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Increased aggression and activity level in 3- to 11-year-old girls with congenital adrenal hyperplasia

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Abstract

Experimental research in a wide range of mammals has documented powerful influences of androgen during early development on brain systems and behaviors that show sex differences. Clinical research in humans suggests similar influences of early androgen concentrations on some behaviors, including childhood play behavior and adult sexual orientation. However, findings have been inconsistent for some other behaviors that show sex differences, including aggression and activity level in children. This inconsistency may reflect small sample sizes and assessment limitations. In the present study, we assessed aggression and activity level in 3- to 11-year-old children with CAH (38 girls, 29 boys) and in their unaffected siblings (25 girls, 21 boys) using a questionnaire that mothers completed to indicate current aggressive behavior and activity level in their children. Data supported the hypotheses that: 1. unaffected boys are more aggressive and active than unaffected girls; 2. girls with CAH are more aggressive and active than their unaffected sisters; and 3. boys with and without CAH are similar to one another in aggression and activity level. These data suggest that early androgens have a masculinizing effect on both aggressive behavior and activity level in girls.

Keywords

activity level; aggression; aggressive behavior; androgens; testosterone; CAH; hormones; sex differences

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INTRODUCTION

Androgen levels during prenatal or neonatal development permanently influence behaviors that show sex differences. In rats, for example, reproductive behaviors, as well as play behavior, aggression, and maze learning show sex differences and are influenced by experimental manipulations of androgen shortly after birth (Casto, Ward, & Bartke, 2003; Collaer & Hines, 1995; Goy & McEwen, 1980). Similar influences of prenatal hormone manipulations have been seen for reproductive behavior and play behavior in non-human primates (Goy, et al., 1980; Wallen, 1996, 2001).

It is unethical to administer hormones during human development for experimental purposes. Therefore researchers interested in the influences of androgen on human development have studied naturally occurring situations (e.g., endocrine disorders) involving prenatal hormone abnormality. In this context, the most commonly studied disorder is classical congenital adrenal hyperplasia (CAH), an autosomal recessive disorder occurring in approximately 1 in 15,000 births (Pang & Shook, 1997). CAH involves enzymatic deficiency in the glucocorticoid pathway (in more than 90% of cases the deficient enzyme is 21-hydroxylase (21-OH)) (White & Speiser, 2000), and results in overproduction of adrenal androgens beginning prenatally (Miller & Levine, 1987). Because of the high levels of androgens, females with classical CAH are typically born with ambiguous genitalia involving varying degrees of clitoral enlargement, partial or total fusion of the labioscrotal folds, and development of a urogenital sinus. They are almost always assigned and reared as females and the external genitalia may be surgically feminized early in life.

In addition to a masculinized appearance at birth, females with classical CAH display increases in some male-typical behaviors from early childhood. For instance, there are consistent reports that girls with the disorder show enhanced preferences for toys and activities normally preferred by boys and for boys as playmates (Berenbaum & Hines, 1992; Dittmann, Kappes, Kappes, Börger, Stegner et al., 1990; Ehrhardt & Baker, 1974; Hines & Kaufman, 1994; Pasterski, Geffner, Brain, Hindmarsh, Brook et al., 2005). Similarly, several studies have found that women with classical CAH show reduced heterosexual interest and orientation (Dittmann, Kappes, & Kappes, 1992; Hines, Brook, & Conway, 2004; Money & Schwartz, 1976; Zucker, Bradley, Oliver, Blake, Fleming et al., 1996). However, evidence of early hormonal influences on some other human behaviors that show sex differences, including interest in infants, activity level, aggression, and cognitive abilities, is less convincing because data are sparse or inconsistent (Collaer & Hines, 1995; Hines, 2004; Hines, Fane, Pasterski, Mathews, Conway et al., 2003).

Both aggressive behavior and activity level show sex differences of moderate size in children, $d (M_1 - M_2 / SD, \text{Cohen, 1988}) = 0.58$ for aggression (Hyde, 1984), and 0.49 for activity level (Eaton & Enns, 1986). In rodents, as in humans, males are generally more aggressive than females, and this sex difference has been linked to androgen prenatally, as well as in adulthood (Simon, 2002). Both male and female animals increase aggression in response to androgen treatment in adulthood and females become more sensitive to these enhancing effects of adult hormone treatment following early treatment with androgen (Simon, 2002). In regard to activity level, normative studies of children show higher activity level in boys than in girls, but a similar sex-difference has not been reported in other mammals. For example, in rats, the amount of general locomotion does not differ between the sexes (Goy & McEwen, 1980); further, open field activity is greater in female rodents than in males (Goy & McEwen, 1980), a sex difference opposite that seen for activity level in children. Nevertheless, research in non-human mammals consistently shows that androgens promote male-typical development across the range of characteristics that show sex differences. Therefore, as for aggressive behavior, one might expect that exposure to androgen prenatally would increase activity level in children.

