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History of Sudden Unexpected Loss Is Associated With Elevated Interleukin-6 and Decreased Insulin-Like Growth Factor-1 in Women in an Urban Primary Care Setting

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Abstract

Objective—To investigate the hypothesis that a history of sudden unexpected loss including number of losses and type of loss (death due to unnatural versus natural causes) would be associated with the magnitude of dysregulation. The sudden unexpected death of a loved one confers risk of morbidity and mortality, perhaps due to dysregulation in the immune/inflammatory and endocrine systems.

Methods—Female primary care patients aged ≥ 40 years ($n = 75$) completed questionnaires, a clinical interview, and a blood draw. Interleukin (IL)-6 and insulin-like growth factor (IGF)-1 were assayed, using standard enzyme-linked immunosorbent assay protocols and anticytokine antibody pairs.

Results—History of sudden loss was positively associated with IL-6 (mean = 4.07 pg/mL; $\log_{10}$ values, $B = 0.314$, $p = .009$) and negatively associated with IGF-1 (mean = 97.05 ng/mL; $B = -0.277$, $p = .023$). A linear relationship parsimoniously captured the association between ordered categories of lifetime loss (0, 1, 2–5, 5+) and increases in $\log_{10}$ IL-6 ($B = 0.107$, $p = .005$) and decreases in IGF-1 ($B = -0.116$, $p = .005$). Adjusting for illness burden, depressive symptom severity, and obesity did not change the observed associations. The hypothesized effect of type of loss was not supported.

Conclusions—These preliminary findings encourage further investigations to elucidate pathways from sudden unexpected loss to biomarker changes that increase risk for morbidity and mortality.

Keywords

interleukin-6; insulin-like growth factor-1; psychoneuroimmunology; sudden unexpected loss; primary care

INTRODUCTION

The death of a loved one is a common life event (1) that confers heightened risk of morbidity and mortality (2–4). Sudden unexpected losses, in particular, increase the susceptibility to illness (5–9) and mortality (3). A putative mechanism for these associations is the effect of loss on specific biomarkers of immune/inflammatory and neuroendocrine

function, which could lead to increased susceptibility to disease (10). Whereas studies of loss-related stress and natural killer cell cytotoxicity, mitogen-induced lymphocyte proliferation, and the number of T-helper or T-cytotoxic lymphocytes in peripheral blood have yielded mixed findings (11,12), studies have consistently shown that the proinflammatory cytokine interleukin (IL)-6 is associated with stress in older adults (13-15), and with morbidity and mortality (16,17). High levels of IL-6 interact with low levels of insulin-like growth factor (IGF)-1, enhancing morbidity and mortality risk in older adults (18). To our knowledge, no studies have examined associations of IL-6 and IGF-1 and exposure to sudden death of a friend or a loved one.

Increased levels of IL-6 and other proinflammatory cytokines indicate systemic inflammation—a risk factor for the development and progression of certain aging-related diseases including Type 2 diabetes, cardiovascular diseases, some cancers, osteoporosis, and rheumatoid arthritis (18-22). The growth factor IGF-1 affects virtually every cell type in the body, and is posited as a protective factor in aging-related diseases (16). IGF-1 has been found to be inversely related to IL-6 with respect to maintenance of muscle strength (23). Both increased levels of IL-6 and decreased levels of IGF-1 are associated with increased prevalence of disability and mortality in older adults (18,19).

The current study is a preliminary examination of the potential links between IL-6 and IGF-1 and sudden unexpected loss among women in an urban primary care center that serves a socioeconomically disadvantaged population. Socioeconomic disadvantage has been consistently found to confer risk for increased exposure to general life stressors, poor health, and higher mortality (24-26), and the risk may be greater among women than men (25). Documenting that the experience of sudden loss is associated with concentrations of biomarkers that are associated with aging (IGF-1) and inflammation (IL-6) would advance our understanding of the development of chronic disease among women seen in urban primary care settings.

