Childhood Parental Loss and Adult Hypothalamic-Pituitary-Adrenal Function

Audrey R. Tyrka, Lauren Wier, Lawrence H. Price, Nicole Ross, George M. Anderson, Charles W. Wilkinson, and Linda L. Carpenter

Background: Several decades of research link childhood parental loss with risk for major depression and other forms of psychopathology. A large body of preclinical work on maternal separation and some recent studies of humans with childhood parental loss have demonstrated alterations of hypothalamic-pituitary-adrenal (HPA) axis function that could predispose to the development of psychiatric disorders.

Methods: Eighty-eight healthy adults with no current Axis I psychiatric disorder participated in this study. Forty-four participants experienced parental loss during childhood, including 19 with a history of parental death and 25 with a history of prolonged parental separation. The loss group was compared with a matched group of individuals who reported no history of childhood parental separation or childhood maltreatment. Participants completed diagnostic interviews and questionnaires and the dexamethasone/corticotropin-releasing hormone (Dex/CRH) test. Repeated measures general linear models were used to test the effects of parental loss, parental care, gender, and age on the hormone responses to the Dex/CRH test.

Results: Parental loss was associated with increased cortisol responses to the test, particularly in men. The effect of loss was moderated by levels of parental care; participants with parental desertion and very low levels of care had attenuated cortisol responses. Adrenocorticotropic hormone responses to the Dex/CRH test did not differ significantly as a function of parental loss.

Conclusions: These findings are consistent with the hypothesis that early parental loss induces enduring changes in neuroendocrine function.

Key Words: Childhood parental loss, cortisol, depression, HPA axis, parental death

Psychosocial stressors, such as childhood parental loss, have long figured prominently in theories and research on the pathogenesis of major depression and related disorders (1–8). Neurobiological systems that regulate stress reactivity are likely involved in the vulnerability to psychiatric disorders after exposure to childhood parental loss. Corticotropin-releasing hormone (CRH) and the hypothalamic-pituitary-adrenal (HPA) axis are activated in response to stress and are thought to play an important role in the pathophysiology of major depression (9–11) and other stress-related psychiatric disorders (12–16). A large body of work in rodents and nonhuman primates demonstrates that early maternal separation results in changes in brain circuitry regulating stress reactivity, mood, and behavior, with associated exaggeration or attenuation of HPA axis activity (17). The direction and pattern of such HPA alterations might depend on the nature and timing of the stressor (17–19).

Unlike other forms of childhood stress, parental death—and to a lesser degree parental desertion—is a discrete and objective event that might be minimally influenced by recall bias or subjective judgments. However, as with other forms of childhood adversity, the study of parental loss is complicated, because: 1) the nature and timing of such losses is highly variable; 2) individuals with parental loss might suffer from psychiatric disorders that can have associated changes in HPA axis function; and 3) parental loss might be linked to other risk factors for psychiatric disorders that might themselves contribute to HPA axis dysfunction, such as poverty and childhood maltreatment.

Children who experienced permanent or long-term separations from parents or parental death have been found to have increases in basal salivary cortisol concentrations (20,21) and cortisol nonsuppression in the dexamethasone-suppression test (22), but decreased morning cortisol concentrations are seen in some cases of separation (20) and in studies of institutionalized children (23–25). Two recent studies of university students with less severe forms of loss have found attenuation of the cortisol response to CRH stimulation in subjects with a childhood history of parental divorce (26) and a decreased awakening cortisol response in students with a history of either parental separation/divorce or death of a very close friend or relative (27). However, reports of adults with a history of childhood parental death have found increased basal (28,29) or psychosocial stress-induced cortisol concentrations (30,31). Luecken *et al.* found that this effect was moderated by the rearing environment such that participants with parental loss who reported low levels of care by the surviving parent (30) or childhood maltreatment (31) had elevated cortisol responses to the speech stressor. Only a few studies have controlled for factors that are associated with parental loss and might themselves be associated with abnormalities in neuroendocrine function, including current and past psychiatric disorders (21,26,28,29), relationships with parents (28,30,31), socioeconomic status (26), and childhood maltreatment (26,31).

In the present study we administered the dexamethasone/CRH (Dex/CRH) test, a sensitive neuroendocrine indicator of psychiatric disorders such as major depression (32), to healthy adults with a history of childhood parental loss and assessed effects of potential confounding factors. We hypothesized that

From the Mood Disorders Research Program and Laboratory for Clinical Neuroscience (ART, LW, LHP, NR, LLC), Butler Hospital; Department of Psychiatry and Human Behavior (ART, LHP, LLC), Brown Medical School, Providence, Rhode Island; Yale Child Study Center (GMA), Yale University School of Medicine, New Haven, Connecticut; Geriatric Research, Education and Clinical Center (CWW), VA Puget Sound Health Care System; Department of Psychiatry and Behavioral Sciences (CWW), University of Washington, Seattle, Washington.

Address reprint requests to Audrey R. Tyrka, M.D., Ph.D., Butler Hospital, 345 Blackstone Blvd., Providence, RI 02906; E-mail: Audrey_Tyrka@Brown.edu.

Received November 7, 2007; revised January 10, 2008; accepted January 18, 2008.

