

# Decreased Cortisol Levels in Adolescent Girls With Conduct Disorder

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**Background:** Female adolescent antisocial behavior is increasing, but little is known about the neuroendocrinologic aspects of this disorder. On the basis of reports of decreased cortisol levels in antisocial males, we investigated morning plasma cortisol levels in adolescent girls with conduct disorder (CD).

**Methods:** Three plasma samples for cortisol levels were taken every 20 minutes between 8 and 9 AM in 47 adolescent girls with CD (mean  $\pm$  SD age, 16.5  $\pm$  0.9 years) and 37 normal control girls (mean age, 16.0  $\pm$  0.8 years). All blood was drawn within 72 hours after the onset of menstrual flow.

**Results:** Girls with CD had significantly lower cortisol levels than girls in the normal control group at all 3 sam-

pling times. This finding was not due to procedural factors, demographic characteristics, or the use of medications. The girls with CD who had no other psychiatric problems had lower cortisol levels than girls with other disorders or those in the normal control group. In the multiple regression analysis, having CD predicted 10% of the variance in cortisol levels.

**Conclusions:** Morning plasma cortisol levels were significantly diminished in adolescent girls with CD. Decreased cortisol levels appear to be most strongly associated with antisocial girls who do not have other psychiatric disorders.

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**F**EMALE ADOLESCENT antisocial behavior is prevalent, whether defined as conduct disorder (CD) or delinquency. Conduct disorder is the second most common diagnosis given to adolescent girls,<sup>1</sup> and one third of adolescent female psychiatric patients receive the diagnosis.<sup>2</sup> In the general population, nearly 10% of 15- to 17-year-old girls meet criteria for CD.<sup>3,4</sup> The delinquency rate for adolescent girls and the proportion of arrests of females for violent crimes have increased dramatically in the past 2 decades.<sup>5,6</sup> Adolescent antisocial behavior is financially and emotionally costly to the teens and their families, and to society.<sup>7</sup> Antisocial girls become women with rates of criminal behavior up to 40 times greater than those of other women, a high risk of early death, complex psychiatric problems, a high rate of substance abuse, poor adult physical health, and intergenerational transmission of antisocial behavior.<sup>8</sup>

Unfortunately, current treatments for female antisocial behavior are ineffective.<sup>9-15</sup> Treatments may fail, in part, because little is known about biological correlates of female antisocial behavior. All

previous research on neuroendocrinologic function in antisocial disorders has studied males.

One of the most provocative neuroendocrinologic abnormalities reported in antisocial males is decreased cortisol secretion. Low plasma cortisol levels in response to experimental stressors was first described among adult male criminals referred to a maximum-security hospital.<sup>16</sup> These men were more violent than a criminal control group, who responded normally to the stressors with an increase in cortisol levels. Ninety-three percent of these hyporesponders had histories of repeated physical violence. Sixty-seven percent of the hyporesponders had committed murder, compared with only 14% of the criminal control group. Similarly, Virkkunen<sup>17</sup> found that violent male criminals had decreased cortisol secretion, but that cortisol levels were normal in nonviolent criminals and noncriminal violent men.

Antisocial behavior in boys has also been associated with low resting cortisol levels, especially in boys exhibiting physical aggression.<sup>18-20</sup> Similarly, both resting salivary cortisol levels and the cortisol response to psychological stimuli were nega-

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## SUBJECTS AND METHODS

### SUBJECTS

We recruited 15- to 17-year-old girls to ensure that as many girls as possible would be in Tanner stage V and yet not out of adolescence. Girls were recruited predominantly from the community, through newspaper ads and posters. The ads sought girls with behavior problems such as "truancy, fighting, stealing, and lying." The ads also indicated that we were interested in girls without these problems. Three hundred fifty-four girls were contacted through ads and posters, through friends already in the study (n=7), or through contacts in clinics (n=6).

