11	0.06 (−0.60, 0.73)	.72	−0.14 (−0.34, 0.07)	.19
Age (years)	−0.02 (−0.14, 0.11)	.81	−0.01 (−0.14, 0.12)	.82	−0.01 (−0.15, 0.12)	.82	−0.01 (−0.10, 0.07)	.76	−0.01 (−0.14, 0.12)	.85	0.12 (−0.03, 0.27)	.10	−0.01 (−0.09, 0.07)	.80	−0.01 (−0.14, 0.12)	.83	0.11 (−0.14, 0.36)	.20	−0.01 (−0.11, 0.08)	.77
Clinical feature of interest	—	—	−0.02 (−0.53, 0.49)	.93	0.00 (−0.14, 0.15)	.95	−0.02 (−0.10, 0.07)	.66	0.05 (−0.08, 0.18)	.41	−0.21 (−0.36, −0.06)	.008	−0.09 (−0.17, −0.01)	.027	0.02 (−0.11, 0.15)	.76	0.31 (0.04, 0.58)	.039	0.00 (−0.10, 0.11)	.95

Clinical variables of interest (i.e., model names) are univariate effects, each from their own model. Intercept values reflect reference valence ratings for males of mean age in the neutral valence and moderate arousal stimulus conditions. Standardized beta (Std. B) and 95% confidence intervals (CI) for each predictor in the model, with the only variable different across models being the clinical feature of interest (e.g., CAH type, testosterone, etc.). Significant P values (P < .05) are bolded. Abbreviations: 17-OHP, 17-hydroxyprogesterone; CAH, congenital adrenal hyperplasia; SD, standard deviation; SV, simple-virilizing; SW, salt-wasting.

Results

Group Differences in Emotion Perception

Results of linear mixed-effect models examining group differences in valence and arousal ratings and reaction times, while controlling for mean-centered age, sex, and valence and arousal image condition with subject ID as the random intercept, are reported in Tables 2 to 5 and visualized in Fig. 2. For valence ratings of IAPS, significant effects were seen for both valence (negative, neutral, positive) and arousal (low, moderate, high) conditions of IAPS (P's < .001), an overall group effect (P = .012), as well as a significant group-by-valence condition interaction (P < .001) (Table 2). As expected, regardless of group, ratings were significantly different for negative, neutral, and positive IAPS images in both CAH and control youth (Table 3). Follow-up post hoc tests revealed that youth with CAH rated negative (P = .007) and neutral (P = .019) valenced images as more negative as compared to control youth (Fig. 2A and Table 3). Yet, youth with CAH did not rate positive images differently than control youth (P = .998) (Fig. 2A and Table 3). In terms of the amount of time that youth took to complete each valence rating of IAPS images, we observed a significant group-by-valence condition effect (P = .009), but no significant main effects in predicting reaction time (Table 2). Follow-up post hoc tests revealed that control youth showed significantly slower rating reaction times for negative vs positive IAPS images (P = .014), whereas youth with CAH did not show significant differences in reaction times between any of the 3 IAPS valence conditions (Table 3).

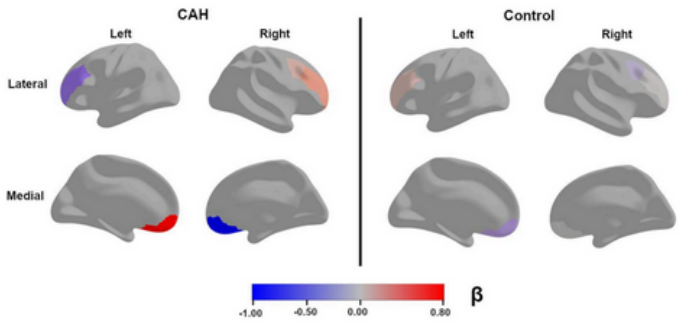

Figure 3. Cortical brain volume associations with valence scores, stratified by group. Beta estimates for regions of interests showing different associations between cortical brain volumes and valence ratings in youth with CAH and control youths. Brain volumes are scaled by a factor of 1,000; each unit in the estimate reflects mean predicted change in valence ratings per 1,000 mm3 increase in subregion brain volume. Blue reflects negative beta estimates whereas red reflects positive beta estimates.

Table 8. Post hoc group contrasts of cortical brain volume effect on valence ratings

	Control	CAH	Group difference	
	Estimate (SE)	Estimate (SE)	Estimate (SE)	*P*
Right CMF	−0.12 (0.09)	0.15 (0.12)	0.22 (0.13)	.07
Right RMF	0.00 (0.08)	0.22 (0.10)	0.22 (0.13)	.10
Left RMF	0.08 (0.09)	−0.46 (0.12)	**−0.54 (0.13)**	**<.001**
Right MOF	0.01 (0.16)	−1.00 (0.28)	**−1.01 (0.32)**	**.002**
Left MOF	−0.42 (0.23)	0.79 (0.21)	**1.21 (0.30)**	**<.001**

Results reflect "emtrends" post hoc group contrasts of the effects of cortical brain volumes predicting valence ratings. Brain volumes are scaled by a factor of 1,000; each unit in the estimate reflects mean predicted change in valence ratings per 1000 mm3 increase in subregion brain volume. Significant contrasts (P < .05) are bolded. Abbreviations: CMF, caudal middle frontal; MOF, medial orbitofrontal; RMF, rostral middle frontal; SE, standard error.

For arousal ratings of IAPS, significant effects were seen for both valence (negative, neutral, positive) and arousal (low, moderate, high) conditions of IAPS (P's < .001), a main effect of increased age being related to decreased arousal ratings (P = .010), as well as a significant group-by-arousal condition interaction effect (P = .020) (Table 3). Follow-up post hoc tests revealed that CAH and control youth rated IAPS images similarly in terms of their arousal for low, moderate, and high arousal images; however, control youth perceived moderate and high arousal IAPS images as significantly different from each other, whereas youth with CAH perceived moderate and high arousal IAPS images similarly in terms of eliciting feelings of excitement or nervousness (Table 4). In terms of reaction times during the rating of arousal of IAPS, we observed significant effects in both valence (negative, neutral, positive) and arousal (low, moderate, high) conditions of IAPS images (P's < .001), as well as a significant group-by-arousal condition interaction effect (P = .031) (Table 4). Follow-up post hoc tests revealed that, while youth with CAH showed slightly faster reaction times than control youth while rating both moderate and high arousal IAPS stimuli, group differences in arousal reaction times were not statistically significant for either of these conditions (Table 5).