We examined three hypotheses. First, we hypothesized that women with a history of sudden loss would have elevated IL-6 and lower IGF-1 levels compared with women without such history. Second, we hypothesized a dose-response relationship between exposure to sudden unexpected loss and the biomarkers of interest. Our reasoning was informed by the concept of “allostatic load” (27). Allostasis (28) denotes a state of balance that is achieved via the interactions of multiple systems including, but not limited to, the autonomic nervous system, neuroendocrine function, and immune function. Repeated or prolonged exposure to stress results in greater “wear and tear” of bodily systems, or allostatic load (29).

Third, we hypothesized that women who have experienced sudden unexpected loss events due to suicide, accident, or homicide (i.e., unnatural) causes would have higher levels of circulating IL-6 and lower levels of IGF-1 than women who had experienced only illness-related (i.e., natural) losses. Deaths due to accident, suicide, or homicide are relatively rare, but their public health implications may be profound. Consequences for individual survivors are often grave. Many feel isolated, as it is difficult to elicit and receive support from others who have first-hand experience grieving in such circumstances (30). Prior research has suggested that bereavement after these deaths is more challenging than bereavement after deaths from other causes (5,30-32).

METHODS

Participants

The sample was composed of 75 female primary care patients, ranging in age from 40 years to 80 years ($M = 52.07$ years, $SD = 9.67$; median age = 49 years). Forty (53.3%) identified

themselves as African American, 32 (42.7%) as white, and three (4%) as American Indian, Alaska native, or multiracial. Mean years of education was 12.7 (SD = 2.67), ranging from 6 to 19 years; about half pursued education beyond high school ($n = 37$, 49.3%). Forty-five (60%) women reported an annual income of <\$20,000 per year. Twenty-three were never married and single (30.7%), 15 were married (20%), 27 were divorced or legally separated (36%), and ten were widowed (13.3%). Thirty women (40%) were living alone and 45 (60%) were living with a significant other, children, family members, and/or friend.

Procedure

This report stems from a larger investigation of stress, individual differences, and health in a middle-aged and older primary care sample. The research protocol was approved by the Institutional Review Board at the University of Rochester Medical Center. Data collection proceeded from September 2006 to August 2007.

Participants were recruited in person during their health visits or via flyers at a family medicine clinic that serves urban, socioeconomically disadvantaged patients. Inclusion criteria were: participants must be receiving care in the Family Medicine Clinic, age ≥ 40 years, and English speaking. Exclusion criteria included: major, uncorrected sensory impairments; severe cognitive deficits that precluded informed consent; severe communication limitations, such as aphasia; active psychosis; and acute substance intoxication at the time of the initial interview. Low literacy was not an exclusion criterion; questionnaires were orally administered if necessary. Exclusion criteria were assessed via clinical interview, chart review, and consultation with potential participants' primary care physician. Patients were informed that the study was to examine the effects of stress including life events, on health across the life span. Patients interested in participating were scheduled for research interviews either in available examining rooms at the clinic, or at the University of Rochester Medical Center's General Clinical Research Center. After obtaining informed consent, we scheduled research appointments consisting of an interview on social circumstances and mental health history, and self-report measures of life events and depressive symptoms. Venipuncture by a trained phlebotomist or research nurse occurred between late morning and late afternoon, after the interview was completed. Participants received \$50.00 compensation.

