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SHORT COMMUNICATION

Diurnal cortisol profiles and evening cortisol in post-pubertal adolescents scoring high on the Children's Depression Inventory

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Summary Early-onset mood disorders have become a significant public health problem in recent years. The Children's Depression Inventory (CDI) is a commonly used self-report measure. We studied the relation of CDI cut-offs to biological markers of depression such as the diurnal cortisol rhythm and evening cortisol. In 58 post-pubertal adolescents (29 boys and 29 girls, M_{age} = 15.1 years), the diurnal cortisol profile was derived from three saliva samples, collected at awakening, at noon and in the evening on a week-end day. Longitudinal repeated measurements regression revealed that the group with CDI > 18 (high depressive symptoms) clearly had a higher and flatter diurnal rhythm with elevated evening cortisol compared to either the group with CDI between 13 and 18 (moderate depressive symptoms) or CDI < 13 (low depressive symptoms). Multinomial logistic regression indicated that evening cortisol was useful in classifying the adolescents in the high depressive symptoms group, while awakening and noon cortisol were not. Our results indicate that the type of high flattened profiles sometimes seen in individuals who are clinically depressed according to diagnostic interviews can also be identified with a self-report inventory, at high levels of symptom reporting. Given the complexity of conducting diagnostic interviews, this result bears clinical relevance.
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1. Introduction

Early-onset mood disorders have become a significant public health problem in recent years. Miller (2007) reviewed epidemiological studies involving more than 2500 youngsters and concluded that approximately 2% of young children, 4% of young adolescents and 16% of older adolescents suffer from a major depressive disorder each year. Early-onset depression is a serious burden for an individual's health for the following reasons: (a) the functional problems of depressed youngsters suggest that the disorder can interfere with developmental milestones; (b) these individuals are likely to show symptoms of anxiety and to develop additional co-morbid disorders such as conduct disorders or substance abuse; (c) early-onset depression may persist into adulthood. Therefore, it is clear that the early recognition of mood disorders should be a priority in primary health care (Hyman, 2001) and that more research on depression prevention and intervention is needed (Kovacs, 2006; Adam et al., 2008). Although clinical interviews are obligatory to diagnose depression, in primary health care and research settings other sound yet less complex and time-consuming instruments are often used. The Children's Depression Inventory (Kovacs, 1992), containing 27 items scored from 0 to 2, is a commonly used self-report measure. As an index of severity of depressive symptoms, a cut-off score of 19 has been found to identify major depressive disorder/clinically depressed children and adolescents, whereas levels between 13 and 18 are regarded as a subclinical or minor depressive episode (Kovacs, 1992).

The usefulness of the CDI (and its cut-off scores) has not been studied in relation to important, non-invasive biological markers of depression such as cortisol assessed with saliva samples; our current study is a preliminary investigation of this issue. For example, depression in adolescent outpatients has been associated with a high, flattened diurnal profile (with elevated afternoon/evening cortisol and awakening levels that may be somewhat lower; Shirtcliff and Essex, 2008) or with elevated evening (peri-sleep-onset) cortisol levels (e.g., Dahl et al., 1991; Goodyer et al., 2001; Kaufman and Charney, 2001; Forbes et al., 2006). Our aims were to examine: (1) the association between the degree of depressive symptomatology (i.e., CDI < 13; CDI between 13 and 18 and CDI > 18) and the diurnal cortisol profile, i.e., whether and in what way the CDI can detect a high flattened diurnal cortisol profile (2) the relative importance of awakening, noon and/or evening cortisol in classifying adolescents into the CDI groups.

2. Method

2.1. Participants

The current study involves 58 participants (29 boys and 29 girls, M_{age} = 15.1 years, S.D. = .26 years; range = 14.5–15.5), whose mothers were recruited during pregnancy in a prospective follow-up study on the association between maternal anxiety during pregnancy and offspring development (Van den Bergh et al., 2008). Most of them had reached Tanner stage four of pubertal development (M = 4.13; S.D. = .526). The local ethical committee approved the study and we obtained informed consent from all adolescents and their parents.