In examining if clinical features related to IAPS valence rating differences noted in youth with CAH as compared to control youth, supplementary analyses showed some clinical features among our sample of youth with CAH were associated with IAPS valence ratings (Table 6). Specifically, we found a positive association between valence ratings and androstenedione levels (P = .027), and negative associations between valence ratings with both glucocorticoid treatment dosage (P = .008) and 17-OHP levels (P = .039), after controlling for age, sex, and stimulus condition. Additionally, after controlling for glucocorticoid treatment dosage, a sex difference emerged in valence ratings, with females having significantly lower ratings than males (P = .050). No significant associations were identified with other clinical variables of interest (Table 6).

Exploratory Brain Analyses

Exploratory stepwise selection resulted in a final model including volumes of the right amygdala, left hippocampus, right caudal middle frontal (CMF), and left and right rostral middle frontal (RMF) and medial orbitofrontal (MOF) cortices, in addition to all aforementioned controlled variables (i.e., age, sex, and valence and arousal image condition), with subject ID as the random intercept. Group-by-brain interaction effects were retained by stepwise selection for the latter 5 brain regions. Notably, we found volumes of the right amygdala, left hippocampus, bilateral RMF, and right MOF to be significantly associated with valence ratings, with larger left hippocampus and right MOF volumes associated with more positive valence ratings, and larger right amygdala volumes associated with more negative valence ratings (Table 7). Moreover, we observed significant group-by-brain volume interaction effects for the right CMF, left RMF, and bilateral MOF cortices, as well as a significant group-by-sex interaction effect on predicted valence ratings (Table 7).

Table 9. Post hoc contrasts of group-by-sex interaction effect on valence ratings

	Control		CAH		Group difference	
	Estimate (SE)	*P*	Estimate (SE)	*P*	Estimate (SE)	*P*
Male	5.04 (0.20)	—	5.09 (0.22)	—	0.06 (0.29)	1.00
Female	4.96 (0.17)	—	3.82 (0.23)	—	**−1.14 (0.29)**	.001
Sex differences	0.07 (0.28)	.99	**1.27 (0.31)**	**<.001**		

Results reflect "emmeans" post hoc tests contrasting valence ratings, averaged over all images, contrasting CAH vs controls and males vs females. Estimates represent estimated mean valence scores (ranging from 1 to 9, negative to positive) and score differences across group/sex. Significant contrasts (P < .05) are bolded. Abbreviations: SE, standard error.

Post hoc comparisons of group-by-cortical brain volume interactions showed that among youth with CAH, higher valence ratings were positively associated with volumes of the left MOF, but negatively associated with volumes of the right MOF and left RMF (Fig. 3A and Table 8). Conversely, associations between valence ratings and cortical volumes in control youth were only significant in the left MOF, where the association was negative (Fig. 3B and Table 8). While group differences were seen in the associations between ratings and brain volumes in the right CMF and right RMF, associations did not reach statistical significance when examining these associations in CAH or control groups alone (Table 8). Lastly, post hoc comparisons of group-by-sex interactions found that, averaged across all image conditions, CAH females rated IAPS images as significantly more negative than both CAH males ($\beta = -1.27$, $t = -4.17$, $P < .001$) and controls of both sexes (vs females: $\beta = -1.14$, $t = -3.97$, $P = .001$; vs males: $\beta = -1.22$, $t = -3.98$, $P = .001$). CAH males, on the other

hand, did not differ significantly from controls of either sex (vs females: β = .13, t = 0.46, P = .97; vs males: β = .06, t = 0.20, P = 1.00), nor did control males and females differ from each other (Table 9).

Discussion

The main finding of our study was that youth with CAH rated the valence and arousal of emotive IAPS images differently than age- and sex-matched controls. In particular, youth with CAH rated negative-valenced and neutral-valenced images as significantly more negative than typically developing controls; this effect was not seen for positive-valenced images. Supplementary analyses revealed that glucocorticoid treatment dosage, androstenedione levels, and 17-OHP levels were significantly associated with valence ratings across all conditions in youth with CAH. In terms of reaction times, control youth took significantly longer to rate negative images as compared to positive images, whereas youth with CAH exhibited no significant differences in reaction time across valence conditions. Control youth rated high arousal IAPS images as significantly higher arousal than moderate arousal IAPS images as expected, whereas arousal ratings across these two conditions did not differ significantly in youth with CAH. There were no significant group differences observed in arousal reaction time. These findings indicate that youth with CAH may perceive signals of negative affect more strongly, while retaining typical ability and speed of emotion perception in other affective domains.

These group differences in emotion perception may be due to previously observed smaller brain volumes in the amygdala, hippocampus, and prefrontal cortex in youth with CAH (15). Exploratory analyses found that brain volumes in these regions, alongside group-by-brain volume interaction effects, significantly predicted valence ratings. In both CAH and control youth, larger left hippocampal volumes were associated with more positive IAPS valence ratings, whereas larger right amygdala volumes were associated with more negative valence ratings. Significant group-by-brain interaction effects were observed in the left rostral middle frontal (RMF) and bilateral medial orbitofrontal (MOF) cortices. Post hoc decomposition of these interaction effects revealed that volumes of the left MOF were positively associated with valence ratings in youth with CAH, but negatively associated with valence ratings in controls. Conversely, larger volumes of the right MOF and left RMF were negatively associated with valence ratings in youth with CAH, but not in controls. These effects all remained significant after controlling for age, sex, total intracranial volume, and image valence and arousal conditions.

The developmental impacts of hormonal imbalances caused by CAH are particularly pronounced in females, due to the virilizing effects of increased androgen levels (1, 2). Exploratory group-by-sex interaction effects found that CAH females rated IAPS images, averaged across all conditions, as significantly more negative than both CAH males and controls of either sex. This effect suggests that CAH girls alone, as opposed to CAH boys and girls, might have rated negative- and neutral-valenced images as significantly more negative. These findings were corroborated by supplementary analyses among youth with CAH, finding that a significant sex difference emerged after controlling for glucocorticoid treatment dosage, with females having significantly lower valence ratings than males. Glucocorticoid treatment dosage may serve as a marker for severity of cortisol deficiency, and thus the amount of prenatal androgens produced as a compensatory mechanism (1, 2). Increased androgen levels having a particularly pronounced virilizing effect on females during development in utero may have downstream effects on brain development and cognitive and affective processing, leading to our observed sex differences in emotion perception (4, 12). Some evidence suggests that cognitive effects of CAH, such as improved spatial reasoning capacity, may be found in CAH females but not males, providing preliminary support for this hypothesis (37–39).