Measures

Sudden Unexpected Loss of a Close Friend or a Loved One—The Traumatic Life Events Questionnaire (33) was administered to patients to assess exposure to potentially traumatic life events. Patients indicated their response to the question “Have you ever experienced the sudden and unexpected death of a close friend or loved one?” by using a rating scale ranging from never to more than five times. Additional questions about the type of loss (accident, murder, illness, and suicide) followed. Three loss variables were used in separate models: 1) *Lifetime history of any sudden unexpected loss*, coded dichotomously (yes/no); 2) *The number of lifetime sudden losses*, which was nonnormally distributed. Thus, the number of losses was grouped into incremental categories of roughly comparable number: once ($n = 23$), two to four times ($n = 23$), and five or more times ($n = 18$). This preserved the ordinality of the data, and permitted us to examine whether biomarkers a) differ in nonlinear fashion as a function of loss category or b) differ linearly as a function of loss category (i.e., linear dose-response). 3) *Type of sudden loss* was unnatural (accident, murder, or suicide) versus natural (illness-related only). Women exposed to both types of losses were categorized in the former; sample size precluded the creation of a separate category combining both types. The small numbers of accidents, murders, and suicide-related losses precluded examination of these specific causes of death separately.

Covariates

Four demographic covariates were included in each model: race, age, education, and household income, to adjust for their potential influences on the associations between predictors related to sudden loss experience, IL-6, and IGF-1. Older adults, compared with younger, typically have higher levels of proinflammatory cytokines (34). Also, some studies showed evidence for higher IL-6 levels in African American women >65 years of age, compared with whites (35,36). Education (in years), race/ethnicity (minority versus white), and household income ($\leq \$20,000$ versus $> \$20,000$) were included as covariates due to their association with increased susceptibility to disease (37), which could affect levels of IL-6 and IGF-1.

To examine the potential confounding role of depressive symptoms and illness burden, secondary analyses controlled for depression, measured by the Center for Epidemiological Studies-Depression Scale-Revised (CES-D-R) (38,39), and illness burden, assessed by a checklist of 45 chronic medical conditions summed to form a morbidity index (40). Chronic medical conditions included respiratory, gastrointestinal, neurological, endocrine, and cardiovascular problems, ranging from hypertension to autoimmune disorders. We also examined specific inflammatory conditions that might either be a cause or result of altered IL-6 levels: diabetes, asthma, arthritis, Parkinson's, psoriasis, chronic obstructive pulmonary disease, lupus, Crohn's disease, human immunodeficiency virus, acquired immunodeficiency syndrome, rheumatism, autoimmune conditions other than previously noted, and cardiovascular disease. Finally, we obtained data on physician-documented obesity from medical charts for all but ten patients; logistic regression predicting absence of data revealed no demographic or biomarker differences between those with and without obesity data. We then examined whether obesity could explain the relationships between loss and cytokines.

Dependent Variable: Proinflammatory Cytokine IL-6

Patients had 30 mL of blood drawn by venipuncture of the antecubital vein. Blood was kept on ice, then centrifuged, and serum stored at -80°C . IL-6 and IGF-1 were assayed, using standard enzyme-linked immunosorbent assay protocols and anticytokine antibody pairs (BD Biosciences, San Diego, California). The absorbance of the color reaction was measured at 405 nm, using an automated Osys MR Microplate Reader (Thermo Labsystems, Chantilly, Virginia). The minimum detectable limit for IL-6 is 0.039 pg/mL and 0.026 ng/mL for IGF-1. The intra-assay variability for both IL-6 and IGF-1 is <4%.

Statistical Analyses

Separate linear regressions were conducted for each loss variable of interest: history of sudden unexpected loss (Model A), frequency of loss (Model B), and type of loss (i.e., suicide, accident, homicide versus illness-related) (Model C). Frequency of loss was modeled in two ways: 1) as a set of dummy variables not imposing a linear relationship between loss frequency and biomarkers (Model B1); and 2) as ordered categories with a linear relationship between loss frequency and biomarkers (0 loss = 0; 1 loss = 1; 2–5 losses = 3; >5 losses = 4). IL-6 was log base-10 transformed to stabilize the variance of residuals. The association between independent variables and outcomes were examined first without adjustment; then, with adjustment for age, years of education, race/ethnicity, and annual household income. Secondary analyses also covaried depression, illness burden in separate regression models, and alternatively fit analyses of covariance. Another set of secondary analyses examined whether obesity, documented in primary care charts and available for all but ten participants (who did not differ from those with available obesity data), explained the relationship between loss and outcomes. Sensitivity analyses examined the effect of missing data on reported associations by including an indicator variable for missing data.

