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Anxiety, Depression, Stress, and Cortisol Levels in Mothers of Children Undergoing Maintenance Therapy for Childhood Acute Lymphoblastic Leukemia

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Abstract

The purpose of this study was to compare anxiety, depression, and stress between mothers of children during maintenance treatment for acute lymphoblastic leukemia (ALL) and matched controls. Twenty-six mothers were recruited from the hematology unit at a children's hospital, and 26 mothers were recruited from the community. Participants were matched to their child's age and gender. Mothers completed the Hospital Anxiety and Depression Scale, the Perceived Stress Scale, and collected salivary cortisol 4 times a day for 3 consecutive days. Compared with mothers of healthy children, anxiety scores did not differ ($P = .10$), but depression scores were higher ($P = .003$) in mothers of children with ALL. More mothers in the ALL group scored above the cutoff of 7 indicating clinical anxiety (46%) and depressive symptoms (27%). A trend toward increased stress was found in mothers in the ALL group. No difference was found in overall daily cortisol (area under the curve), daily decrease in cortisol (slope), and cortisol awakening response. Mothers of children with ALL experienced emotional symptoms many months after the initial diagnosis.

Keywords

acute lymphoblastic leukemia; ALL; depression; maintenance; salivary

Introduction

Acute lymphoblastic leukemia (ALL) is a life-threatening illness that is diagnosed in 2400 children each year and accounts for about 75% of pediatric leukemia diagnoses (Ries et al., 1999). ALL is more likely to occur in young children between 2 and 5 years of age, but it is

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seen across the entire pediatric age spectrum (Pieters & Carroll, 2008). Duration of treatment for childhood ALL currently ranges from 30 to 36 months. Examples of medications commonly used in leukemia therapy include L-asparaginase, methotrexate, mercaptopurine, daunorubicin, and vincristine and steroids. Prophylactic treatment to protect the central nervous system (intrathecal chemotherapy) also is given.

The shock of a life-threatening event in their child's life and subsequent intense treatment is understandably traumatic for mothers of children with ALL. Little research has been reported on the effects of the specific diagnoses of childhood ALL on mothers, but in one study, mothers reported feeling overwhelmed, stressed by the uncertainty of the situation, and feeling trapped by the emotional ups and downs during the initial stages of their child's ALL treatment (McGrath, 2002).

Although treatment varies somewhat among treatment centers, maintenance therapy follows the first months of intense treatment and lasts for approximately 24 to 30 months. Typically, treatment frequency decreases from weekly to monthly, but the child continues to receive oral chemotherapy with mercaptopurine and methotrexate, monthly vincristine and steroid pulses, and intrathecal chemotherapy every 3 months (Pieters & Carroll, 2008). Although most children are able to resume the majority of their normal activities, including school and sports, mothers still need to be vigilant in recognizing symptoms of infection. Mothers of 80% of children can expect their child to experience a relapse-free survival and a normal lifespan, but relapse is a possibility during maintenance treatment (Pieters & Carroll, 2008). Cardiac toxicity from anthracyclines, osteopenia or osteonecrosis from steroid exposure, potential for neurocognitive effects, and psychosocial sequelae also may occur during maintenance (Hobbie, Carlson, Harvey, Ruccione, & Moore, 2011). Thus, although the maintenance phase of ALL treatment is less intense and tumultuous, threats to the child's life and well-being remain.

The trauma of ALL diagnosis and months of intense treatment are understandably stressful to mothers of children with ALL. Stress is the perception that the demands (or anticipated demands) of the environment exceed an individual's ability to cope (Lazarus & Folkman, 1984; Lupien, King, Meaney, & McEwen, 2001). The uncertainty of relapse, the possibility of serious infection, and the adverse effects of drugs are factors that may affect mothers' perception of their ability to cope, resulting in stress extending from initial diagnosis through maintenance treatment to becoming chronic.