Independent of sex differences, our findings are consistent with previous observations showing that youth with CAH have altered perception and memory encoding of negative (i.e., angry or fearful) facial stimuli, corresponding with altered function in brain regions of interest, most notably the amygdala and hippocampus (19, 20). We also expand on these observations in three notable ways. First, we show that youth with CAH respond differently to negative affect not only in emotive faces, but to affective stimuli more generally, as in the case of the IAPS dataset (21). Second, we show that altered behavior and emotion perception in CAH may be related not only to group differences in functional activation (19, 20) or functional connectivity (40), but also to previously noted structural brain differences (15). Third, our study provides preliminary evidence that previously studied differences in CAH cognitive and emotional processing may be stronger in, or even unique to, females with CAH.

Beyond the paucity of research on CAH and emotion perception, these findings may be understood in relation to a broader literature linking structural brain differences to differences in emotion processing. For example, several studies have associated smaller amygdala volumes, or lesioned amygdalae, with altered processing of negative-valenced affective stimuli but intact processing of positive stimuli (41, 42). Moreover, past research on psychopathy has identified structural correlates between emotion perception and volumes in the amygdala and prefrontal cortex regions, including the MOF cortex, with differential associations for negatively and positively valenced stimuli (43). It is possible that smaller brain volumes in the amygdala, hippocampus, and prefrontal cortex in our sample of youth with CAH may partially explain our findings of altered perception of valence and arousal in IAPS images (15). Consistent with these findings, volumes of the hippocampus, amygdala, right RMF cortex, and bilateral MOF cortices predicted valence scores in CAH, even after controlling for age, sex, and total intracranial volume. Our findings are notable in demonstrating differential main effects on emotion perception of opposite directions in three distinct cortical regions (i.e., left RMF and bilateral MOF) across CAH and control youth. Additionally, within both CAH and control groups, we observed opposite-direction relationships with valence ratings across the left and right MOF cortex, highlighting the importance of bilateral segmentation in revealing more nuanced structural correlates of brain functioning.

There are several methodological limitations in both this study and the CAH literature at large that should be addressed in future research. Firstly, our sample size is relatively small, consisting of only 27 CAH and 35 control participants. Future research should aim for larger sample sizes to increase both reliability and power to detect small effect sizes. This is especially important when examining sex differences in the effects of CAH, which result in reduced statistical power by splitting sample sizes in half. Secondly, while supplementary analyses revealed some clinical features of CAH (i.e., glucocorticoid treatment dosage, androstenedione levels, and 17-OHP levels) were related to overall valence rating behavior, many others did not. Yet, the current sample size may be underpowered to detect small or medium effects, suggesting further research is needed to understand the potential moderating roles of adrenal crises, CAH type, hormone levels, and/or treatment in youth with CAH and emotion perception. Finally, while novel in its approach of relating emotion processing differences to structural brain differences, it is unclear to what degree these findings are reflective of underlying differences in brain function or connectivity. Therefore, future neuropsychological research in CAH should seek to also examine brain function, using fMRI or related methods, as they relate to cognitive and behavioral group differences.

In conclusion, we found significant group differences in emotion perception between youth with CAH and typically developing controls, which were associated with structural differences in key brain regions of interest. Our study, though correlational in design, highlights how differences in brain structure may contribute to other cognitive differences in CAH, such as reduced working memory capacity (6, 7). Identifying which brain subregions are associated with cognitive and behavioral differences in CAH may also shed light on the developmental trajectory by which CAH influences the brain. Future study is merited to examine the degree to which altered emotion perception, particularly in responding to negative stimuli, may relate to established affective and behavioral differences in children with CAH, such as increased aggression (9, 10). It remains unclear whether these observed differences are mediated primarily by hormonal imbalances prenatally and/or in early development, differences in pubertal development, or long-term neurophysiological

changes brought on by medical interventions such as glucocorticoid treatment (12). Additionally, it is unclear whether the present findings represent true neuropsychological changes brought on by altered brain structure in CAH, or whether this relationship is merely a marker for broad-scale impacts of hormonal imbalances in both the domains of emotion perception and brain structure. To answer these questions, future longitudinal research should seek to relate behavior, brain structure, and brain function in patients with CAH to their past or present hormonal imbalances, particularly considering the effects of androgen levels, glucocorticoid treatment, and CAH phenotypes and genotypes on structural and functional brain development.

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Data Availability
Restrictions apply to the availability of data generated or analyzed during this study to preserve patient confidentiality or because they were used under license. The corresponding author will on request detail the restrictions and any conditions under which access to some data may be provided.

(Full Article & References)

RESEARCH

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- **2 Adult Panelists**
  - **Adult with Hemophilia at time 00:37**
  - **Adult with Fredrich's Ataxia at time 1:33**

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CLAY SHOOT for CARES

Thank you to everyone that attended the 8th Annual Clay Shoot for CARES in Coplay, PA!

This year we had over 100 people take part in this event. So far, we have raised upwards of $150,000 since the Clay Shoot began in 2015. Thank you to all of our event sponsors and donors for your support!

Congratulations to all of our awards winners! We look forward to seeing you back next year, and hope that more of the CAH Community will join us for this successful and fun event!

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September 26, 2024

Reach out to john@caresfoundation.org to be notified when registration opens!

IT WAS A VERY SUCCESSFUL WALK SEASON THIS SUMMER & FALL THANKS TO EVERYONE'S SUPPORT!

If you are interested in hosting a walk in your area in 2024, please contact dina@caresfoundation.org for more information.