RESULTS

Descriptive Statistics

Table 1 shows IL-6 and IGF-1 levels (raw scores) and lifetime history of sudden unexpected loss, frequency of sudden unexpected loss, and type of loss. Eleven of 75 women reported no lifetime sudden unexpected losses. Fifteen women experienced accident-related losses, 11 suicide-related losses, and ten murder-related losses. Five women who reported a sudden loss did not respond to the question about the cause of death, and nine did not respond to the question about the age when the loss happened. Comparison of demographic factors between women with loss exposure who reported its features (cause of death, age during the loss) and those who did not showed no significant demographic differences. Patients had an average of 4.35 (SD = 3.67) chronic conditions (median = 3), with the three most common being arthritis (52.7%), hypertension (39.2%), and gastroesophageal reflux (26.7%).

Associations Between Sudden Unexpected Loss and IL-6

Table 2 reports the results of separate regression models examining the hypotheses about the associations of IL-6 and IGF-1 with lifetime history of sudden unexpected loss and its features, controlling for covariates.

The first hypothesis was supported. Findings from Model A show that women with a history of sudden unexpected loss had higher IL-6 and lower IGF-1 levels compared with women without a history of sudden loss. With respect to clinical significance, a prior study found that all-cause mortality risk doubles at the IL-6 threshold of 3.19 pg/mL (20). (Comparable epidemiologic data on IGF-1 do not exist.) The data in Tables 1 and 2 suggest that women exposed to any sudden loss have, on average, IL-6 levels that exceed this threshold.

The second hypothesis also received support. Results of Kruskal Wallis test showed that number of losses was significantly associated with IL-6 ($\chi^2 = 7.938$, $df = 3$, $p = .047$) and IGF-1 ($\chi^2 = 9.663$, $df = 3$, $p = .02$). As shown in Table 2 (Model B1), relative to no losses, a single loss was associated with elevated IL-6 and decreased IGF-1, at a trend level, and women exposed to two to four losses and five or more losses were more likely to have higher IL-6 and lower IGF-1 levels than those with no reported loss. The coefficients suggested the greatest increase in IL-6 and decrease in IGF-1 levels for those women with five and more losses, with IL-6 levels increasing in small increments for individuals who experienced one loss and two to four losses; however, the difference in magnitude of IL-6 increase and IGF-1 from one loss category to another was not statistically significant, suggesting that a linear association more parsimoniously characterizes the relationship (Model 2B). In this model, advancing one category (e.g., from category 1 to category 2) was strongly related to a constant increment in IL-6 and decrement in IGF-1 (Fig. 1).

The third hypothesis was not supported. As shown in Table 2 (Model C), women who reported exposure to suicide, homicide, or accidental (unnatural) deaths did not have significantly higher IL-6 and lower IGF-1 levels when compared with those who had only been exposed to natural deaths. Further analysis with a reference group of *no history of sudden loss* showed that women with exposure to sudden losses due to unnatural death had greater levels of IL-6 ($B = 0.35$, standard error [SE] = 0.11, $p = .002$) and lower levels of IGF-1 ($B = -0.397$, SE = 0.107, $p = .001$), as would be expected from the results of Model A. Also consistent with model A, women exposed to sudden losses due to natural deaths had higher IL-6 ($B = 0.258$, SE = 0.115, $p = .031$) and lower IGF-1: $B = -0.211$, SE = 0.081, $p = .011$).