The hypothalamic-pituitary-adrenal axis (HPA) is an important endocrine system that regulates responses to physical and mental stress to facilitate the maintenance of physiologic homeostasis (Tsigos & Chrousos, 2002). Cortisol, the hormonal end product of the HPA axis, mobilizes energy, increases cerebral perfusion and glucose utilization, and enhances cardiovascular function to help the individual adjust to real or perceived threats. The paraventricular nucleus in the hypothalamus responds to a threat by secreting the corticotropin-releasing hormone that stimulates the anterior pituitary to synthesize adrenocorticotropin (ACTH) that promotes cortisol release from the adrenal glands. The increasing cortisol levels downregulate the blood concentration of corticotropin-releasing hormones, ACTH, and cortisol via negative feedback loops (Habib, Gold, & Chrousos,

2001; McEwen, 1997; Papadimitriou & Priftis, 2009). Thus, when stress is short term or mild, cortisol levels increase and return to normal when the challenge is over.

One feedback mechanism is in the pituitary gland (Gupta, Aslakson, Gurbaxani, & Vernon, 2007). When cortisol levels increase in response to stress, cortisol binds with the glucocorticoid receptor in the pituitary, resulting in an increase in the number of glucocorticoid receptors and decreased ACTH production and cortisol synthesis. When stress is prolonged, cortisol levels remain high to provide continuous energy to the body (Miller, Chen, & Zhou, 2007). Ongoing stimulation of glucocorticoid receptor synthesis by cortisol, which may occur with chronic stress, inhibits ACTH, resulting in lower cortisol production. This state of inhibition may remain even after the stress ceases and a new stable state—hypocortisolism—occurs (Fries, Hesse, Hellhammer, & Hellhammer, 2005; Gupta et al., 2007; Kugler, Zarzer, Puchinger, & Kohler, 2013).

The normal functioning HPA system has a diurnal pattern with higher secretory activity that occurs in the morning, and it decreases during the day. In addition to the diurnal cycle, an abrupt rise in cortisol release occurring in the first 30 minutes after awakening in the morning increases cortisol secretion by 38% to 75%. This is termed the cortisol awakening response (CAR) that is thought to be distinct from the diurnal pattern of HPA axis activity and is associated with the expectation of the demands of the upcoming day (Fries, Dettenborn, & Kirschbaum, 2009). Much intra-individual variability has been found in day-to-day CAR, but several studies have shown lower CAR in people with chronic stress (Neylan et al., 2005; Rohleder, Joksimovic, Wolf, & Kirschbaum, 2004; Wessa, Rohleder, Kirschbaum, & Flor, 2006). Lowered CAR has been hypothesized to occur because of the development of a hypoactive HPA axis activity (Fries et al., 2005).

Little research has been done to address the anxiety, depression, and stress specifically among mothers of children with ALL. Physiologically, only the association between cortisol levels and posttraumatic stress disorder (PTSD) in parents of children with mixed cancer diagnoses has been investigated (Glover & Poland, 2002; Stoppelbein, Greening, & Fite, 2010). The clinical team in the oncology unit where children were recruited for this study expressed concern about placing any extra burdens (eg, participating in research) on families during the initial treatment phases. Although emotional turmoil was expected during the initial phase, the clinicians wondered if maternal emotional state normalized during maintenance. Maintenance is an understudied phase of treatment that lasts for an extended period of time. If evidence supports the existence of emotional difficulties during maintenance treatment, the implementation of interventions might be most appropriate and effective during this time.

The purpose of this study was to compare physiologic and emotional stress of mothers of children during maintenance treatment for ALL with matched control mothers. We hypothesized that when compared with mothers of healthy children, mothers of children with ALL during maintenance treatment would (a) report greater anxiety and depressive symptoms, (b) report greater overall stress, and (c) display lower salivary cortisol levels as evidenced by the area under the curve (AUC), the CAR, and the diurnal slope, indicating chronic stress.

Methods

Participants

A power analysis revealed that a sample size of 50 (25 per group) will give 80% power at $\alpha = .01$ (correcting for multiple tests). From 35 mothers approached in the hematology practice of a children's hospital in a mid-sized city in the western United States, 26 consented to participate in this study. Mothers of 29 healthy children who were recruited from the community through ads, brochures, or university e-mail expressed interest in the study, and 26 consented to participate. Mothers were matched by their children's sex and age. Inclusion criteria were as follows: (a) mothers were primary caregivers of the children between the age of 3 and 12 years, (b) mothers spoke and wrote English, (c) children were in the maintenance phase of therapy and had no other concurrent, major illness or disability, (d) children were standard risk, and (e) mothers in the control group had children without chronic disease or disability. Exclusion criteria were as follows: (a) serious, unstable physical or mental illness in mother or child or (b) mothers taking steroid medication.