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2ND ANNUAL LONG ISLAND, NY CAH AWARENESS WALK



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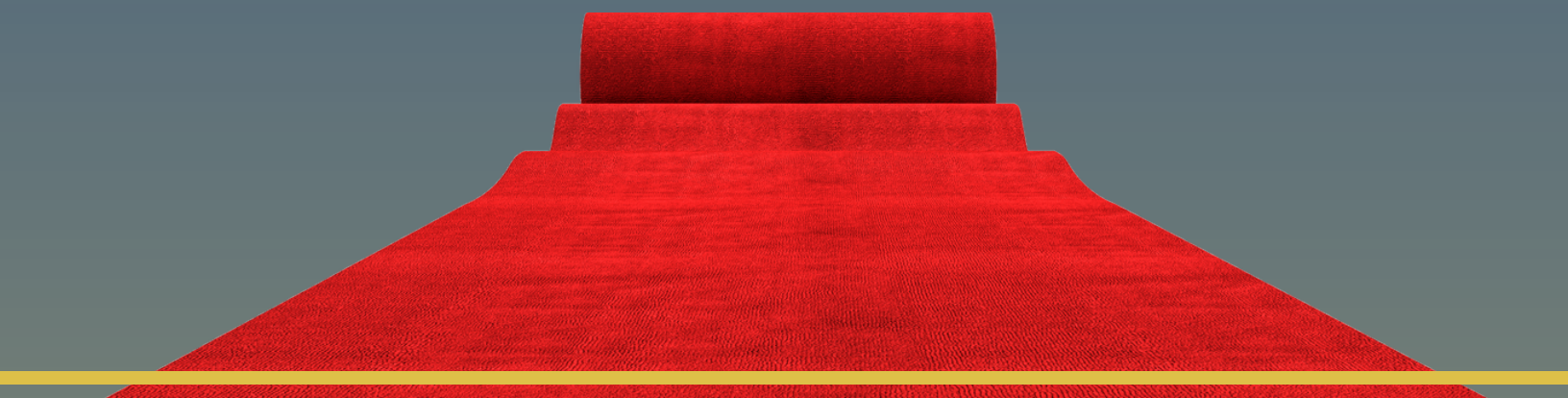
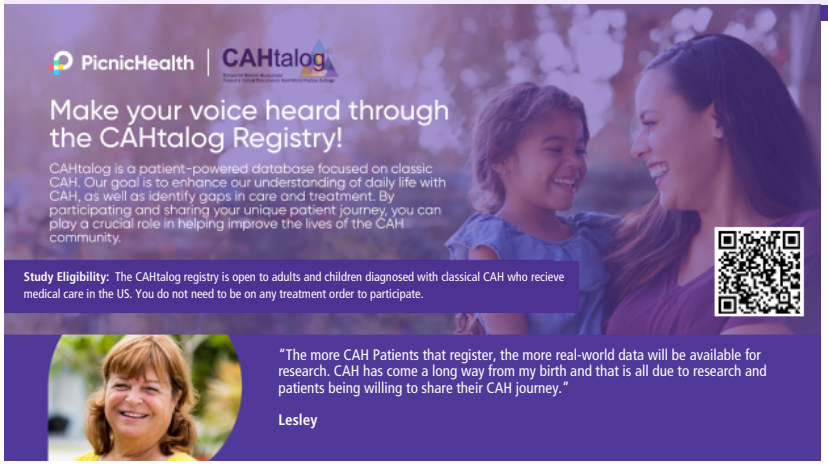
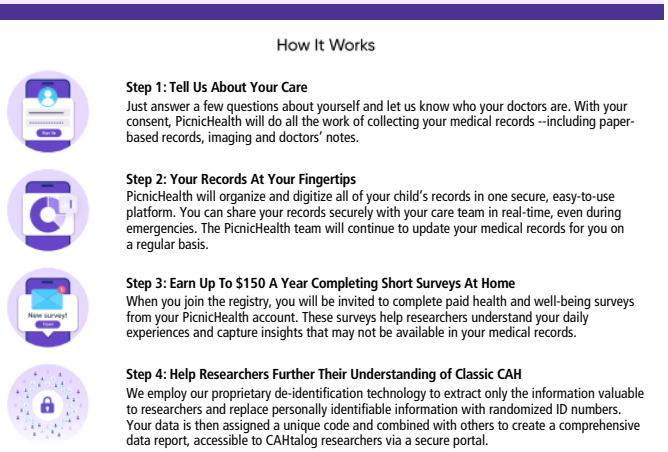


What is the CAHtalog Patient Registry?

CARES Foundation, partnering with Neurocrine Biosciences and PicnicHealth, has established the CAHtalog (Congenital Adrenal Hyperplasia: Patient and Clinical Outcomes in Real-World Practice Settings) registry. The goal of the registry is to support patient-centered research that will enhance the scientific community's foundational knowledge of classic CAH and ultimately improve the lives of patients who live with it every day. Participants can contribute to classic CAH research and share their unique patient journey and voice without the need for in-person visits - and all information will be kept private and secure. After enrollment, participants will have ready access to their digital medical records in one place.





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See how Eton Cares helps deliver accurate, individualized treatment for adrenal insufficiency: https://www.alkindisprinkle.com/support/

†Restrictions, limitations, and/or eligibility requirements apply.
‡Anovo will work with doctors to obtain insurance coverage. If insurance is denied, patients may apply to the Patient Assistance Program.
§For newborns awaiting hospital discharge, medication may be delivered in as soon as 24 hours. Typical delivery is 3 to 7 days.

USE & IMPORTANT SAFETY INFORMATION

USE

ALKINDI SPRINKLE is a prescription medicine used in children from birth to less than 17 years old as replacement therapy when the adrenal gland is not making enough cortisol.

IMPORTANT SAFETY INFORMATION

Always give ALKINDI SPRINKLE exactly as your doctor has directed.

Do not take ALKINDI SPRINKLE if you are allergic to hydrocortisone or any of its other ingredients.

Adrenal Crisis: giving too low a dose or stopping medication can cause low levels of cortisol, which can result in serious illness or death. Treatment with intravenous hydrocortisone should be started immediately. When switching fromanother type of hydrocortisone to ALKINDI SPRINKLE,watch your child closely for any changes. If your child doesn't get the entire dose of ALKINDI SPRINKLE because of vomiting or spitting some granules out, contact your doctor to see if another dose is needed.

Infections: all infections should be treated seriously, and stress dosing of hydrocortisone shouldbe started early.Taking ALKINDI SPRINKLEshould not stop your child from being vaccinated but let your healthcare provider know prior to vaccination.

Growth Retardation: the long-term use of corticosteroids in high doses may cause growth retardation in children.

Decrease in Bone Density: corticosteroids can affect your child's bone growth and strength.

