Brief Report: Role of Cortisol in Posttraumatic Stress Symptoms among Mothers of Children Diagnosed with Cancer

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Objective To examine the role of cortisol in posttraumatic stress symptomatology among mothers of children newly diagnosed with cancer. **Methods** Mothers ($N = 27$) completed standardized measures of posttraumatic stress symptoms and provided salivary cortisol samples at the time of their child's cancer diagnosis and then monthly for 1 year. **Results** Random effects regression analyses of 351 person-by-time observations revealed that high levels of cortisol were associated with higher levels of posttraumatic stress symptoms ($B = .12$, $p < .02$). The mothers who exhibited higher cortisol levels at the time of their child's diagnosis showed statistically significant declines in symptomatology from diagnosis to 12 months postdiagnosis ($B = .97$, $p < .0001$) compared to mothers who exhibited lower cortisol levels at diagnosis ($B = .003$, $p < .05$). **Conclusions** These findings offer some suggestions into possible neurobiological processes underlying posttraumatic stress symptoms and directions for future research and clinical intervention.

Key words cancer; cortisol; pediatric; posttraumatic stress; women.

Although not all parents of children newly diagnosed with cancer are at risk for posttraumatic stress disorder (PTSD), as much as 50–62% meet diagnostic criteria for acute stress disorder (Lutz Stehl et al., 2008; Patino-Fernandez et al., 2008) and up to 99% can exhibit posttraumatic stress symptoms (PTSS; Kazak et al., 2004). Mothers who exhibit traumatic symptomatology during their child's medical illness have been found to be significantly more likely to develop PTSD later (Manne, 2009). Hence, although PTSS is clinically and conceptually different from PTSD, research on PTSS among medical populations could potentially offer an opportunity to examine factors related to the development of PTSD. Investigating psychological and biological factors underlying their vulnerability to these symptoms will help identify risk factors and thus, advance our understanding about possible causes and treatments for PTSS.

One biological theory proposed to explain PTSD is the dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis, which is known as the response center for ''fight or flight'' reactions to stressors. Cortisol, one component of the HPA axis feedback loop, is released from the adrenal glands in response to a stressful stimulus. A number of studies in the last decade have linked *hypo*cortisolism to PTSD in survivors of traumatic events including mothers of pediatric cancer survivors (Delahanty, Raimonde, & Spoonster, 2000; Glover & Poland, 2002; Luecken, Dausch, Gulla, Hong, & Compas, 2004); thus suggesting that PTSD may be a function of a dysregulated HPA axis. However, methodological limitations including evaluating mothers over a year postcancer diagnosis and the use of cross-sectional designs preclude drawing conclusions for this particular population. In addition, a number of studies have linked PTSD to *hyper*cortisolism (Delahanty, Nugent, Christopher, & Walsh, 2005; Resnick, Yehuda, Pittman, & Foy, 1995), which is more consistent with a biological hypothesis which postulates that heightened arousal precipitated by cortisol secretion enhances traumatic memories (McCleery & Harvey, 2004).

Linking cortisol, whether it be hypo- or hypercortisolism, to PTSD could provide support for biological theories implicating alterations in the HPA axis as a

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Journal of Pediatric Psychology 35(9) pp. 960–965, 2010
doi:10.1093/jpepsy/jsp139
Advance Access publication January 12, 2010

possible underlying mechanism for symptomatology and thus, offer directions for possible pharmacological treatments. Manne (2009) also recently discussed the need for further research investigating possible neurobiological underpinnings for PTSS. Hence, the purpose of the present study was to examine cortisol in mothers from the time their children were diagnosed with cancer to 12 months postdiagnosis so that we might ascertain a developmental perspective on how cortisol might relate to PTSS. This sample provides a unique opportunity to conduct a longitudinal study which, to date, has not yet been conducted. Another advantage of this study is that random effects regression analyses were used to examine the role of cortisol because it allowed us to model individual change, reduce the risk of error in the model, and increase statistical power to detect effects (Raudenbush & Bryk, 2002). There have been theoretical discussions and equivocal data about parents of pediatric cancer survivors being a valid trauma group (Kazak et al., 2004; Phipps, Long, Hudson, & Rai, 2005; Stoppelbein, Greening, & Elkin, 2006). Nevertheless, as outlined by Kazak et al. (2006) reactions to pediatric illnesses have been conceptualized within a traumatic stress model.