Instruments

Demographic Information—A demographic form included maternal and child age; child's sex; mother's marital status, race/ethnicity, employment status, and highest educational level completed; duration of child's maintenance treatment for ALL; and a checklist of medical conditions and medications taken by the mother.

Hospital Anxiety and Depression Scale (HADS)—The HADS is a self-report questionnaire consisting of 14 items divided into 2 subscales, anxiety and depression (Zigmond & Snaith, 1983). The maximum score for each subscale is 21. A score of 7 or greater on each subscale suggests the presence of clinical levels of anxiety or depression. Scores between 8 and 10 suggest the presence of anxiety or depression, while scores greater than or equal to 11 indicate probable mood disorder (Snaith, 2003). Moorey et al. (1991) reported internal consistency of .93 for anxiety and .90 for depression. Concurrent validity (assessed by comparison with psychiatric rating scales) is $r = .54$ for anxiety and $r = .79$ for depression (Zigmond & Snaith, 1983). Validity also has been shown when used with a community sample. Sensitivity was 88% for the anxiety subscales and 90% for depression, while specificity was 91% for both subscales (Abiodun, 1994). When used in primary care, internal consistency was $\alpha = .89$. Convergent validity between the Patient Health Questionnaire-9 and the HADS anxiety scale ($r = .81$) and HADS depression scale ($r = .77$) was adequate (Cameron, Crawford, Lawton, & Reid, 2008).

Perceived Stress Scale (PSS)—The PSS is a widely used questionnaire for measuring perception of stress. Each of the items is a 5-point scale in which respondents rate the prevalence of each item during the past month from 0 = *never* to 4 = *very often*. Items address how unpredictable, uncontrollable, and overloaded respondents find their lives. The scale also includes direct queries about current levels of experienced stress. The 10-item short-form version has internal consistency ranging from .75 to .86 and test-retest reliability of .85 over 2 weeks (Cohen & Williamson, 1988). Higher scores indicate more distress.

Salivary Cortisol—Saliva for salivary cortisol was collected on special filter paper as described elsewhere (Laudenslager, Calderone, Philips, Natvig, & Carlson, 2013; Neu, Goldstein, Gao, & Laudenslager, 2007). A commercial expanded-range high-sensitivity EIA kit (No. 1-3002/1-3012, Salimetrics, LLC, State College, PA) detects cortisol levels in the range of .003 to 3.0 µg/dL (0.083–82.77 nmol/L), and it was used to determine cortisol concentration. The low-end detection limit after extraction was approximately 0.019 µg/dL (0.52 nmol/L). Unknowns were determined using commercial software (Gen 5, Biotek Instruments, Winooski, VT) for the ELISA plate reader (PowerWave 340, Biotek Instruments, Winooski, VT). Laboratory controls were run on every plate for determination of inter- and intra-assay coefficients of variability, which were generally less than 5% and 9%, respectively. Subject's samples were not split across different assay plates.

Procedure

Human subject approval was obtained and mothers signed informed consent. Mothers received \$40 for participation. A research assistant visited mothers in their homes or in the hematology clinic. Mothers completed the HADS and PSS. The research assistant explained how to collect saliva and provided written instructions and a phone number if the mother had any questions. Mothers were asked to use filter paper to collect salivary cortisol 4 times a day (on awakening, 30 minutes post awakening, before lunch, and 10 hours after awakening) for 3 consecutive days during the following week. Mothers were instructed not to brush their teeth, or eat or drink anything except water, for an hour prior to salivary cortisol collection. A diary was supplied that included the time when food or drink was taken, when the mother exercised, and if medications were taken. The research assistant or investigators demonstrated how to collect the saliva, by placing the filter strip on their tongue for 10 to 20 seconds and completely saturating at least halfway up the strip.