Intake appointments were made after a brief telephone screening and explanation of the project. One hundred fifty-one girls completed intake appointments. Each girl was interviewed concurrently with a parent or guardian who knew her history (the majority of adult informants were mothers or fathers). The intake appointment was used to determine eligibility for the study and to collect baseline nonbiological data.

In addition, a structured psychiatric interview (see below) was used to classify girls into the conduct disorder (CD) or normal control (NC) group. Exclusion criteria for both groups were age outside the 15- to 17-year range, pubertal development less than Tanner stage V, history of head trauma with loss of consciousness for more than 15 minutes, serious medical illness that could affect hypothalamic-pituitary-adrenal (HPA) axis function (eg, diabetes, thyroid disorders, renal disease), IQ less than 65, or a history of psychosis. Additional exclusion criteria for the NC group were the presence of any lifetime psychiatric disorder or any symptom of CD. Since we were trying to recruit a sample that would be as representative as possible of girls in the general population who matched girls with CD, we did not exclude girls in the NC group who smoked cigarettes or had experimented with alcohol, marijuana, or other drugs. We defined experimentation as not having used these substances more than 5 times throughout a girl's life and having no social or physical sequelae of use; no NC girl exceeded these criteria.

Ninety-three girls (52 in the CD group and 41 in the NC group) were found eligible and agreed to participate. We

dropped 5 girls (3 in the CD group and 2 in the NC group) from the neuroendocrine protocol because we could not obtain a blood sample within 4 menstrual cycles of the baseline data collection. Four girls (2 in the CD group and 2 in the NC group) refused to give blood either initially or after an adverse event (vein collapsing, fainting). Thus, the final sample size for the neuroendocrine data presented in this article was 84 (47 in the CD group and 37 in the NC group).

### ASSESSMENTS

After explaining both stages of the study, we obtained written, informed consent from each girl and her parent or guardian. The intake interview was conducted separately with each girl and her parent. Data were collected about the following topics: family demographics, medical and developmental history of the girl, school experiences, psychosocial history, family function, family psychiatric history (parent only), and Tanner pubertal stage self-report (girl only). Psychiatric diagnosis was determined from the computerized version of the NIMH (National Institute of Mental Health) Diagnostic Interview Schedule for Children, Version 2.3 (DISC), Parent and Youth Versions.<sup>24</sup> All interviewers held bachelor's or postgraduate degrees. They were trained by the principal investigator (K.P.), who in turn had been trained by the developers of the DISC.

As indicated above, the DISC was used to classify girls into 2 groups. On the basis of concerns regarding the validity of using the aggression and age at onset *DSM-IV* criteria to diagnose female CD,<sup>1</sup> we modified the DISC slightly. First, we rephrased the question on fighting to read "Do you often get into fights?" rather than "Do you often start fights?" Second, our diagnostic algorithm required that antisocial behaviors be demonstrated for at least 1 year before the interview, but onset before age 13 years was dropped from the items to which it is attached in the *DSM-IV* criteria.

Subjects were given a diagnosis based on meeting criteria from either the youth or the parent report. It is difficult to know who is the more accurate informant at this age because some adolescents may share their feelings and activities with their parents, and others may not. Moreover, some adolescents exaggerate reports of what they do, while others minimize them. Therefore, we considered data from all sources to be equally valid.

tively correlated with symptoms of CD in aggressive and impulsive sons of substance-abusing fathers.<sup>21,22</sup>

Given that low cortisol levels have been found in antisocial males, we investigated whether they are also low in antisocial females. We chose to determine morning cortisol levels because cortisol secretion follows a circadian rhythm and secretion peaks in most people between 8 and 9 AM.<sup>23</sup> We focused on teenage girls who were in the final stage of puberty, and who met criteria for repeated antisocial behavior.