The study hypotheses were that (a) the mothers would report higher levels of PTSS at diagnosis, because of the initial shock of their child's diagnosis, rather than later in the year, and (b) that their PTSS would decline across the next 12 months. Although hypo- and hypercortisolism have been linked to PTSS, we hypothesized that (c) cortisol would be positively related to the mother's PTSS at diagnosis and up to 12 months, and that (d) higher cortisol levels would predict PTSS because hypercortisolism has been linked to PTSD among first time trauma survivors (Resnick et al., 1995). Since the directionality of the relation between cortisol and PTSS cannot be ascertained from the cross-sectional research conducted to date, we also tested PTSS as a predictor of higher cortisol levels to evaluate its merit as a competing hypothesis.

Methods

Participants

Mothers of 33 consecutive patients admitted to an inpatient pediatric oncology unit over a 12-month period were recruited. Inclusion criteria included (a) child's diagnosis of cancer occurring within the previous 2 weeks, (b) no prior diagnoses of pediatric diseases in the family, (c) child was between 2 and 17 years of age, and (d) English is primary language. Exclusion criteria included, (a) not being the biological mother, (b) history of a psychiatric diagnosis or substance abuse, (c) history of an endocrine disorder or use of synthetic glucocorticoid or exogenous steroid treatment, (d) history of trauma exposure within the past month other than the child's diagnosis, and (e) cognitive impairment for parent or child.

One parent declined participation, and five were excluded based on exclusion criteria. Nonparticipants did not differ from participants in either age, ethnicity, or socioeconomic status (SES). Of the remaining 27 participants ($M_{age} = 30.13$ years, range = 22–43), 1 discontinued participation after 4 months and another after 11 months because their children died, leaving 27 mothers up to 4 months, 26 up to 11 months, and 25 at 12 months. The bereaved mothers were not included in analyses after their child's death because their loss was a possible confound. The children were on average 7.5 years old at the time of their diagnosis ($SD = 5.90$, range = 2–17); and the mothers were either African-American ($n = 14$) or Caucasian ($n = 13$). Thirteen mothers were married to the child's father, seven were either separated or divorced, five had never married, and two had remarried. The children were diagnosed with either acute lymphoblastic leukemia ($n = 9$), solid tumors ($n = 9$), acute myeloid leukemia ($n = 6$), or Hodgkin lymphoma ($n = 3$). By the end of the study, all of the children had been treated with chemotherapy and four had also received radiation. The demographic and diagnostic composition of the sample is representative of the hospital's patient population.

Measures

Demographic and Health Interview

Participants completed a brief interview about their child's disease, demographic data (e.g., age, marital status, etc.), and maternal health information that can affect cortisol level, i.e., smoking and phase of menstrual cycle. Phase of menstrual cycle was determined from the start date of the mother's last menses. Demographic data were used to compute a Hollingshead Index as a measure of SES.

Life Events Checklist

The Life Events Checklist (LEC) is a 17-item list of traumatic events patterned after Breslau's (2001) measure of trauma exposure. The events have been linked to PTSS and are considered qualifying events for a PTSD diagnosis. Respondents indicated if they experienced or witnessed someone experience an event and how long ago. This measure was used to screen for previous trauma exposure. Test–retest reliability was high, .90, $p < .0001$; and the mean number of events endorsed (4.04) is consistent with epidemiological data (Breslau, 2001).

Posttraumatic Stress Disorder Checklist-Civilian Version

The Posttraumatic Stress Disorder Checklist-Civilian version (PCL-C) is a 17-item self-report measure of PTSS and PTSD (Weathers, Litz, Herman, Huska, & Keane, 1993). Respondents rated on a 5-point scale ranging from 1 (*not at all*) to 5 (*extremely*) how much they endorse PTSS that occurred since and in response to their child's pediatric cancer diagnosis. A score $\geq$50 merits a PTSD diagnosis (Weathers et al., 1993). The PCL-C has good sensitivity (.71) and specificity (.87; Stoppelbein & Greening, 2007). Internal consistency is high, Cronbach $\alpha = .94$, and was high for the present sample, $\alpha = .95$. Total PCL-C scores were used in analyses.