Cushing's Syndrome Due to High Doses of Corticosteroids: treatment with high doses of corticosteroids can cause Cushing's Syndrome. Treatment should be limited to the smallest dose required, and your child's growth and development monitored appropriately.

Changes in Vision: tell your doctor if your child has blurred vision or other vision problems during treatment with ALKINDI SPRINKLE.

Psychiatric Changes: corticosteroids can change your child's behavior or mood. Tell your doctor if your child has periods of extreme happiness, extreme sadness, hallucinations, or depression.

Gastrointestinal Reactions: tell the doctor if your child has stomach pain, upset stomach,black, tarry stools,or vomiting of blood. These could be signs of ulcers or tears in the stomach or intestines. Taking anti-inflammatory nonsteroidal drugs, like ibuprofen, naproxen, or aspirin, can increase the risk of ulcers or tears.

The most common side effects of ALKINDI SPRINKLE include retaining fluids, changes in glucose tolerance, high blood pressure, behavioral and mood changes, greater appetite, and weight gain.

Please visit ALKINDISPRINKLE.com/patient for more information

You are encouraged to report negative side effects of prescription drugs by contacting Eton Pharmaceuticals, Inc. at 1-855-224-0233 or the U.S. Food and Drug Administration (FDA) at www.fda.gov/safety/medwatch or call 1-800-FDA-1088.

Please see full Prescribing Information for more information.

(https://www.alkindisprinkle.com/wp-content/themes/alkindisprinkle/assets/pdfs/2c0fb3caa7a6f765db1805032e228555/alkindi-sprinkle-prescribing-information-02-2022.pdf)

Reference: 1. ALKINDI SPRINKLE. Package insert. Eton Pharmaceuticals, Inc; 2022.

1501-v1

Preventing Adrenal Crisis Events

PACE App

Have you downloaded it yet?

The Preventing Adrenal Crisis Events (PACE) app is available to patients, parents/caregivers, and medical professionals and is designed to provide readily accessible information and instructions for effectively managing AI (Adrenal Insufficiency). The app will include stress dosing and intramuscular injection techniques as well as other helpful tools.

AVAILABLE IN SPANISH IN JANUARY 2024!

Sponsored by:

NEUROCRINE BIOSCIENCES Walmart

Email support@caresfoundation.org for the Access Code

(Apple App Store Only)
https://apps.apple.com/us/app/pace-by-chaicore/id1490431010

(Android App Store Only)
https://play.google.com/store/apps/details?id=com.jafproductions.PACEAndroidNew&pcampaignid=web_share

Externally-Led Patient Focused Drug Development Meeting

CARES Foundation is planning to host an externally-led Patient-Focused Drug Development (EL-PFDD) meeting in 2024. The meeting will mark a milestone for the Congenital Adrenal Hyperplasia (CAH) community, as it will engage patients directly in the process of drug development. The PFDD meeting will afford CAH patients and their families an opportunity to provide the Food and Drug Administration (FDA), drug developers, and NPC stakeholders with community perspectives on a number of important issues affecting the lives of those living with the condition.

IMPORTANT DATES

2024 PATIENT EDUCATION CONFERENCE

SEPTEMBER 21 & 22, 2024

ROBERT WOOD JOHNSON UNIVERSITY HOSPITAL, NEW BRUNSWICK, NJ

If you are interested in participating please reach out to john@caresfoundation.org to be notified when registration opens!

PATIENT ADVISORY SUMMIT

SEPTEMBER 20, 2024
NEW BRUNSWICK, NJ

If you are interested in receiving a scholarship to attend this event, please reach out to contact@caresfoundation.org

COMPREHENSIVE CARE CENTER DIRECTORS MEETING

SEPTEMBER 23, 2024
NEW BRUNSWICK, NJ

If you are interested in sponsoring this event please reach out to john@caresfoundation.org!

GET READY TO LACE UP IOWA!

THE FIRST ANNUAL IOWA CAH AWARENESS 5K WILL BE HELD ON

MAY 18, 2024

DES MOINES WATER WORKS, DES MOINES, IOWA

CHECK-IN: 9:00AM WALK STARTS: 10:00AM

VISIT: HTTPS://CARESFOUNDATION.ORG/DESMOINESCAH5K/ TO REGISTER TODAY!

NOTEWORTHY

NEW PODCAST: CAH Pulse

Co-Hosted by Dina Matos and Stephanie Erb

Each month we will bring attention to the the many facets of a patient's journey. Patients and caregivers will share their experiences and advice, and explain the challenges of living with congenital adrenal hyperplasia. We will also be joined by medical professionals and researchers to talk about their work in the CAH Community.

Please reach out to dina@caresfoundation.org if you would like to be a guest on the podcast!

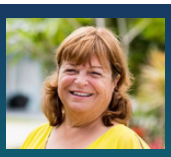
CAH Pulse is available on all platforms!

Solu-Cortef® Updates

UPDATE: PFIZER HAS EXTENDED SHELF FOR SOLU-CORTEF® BY SIX MONTHS!

Having trouble getting Solu-Cortef®? Please let us know.
Send us the name of your pharmacy, city and state to
support@caresfoundation.org

Rare Compassion Program



Lesley Holroyd has begun the second phase of her work with Global Genes' Rare Compassion Program.

Earlier in the year, she was partnered with a 1st-year medical student who learned first-hand from Lesley about living with a rare disease from the perspective of a patient, while also learning how to advocate for the rare disease patient. Lesley and Kayla, the medical student with whom she was partnered with, were asked to create a short video for Global Genes as part of their Rarely Told Stories program. Their video was 1 of only 5 videos selected from hundreds that were submitted to be presented at their annual fall conference in San Diego in September. Following the conference, the American Medical Women's Association (AMWA) posted the video on their social media channels.

During this second phase, Lesley is partnered with a 4th-year medical student and is looking forward to teaching her about life with a rare disease and the importance of advocating for patients.

Lesley's participation in this program has led to her being invited to present her CAH journey to a group of medical students in Miami who are learning about rare diseases!

Thank you Lesley for all you do on behalf of the CAH community!

2023 Giving Campaign
Support Our Growth

This year we have witnessed significant advances in CAH research thanks to our industry partners who are bringing new hope to the community, and to the brave patients who participate in trials. New treatments are only possible because of the individuals who actively participate in CAH research.

