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Catecholamine predictors of complicated grief treatment outcomes

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ABSTRACT

Could sympathetic hyperarousal limit treatment success in complicated grief? The present study investigated persons with complicated grief, a chronic condition with distinct symptoms including persistent intense yearning and longing for the person who died, avoidance of reminders that the person is gone, deep relentless sadness, self-blame, bitterness, or anger in connection with the death, and an inability to gain satisfaction or joy through engaging in meaningful activities or relationships with significant others. Length of bereavement did not correlate with complicated grief scores. Catecholamines (i.e., epinephrine, norepinephrine, dopamine) in plasma were assessed pre- and post-psychotherapeutic treatment. Participants with the highest levels of epinephrine at pre-treatment had the highest levels of complicated grief symptoms at post-treatment, accounting for baseline levels of symptoms. This predictive relationship was not seen for depressive symptoms. The present study supports the hypothesis that catecholamine levels are affected by bereavement, and in turn, can affect the ability of those with complicated grief to benefit from psychotherapy.

No one ever told me that grief felt so like fear.
C. S. Lewis, from *A Grief Observed*

1. Introduction

The death of a loved one is a highly stressful event because of the permanent loss of an attachment figure. The attachment model states that when the loved one is unavailable, there is a resulting strong desire to be with the person and a sense of insecurity (Bowlby, 1969). There is evidence for the role of attachment relationships in autonomic regulatory processes (for a review, see Hofer, 1984). Bereavement triggers acute grief, a unique biobehavioral response (Shear and Shair, 2005). Acute grief is intensely painful and disruptive, but for most people, a natural healing process slowly integrates the reality of the death. However, for a subset of bereaved people, dysfunctional thoughts, maladaptive behaviors or ineffective emotion regulation complicate and prolong the process, resulting in a disorder termed complicated grief. Little information is available regarding autonomic regulatory processes in complicated grief, but there is some evidence for increased sympatho-adrenal-medulla (SAM) system activation with acute grief, and this could be a contributor to complicated grief. The present paper investigates whether sympathetic hyperarousal limits treatment success in complicated grief.

Prior research demonstrates that acute grief is associated with increased urinary catecholamines (Jacobs, et al., 1986), increased heart rate (Buckley, et al., 2012a; O'Connor et al., 2002), and cardiovascular disorders, including high blood pressure (Buckley, et al., 2011), stress cardiomyopathy (Wittstein, et al., 2005) and sudden cardiac death (Stroebe et al., 2007). During emotional activation, the SAM system releases epinephrine and norepinephrine, which increases heart rate. In addition, epinephrine increases peripheral resistance, and therefore increases blood pressure. In instances of stress cardiomyopathy (usually occurring after an acute emotional trigger, most frequently, notification of the death of a loved one), plasma catecholamine levels are extremely high from SAM activation (Wittstein, 2012).

Higher grief intensity, as well as persistence and chronicity, is associated with greater physiological stress responsivity. In a small naturalistic study (n = 56) of adaptation at 1 and 2 months after bereavement, Jacobs and colleagues found that the subgroup whose separation anxiety symptoms worsened over the month (n = 24) compared to those that did not (n = 32) had higher urinary free cortisol levels (Jacobs, et al., 1987). In another study the stress of losing a family member was associated with the development of essential hypertension in the absence of other cardiovascular risk factors (Santic et al., 2006). These authors found that family members of deceased soldiers had a higher prevalence of arterial hypertension, accounting for a host of other cardiovascular risk factors and post-traumatic stress disorder

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(50.7% vs. 39.0%, p<0.001.). The prevalence of hypertension decreased over time only in the bereaved group.

Complicated grief, which affects about 10% of bereaved people, has been recognized for only a short time and is not yet in the official diagnostic nomenclature. As a result, there has been little study of the physiological profile of this chronic disabling condition (Shear et al., 2011). Complicated grief is characterized by a prolonged acute grief accompanied by dysfunctional thoughts, behaviors or emotions related to the death that interfere with the process of adaptation. One longitudinal study found that those with complicated grief at 6 months post-loss showed higher levels of hypertension at thirteen months (Prigerson, et al., 1997). We hypothesize that individuals with complicated grief continue to experience sympathetic stimulation generated by the emotional distress.

The parent study (NIMH MH70741) for the current report is investigating the efficacy of complicated grief treatment in older adults. We conducted a pilot study of plasma catecholamines among a subgroup of participants in this study (n = 16) treated with either Complicated Grief Treatment (Shear et al., 2005) or Interpersonal Psychotherapy (Shear et al., 2005).[1] The present paper reports results of baseline and post-treatment catecholamines in order to explore hypotheses about baseline catecholamines affecting responsiveness to treatment. To do so we measured peripheral epinephrine, norepinephrine and dopamine at pre- and post-treatment.