Secondary analyses covarying CES-D scores and illness burden did not change the pattern of results and significance reported in Table 2; none of the coefficients related to loss

variables changed by >10%. Depression scores were not significantly associated with IL-6 ($r = .03, p = .78$) and IGF-1 ($r = -.06, p = .62$). A Kruskal-Wallis test showed a significant association with the number of losses and inflammatory/autoimmune conditions ($\chi^2 = 12.43, df = 3, p = .006$). No differences in the number of inflammatory or autoimmune conditions were observed between women with a history of loss and those without, however. Controlling for the number of chronic inflammatory or autoimmune conditions did not change the β estimates of loss variables >10%. Similar analyses revealed that obesity explained roughly 5% of the association between loss and IL-6, and 9% for IGF-1. Sensitivity analyses accounting for missing data revealed no significant changes for the association between type of loss and IL-6 and IGF-1.

DISCUSSION

Consistent with our first hypothesis, women with a history of sudden unexpected loss of a friend or a loved one had higher levels of the proinflammatory cytokine IL-6 and lower levels of anti-inflammatory IGF-1 compared with those who did not report such events. With respect to the second hypothesis, findings are consistent with the concept of allostasis and the idea that susceptibility to inflammation and aging-related disease increases as lifetime stressors accumulate. The third hypothesis was not supported. Women who reported exposure to unnatural deaths did not have significantly higher IL-6 and lower IGF-1 levels than those who experienced deaths due to natural causes. Significant associations between sudden unexpected loss and biomarkers were maintained in secondary analyses that controlled for depressive symptom severity, health status, and obesity.

These preliminary findings encourage further investigations to elucidate pathways from unexpected loss to changes in inflammatory and endocrine function, which could lead to increased morbidity and mortality in psychosocially and economically vulnerable middle- and older age adults. Interrelated biopsychosocial mechanisms may explain the associations between sudden unexpected loss and biomarkers. Repetitive sudden losses could result in diminished social support and increased loneliness. Links between social support, health, and longevity have been established as well as associations between social support and immune and neuroendocrine function (41,42). Sudden unexpected loss also could lead to negative emotions including grief and increased emotional stress, which in turn may disrupt functioning of immune and neuroendocrine systems (10). Intrusive thoughts are more likely to follow unexpected or violent deaths (6,32), and have been associated with dysregulations in immune and neuroendocrine systems (43,44). In addition to these psychological factors, poor health behaviors, such as increased alcohol or tobacco consumption and poor eating habits, could influence associations between sudden loss, IL-6, and IGF-1 (10).

Study findings must be considered in the context of certain limitations. The cross-sectional design does not allow conclusions regarding causal relationships. A relatively small and racially diverse yet socioeconomically homogeneous sample may have limited power and applicability to other demographic groups. The associations between sudden unexpected loss and biomarkers could be affected by any of several unexamined features of the loss including the nature of the relationship to the deceased (45) and time since death. The grief experience may also affect the observed relationships including the type and intensity of emotional response to loss (46-48), and the presence of complicated or traumatic grief. Although we examined the effects on the observed associations of physician-documented obesity, rigorous and systematic data on body mass index were unavailable (49). Participants were not asked to refrain from use of medications, alcohol consumption, and food intake before the blood draw, nor were they excluded for having active infectious or inflammatory disease. The reasons for clinic visits were not documented. Thus, the nature of the clinic visit varied across study patients (e.g., routine check-up versus acute illness

including an acute infection). However, we are not aware of any reason such factors would vary systematically across loss history, and if they do not, they cannot explain observed associations. Similarly, the timing of blood draws varied between late morning and late afternoon (during which IL-6 levels might have been higher due to diurnal variation). Yet, in order for time of blood draw to confound the association, it must be related not only to IL-6 but also to loss history. Persons with a greater history of loss were unlikely to have systematically scheduled late afternoon interviews. Artificially higher IL-6 measurements in this group are possible but highly improbable. Finally, in a cross-sectional context, it is not clear if inflammatory conditions may prove to be significant mediators of loss and IL-6, or if IL-6 may significantly mediate loss and inflammatory condition associations. Future longitudinal work in larger samples may help clarify this.