Mothers received one Saliva Procurement and Integrated Testing booklet for each of the 3 collection days. The booklets are described in Laudenslager et al. (2013). Four filters (Whatman grade 42 filter paper, 2.54 cm, 9.0 cm, GE Healthcare, Waukesha, WI) were contained in each booklet, with a color-coded circle matched to the collection time. Mothers recorded the date and time of each collection on the booklet and stored the booklets at room temperature in a plastic bag with holes cut into the bag to facilitate the drying of the filter paper. A reliable relationship of $r^2 = .98$ was observed between the time recorded by the subject directly on the booklet and the time recorded by an electronic collection device for 286 observations (Laudenslager et al., 2013).

Data Analysis

Three cortisol calculations—CAR, slope, and AUC—were done for the 3 days of salivary data collection. CAR was chosen as a measure to assess the mother's morning cortisol surge needed to meet the demands of the day (Thorn, Hucklebridge, Evans, & Clow, 2006). The slope was used to assess the decline of cortisol over the day (Cohen et al., 2012), and AUC measured the overall cortisol level throughout the day (Pruessner et al., 1997). Mothers had collected cortisol samples 4 times a day for 3 days, a total of 12 possible samples. For each of the 4 collection times, samples were averaged across all 3 days of data collection so that there was an average cortisol level for wake, another for 30 minutes after waking, another

for noon, and finally for 10 hours after wake. CAR was calculated from the samples taken from waking to 30 minutes after waking, and it was expected to be positive. The slope of the cortisol curve was calculated from waking to the last observation of the day (wake, noon, and 10 hours after wake) and was expected to be negative. AUC was calculated using the 3 time points (wake, noon, and 10 hours after wake).

Analysis of covariance controlling for demographic covariates that differed between groups (age and educational level) was used to assess differences between mothers of children with ALL and mothers of healthy children on the 3 psychological self-report variables and on physiologic stress measured by the 3 cortisol variables described above. The psychological variables were anxiety and depressive symptoms, assessed by the HADS, and overall stress, assessed by the PSS. Alpha was adjusted using Bonferroni correction to .017 for all tests to maintain a family-wise Type I error rate of .05 within the 3 psychological measures and the 3 cortisol measures, respectively. Missing data were handled through multiple imputation (Collins, Schafer, & Kam, 2001), a strategy that minimizes bias because of missing values and provides better estimates of true population parameters.

Results

Enrollment and Maternal Characteristics

Table 1 shows maternal characteristics of both groups. The mothers of children with ALL were younger than the mothers of healthy children, $t(50) = 2.02$, $p = .049$, $d = 2.02$. Educational level also differed between groups, $\chi^2(5) = 12.3$, $p = .03$, $\phi = .49$, with the mothers of children with ALL having lower educational attainment than the mothers of healthy children. Educational level and age were included as covariates in all subsequent tests of between-group differences. Other demographic characteristics did not differ significantly between groups. At the time of data collection, children had been in treatment (diagnosis to maintenance) from 7 to 38 months (mean [M] = 15.2, standard deviation [SD] = 8.5). Maintenance treatment ranged from 1 to 32 months (M = 9.2, SD = 8.6) with a median of 6 months. Fifteen children (58%) received maintenance 6 months.

Anxiety, Depression, and Stress

As seen in Table 2, although HADS anxiety scores were higher in the ALL than in the control group, no difference was found when covariates of maternal age and education were included in the analysis. HADS depression scores were significantly higher in mothers of children with ALL than in mothers of healthy children. More mothers in the ALL group scored above the cutoff of 7, which indicated clinical anxiety and depression than in the matched group. Because of the adjusted α of .017, although maternal scores on the PSS were higher in the ALL group than the control group, the difference ($P = .025$) was not significant between groups.