2.2. Measures

The CDI was used to measure the severity of depressive symptoms over the last 2 weeks in this non-clinical sample of post-pubertal adolescents. Adolescents with CDI > 18 formed the high depressive symptoms group (HDSG), those with CDI between 13 and 18 the moderate depressive symptoms group (MDSG), and those with CDI < 13 the low depressive symptoms group (LDSG). The participants were asked to complete the questionnaire on the day they collected saliva. For reasons of feasibility, we planned the saliva collection on a week-end day, at home. We used a short version of the daytime cortisol profile (cf. Wüst et al., 2000) and samples were collected upon awakening (before brushing teeth and having breakfast), around noon and in the evening (approximately 4 and 12 h after awakening, respectively). Samples were collected by spitting in a small plastic tube (Sarstedt, Germany), without using swabs or aids to salivation. Cortisol was analyzed with a revised version of the protocol provided by the manufacturer of the Coat-a-Count Radio-Immuno-Assay Kit (Euro DPC, Llanberis, Wales). The method was sensitive to as low as 0.3 nmol/L; all cases below this threshold were set at zero.

2.3. Statistical analysis

For the first aim, longitudinal repeated measurements (LRM) regression analysis was used. The associations among the cortisol measurements at different times of the day – i.e., at awakening (time = 0 in the analysis), noon (time = 4) and evening (time = 12) – were best modeled using a heterogeneous first-order autoregressive covariance structure (Verbeke and Molenberghs, 2000). We investigated the main effect of CDI groups, the linear and quadratic time effects of cortisol (to investigate how the cortisol level evolves during the day), and the interaction effects of the CDI with the linear and quadratic time effects (to investigate whether the cortisol evolution depends on CDI). Cortisol was log transformed to account for observed skewness in the distribution, mainly for the noon and evening levels. It is useful to mention at this point that the three CDI groups were best modeled as categorical (i.e., LDSG, MDSG, HDSG) rather than numerical (i.e., 1, 2, 3), and that there were no effects (main or interaction) involving gender.

For the second aim, a multinomial logistic regression model was built to predict CDI group. Using the Bayesian information criterion and the likelihood-ratio p-values, variable selection was carried out in order to investigate the importance of morning, noon and evening cortisol. The final model yielded predicted probabilities for each CDI group, and these were used to construct the area under the receiver operating characteristic curve (AUROC) (Lasko et al., 2005). An AUROC of 1 represents a model that perfectly discriminates between two classes of adolescents in the data set (those belonging to that CDI group versus those belonging to the other groups), whereas an AUROC of .5 represents a model with random performance.

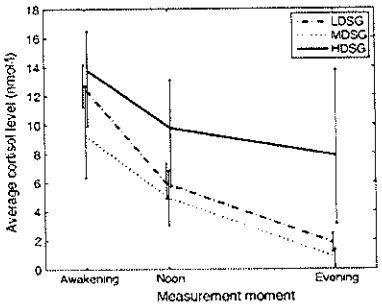

Figure 1 Diurnal cortisol profiles (i.e., average cortisol level at awakening, noon and evening, with their 95% confidence intervals) in the high depressive symptoms (HDSG; CDI > 18), moderate depressive symptoms (MDSG; CDI between 13 and 18) and low depressive symptoms (LDSG; CDI < 13).

3. Results

3.1. Aim 1

Fig. 1 shows the average cortisol profiles for the three CDI groups. The 95% confidence intervals were obtained using the bias-corrected bootstrap method using 1000 bootstrap samples to account for skewness and to ensure non-negative intervals (Efron and Tibshirani, 1993). The profile for HDSG ($n = 5$; $n = 4$ females) was flatter and higher than the profiles for MDSG ($n = 8$; $n = 4$ females) or LDSG ($n = 45$; $n = 21$ females). The LRM (see Table 1) revealed that the log-transformed cortisol level decreased throughout the day (cf. the linear time effect, $p < .001$) with the decrease slowing down as the day progressed (cf. the quadratic time effect, $p = .039$). Further, the diurnal cortisol decrease was stronger for MDSG and LDSG versus HDSG (cf. the interaction between CDI and the linear time effect, $p = .016$). Thus, the HSDG had a flatter profile. The interaction between CDI and the quadratic time effect was weak and was dropped from the model. The main effect of CDI was weak ($p = .195$), suggesting that there were no strong differences in awakening cortisol (for awakening, time = 0 so the effect involving time drop out). Thus, the flattened profile appears to be the result of elevated evening cortisol levels. This is confirmed by post-hoc regression analyses, where CDI groups only differed with respect to evening cortisol (ω^2 estimate of explained variation = .20, $p = .001$). Tukey–Kramer paired comparisons suggested that, regarding evening cortisol, the HDSG differed from the MDSG ($p = .002$) and the LDSG ($p = .002$) whereas the two latter groups did not differ much ($p = .531$).