Cortisol

Salivary cortisol provides a reliable index of free plasma cortisol and avoids confounds that could arise from the stress of blood draws (Bhagwagar, Hafizi, & Cowen, 2002). Approximately 2 ml of saliva were collected from each participant using a preweighed Salivette kit and stored in a subzero freezer at −80°C. Cortisol samples were analyzed as a group in a single assay after completing data collection to prevent possible confounds with inter-assay variability. Samples were assayed in duplicate and the average for the duplicate was used for analyses. Samples were analyzed with the Salimetrics HS Salivary Cortisol EIA kit for unbound cortisol using kit instructions. The Salivary Cortisol EIA kit has intra-assay coefficients of variation ranging from 3.35% to 3.65% and the intra-assay variability of 3.46% for the current study is similar to that reported by the kit manufacturer. Salivary cortisol as analyzed using the kit is highly correlated with serum cortisol ($r = .91$, $p < .0001$).

Procedure

After obtaining Institutional Review Board approval, mothers of consecutive inpatient admits with new-onset pediatric cancer were invited to participate within 1–2 weeks of their child's hospitalization. Mothers provided written informed consent and completed the demographic interview, LEC, and the PCL-C, after which a researcher collected a saliva sample between 3:00 and 5:00 p.m. The researcher collected two additional saliva samples between 6:00–8:00 a.m. and 3:00–5:00 p.m., respectively, the next day during admission, so that all three saliva samples were collected across 2 days. At subsequent monthly intervals for up to 12 months, the mothers completed the PCL-C in addition to collecting three saliva samples at the same time of the day as conducted for the initial assessment. The measures and Salivette kits were given to the mothers at monthly outpatient appointments to complete at home unless their child was hospitalized for a medical procedure, in which case the monthly assessment was collected by the researcher during admission. Each child was hospitalized randomly throughout the study and for different lengths of time. Hence, the location of data collection (i.e., inpatient vs. outpatient) and the length of hospital stay were considered random variance. If measures were collected at home, the mothers were telephoned to remind them of the time to collect saliva samples. The mothers stored their samples in a freezer at home until a courier arrived within 24 hr to collect them. Salivary cortisol is stable at room temperature or colder for 2–3 weeks (Groschl, Wagner, Rauh, & Dorr, 2001). All saliva samples received by the researchers were stored in a subzero freezer until completion of follow-up data collection. Participants were compensated for their participation.

Data Analyses

Preliminary analyses included examining the participant's mean PCL-C score and calculating the area under the curve (AUC), which is used to assess total hormonal output over a 24-hr period. AUCs were calculated from three cortisol assessments that were collected at monthly intervals up to 12 months for a total of 12 AUCs. The AUC was chosen to represent cortisol secretion over other statistics because it transforms multivariate data into a univariate form, thereby minimizing the risk of Type I error. Demographic variables, phase of menstrual cycle, smoking, and LEC score, were also examined in correlational analyses as possible covariates.

A series of random effects regression models were estimated to examine the hypothesis that cortisol AUC is linked to PTSS across time. Random effects regressions were estimated because the data were nested (repeated measures nested within mothers). When considering sample size for random effects models that examine individual change over time, it is recommended that the person-by-time observations be used to determine power (Muthen & Curran, 1997). The present study's 351 person-by-time observations offer more than adequate power to detect effects in spite of the relatively small sample size (Raudenbush & Bryk, 2002). Models were estimated using SAS Proc Mixed version 9.1 with Restricted Maximum Likelihood Estimation; and the Kenward–Rodgers method was used for estimating the degrees of freedom. Models included a random intercept, which permits estimation of individual variability. In addition, time-varying predictors (i.e., cortisol and PTSS) were included in the models.