## RESULTS

### SUBJECT CHARACTERISTICS

The girls in the CD group were, on average, 6 months older than the NC girls (**Table**). Because all girls were

in Tanner stage V, we doubt that this finding is clinically significant. The CD group included slightly higher proportions of African American girls and girls of lower socioeconomic status. Rates of smoking, alcohol, and drug experimentation were also higher among girls with CD, particularly experimentation with drugs other than marijuana (primarily hallucinogens). Girls with CD had high rates of comorbid substance abuse, internalizing, and oppositional defiant disorders, although few of the girls with CD had comorbid attention-deficit/hyperactivity disorder.

### CD VS NC DIFFERENCES IN PLASMA CORTISOL

Mean plasma cortisol levels were significantly lower in the CD group at all 3 time samples (**Figure**). A repeated-measures analysis of variance was performed, and the ef-

## PROCEDURES

If a girl met criteria for either group, she was asked to participate in neuroendocrinologic testing. To control for any menstrual cycle effects on HPA axis activity, we drew all blood within the first 72 hours after the onset of menstrual flow.<sup>25-28</sup> Each girl participating in stage 2 was asked to call the study office as soon as she started her next menstrual period. When contacted, we arranged for an early-morning phlebotomy appointment within 72 hours of when she had begun her period. Fifty-two percent of the subjects had their blood drawn in their homes or at another designated meeting place (eg, school). The others were done at the study office. We inserted an indwelling catheter into the antecubital fossa of one arm. Samples were taken immediately on insertion (time 0), 20 minutes later (time 1), and 40 minutes later (time 2). Time 2 samples were used in the analyses. They were likely to be the most reliable estimates of morning basal secretion, since 40 minutes should have allowed the HPA axis to recover from the stress of catheter insertion. The catheter was kept patent with a saline flush between samples. Sixty-seven percent of the blood draws occurred before 9 AM (this time, however, was not significantly associated with CD vs NC status). However, because of the unpredictable schedules and behavior of these subjects, some girls had their blood drawn later than 9 AM, with starting times ranging to 11:15 AM. Most girls were studied within 1 menstrual cycle of baseline data collection, but erratic menses and scheduling difficulties resulted in some subjects having their blood drawn 2 to 4 cycles later.

All cortisol assays were performed without regard to diagnostic status. Plasma cortisol levels were determined with radioimmunoassay by means of a commercially available kit (Nichols Institute, San Juan Capistrano, Calif). Interassay variability, intra-assay variability, and assay sensitivity were 6.1%, 4.7%, and 1.4 nmol/L, respectively.<sup>29</sup>

Ten girls were taking medroxyprogesterone acetate and 5 were using oral contraceptives. One girl in the NC group signed up for the study and was pregnant by the time she was ready for neuroendocrinologic testing. Since the menstrual cycle in all 16 of these girls was suppressed, we drew blood when it was convenient for them, and as close as possible to the intake interview. We then tested for effects of these variables in the data analysis.

Effect of group status was significant:  $F_{1,82}=8.40$ ,  $P=.005$ . Results of  $t$  tests on log-transformed cortisol variables, which included corrections for unequal within-group error variances, showed  $t_{71.3}=2.13$ ,  $P=.04$  at time 0;  $t_{75.8}=2.74$ ,  $P=.008$  at time 1; and  $t_{78.4}=3.08$ ,  $P=.003$  at time 2. The fractional degrees of freedom reflect corrections for unequal variance. Results were similar when the analysis was repeated without the girl who was pregnant. They were also similar when analyses were repeated without a girl who took lithium carbonate, a girl who took sertraline hydrochloride, girls who took oral contraceptives, girls who took medroxyprogesterone, and girls with PTSD. The effect sizes were substantial: time 0,  $d=0.48$ ; time 1,  $d=0.61$ ; and time 2,  $d=0.67$ ; where  $d=(\bar{x}_{CD}-\bar{x}_{NC})/SD_{pooled}$ . Cortisol level was not significantly associated with age, ethnicity, socioeconomic status, or use of oral contraceptives.