Prior studies of aggressive behavior in children with CAH have produced mixed results (Berenbaum & Resnick, 1997; Ehrhardt, et al., 1974; Ehrhardt, Epstein, & Money, 1968) (Table 1). One study suggested increased aggression in females with CAH (Berenbaum & Resnick, 1997), a second study found a similar, though statistically non-significant, trend (Ehrhardt & Baker, 1974), and two studies found no effects (Ehrhardt, et al., 1968; Money, et al., 1976). In general, these studies relied on small samples ($n = 11$ to 20 females with CAH and 5 to 15 controls) and measurement of aggression often involved responses of mothers to single interview questions. In addition, one study had no control group (Money, et al., 1976). Retrospective parental report also may have contributed to the lack of consistent findings. The one study that found a significant effect (Berenbaum, et al., 1997) used systematic assessment tools, but, even in this study, results were not consistent across three samples of individuals with CAH. In one sample, adolescent and adult females with CAH scored higher than controls on the aggression subscale of the Multidimensional Personality Questionnaire (MPQ) (Tellegen, 1982); however, a second sample of similarly-aged females with CAH showed no differences on the MPQ, although they scored higher than controls on a different measure of aggression, the Reinisch Aggression Inventory (RAI) (Reinisch, 1981). In a third sample, this time of young children, no differences were seen between girls with and without CAH on the RAI. No differences were found between males with and without CAH on either measure in any of the three samples.

Prior studies of activity level in children with CAH also have produced mixed results. One study reported increased activity level in girls with CAH (Ehrhardt & Baker, 1974), two found no effect (Dittmann, et al., 1990; Ehrhardt, et al., 1968), and one reported high activity level in girls with CAH, but did not include a control group (Money & Schwartz, 1976). (Table 2). The single study that included boys reported that boys with CAH showed higher activity level than male controls (Ehrhardt & Baker, 1974). This finding is unique in that it is the only report of enhanced male-typical behavior of any sort in males with CAH. Prior studies of activity level, like studies of aggression, used relatively small sample sizes, ranging from 15 to 33 individuals with CAH and 11 to 15 controls, and the one relatively large study of 33 participants divided the sample into 5 age groups for analyses. Other methodological limitations, such as retrospective reporting, reliance on single interview items for measures, and, in one case, no control group, may also have limited the power of the studies.

The current study was designed to provide more definitive information on the effects of early androgen exposure on aggression and activity level by using a larger sample than in prior studies and by using a standardized questionnaire measure of current behavior. In addition to avoiding problems associated with retrospective assessment, the questionnaire reduced social desirability biases that can be associated with face-to-face interviews (see Richman, Kiesler, Weisband, & Drasgow, 1999). We evaluated three hypotheses: 1. that boys show more aggression and higher activity level than girls; 2. that girls with CAH show more aggression and higher activity level than girls without CAH; and 3. that boys with and without CAH do not differ in either aggression or activity level. These hypotheses were based on research in humans showing sex differences in aggression and activity level, on research in non-human animals showing that early androgen exposure increases male-typical behavior and on prior human studies showing that girls, but not boys, with CAH show increased male-typical behavior in other areas.

METHOD

Participants

One hundred thirteen, three- to 11-year old, children (38 girls, 29 boys with CAH; 25 unaffected sisters, 21 unaffected brothers) and their mothers took part in the study. Forty children were recruited through pediatric endocrinologists in Los Angeles, California and participated at

University of California, Los Angeles, United States (US) and 73 children were recruited through pediatric endocrinologists in London, United Kingdom (UK), or through a CAH support group in the UK, and participated at City University, London. Fifty-nine (95%) of the children with CAH had the more severe, salt-wasting form of CAH and 3 (5%) had the less severe, simple virilizing form of CAH. Forty-seven percent of the Los Angeles sample was Hispanic, 38% was White, and 15% was African-American. All but two of the London sample were White (of British or other European descent). Two brothers were of mixed (Black/White) race.

Procedure and Materials

Procedures for the study were approved by institutional review boards in the US and in the UK and informed consent was obtained prior to participation. Participants were part of a larger study, from which data on toy choices and parental responses to sex-typical and sex-atypical toy choices have been reported previously (Pasterski, et al., 2005).