3.2. Aim 2

Entirely consistent with the previous results, the multinomial logistic regression analysis revealed that only evening cortisol was useful in detecting CDI group ($p = .002$). More specifically, evening cortisol predicted HDSG (AUROC .88), but not LDSG or MDSG (AUROCs .50 and .66, respectively). All five HDSG adolescents had an evening cortisol of at least 2.5 nmol, while 40/53 (75%) LDSG/MDSG adolescents had a lower evening cortisol.

4. Discussion

The results regarding our two aims suggest that: (1) there is an association between the degree of depressive symptomatology and the diurnal cortisol profile: adolescents with a CDI > 18 showed a high, flattened cortisol profile; (2) evening cortisol is useful in identifying adolescents with CDI > 18 while morning and noon cortisol are not.

Depression has been linked with changes in the activity of the hypothalamus–pituitary–adrenocortical (HPA)-axis activity and several lines of evidence indicate that these alterations are not merely epiphenomena of the disorders but may play a role in the pathophysiology of depression (Van Praag et al., 2004). The flattened profile may reflect the failure of the HPA-axis to maintain a normal diurnal rhythm or efficiently manage the response to challenge, even in the absence of excessive stressful events (McEwen and Wingfield, 2003). Our results are in line with other research on the association between depression and either flattened cortisol rhythms or evening cortisol (see Section 1).

Table 1 Results of the longitudinal repeated measurements regression of log(cortisol + 1) on time effects and self-reported symptoms of depressed mood.

Effect	CDI-group*	Estimate (SE)	F-value (df1, df2)	P-value
Final model				
Intercept		2.66 (.195)		
CDI	LDSG	−.134 (.204)	1.69 (2, 55)	.195
	MDSG	−.404 (.247)		
	HDSG	0		
Linear time effect		−.109 (.0374)	37.60 (1, 112)	<.001
Quadratic time effect		.0042 (.0020)	4.37 (1, 112)	.039
CDI × linear time effect	LDSG	−.0874 (.03)	4.31 (2, 112)	.016
	MDSG	−.0870 (.0363)		
	HDSG	0		

* CDI = Children's Depression Inventory; LDSG = low depressive symptoms group; MDSG = moderate depressive symptoms group; HDSG = high depressive symptoms group.

However, our study shows limitations that warrant some caution in interpreting the results. (1) The sample size was small; (2) the study used single day samples and did not use monitoring devices or adjust the analyses for exact time of sampling; (3) we did not measure potentially confounding factors such as nicotine and caffeine use, use of steroid based medications, presence/absence of a menstrual cycle and menstrual timing; therefore we did not demonstrate that the association between the CDI and diurnal cortisol was independent of these confounding variables.

Our results indicate that the type of high flattened cortisol profile sometimes seen in individuals who are clinically depressed according to diagnostic interviews can also be identified with a self-report depression inventory, at high levels of symptom reporting. Given the complexity of conducting diagnostic interviews, the fact that a self-report questionnaire can be used to study associations between the HPA axis and depression is an important result that bears relevance for clinical practice. Our preliminary findings may stimulate further research on biological markers of depression. Besides replicating the concurrent associations between the CDI and cortisol measures, it would be interesting to study whether a high, flattened cortisol profile or elevated evening cortisol are predictive of a future depression in adolescents, as observed by Shirtcliff and Essex (2008), because prospective studies most often found associations between morning cortisol and subsequent depression (Adam et al., 2008).

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Conflict of interest

None of the authors has a potential conflict of interest.

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