Because hypocortisolemia in antisocial men may be particularly related to violence, we categorized the girls with CD as aggressive or nonaggressive on the basis of the presence of 1 or more aggressive behaviors in either the parent or youth DISC report (fighting, cruelty to animals or people, carrying or using a weapon, fire-setting, stealing with confrontation, police arrests for assault). Each behavior described by the girl or her parent was assigned 1 point, and the final score for aggressive CD was the sum of these points. Girls with CD were also divided into 3 groups defined by the presence of psychiatric comorbidity: CD and no comorbidity, CD and oppositional defiant disorder only, and CD and multiple diagnoses.

The protocol was approved by the institutional review boards at Allegheny General Hospital and the University of Pittsburgh Medical School, Pittsburgh, Pa. The girls and their parents were paid \$20 for baseline testing, and each girl received \$50 on completion of the neuroendocrinologic testing.

## DATA ANALYSIS

Any variable not displaying a normal distribution was log-transformed, including plasma cortisol level. Comparisons between the 2 groups were tested for statistical significance by using unpaired  $t$  tests, univariate and repeated-measures analyses of variance, correlation coefficients, or  $\chi^2$ , depending on whether the variables were interval or nominal. All tests were 2-tailed, and statistical significance was set at  $P\leq.05$ .

Cortisol levels are associated with many factors, including the time of day, time of year, and place when blood was drawn,<sup>30</sup> demographic factors,<sup>31-36</sup> taking oral contraceptives,<sup>28,37</sup> being pregnant,<sup>38-40</sup> and other psychiatric conditions, including posttraumatic stress disorder (PTSD).<sup>41</sup> Statistically controlling for all of these factors would absorb more degrees of freedom than we could afford with our sample. Therefore, we calculated propensity scores<sup>42</sup> (ie, the probability of CD vs NC membership) by logistically regressing group status on the above covariates. We then controlled for CD vs NC differences on the covariates by calculating a linear regression of cortisol on group status and the propensity score. By including the propensity score in the regression, we controlled for that information in the covariates that increased the likelihood of group membership. SPSS (SPSS Inc, Chicago, Ill) was used to conduct the analyses.

To control for NC vs CD differences on other variables that might affect cortisol level, we estimated propensity scores to summarize these differences (see above). We then computed a linear regression of time 2 cortisol level on CD vs NC group status and the propensity score. In this regression, belonging to the CD group lowered cortisol level by 185.1 nmol/L ( $t_{81}=2.53$ ;  $P=.01$ ), despite our having controlled for the group differences represented by the propensity score.

## PLASMA CORTISOL: AGGRESSION AND PSYCHIATRIC COMORBIDITY

Thirty-seven girls met the criteria for aggressive CD, with the number of aggressive behaviors ranging from 1 to 10 (mean and median, 3 behaviors). The mean of the plasma levels of cortisol in the aggressive CD group ( $n=37$ ) was

### Subject Characteristics\*

	CD (n = 47)	NC (n = 37)	P
Age, mean ± SD, y	16.5 ± 0.9	16.0 ± 0.8	.01
Lower SES†	41 (87.2)	26 (70.3)	.06
Ethnicity			
White	28 (59.6)	26 (70.3)	.31
African American	19 (40.4)	11 (29.7)	
Nicotine use‡	35 (74.5)	22 (59.5)	.15
Alcohol experimentation§	42 (89.4)	31 (83.8)	.45
Marijuana experimentation§	31 (66.0)	19 (51.4)	.39
Other drug experimentation	15 (31.9)	1 (2.7)	.001
ODD	20 (42.6)	0	NA
ADHD	3 (6.4)	0	NA
Depression	5 (10.6)	0	NA
Anxiety disorders	12 (25.5)	0	NA
Posttraumatic stress disorder	2 (4.3)	0	NA
Alcohol abuse/dependence	10 (21.3)	0	NA
Marijuana abuse/dependence	16 (34.0)	0	NA
Other drug abuse/dependence	1 (2.1)	0	NA
Diagnosis other than CD/ODD	29 (61.7)	0	NA

\*All variables except age are expressed as number (percentage). CD indicates conduct disorder; NC, normal control; SES, socioeconomic status; NA, not applicable; ODD, oppositional defiant disorder; and ADHD, attention-deficit/hyperactivity disorder.