Aggression and activity level were assessed using the Activity Level/Extraversion Questionnaire (Zucker & Bradley, 1995). This instrument includes 17 items for which a parent indicates on a 5-point scale (1 = not at all like my child to 5 = a lot like my child) how similar their child's behavior is to the behavior described. Example items are "My child is very energetic" and "My child is physically aggressive," (Table 3). The 17 items were originally extracted from a temperament questionnaire and were considered to be a measure of activity level/extraversion (Zucker, et al., 1995). However, some of the items appear to measure aggression, whereas others measure activity level. Therefore, we performed a factor analysis requesting the extraction of two factors, with the anticipation that items related to aggression would load on one factor and items related to activity level would load on the other. Principal components analysis revealed a two factor solution where both factors had eigenvalues exceeding 1; the first explained 36.59% and the second explained 11.45% of the variance. All items loaded substantially and primarily on one of the two factors, and items were assigned to the factor for which the loading was higher. The interpretation of component 1 as activity level and component 2 as aggression has face validity and each factor had high internal consistency reliability, $\alpha = .87$ for activity level and $.81$ for aggression (Table 3).

RESULTS

We first screened data for group differences in age. Means, SDs and ranges for age (in months) were 72.0, 24.8, 37–118 for unaffected girls; 82.4, 27.0, 36–139 for girls with CAH, 89.6, 29.4, 36–129 for unaffected boys; and 88.5, 23.7, 48–128 for boys with CAH. A 2 (sex) \times 2 (CAH Status) ANOVA revealed a main effect of sex, $F(1, 109) = 5.53, p = .020$, indicating that boys in our sample (both with and without CAH) were older than girls. Therefore, we entered age as a covariate for subsequent group comparisons

Two-way (sex \times CAH status) ANCOVA was performed for each of the two dependent variables, aggression and activity level. To follow up on these ANCOVAs and to test specific hypotheses, group differences were assessed using one-tailed t-tests for directional hypotheses and two-tailed t-tests where no difference was predicted. See Table 4 for a summary.

For aggression, the 2 (sex) \times 2 (CAH status) ANCOVA revealed a main effect of sex, $F(1, 108) = 5.83, p = .017$, and a sex \times CAH status interaction, $F(1, 108) = 13.49, p < .001$. Mothers rated their sons as more aggressive than daughters, regardless of whether or not they had CAH. Simple effects analysis of the two-way interaction revealed the hypothesized effects. Unaffected boys were more aggressive than unaffected girls $t(44) = 4.22, p < .001$, girls with CAH were more aggressive than unaffected girls, $t(61) = 4.25, p < .001$, and boys with CAH

did not differ from unaffected boys. Girls with CAH, boys with CAH, and unaffected boys did not differ from one another.

For activity level, the $2(\text{sex}) \times 2(\text{CAH status})$ ANCOVA revealed a main effect of the covariate (age), $F(1, 108) = 6.74, p = .011$, and a $\text{sex} \times \text{CAH status}$ interaction, $F(1, 108) = 13.12, p < .001$. Further analysis indicated that younger children were more active than older children, $r = -.20, p = .038$. Simple effects analysis of the two-way interaction revealed the hypothesized effects. Unaffected boys were more active than unaffected girls, $t(44) = 2.01, p = .013$, girls with CAH were more active than unaffected girls, $t(61) = 2.15, p = .009$, and boys with CAH did not differ from unaffected boys. Girls with CAH, boys with CAH, and unaffected boys did not differ from one another.

DISCUSSION

Our results suggest that the prenatal elevation in androgen that is experienced by females with CAH is associated with increased aggressive behavior and activity level in childhood. The girls with CAH in our sample were reported by their mothers to be significantly more aggressive and active than unaffected sisters. In addition, unaffected boys were rated as being significantly more aggressive and active than were unaffected girls. There were no significant differences in either aggressive behavior or activity level for boys with versus without CAH. Thus, all three hypotheses tested were supported for both aggression and activity level. These findings resemble prior findings for childhood play behavior (e.g., toy and playmate preferences) in children with CAH (Berenbaum, et al., 1992; Pasterski, et al., 2005), and for sexual orientation in women with CAH (Hines, et al., 2003). Thus, our findings suggest that the range of affected behaviors in females with CAH should be extended to include aggression and activity level in childhood. Prior studies may have failed to find similar results because of methodological limitations (e.g., small samples, insensitive measures, retrospective assessments and social desirability biases).