Salivary Cortisol

Two mothers in the ALL group did not provide cortisol so the sample consisted of 24 in the ALL group and 26 in the control group. One mother stated that she was too busy and overwhelmed at the time of the study to collect the samples. The other mother explained that

she collected the samples but mislaid them. She said she was too busy to recollect them. Of the possible 288 samples (24 mothers $\times$ 12 samples) in the ALL group, 50 samples (17%) were not collected. As previously stated, there was an average cortisol level for wake across all 3 days of data collection, another for 30 minutes after waking, another for noon, and a final average for 10 hours after wake, resulting in 96 data points (24 mothers $\times$ 4 collection times). Because of the missed collections, averages were done with 2 samples for each collection time (eg, 26 of these data points [27%], and 1 sample was used for 6 [6%] of the data points). When the averages for each collection time were completed, 4 mothers were missing data for 10 hours after wake. These values were imputed using multiple imputation based on all available data. Of the possible 312 samples (26 $\times$ 4 samples) in the control group, 13 (4%) were missing. There were 104 possible data points in the control group (26 mothers $\times$ 4 collection times). Averages were made from 2 samples for 8 data points (8%) and from 1 sample for 3 data points (3%). No imputation was necessary for the control group.

As shown in Table 2, no significant differences were found between mothers of children with ALL and mothers of healthy children in the mean morning rise, in the slope from 30 minutes post awakening to the end of the day, or in the overall AUC measure.

Discussion

This study was conducted to compare anxiety, depressive symptoms, and emotional and physiologic stress between mothers of children during maintenance treatment for ALL and matched controls. We hypothesized that mothers of children with ALL during maintenance treatment compared with control mothers would (a) report more anxiety and depressive symptoms, (b) report greater overall stress, and (c) display lower salivary cortisol levels as evidenced by AUC, CAR, and the diurnal slope. Mothers of children with ALL had significantly higher scores for depressive symptoms but not anxiety than the matched sample. They were more likely, however, to have scores above the clinical cutoff of 7 on the HADS for both anxiety and depression. Mothers also showed a trend for greater perceived stress over the past month but did not show significant cortisol differences compared with the matched sample. These findings suggest that mothers are continuing to experience emotional distress months after the initial diagnosis.

Other researchers have found higher levels of anxiety and depression in mothers of children with cancer. Demirtepe-Saygili and Bozo (2011) reported that 47% of 100 mothers in a Turkish study had scores indicating depression and 42% had elevated anxiety scores. Mothers completed questionnaires 1 to 81 months after diagnosis, and 75% of the children had some form of leukemia. Low educational levels and younger maternal age were associated with heightened anxiety and depressive symptoms. In an Israeli study, 22% of 32 mothers reported depressive symptoms. Parents were recruited after 1 month of treatment, but the average length of treatment when mothers were assessed was 16 months. Fifty percent of the children had some form of leukemia (Benaroya-Milshtein et al., 2013). Dolgin et al. (2007) reported that 68% of mothers had moderate depression scores 6 months after their child's cancer diagnosis. Although not stated, this would be close to the beginning of

the maintenance phase of treatment in many treatment centers. Fifty percent of the children had either leukemia or lymphoma (Dolgin et al., 2007).

In the aforementioned studies, mothers of children with a mixture of cancer diagnoses were included in the sample. The diagnosis of leukemia included children with ALL and other forms of leukemia. A variety of assessment measures were used. Studies included mothers of children in treatment phases spanning from soon after diagnosis through the maintenance phase and in one study after completion of treatment (Demirtepe-Saygili & Bozo, 2011). Cultural differences also may have existed among studies. Although these factors make direct comparison of findings among studies difficult, a high percentage of mothers showed elevated anxiety and/or depression in all studies, including the current study.

When directly compared with mothers of children with complex cancer diagnoses (eg central nervous system and bone tumors), mothers of children with ALL recounted significantly ($P = .014$) less depressive symptoms and a trend toward higher anxiety scores ($P = .095$). However, the sample was large ($n = 321$), and the mean depression scores of 2.14 in the ALL group did not seem clinically different from the score of 2.25 in the complex cancer group (Hovén, Anclair, Samuelsson, Kogner, & Boman, 2008).

Iqbal and Siddiqui (2002) found that 57% of mothers of children with ALL ($n = 37$) reported depressive symptoms 1 month after their child achieved their first remission. This study was conducted in Pakistan, and 60% of the sample had educational levels less than 10th grade. The percentage of elevated depression scores is higher than in the current study (27%) in which all but 2 mothers in the ALL group completed high school and 69% were educated beyond high school. Educational level plus possible cultural differences and the use of a different measurement tool may have contributed to the discrepancy in the findings.