†The SES categories 4, 5, and 6.

‡Girls were defined as nicotine users if they reported daily smoking.

§Experimentation was defined as not having used these substances more than 5 times throughout a girl's life.

||The NC girls were recruited on the basis of absence of these disorders.

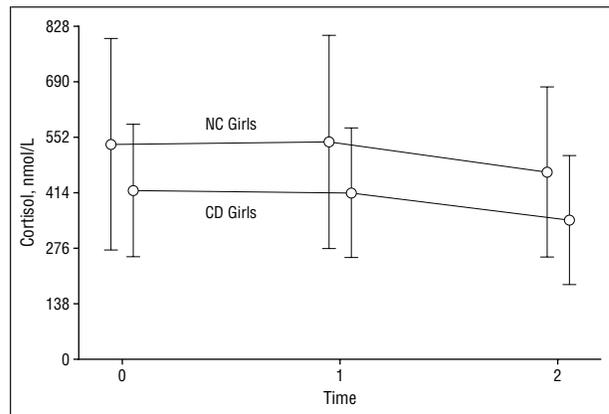
336.9 ± 173.5 nmol/L compared with a mean of 386.5 ± 102.6 nmol/L in the nonaggressive CD group (n = 10). However, this difference was not statistically significant ( $t_{45} = 1.92$ ;  $P = .07$ ).

To determine whether decreased cortisol level was simply a correlate of severe psychopathology, as manifested by multiple diagnoses, we examined the mean cortisol levels in the following groups: NC (n = 37) (467.4 ± 212.2 nmol/L), CD with no comorbidity (n = 12) (291.9 ± 131.6 nmol/L), CD with ODD only (n = 6) (338.8 ± 103.2 nmol/L), and CD with multiple diagnoses (n = 29) (372.2 ± 179.1 nmol/L). It is clear that the girls with CD who had no comorbidity, not the girls with multiple comorbid diagnoses, had the lowest mean cortisol level. Only 2 girls had comorbid PTSD, but their cortisol levels were the lowest 2 in the sample. However, these 2 subjects also met criteria for major depression, separation anxiety disorder, and generalized anxiety disorder.

### COMMENT

This is the first study, to our knowledge, of cortisol levels in antisocial girls. It confirmed our hypothesis that adolescent girls with CD would have lower morning cortisol levels than girls without any psychiatric disorder. Thus, it appears that adolescent antisocial girls may have HPA axis dysregulation similar to that found in antisocial boys and men.

The difference in mean cortisol levels between the CD and NC groups is much larger than those reported in previous studies on males.<sup>16,17</sup> Not all researchers have found a negative correlation between cortisol levels and



Cortisol levels in the girls with conduct disorder (CD) vs the normal control (NC) group. Each error bar represents 1 SD.

antisocial behavior in boys. Mean plasma cortisol levels drawn for morning baseline levels before a fenfluramine challenge were not different in a mixed group of prepubertal and adolescent boys who had “disruptive behavior disorders” compared with normal controls.<sup>43</sup> In 2 samples of boys with attention-deficit/hyperactivity disorder, the majority of whom had comorbid CD or oppositional defiant disorder, urinary free cortisol levels<sup>44</sup> and plasma cortisol levels<sup>45</sup> were no different than levels in NC subjects. However, all of these samples were composed of boys spanning the age range from latency to adolescence and who had been selected on the basis of disruptive behavior or attention-deficit/hyperactivity disorder, rather than repeated acts of antisocial behavior. Our more robust effect may be due to our sampling strategy, which selected a homogeneous group of late-adolescent girls who were in Tanner stage V and who had exhibited a pattern of repeated antisocial acts for at least 1 year. Our design further limited intersubject variance secondary to sampling time and menstrual cycle effects by standardizing these factors across subjects. However, it is also possible that the difference in cortisol levels between antisocial and normal subjects may be more pronounced in females because normal women have higher basal and reactive levels of cortisol than do normal men.<sup>46-48</sup>