We have plans to add more centers of excellence; increase participation in the CAHtalog patient registry; support advances in new research, continue to push for an autoinjector; grow our EMS campaign; and develop new tools, including a patient education guide, to improve the quality of life for patients and families.

None of what we have accomplished since our founding in 2000 was possible without your support. We value your partnership and invite you to remain on this journey with us!

Please consider helping to support our growth by visiting: (https://charity.pledgeit.org/c/XBmu1lRIKD)

CARES Foundation Endowment Fund

Leave a meaningful gift that will have an enduring impact on the CAH community!

We have created an endowment fund account at the Community Foundation of New Jersey to ensure the longevity of our organization. Please consider giving to it.

A bequest can be arranged in a variety of ways. It can take the form of cash, property, or a part of your estate's remaining value. Including the CARES Foundation Congenital Adrenal Hyperplasia Endowment Fund into your Will could be a beneficial component of your plans, lowering your taxable estate while achieving your philanthropic objectives.

If you would like to name us in your Will or IRA, please add the following as a beneficiary:
Community Foundation of New Jersey
c/o CARES Foundation Congenital Adrenal Hyperplasia Fund
EIN 22-2281783

Ways to Contribute

- **Name us in your Will or estate**
- **Real Estate**
- **Shares of appreciated stock**
- **IRA RMDs**
- **Cash**
- **Interest or Shares of Operating Business**

For more information regarding this process or specific donations, please contact:

COMMUNITY FOUNDATION OF NEW JERSEY Phone: 973.267.5533 Toll-Free: 800.659.5533 Fax: 973.267.2903

Thank you for considering CARES Foundation!

November 28, 2023

GIVING TUESDAY

ALL DONATIONS MADE ON GIVING TUESDAY WILL BE MATCHED - UP TO $25,000!

Please consider GIVING to CARES so that we can continue to improve the lives of the congenital adrenal hyperplasia community!

CARES CONGENITAL ADRENAL HYPERPLASIA FOUNDATION

DOUBLE H RANCH Adaptive Winter Sports PROGRAM

Double H is excited for our upcoming winter season! The day program and family weekends are designed for medically qualifying campers, aged 6-16 and their families to enjoy the magic of winter in the Adirondacks together.

Activities include 1:1 instruction in alpine skiing or snowboarding with trained adaptive instructors and National Ski Patrol onsite. On family weekends, campers' family members can also take to the hill for group lessons.

Families are given private accommodations in camper cabins with meals provided FREE OF CHARGE.

Use the link below or QR code for more information

https://www.doublehranch.org/programs/winter/

Medical Advice from Medical Experts

ask the expert

Questions answered, worries alleviated, suggestions offered, CAH medical advice for your loved ones.

Dr. Karen Lin Su
CARES MEDICAL DIRECTOR

Dr. Alejandro Diaz
Director of the Division of Endocrinology at Nicklaus Children's Hospital in Miami.

pregunta el experto

Do you need expert medical advice before your next appointment?

Do you have unanswered questions about your treatment?

Then, DON'T FORGET about our program!

CLICK HERE: https://caresfoundation.org/ask-the-expert/ to visit this page

Haga clic aquí: https://caresfoundation.org/pregunta-el-experto/ para visitar esta pagina.

You must be registered with CARES to use this service. To join, click: https://caresfoundation.org/join-the-cares-community/

cares SUPPORT

Support Group Leaders

CARES support groups and private Facebook groups are available in a wide variety of demographics for any type of CAH patient or caregiver. Some groups meet for beneficial discussions that ultimately have the goal of providing necessary support in the areas you may need! Share your experience.

Leaders are also organized by topics like "Women", "Teens & Young Adults", "Parents of Newborns", "Parents of Teens & Young Adults", "Men", etc. We hope that you will take advantage of this program. We appreciate our leaders and know that they are there for you when you need extra support!

Support Group Meetings

Don't forget to check out our monthly, bi-monthly, & regularly scheduled Support Group Meetings. These meetings are hosted on Zoom and there is always a CAH-expert medical professional there to answer your questions in between doctor appointments or in times of worry or concern.

Use our Event Calendar (https://caresfoundation.org/calendar/) regularly for upcoming dates for these meetings. Registration in advance is required and all you have to do is send an email to support@caresfoundation.org with the date of the meeting you'd like to attend. To attend, you must first Join the CARES Community. (https://caresfoundation.org/join-the-cares-community/).

Please visit our support pages on our website to see if there is a leader in your area. https://caresfoundation.org/support/

Upcoming Support Group Meetings

December 7, 2023

SUPPORT GROUP MEETING* for Parents of School-aged Children, Teens & Young Adults, 8:30PM (ET)

December 14, 2023

SUPPORT GROUP MEETING* for CAH children, newborn-Age 5, 9PM (ET)

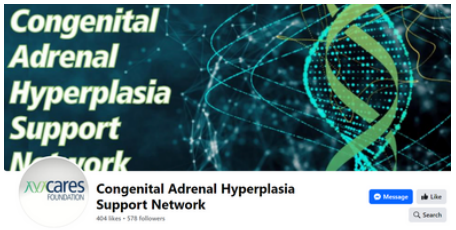
Please contact support@caresfoundation.org to confirm your attendance at any of the above meetings!

Support can also be found on our Facebook page.

Congenital Adrenal Hyperplasia Support Network Facebook Page

Here you will find several private groups where members share stories and experiences! Click the link below to be taken directly to our profile:

https://www.facebook.com/profile.php?id=100088886342973



We remind you not to give medical advice here. All medical questions should be addressed by a physician or other healthcare professional. We offer an Ask-the-Expert program on our website where you can email your questions/concerns to Drs. Su and Diaz. https://caresfoundation.org/ask-the-expert/

Thank you for your continued support!

WE ARE MOVING ALL PRIVATE FACEBOOK GROUPS TO CONGENITAL ADRENAL HYPERPLASIA SUPPORT NETWORK

If you would like to join any of the below listed Private Facebook Groups, please click the link provided in this post https://www.facebook.com/profile.php?id=100088886342973 and request access to join a specific group/groups directly through our profile by selecting 'More' and then 'Groups'. (If you are on a mobile device, select 'About' then 'Groups').