Models that examined cortisol AUC as a predictor of PTSS based on total PCL-C score were first estimated. These models were estimated in three steps. First, linear and quadratic effects of time were entered into the model to determine how PTSS changed over time. After the best fitting model for time was established, cortisol was added as a time-varying predictor to determine whether cortisol predicted PTSS within time. Finally, the Time × Cortisol interaction was tested to examine whether the level of PTSS depended on the level of cortisol across time. These analyses were repeated with PTSS as the independent variable and cortisol as the dependent variable to rule out the competing hypothesis that PTSS predicts cortisol level.

Results

Total *mean* PCL-C scores fell below the clinical score of 50 at all assessments (M's = 28.40–39.90, SD = 11.21–15.65) with the highest scores occurring at diagnosis; 7 mothers scored >50 at diagnosis and 1 at 12-months. Cortisol levels ranged from 0.12 to 2.10 μg/dl across all assessments (SD = 0.21–0.32). PCL-C and cortisol variables were normally distributed. Correlational analyses revealed that LEC score, age, SES, smoking, and stage of menstrual cycle were not significantly related to cortisol AUC or to PCL-C score and, therefore, were not included as covariates. Cortisol AUC and PCL-C scores were significantly related at each assessment (r's = .44–.80, $p < .05$) with the exception of months 1, 2, and 5, which were marginally significant ($p < .10$). Since types of cancer and treatment variables have not consistently been linked to PTSS/PTSD, they were not examined (Alderfer, Cnaan, Annunziato, & Kazak, 2005; Jurbergs, Long, Ticona, & Phipps, 2009).

Change in PTSS followed a linear trend, such that PTSS decreased across time ($B = -.59$, $SE = .12$, $p < .0001$). The addition of the quadratic effect was not significant ($B = .01$, $SE = .03$, $p > .05$). Therefore, only the linear effect of time was retained in subsequent models. Models included a significant random intercept, $z = 3.14$, $p = .001$, suggesting individual variability in overall levels of PTSS. Cortisol AUC was added to the model and emerged as a significant predictor of PTSS, such that higher levels of cortisol AUC were associated with higher levels of PTSS while controlling for time ($B = .12$, $SE = .05$, $p = .02$). Finally, the interaction variable, Time × Cortisol AUC, was included in the model, revealing a significant interaction ($B = -.05$, $SE = .02$, $p = .006$). The model was conditioned at high and low levels of cortisol AUC to examine the nature of the interaction, and revealed that PTSS decreased across time at high levels of cortisol AUC, ($B = -.97$, $SE = .18$, $p < .0001$). However, PTSS did not change across time at low levels of cortisol AUC, ($B = .003$, $SE = .25$, $p > .05$). Analyses testing the competing hypothesis that PTSS predicts cortisol did not yield significant findings.

Discussion

Consistent with the study hypotheses, regression analyses revealed (a) a significant linear trend with mothers reporting more PTSS at diagnosis than 12 months later, (b) this significant linear trend supports a decline in PTSS from diagnosis to 12-months postdiagnosis, (c) cortisol was positively related to PTSS independent of time, and lastly (d) cortisol predicted PTSS, with higher levels predicting more symptoms. Regression analyses with PTSS as the predictor revealed that PTSS did not predict cortisol further supporting a causal relation between cortisol and PTSS. Support for hypercortisolism as a predictor is in contrast to Glover and Poland's (2002) finding of hypocortisolism in mothers with PTSD versus controls. However, methodological differences, including Glover and Poland evaluating mothers of children not in treatment and more than 1 year postdiagnosis, may have accounted for the different outcomes. Glover and Poland also examined PTSD, whereas PTSS was examined in the present study.

Interestingly, mothers with higher cortisol levels showed a decline in PTSS as time elapsed. Jurbergs et al. (2009) noted a similar decline, suggesting that parents become habituated to their child's diagnosis as time passes. Yet, the decline could just as likely be a regression to the mean.

Although the present findings provide support for neurobiological correlates for PTSS, further research is needed to examine how cortisol influences PTSS. McCleery and Harvey (2004) suggest that heightened arousal in response to trauma enhances trauma memory as a result of, in part, increased cortisol secretion; and that if arousal persists with high-risk psychosocial factors (e.g., repeated traumas, poor coping) then the risk of PTSS increases. Perhaps the mothers' heightened arousal as manifested by elevated cortisol contributed to their PTSS; yet these mothers may have adapted to their child's diagnosis or else they relied on adaptive coping strategies to minimize their PTSS in the ensuing year (Greening & Stoppelbein, 2007). Although research is recommended to test this model, there is a debate about pediatric cancer being a valid trauma, which is beyond the scope of this report.