To our knowledge, this is the first study to examine potential associations between IL-6 and IGF-1 and the all too common human experience of sudden unexpected loss. Significant associations were found in this sample which, by virtue of its relatively lower socioeconomic status, has higher propensity for psychosocial adversity and health problems (24-26). Findings are of potential clinical significance given prior research on the association between IL-6 and all-cause mortality (20). If future research confirms the role of sudden unexpected loss in the pathway to immune and neuroendocrine alterations and poor health outcomes, it would alert health professionals to the importance of assessing sudden unexpected loss as part of general health inquiries. Persons with greater cumulative loss may benefit from closer health monitoring. Clinicians may decide to tailor their treatment plans for suddenly bereaved individuals and consider watchful waiting along with advising patients about the availability of low-cost treatment options, such as support groups. The effectiveness of formal interventions after loss is debatable (50,51), although there is empirical support for individual (52,53) and family (54) interventions. Future research on the effectiveness of interventions after sudden loss is needed.

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Glossary

IL-6	interleukin-6
IGF	insulin-like growth factor

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Figure 1. Linear dose-response relationship between ordered loss categories and log₁₀ interleukin (IL)-6 and insulin-like growth factor (IGF)-1. *Shaded area* is 95% confidence interval around regression line. Adjusted for age, education, income, and race/ethnicity. $n = 75$.

TABLE 1

Descriptive Statistics for Features of Sudden Unexpected Loss, IL-6, and IGF-1

	<i>n</i>	%	IL-6 (pg/mL)		IGF-1 (ng/mL)	
			M	SD	M	SD
Sudden loss (<i>n</i> = 75)						
Yes	64	85.3	4.39	2.80	91.83	30.60
No	11	14.7	2.22	1.38	127.42	43.72
Number of sudden losses (<i>n</i> = 64)						
1	23	35.94	3.86	2.35	98.87	37.14
2-4	23	35.94	4.34	2.81	89.16	25.28
≥5	18	28.13	5.13	3.26	86.26	27.33
Type of sudden loss (<i>n</i> = 59) ^a						
Natural death	28	47.46	4.01	2.84	97.96	34
Unnatural death ^b	31	52.54	4.99	2.82	85.05	23.70

IL = interleukin; IGF = insulin-like growth factor; SD = standard deviation.

^aFive women do not have data for the type of loss.^bThis group includes 19 women who were exposed to sudden losses due to unnatural causes only (unnatural only group), and 12 were exposed to both unnatural and natural death (combined group).

Unstandardized (b) and Standardized (B) Regression Coefficients and Standard Error (SE) Testing Hypothesized Associations With Log₁₀ IL-6 and IGF-1

TABLE 2

Variable	Log ₁₀ IL-6			IGF-1		
	b (SE)	B	p	b (SE)	B	p
Model A ^a : History of Loss (Reference Group: No Loss)						
Sudden loss	0.283 (0.106)	0.314	.009	-0.132 (0.057)	-0.277	.023
Model B1 ^a : Number of Sudden Losses (Reference Group: No Loss); No Assumption of Linear Relationship Between Ordered Loss Category and Biomarker						
1	0.223 (0.117)	0.323	.061	-0.106 (0.064)	-0.291	.099
2-4	0.298 (0.118)	0.430	.014	-0.147 (0.064)	-0.402	.024
≥5	0.356 (0.125)	0.476	.006	-0.149 (0.067)	-0.378	.030
Model B2 ^a : Number of Sudden Losses; Linear Relationship Assumed Between Ordered Loss Category and Biomarker						
Increase of 1 loss category	0.107 (0.038)	0.336	.005	-0.11 (0.005)	-0.335	.005
Model C ^b : Type of Sudden Loss (Reference Group: Natural Death)						
Unnatural death	0.129 (0.083)	0.210	.128	-0.059 (0.043)	-0.186	.174

IL = interleukin; IGF = insulin-like growth factor.

^a_n = 75.

^b_n = 59.

The models were tested in separate regression analyses. Each analysis adjusted for the effects of age, years of education, annual household income, and racial/ethnic origin.