A prior study reported some evidence of increased aggression in adolescent and adult females with CAH, but not in younger girls with CAH (Berenbaum & Resnick, 1997). Based on this result, the authors suggested that activational influences of androgen after puberty might be necessary for the prenatal influences of androgen to manifest on aggression. Our results argue against this suggestion. Because we found increased aggression in three- to 11-year-old girls with CAH (mean age, 6 years, 10 months), it appears that the early influences of androgen on aggression can manifest without postpubertal hormone activation. Evidence that children show sex differences in aggression, and that, indeed, sex differences in aggression are larger in children than in adults (Hyde, 1984), also argues against the necessity for post-pubertal hormones to activate sex differences in human aggression. Alternative explanations for the lack of increased aggression in girls with CAH in the prior study include the small sample and the possibility that parents are reluctant to admit, in a face-to-face interview, that their daughters with CAH are aggressive.

Concentrations of androgen present prenatally may influence human behavior postnatally because androgens, and hormones derived from them, direct certain aspects of brain development during the prenatal period. Experimental research in other species has shown that manipulating androgen during comparable developmental periods influences fundamental processes of neural development and differentiation, including cell survival, neural connectivity, and neurochemical characterization (De Vries & Simerly, 2002). It is possible that the prenatal androgen exposure associated with CAH influences human behavior through similar mechanisms. However, the neural systems that regulate many of the behaviors that are altered in females with CAH are largely unknown. In the case of aggression, however, the medial amygdaloid nucleus (MA) could be a locus for hormonal influence. High density of

androgen receptors has been found in the MA of non-human mammals, including rodents and primates (McGinnis & Katz, 1996; Michael, Clancy & Zumpe, 1995) and it exhibits structural sexual dimorphism both in rodents (Hines, Allen, & Gorski, 1992; Mizukami, Nishizuka, & Arai, 1983) and in humans (Goldstein, Seidman, Horton, Makris, Kennedy et al., 2001). In addition, lesion and implant studies have implicated the MA in aggressive behavior in rodents and non-human primates (Meaney & McEwen, 1986; Meunier, Bachevalier, Murray, L., & Mishkin, 1999). There also is evidence that the MA is reduced in volume in individuals with CAH (Merke, Fields, Keil, Vaituzis, Chrousos et al., 2003). However, reduced MA volume appears to occur in both males and females with CAH, whereas we find that only females, not males, with CAH show increased aggression.

An alternative possibility to a direct influence of androgen on brain regions underlying aggression (or activity level) is that alterations in these behaviors are secondary to other consequences of CAH. For instance, the preference of girls with CAH for playing with boys and with boys' toys could expose them to the high levels of aggression and activity typical of boys, and thereby increase their own levels of these behaviors. It also has been suggested that parents of girls with CAH might promote male-typical behavior in their daughters (Quadagno, Briscoe, & Quadagno, 1977). However, parents report that they do not treat their daughters with CAH in a more male-typical way (Berenbaum & Hines, 1992; Ehrhardt & Baker, 1974), and an observational study of parental responses to sex-typical and -atypical play in girls with CAH, found no evidence for parental encouragement of cross-gendered behavior. Instead, parents were found to give their daughters with CAH stronger encouragement of female-typical behavior than their unaffected daughters (Pasterski, et al., 2005).

Although we found that girls with CAH showed higher levels of aggression and activity than did unaffected girls, similar increases were not seen for either aggression or activity level in boys with CAH. This result resembles results for other behaviors in males with CAH (Berenbaum & Hines, 1992; Ehrhardt & Baker, 1974; Pasterski, et al., 2005). The lack of behavioral changes in males with CAH is often attributed to feedback mechanisms that reduce testicular androgen production in response to the adrenal increase, an explanation consistent with evidence that male fetuses with CAH have androgen concentrations that are generally within the normal male range (Pang, Levine, Cederqvist, Fuentes, Riccardi et al., 1980; Wudy, Dörr, Solleder, Djalali, & Homoki, 1999). In contrast to findings of unaltered behavior in boys with CAH, Reinisch (1981) reported increased physical aggression in males as well as females who were exposed prenatally to androgenic progestins, because their mothers were prescribed these hormones during pregnancy. One possibility is that medical treatment with androgenic progestins produces more dramatic androgen exposure than that caused by CAH and prevents complete compensation by testicular decreases in androgen production. Alternatively, the finding suggesting increased aggression in boys exposed prenatally to androgenic progestins may have been spurious, given that only 8 progestin-exposed boys were studied.

In summary, our findings suggest that prenatal concentrations of androgens influence the development of aggressive behavior and activity level in children, and that girls with CAH might be expected to show elevated levels of these male-typical behaviors. Future studies are needed to identify the precise neural or social mechanisms that underlie these relationships between prenatal androgen and postnatal behavior. In addition, our study focused on reports of specific forms of aggression and activity level (i.e., direct aggression and general activity level). Future studies might investigate relationships between prenatal androgen exposure and other types of aggression and activity, such as indirect or relational aggression, or discrete physical activity.