Surprisingly, past trauma was not related to PTSS or cortisol. Perhaps the impact of past traumas was too low or too few parents experienced high-impact events. Another plausible explanation could be that the parents experienced posttraumatic growth instead (Barakat, Alderfer, & Kazak, 2006). Survivors of single versus multiple past traumas should be differentiated in the future because of possible differences in how cortisol is related to PTSS for these two groups (Resnick et al., 1995).

Although the study's small sample size raises questions about the study's power to detect effects, the 351 person-by-time observations used in analyses were adequate for detecting significant effects (Raudenbush & Bryk, 2002). Other methodological limitations including (a) few cases of PTSD by 12 months, (b) failing to control for other comorbid symptoms and length of hospital stays, (c) using self-report measures, and (d) the lack of a nontrauma/stressed control group, should be addressed in future replications. Although the racial composition of the present sample (50% African American) limits generalizations to cancer populations which are largely Caucasian (National Cancer Policy Board, 2003), it enhances generalizations to minorities.

The present findings offer some support for biological underpinnings for PTSS and thus, provide some directions for prevention and treatment including pharmacological agents that affect cortisol. Medications that lower plasma cortisol (i.e., α_2 agonist), for example, have been found to reduce PTSS in war veterans and abuse survivors (Strawn & Geracioti, 2008). However, it is important to note that the HPA axis is a complex system in which other neurotransmitters and biological processes need to be considered and investigated.

In conclusion, the present longitudinal study sought to overcome methodological limitations of cross-sectional studies evaluating the role of cortisol in PTSS. Although exploratory, the findings offer support for further research with larger samples to validate the clinical significance of cortisol. Prospective studies might also examine cortisol while evaluating other neurobiological processes that co-occur with and in response to cortisol secretion to further ascertain the underlying biological mechanism. Such findings might support theoretical and clinical implications for triage and the prevention of PTSS including pharmacotherapy.

Acknowledgments

We would like to thank those who assisted in data collection as well as the families who participated in the study.

Funding

This work was supported by the Center for Psychiatric Neuroscience, University of Mississippi Medical Center, Institutional Development Award Program of the National Center for Research Resources (P20 RR17701).

Conflicts of interest: None declared.

Received August 3, 2009; revisions received December 15, 2009; accepted December 16, 2009

References

Alderfer, M. A., Cnaan, A., Annunziato, R. A., & Kazak, A. E. (2005). Patterns of posttraumatic stress symptoms in parents of childhood cancer survivors. *Journal of Family Psychology, 19*, 430–440.

Barakat, L. P., Alderfer, M. A., & Kazak, A. E. (2006). Posttraumatic growth in adolescent survivors of cancer and their mothers and fathers. *Journal of Pediatric Psychology, 31*, 413–419.

Bhagwagar, Z., Hafizi, S., & Cowen, P.J. (2002). Acute citalopram administration produces correlated increases in plasma and salivary cortisol. *Psychopharmacology, 163*, 118–120.

Breslau, N. (2001). The epidemiology of posttraumatic stress disorder. *The Journal of Clinical Psychiatry, 62*, 16–22.

Delahanty, D. L., Nugent, N. R., Christopher, N. C., & Walsh, M. (2005). Initial urinary epinephrine and cortisol levels predict acute PTSD symptoms in child trauma victims. *Psychoneuroendocrinology, 30*, 121–128.

Delahanty, D. L., Raimonde, A. J., & Spoonster, E. (2000). Initial posttraumatic urinary cortisol levels predict subsequent PTSD symptoms in motor vehicle accident victims. *Biological Psychiatry, 48*, 940–947.

Glover, D. A., & Poland, R. E. (2002). Urinary cortisol and catecholamines in mothers of child cancer survivors with and without PTSD. *Psychoneuroendocrinology, 27*, 805–819.