2. Methods

The data in the present report is from an ancillary study of a larger randomized clinical trial comparing Complicated Grief Treatment to Interpersonal Therapy for the treatment of complicated grief. Entry into the parent study was based upon a score of at least 30 on the 19-item Inventory of Complicated Grief (ICG; Prigerson, et al., 1999). All participants gave informed consent, and the New York State Psychiatric Institute Institutional Review Board approved the study. The biomarker data presented here are from a subset of participants who consented to have blood drawn for neuroendocrine measures and who currently have pre and post-treatment data. The clinical trial is ongoing, and so we provide no information about which treatment the participant received. Blood for biomarkers and the ICG were measured at study intake, which occurred up to 4 weeks before the first therapy session. The Beck Depression Inventory-II (BDI-II) was completed at the first therapy session, and the ICG and BDI-II were given at week 20, following the termination of treatment.

Participants included 14 women and 2 men. This is the same percentage of males as previously seen in a randomized clinical trial of treatment for complicated grief (12%; Shear et al., 2005). They were asked not to eat or drink caffeine and not to smoke for at least 4 h prior to blood sampling. All blood samples were drawn between 10 am and 3:30 pm. Participants were in the clinic for a minimum of 45 min prior to the blood draw, while treatment study assessment procedures were conducted. All participants were seated during the blood draw. Venipuncture collection of 4 mL whole blood was drawn in k2EDTA tubes. Samples were placed on ice immediately, and plasma was separated in a 4 °C centrifuge within 2 h after sampling. Plasma was initially stored at −20 °C, and then stored at −80 °C until the end of the study so that all samples could be assayed simultaneously.

Enzyme-linked immunoassay (ELISA) with a microtiter plate format was used (ALPCO Diagnostics, Salem, NH). Norepinephrine, epinephrine and dopamine were assayed. All samples were analyzed in duplicate in the same assay to minimize variability. Values below the detectable limit of the assays made up 11.8% of samples. The biomarker values were log transformed to adhere to the assumptions of parametric statistical analysis.

3. Results

At the pre-treatment baseline, participants had a mean age of 64 (SD = 4.3). Participants were grieving the loss of a close relative or friend, including loss of a parent (44%), spouse (31%), child (6%), sibling (13%), or others (e.g., close friend). The length of bereavement varied widely, with a mean of 87 months (SD = 123.9), but a median of 38 months. However, the length of bereavement did not correlate with depression or complicated grief scores at pre-treatment or at post-treatment, and did not correlate with any of the biomarkers. The mean BMI was 25.7 (SD = 4.4). The paired-sample *t*-test for the BDI was significant (t = 8.03, p<.001). Additional demographics are in Table 1.

The mean BDI score was 26.2 (SD = 7.5) at pre-treatment and 10.6 (SD = 6.5) at post-treatment. We grouped depression at post-treatment as high (BDI score of >21) and low (BDI of <21). Only one of the participants had a high level at post-treatment (although the BDI declined from 36 to 23). Two participants showed particularly long time since the death (425 and 344 months), and one of these had persistent levels of high depressive symptoms.

The mean level ICG score at pre-treatment was 44.6 (SD = 11.5) and 23.5 (SD = 11.0) at post-treatment. The paired-sample *t*-test for the ICG was significant (t = 7.44, p<.001). We grouped ICG scores at post-treatment as high (ICG > 30) or low (ICG < 30), and 64.7% (n = 11) were low. The length of bereavement was not different between those with high or low post-treatment levels ($F = 1.31$, $p = 0.27$). Cronbach's alpha for the ICG was 0.84 at pre-treatment, and 0.88 at post-treatment and the two scores correlated at r = 0.45, p = 0.08.

3.1. Biomarkers

Levels of plasma catecholamines can be seen in Table 2. To determine whether the biomarkers predicted treatment outcome, regression analyses were used. Epinephrine at pre-treatment predicted the post-treatment ICG score, accounting for the pre-treatment ICG score ($F(16, 2) = 6.68$, $p = 0.01$, $\beta_{logE} = 0.53$, $\beta_{ICG} = 0.48$). Those participants with the highest levels of epinephrine at pre-treatment had the highest levels of complicated grief symptoms at post-treatment. Outlying values did not account for the relationship (Fig. 1). Norepinephrine and dopamine at pre-treatment were not significant predictors of

Table 1
Demographic characteristics.

	Percentage
Gender (female)	88%
Ethnicity	
Caucasian	81%
African-American	19%
Marital status	
Never married	19%
Married	19%
Separated	6%
Divorced	25%
Widowed	31%
Education	
Some college/AA	13%
College degree	13%
Some graduate school	18%
Graduate/professional degree	56%
Employment	
Full-time	18%
Part-time	38%
Retired	38%
Unemployed	6%

AA = associates degree.

[1] The study is ongoing so the blind cannot be broken.