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Table 1

Studies of Early Androgen Exposure and Childhood Aggressive Behavior

Study	Assessment Method	Measure	Clinical condition (Control group)	N's, Probands (controls)	Study outcome Aggressive behavior ^a	
					females	males
Berenbaum & Resnick (1997)	Self-report	MPO aggression subscale ^d	CAH (Sibling controls)	18 F, 11 M (13 F, 5 M)	CAH > control *	ns
sample 1	Self-report	MPQ aggression subscale	CAH (Sibling controls)	11 F, 17 M (5 F, 10 M)	ns	ns
sample 2	Retrospective self-report	RAI ^b	CAH (Sibling controls)	11 F, 17 M (5 F, 10 M)	CAH > control **	ns
sample 3	Parent-report	RAI	CAH (Sibling controls)	20 F, 15 M (10 F, 20 M)	ns	ns
Ehrhardt & Baker (1974)	Self- and parent-report	Semi-structured interview	CAH (Sibling controls)	17 F, 10 M (11 F, 16 M)	CAH > control, ns	ns
Ehrhardt, Epstein, & Money (1968)	Self-report	Semi-structured interview	CAH (matched controls)	15 F (15 F)	ns	---
Money & Schwartz (1976)	Retrospective self- and parent-report	Interview	CAH girls (no control group)	15 F	ns ^c	---

* p < .05

** p < .01

*** p < .001

^aMPQ - Multidimensional Personality Questionnaire (30). Participants rated how aggressive, vindictive, or revengeful they are.^bRAI - Reinisch Aggression Inventory (26). This measure assesses potential for aggressive behavior in hypothetical conflict situations.^cNo control group was employed and no statistics were reported; authors concluded that there was no effect on aggressive behavior given the low prevalence in their sample.

--- indicate that this group was not included in the study.

Table 2

Studies of Early Androgen Exposure and Childhood Activity Level

Study	Assessment Method	Measure	Study Population (control group)	N's, Probands (controls)	Activity Level	
					females	males
Dittmann, et al. (1990b)	Retrospective mother-report	Semi-structured interview	CAH (Sibling controls)	33 F, 14 F	ns	---
Ehrhardt and Baker (1974)	Self-report	Semi-structured interview	CAH (Sibling controls)	17 F, 10M (11 F, 16 M)	CAH > control ^{***}	CAH > control [*]
Ehrhardt, Epstein, and Money (1968)	Self- and mother-report	Semi-structured interview	CAH (matched controls)	15 F (15 F)	CAH > control, ns	---
Money and Schwartz (1976)	Retrospective self-report	Interview	CAH girls (no control group)	15 F	CAH high [†]	---

* p < .05

** p < .01

*** p < .001

[†] Thirteen out of 15 participants indicated vigorous energy expenditure.

--- indicate that this group was not included in the study.

Table 3
Two factor solution for Activity Level/Extraversion items

Item	Component 1 Activity level	Component 2 Aggressive behavior
03. My child is always on the go.	.78	
01. My child is very energetic.	.77	
05. In the playground, my child runs, climbs, and swings and is constantly on the go.	.77	
02. My child is off and running as soon as s/he wakes up in the morning.	.73	
04. When my child moves about, s/he usually moves about slowly.*	.68	
11. My child is bold and adventurous.	.59	
10. My child performs strenuous activities for long periods of time.	.55	
08. When outdoors, in a playground or in a park, my child plays quietly with toys.*	.52	
06. When my child moves about in the house, s/he runs rather than walks.	.51	
12. My child is noisy.	.47	
15. My child likes rough-and-tumble play.	.47	
07. My child splashes hard in the bath.	.44	
14. My child is curious and explores things.	.37	
16. My child fights.		.93
17. My child gets into fights with other children.		.83
13. My child is physically aggressive with peers.		.61
09. My child is physically aggressive.		.51
% of variance explained	36.59%	11.45%
Cronbach's alpha	.87	.81

*Reverse-scored

Table 4
Sex differences and CAH-control comparisons for activity level and aggressive behavior

	Females			Males			Sex diff. Controls			
	Control	CAH	d	Control	CAH	d	p	d	p	d
Activity level										
M	3.65	4.01	.55	4.04	3.79	.33	.236		.050	.59
SD	.65	.65		.68	.82					
N	25	38		21	29					
Aggressive behavior										
M	1.76	2.72	1.02	2.86	2.46	.38	.189		.000	1.34
SD	.64	1.14		1.04	1.08					
N	25	38		21	29					

d = mean difference divided by the weighted standard deviation (41).