Greening, L., & Stoppelbein, L. (2007). Pediatric cancer, parental coping style, and risk for depressive, posttraumatic stress, and anxiety symptoms. *Journal of Pediatric Psychology, 32*, 1272–1277.

Groschl, M., Wagner, R., Rauh, M., & Dorr, H.G. (2001). Stability of salivary steroids: The influences of storage, food and dental care. *Steroids, 66*, 737–741.

Jurbergs, N., Long, A., Ticona, L., & Phipps, S. (2009). Symptoms of posttraumatic stress tin parents of children with cancer: Are they elevated relative to parents of healthy children. *Journal of Pediatric Psychology, 34*, 4–13.

Kazak, A.E., Alderfer, M., Rourke, M., Simms, S., Streisand, R., & Grossman, J. (2004). Posttraumatic stress symptoms (PTSS) and posttraumatic stress disorder (PTSD) in families of adolescent childhood survivors. *Journal of Pediatric Psychology, 29*, 211–219.

Kazak, A.E., Kassam-Adams, N., Schneider, S., Zelikovsky, N., Adlerfer, A.S., & Rourke, M. (2006). An integrative model of pediatric medical traumatic stress. *Journal of Pediatric Psychology, 31*, 343–355.

Luecken, L. J., Dausch, B., Gulla, V., Compas, B., & Hong, R. (2004). Alterations in morning cortisol associated with PTSD in women with breast cancer. *Journal of Psychosomatic Research, 56*, 13–15.

Lutz Stehl, M. J., Kazak, A. E., Hwang, W. T., Pai, A. L. H., Reilly, A. F., & Douglas, S. D. (2008). Innate immune markers in mothers and fathers of children newly diagnosed with cancer. *Neuroimmunomodulation, 15*, 102–107.

Manne, S. (2009). Commentary: Adopting to a broad perspective on posttraumatic stress disorders, childhood medical illness and injury. *Journal of Pediatric Psychology, 34*, 22–26.

McCleery, J. M., & Harvey, A. G. (2004). Integration of psychological and biological approaches to trauma memory: Implications for pharmacological prevention PTSD. *Journal of Traumatic Stress, 17*, 485–496.

Muthén, B. O., & Curran, P. J. (1997). General longitudinal modeling of individual differences in experimental designs: A latent variable framework for analysis and power estimation. *Psychological Methods, 2*, 371–402.

National Cancer Policy Board. (2003). *Childhood cancer survivorship*. Washington DC: National Academic Press.

Patino-Fernandez, A. M., Pai, A. L. H., Alderfer, M., Hwang, W. T., Reilly, A., & Kazak, A. E. (2008). Acute stress in parents of children newly diagnosed with cancer. *Pediatric Blood & Cancer, 50*, 289–292.

Phipps, S., Long, A., Hudson, M., & Rai, S.N. (2005). Symptoms of post-traumatic stress in children with cancer and their parents: Effects of informant and time from diagnosis. *Pediatric Blood & Cancer, 45*, 952–959.

Raudenbush, S. W., & Bryk, A. S. (2002). *Hierarchical linear models: Applications and data analysis methods 2nd edition*. Thousand Oaks, CA: Sage Publications.

Resnick, H., Yehuda, R., Pitman, R. K., & Foy, D. W. (1995). Effect of previous trauma on acute plasma cortisol level following rape. *American Journal of Psychiatry, 152*, 1675–1677.

Stoppelbein, L., & Greening, L. (2007). The risk of posttraumatic stress disorder in mothers of children diagnosed with pediatric cancer and type I diabetes. *Journal of Pediatric Psychology, 32*, 223–229.

Stoppelbein, L., Greening, L., & Elkin, D. (2006). Risk of posttraumatic stress symptoms: A comparison of child survivors of pediatric cancer and parental bereavement. *Journal of Pediatric Psychology, 31*, 367–376.

Strawn, J. R., & Geracioti, T. D. (2008). Noradrenergic dysfunction and the psychopharmacology of posttraumatic stress disorder. *Depression and Anxiety, 25*, 260–271.

Weathers, F., Litz, B., Herman, J., Huska, J., & Keane, T. (1993). *The PTSD checklist (PCL)*. San Antonio: TX, Paper presented at the 9th Annual Conference of the ISTSS.