- CAH Women 50+
- CAH-X (CAH + EDS)
- Mexico CAH
- CAH Athletes
- Parents of Young Adults (Ages 25-35)
- Adoption & CAH
- Newborns
- Classic CAH Women
- CAH Partners/Spouses 17 Hydroxylase
- Parents and Caregivers of Girls with NCAH
- CARES Support Group Leaders
- Men & Dads with Sons with CAH
- Teens with CAH
- Surgery
- Parents/Caregivers of Teens with CAH
- Grandparents of CAH Children
- Parents of Kids with NCAH
- Men with CAH
- 3 Beta Women
- Bereavement Support Group
- 11 Beta
- Parents of Kids with CAH
- LGBTQIA+

If you are having trouble, or have any questions, please reach out to john@caresfoundation.org

YOU MUST BE A MEMBER OF THE CARES COMMUNITY TO JOIN ANY PRIVATE FACEBOOK GROUPS
JOIN FOR FREE HERE: https://caresfoundation.org/join-the-cares-community/

COMPREHENSIVE CARE CENTERS for CAH

Centers of Excellence

If you are seeking expert CAH medical care, then plan a visit to one of 8 CARES-designated Comprehensive Care Centers for CAH. These are highly specialized care centers that offer care throughout a patient's life cycle.

Children's Health/UT Southwestern Medical Center
1935 Medical District Dr
Dallas, Texas 75235

For appointments, contact Merritt Lamm or Emily Silva, (214) 456-5980
VISIT WEBSITE

Children's Hospital Los Angeles
4650 Sunset Blvd
MS #61
Los Angeles, CA 90027

University of Southern California/Keck Medical Ctr
8700 Beverly Blvd
Los Angeles, CA 90048

For appointments contact: Janet Guerrero, Comprehensive Care Center Coordinator, 323-361-4630 janguerrero@chla.usc.edu

VISIT WEBSITE

Children's Hospital of Philadelphia/ Main Hospital
3401 Civic Center Blvd.
Philadelphia, PA 19104
Penn Med – Philadelphia, PA

For appointments, 215-590-3174
VISIT WEBSITE

Cook Children's Medical Center
801 7th Avenue
Fort Worth, TX 76104

VISIT WEBSITE

New York-Presbyterian/Weill Cornell Medical Center
525 E 68th St,
New York, NY 10065

646) 962-3442, Option 1
Email, Attn: Koree Richardson, Coordinator
kor2005@med.cornell.edu

VISIT WEBSITE

Riley Hospital for Children/ Indiana University Health
705 Riley Hospital Dr
Indianapolis, IN 46202

Comprehensive Care Center Coordinator – Heather Frady, RN - Email Heather Frady
(317) 412-1206
VISIT WEBSITE

Seattle Children's Hospital and University of Washington
Medical Center
4800 Sand Point Way NE
Seattle, WA 98105

For appointments: (206)987-0304 or toll free, (866)987-2000
VISIT WEBSITE

Rutgers-Robert Wood Johnson Medical School (RWJMS), Child Health Center of New Jersey (CHINJ)
200 Somerset Street
New Brunswick, NJ 08901

VISIT WEBSITE

VISIT OUR CENTERS OF EXCELLENCE WEBPAGE FOR MORE INFORMATION ON OUR COMPREHENSIVE CARE CENTERS: https://caresfoundation.org/centers-of-excellence/

A Personal Story

From ever since I can remember I've seen myself as a little different from the other people around me. I pop pills multiple times a day, I carry a needle and medicine in my purse, and I enjoy putting salt on absolutely everything. Such is life with salt wasting CAH and it started on day one!

When I was born in Washington state in 1986 the state's universal newborn screening for CAH was almost brand new. My parents had moved to Fairchild AFB, just outside Spokane, from Maine. Unbeknownst to the Air Force, the move was probably a life saver for me. Washington began its universal newborn screening program in 1984 while Maine waited until 1998 to start their program. I was born with atypical genitalia so it was clear that there was some kind of serious problem but I was not sure what it was. The CAH screening program almost certainly shortened the time between my birth and my diagnosis and possibly saved my life.

As a child my medical situation was a significant part of my life (as it is today). I had to take pills and liquid medicine several times a day, which meant going to the nurses' office at school. So embarrassing! My medic alert bracelet didn't help me feel "normal" either. On top of that I had an adrenal crisis once or twice a year until I was around twelve so ER visits and over night hospital stays were almost normal. The most difficult part of it all for me was how I felt about my body. The inspections at the doctor's office and the surgery when I was twelve were some of the worst parts of my childhood, honestly. Looking back on it now it seems like it would have overshadowed my life and caused my parents so much worry, but that really wasn't the case.

My CAH was only a small part of our family life and my parents never held me back from doing anything because of my CAH. They did take my CAH seriously but it didn't hinder our family from rock climbing, camping, white water rafting, or hiking all the trails we could find. In high school I ran cross country and track; in college I went backpacking twice a year with friends for fall and spring breaks. One of my favorite memories was hiking part of the Appalachian trail in Great Smoky Mountains National Park. Between high school and college I even spent six months in Japan, thousands of miles from my parents or anyone they knew. I even went to the ER in adrenal crisis in Japan due to my own careless choices. But my parents didn't panic and demand my return to the US. Their confidence in me, seeing me as a "normal person", taught me not to be afraid of life because of my CAH.

It was easy for me to see myself as no different from others when it came to sports or making friends but the romance area of my life was different. I didn't have a menstrual cycle until I was twenty five and worried that I'd never have children. A few years after college I went to a talk therapist worked to get past the intense fear I felt when men expressed interest in me, which was a product of the combination of trauma from a very coercive medical genital examination as a child and my own unresolved fears about that part of my body. I can testify that a psychologist or counselor really is an important part of the treatment team for CAH patients. I'm happy to say that now those struggles are a thing of the past. Because I was able to accept myself and my CAH, I was emotionally ready to fall in love when the right man came along.

Today I'm married to a kind hearted, devoted husband and I'm the mother of a wonderful, healthy two year old boy. Early on in the pregnancy we met with a genetic counselor and underwent carrier screening for a long list of genetic disorders. To my surprise my husband wasn't a carrier for a single genetic disorder! What a relief!

Today I see myself as almost the same as everyone else except for the facts about my CAH, which I keep private. My CAH still doesn't stop me from doing the sports or travel I enjoy. It tried to block me from romantic love but with help I faced my feelings and overcame them. An unexpected gift of my experiences is a genuine empathy for other people facing physical or mental health struggles.