0006-3223/08/$34.00
doi:10.1016/j.biopsych.2008.01.011

Table 1. Loss Characteristics

Death ($n = 19$)	
Age at loss, mean (SD)	9.2 (4.5)
Range	3–17
Gender of loss parent, *n* (%)	
Mother	2 (10.5)
Father	17 (89.5)
Type of death, *n* (%)	
Illness/disease	16 (84.2)
Accident	2 (10.5)
Suicide	1 (5.3)
Desertion ($n = 25$)	
Age at loss, mean (SD)	5.2 (4.8)
Range	0–14
Gender of loss parent, *n* (%)	
Mother only	4 (16.0)
Father only	13 (52.0)
Both	6 (24.0)
Father + stepfather	2 (8.0)
Circumstance at time of loss, *n* (%)	
Following divorce	8 (32.0)
At birth	5 (20.0)
Unknown	12 (48.0)
Duration of separation, *n* (%)	
Permanent	22 (88.0)
Nonpermanent	3 (12.0)

Death from illness or disease included heart disease, $n = 4$; cancer, $n = 4$; liver disease, $n = 2$; vascular disease, $n = 2$; "natural causes," $n = 2$; blood disorder, $n = 1$; and renal failure, $n = 1$. Permanent desertion included one subject who was adopted from Korea 6 months after birth. Nonpermanent desertion included one that occurred at age 2 and lasted 4 years, one that occurred at age 13 for 6 months, and one with an 8-month separation from the mother at age 9, followed by separation from the father with twice yearly contact thereafter.

parental loss would be associated with elevated adrenocorticotropic hormone (ACTH) and cortisol responses and that the quality of parental care would moderate these effects.

Methods and Materials

Subjects

Eighty-eight adults with no current Axis I psychiatric disorder participated in this study. Flyers and advertisements on the Internet and in local newspapers for several thematically and methodologically related studies advertised for: 1) healthy adults, 2) individuals with a history of early parental loss, and 3) adults with a history of early-life stress. Participants were included in the present study if they met the inclusion and exclusion criteria detailed in the following text. Subjects underwent physical and neurological examinations, an electrocardiogram, and laboratory studies for complete blood count, electrolytes, thyroid stimulating hormone, urine toxicology, and urinalysis. Subjects were excluded if they worked night shifts, met criteria for a current Axis I psychiatric disorder, or had one or more of the following conditions: acute or unstable medical illness, a history of brain injury, seizure disorder, endocrine disease, or substance abuse. Also excluded were individuals undergoing treatment with drugs that might influence HPA axis function, including psychotropics, beta blockers, angiotensin-converting enzyme inhibitors, ketoconazole, metyrapone, and corticosteroids. Subjects were free of these medications for at least 2 weeks (6 weeks for fluoxetine) before participation. Oral contraceptives (OCs) were allowed. All subjects gave voluntary written informed consent to participate in this study, which was approved by the Butler Hospital Institutional Review Board.

Forty-four individuals who had experienced either parental death ($n = 19$, Parental Death group) or prolonged separation or desertion of a parent ($n = 25$, Parental Desertion group) before the age of 18 were considered to have parental loss (Loss group). Participants were considered to have prolonged parental separation or desertion if they identified a parent as having left them without attempting to contact them or responding to attempts at contact for at least 6 months. Table 1 shows the details of the loss characteristics for these groups.

The Loss group was matched with respect to gender to 44 subjects with no childhood parental separation, including divorce (No Loss group). To minimize the likelihood of childhood stress in this group, participants who reported a history of childhood neglect or abuse were not included in this group. A Parental Loss variable was created that included three categories: Parental Death, Parental Desertion, and No Loss. Demographic characteristics for all subjects are presented in Table 2.

Measures

Socioeconomic Adversity. Socioeconomic adversity in the childhood home was determined if participants scored in the adverse direction on either of the following true/false statements:

Table 2. Subject Characteristics

	No Loss ($n = 44$)	Death ($n = 19$)	Desertion ($n = 25$)
Subject Age, yrs, mean (SD)	27.3 (9.2)	28.3 (9.3)	32.4 (11.2)
Range	18–55	19–45	19–52
Gender; *n* female (%)	29 (65.9)	11 (57.9)	17 (68.0)
Race, *n* (%)			
White	37 (84.1)	18 (94.7)	18 (72.0)
Black	1 (2.3)	0	3 (12.0)
Asian	2 (4.5)	0	1 (4.0)
Native American	0	0	1 (4.0)
Other	3 (6.8)	1 (5.3)	2 (8.0)
Not reported	1 (2.3)	0	0
Socioeconomic Adversity, *n* (%)	2 (4.5)	1 (5.3)	12 (48.0)[a]
Multiple Loss, *n* (%)	0	1 (5.3)	6 (24.0)[a]
Foster Care, *n*, (%)	0	0	4 (16.0)[b]
Reported Abuse/ Neglect, *n* (%)			
Emotional Abuse	0	3 (15.8)[b]	12 (48.0)[a]
Physical abuse	0	1 (5.3)	6 (24.0)[a]
Sexual abuse	0	3 (15.8)[b]	7 (28.0)[a]
Emotional neglect	0	5 (26.3)[a]	10 (40.0)[a]
Physical neglect	0	2 (10.5)[c]	8 (32.0)[a]
Compound Stress, *n* (%)	0	3 (15.8)[b]	10 (40.0)[a]

Abuse or neglect considered present when the Childhood Trauma Questionnaire subscale score reached threshold for "moderate" or "severe." Compound stress considered present when three or more of eight stressors were reported: multiple loss, foster care, socioeconomic adversity, and reported abuse or neglect on each of the five types of maltreatment. Analysis of variance with post hoc Tukey Honestly Significantly Different (HSD) tests and χ^2 tests were used to compare groups. The Desertion and Death groups were significantly different from each other with respect to Emotional Abuse ($p < .05$) and Socioeconomic Adversity ($p < .005$). There were trend-level differences between the Desertion and Death groups on Multiple Loss, Foster Care, Physical Neglect, and Compound Stress ($p < .10$). Multiple Loss, subjects who reported the loss of a parent plus the loss of at least one additional caregiver.

Symbols refer to comparisons with the No Loss group:
[a] $p < .001$.
[b] $p < .01$.
[c] $p < .05$.