The girls with CD displayed substantial psychiatric comorbidity, a finding consistent with other reports in the literature.<sup>49-52</sup> Nonetheless, we were able to demonstrate that the relationship between cortisol level and CD was not simply a reflection of severity of psychopathology, because subjects without other diagnoses actually had the lowest mean cortisol levels.

The finding that antisocial females have low cortisol levels raises important clinical questions. First, low cortisol levels may put these girls at risk for later autoimmune diseases, some types of atopic illnesses, increased inflammation, and infections with extracellular pathogens.<sup>53-61</sup> This may partially explain the poor adult health of women who had been antisocial adolescents.<sup>8,62-66</sup>

Second, low cortisol level may be a diagnostic marker for subtypes of girls with CD. To determine whether a biological correlate of a behavioral syndrome is a diag-

nostic clinical marker, one must first show that the relationship between the two is not due to a confounding factor. We have extended the previous work in males by demonstrating that the association between cortisol and CD is not due to factors such as season or race. The next step is to demonstrate that the biological finding discriminates between subgroups within the spectrum of a diagnostic category.<sup>67,68</sup> We did find that girls with aggressive CD had lower mean cortisol levels than girls with nonaggressive CD did, but this difference was not statistically significant. However, only 10 girls with CD were not aggressive. Thus, the question of whether low cortisol level is a marker for aggressive CD in girls remains unanswered.

On the basis of a study reporting a high rate of PTSD in a sample of incarcerated adolescent females<sup>69</sup> and data suggesting low cortisol levels in subjects with PTSD,<sup>41</sup> we also investigated whether low cortisol level was a marker for antisocial girls with PTSD. The girls with CD with comorbid PTSD had the lowest cortisol levels in our sample, but there were only 2 of them and they also met criteria for several other diagnoses. Furthermore, the NC vs CD differences remained when these 2 cases were deleted from analyses. This important issue should be addressed in a study with larger numbers of antisocial girls with PTSD.

Our design permitted us to examine many alternative explanations for the group difference in cortisol levels. One limitation of our study, however, is that we could not exclude sleep disturbance as an explanation for the difference between the CD and NC groups. If the girls with CD are less well supervised and their lives more chaotic, it is possible that, as a group, they may routinely go to sleep later than midnight. This could shift their circadian rhythm such that the 8 to 9 AM blood-drawing time may still be in the prepeak phase of their HPA axis cycle.<sup>70</sup> This question merits further research.

To date, there have been no studies of the mechanisms underlying decreased cortisol levels in antisocial subjects. However, animal and human data suggest that the ratio of corticotropin-releasing hormone to arginine vasopressin may be lower than normal in aggressive subjects, particularly in animals who have been bullied and become bullies themselves.<sup>71,72</sup> This explanation may account for both the aggression and PTSD aspects of our findings. Although this research has focused on males, one clinical study of pregnant teens did report that the girls with CD had lower plasma levels of corticotropin-releasing hormone than the pregnant controls without CD.<sup>73</sup>

Future studies on HPA axis function in these girls should focus on describing the basal state of cortisol secretion throughout the rest of the 24-hour cycle, determining if their HPA axis responds normally to experimentally induced stressors, and methodically investigating the function of each component of the HPA axis (eg, response to corticotropin-releasing hormone, assessment of glucocorticoid receptor function). Research on potential mechanisms may result in more effective pharmacologic interventions or facilitate the identification of subgroups of girls with CD who respond to different types of treatments.

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