Finally, I'd like to pass what I've learned after 37 years of experience with CAH: Always wear your med alert! No matter what, find a doctor you trust. Educate yourself about CAH! It's your life and you can keep it as private as you want. Most importantly, a person who really loves you will accept all of you, including the CAH.

Special thank you to Lydia Mather for sharing her story!

THE DOCTOR IS IN

Dr. Karen Lin Su

CARES Medical Director

Vaccinations in CAH

Introduction

Vaccines provide a way for people to produce immunity (the body's natural defense) against infectious diseases. They work by teaching one's own immune system to develop natural defenses against pathogens by mimicking a natural infection.

Types of Vaccines

1. Live, attenuated vaccines

- Contain a version of the living pathogen that has been weakened, so it does not cause disease
- Closest to a natural infection, so very effective at conferring long-lasting immunity with only one or two doses
- Individuals with compromised immune systems should not be given live vaccines because of the remote possibility that the attenuated pathogen could mutate and cause disease
- Examples: measles, mumps, rubella, varicella (chicken pox), yellow fever

2. Messenger RNA (mRNA) vaccines

- A piece of mRNA that corresponds to a viral protein (such as the COVID-19 spike protein) is introduced into muscle cells
- The muscle cells use information from the mRNA to produce the protein and then quickly break down the mRNA. The mRNA does not enter the nucleus and does not alter DNA.
- Examples: Pfizer-BioNTech and Moderna COVID-19

3. Inactivated vaccines

- Contain killed microbe that cannot mutate back to disease-causing state
- Stimulate a weaker response than live vaccines, so require multiple doses and booster shots to maintain immunity
- Examples: RSV, influenza (flu), pertussis, typhoid, cholera, inactivated polio virus

4. Subunit/conjugate vaccines

- Include only the parts of the pathogen (called antigens) that best stimulate the immune system
- Not effective in infants and young children (under 18-24 months)
- Induce only short-term immunity
- Examples: hepatitis B, meningococcus, pneumococcus, Novavax COVID-19

5. Toxoid vaccines

- Used when a bacterial toxin is main cause of illness
- Toxin is inactivated into a "toxoid" and is then safe for use in vaccine
- Examples:
  - tetanus
  - diphtheria

Can CAH patients on steroid treatment be vaccinated?

Yes, CAH patients can and should receive vaccinations because vaccines protect against debilitating and potentially life-threatening diseases.

Stress-dosing for routine vaccinations is not necessary unless a fever develops.

While live vaccines should not be given to immunocompromised patients, CAH patients are typically treated with replacement doses of steroid, so they are not usually considered to be immunosuppressed. However, if someone is chronically treated with very high doses of steroids, they may be immunosuppressed and live vaccines should be used with caution.

EMS Advocacy 2023

Thank you Gretchen and all who had participated in our Summer of Change EMS Advocacy master class sessions! Stay tuned for more EMS advocacy in 2024!

For more information on any free online webinars throughout the year, make sure to be on the lookout for any social media posts, emails, or updates to our event calendar!

www.caresfoundation.org/calendar

Ways to Support CARES

HOST A FACEBOOK FUNDRAISER!

Have you got a birthday coming up, or a wedding anniversary, retirement, or other special occasion? To honor this special event, try raising money for CARES on Facebook. It's easy to do and Facebook takes you through setting up a fundraiser step-by-step. They even published a guide for your convenience: https://tinyurl.com/pvub644a Make sure to share your fundraiser and use hashtags to bring attention to the CARES community & others with CAH. (#caresfoundation, #congenitaladrenalhyperplasia, #CAH, etc.)

Please keep us in the know by tagging CARES Foundation in your fundraiser post!

Thank you to everyone who has raised money so far!

If you've already hosted a Facebook fundraiser for CARES please let us know that too. We'd like to show our gratitude.

Walmart SPARK | **cares** CONGENITAL ADRENAL HYPERPLASIA FOUNDATION

Every time you shop at Walmart.com, you are able to round up and direct Network for Good to support CARES Foundation!

Visit the link or QR Code to see our Page!
https://www.walmart.com/nonprofits/5c53a68e-bace-4c07-a4d2-4ba53a91df19/profile

THE CARES SHOP

https://caresfoundation.org/cares-shop-ii/

In our online store you can find helpful tools and resources that can make living with CAH a little bit easier. Check out our assortment of items that promote raising awareness for CAH throughout everyday activities.

Traveling with CAH/AI Packet Printed with Shot Kit

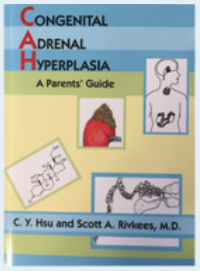
Traveling with CAH/Adrenal Insufficiency (AI) is all about being prepared, taking the proper precautions, and most of all, having fun! CARES Foundation's "Traveling with CAH Packet" will help you plan for a safe and healthy trip.

Medical I.D. Shoe Tags

Medical ID Shoe Tags are 2-ply red plastic oval tags (1"x1 1/2") with two holes (each 3/16" diameter). Laser engraved with medical id logo on front side and personal info on back side for privacy.

Emergency Response Kit (Set of 3)

Clear, plastic, water-resistant bags just the right size for your Emergency Response Kit. Emergency wallet card and Emergency Instructions brochure are included.



Congenital Adrenal Hyperplasia: A Parents' Guide

A nuts-and-bolts look at CAH-what this condition is, how it is inherited, and how it is treated and monitored. This new book on CAH written for a lay audience will be welcomed by all patients, parents, caregivers, and healthcare professionals.

CARES Foundation Ceramic Mug

Beautiful 17 oz. ceramic mug with CARES logo, website and signature heart! Use at home or at the office - a conversation starter for CAH awareness! Price include Shipping & Handling!

CARES Emergency I.D. Luggage Tag

Luggage tag good for a purse/bag, backpack or suitcase. Includes emergency instruction card.

Please remember that CARES Foundation newsletters have "gone green" and are available digitally. Please make sure we have your current email address to ensure that you continue receiving newsletters and other important information from CARES. Send any updates to john@caresfoundation.org.

cares CONGENITAL ADRENAL HYPERPLASIA FOUNDATION

www.CARESFoundation.org

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Email: contact@caresfoundation.org