Dolgin et al. (2007) examined PTSD symptoms in mothers of children with various cancer diagnoses and found that 49% of mothers reported moderate stress scores after 6 months of treatment. In the current study, maternal perception of stress was measured, not specific stress symptoms. Scores trended to be higher in the ALL group in the current study, but the PSS used in the current study does not have a suggested score for PTSD or clinical stress condition.

In a qualitative study, mothers of children with ALL were asked to describe stressors during maintenance treatment. They related in detail that the difficulty of coping with the child's aggressive and hostile behavior when on steroids was extremely stressful (McGrath & Rawson-Huff, 2010). Most of the children were on dexamethasone that is used in cancer treatment because it is associated with better event-free survival than prednisone. However, behavior problems are a common side effect of dexamethasone, and in children more than 10 years of age, the drug can cause osteonecrosis. Thus, prednisone is typically given to children who are more than 10 years of age (Gramatges & Rabin, 2013). In the current study, 20 (77%) of the children with ALL were on dexamethasone. The stress of dealing with the child's problematic behavior is likely one factor that contributed to the stress of parents in the current study, but it was not captured in the questionnaire.

Even though maternal scores on the PSS were higher in the ALL group than the matched controls, mean AUC, CAR, and slope were not significantly lower in the ALL group, suggesting that the mothers had not developed patterns of hypocortilism. Several reasons may have contributed to the lack of difference between groups. Much cortisol variability was observed in the current study, and 2 mothers did not collect samples, which reduced the ALL group size. The sample was not large enough to make meaningful comparisons within the ALL group on factors that might have influenced stress and cortisol levels, such as maternal age, education, work status, or length of time in maintenance. In this study, mothers did not record whether they collected cortisol on workdays or when they were off. Cortisol levels and morning rise tend to be lower on nonworking days (Law et al., 2013). Mothers in the ALL group may have collected their samples on quieter days. Mothers of children with very high stress levels may not have agreed to participate in this study.

Stoppelbein et al. (2010) also assessed salivary cortisol, but in mothers of children with a variety of cancer diagnoses. Mothers with PTSD symptoms had higher daily levels of cortisol. This was a longitudinal study with 3 cortisol samples measured at the initiation of treatment and monthly for the next 12 months. Samples were obtained from 3 to 5 PM for 2 evenings and from 6 to 8 AM in the morning between the evening samples. It was not stated how the morning collection time related to time of awakening, and each of the 12 AUC analyses was based only on 3 samples collected over one 24-hour period. It is possible that instead of providing a sample on awakening, some mothers may have sampled cortisol during CAR. In the current study, mothers collected samples for 3 days, and an average of the 3 days for each time point was done. This would lessen the effect of any one sample being artificially high.

Glover et al. (2006) reported that mothers with PTSD ($n = 14$) whose children survived cancer had lower urinary cortisol levels ($P < .05$) than mother without PTSD whose children survived cancer ($n = 7$) and mothers without PTSD who had healthy children ($n = 8$). Cortisol was obtained from 1 nightly sample consisting of all urine collected during that night from 7 PM through 7 AM and was indicative of overall HPA activity.

Stoppelbein et al. (2010) and Glover et al. (2006) assessed PTSD in the mothers suggesting a more serious chronic stress response than perception of stress over the past month as measured in the current study. Using a measurement of PTSD would have made comparison more feasible with the current study.

The presence of emotional symptoms in mothers of children with ALL is concerning. Depression is associated with lower quality of life, lower functioning, greater health care utilization, morbidity, and mortality (Imam, Salam, Algin, & Ali, 2013; Sprangers et al., 2000; Wells & Sherbourne, 1999). Anxiety has been found to negatively impact sleep, cognitive functioning, and physical health (Cornwell, Mueller, Kaplan, Grillon, & Ernst, 2012; Jansson-Frojmark, Harvey, Lundh, Norell-Clarke, & Linton, 2011; Zavagli, Varani, Samosky-Dekel, Brighetti, & Pannuti, 2012), and chronic stress may result in health problems such as gastrointestinal alterations, obesity, or cardiovascular disease (Huang, Webb, Zourdos, & Acevedo, 2013; Huerta-Franco et al., 2013; Kubzansky et al., 2013).

Screening for depression, anxiety, and stress for mothers and encouraging treatment if scores are high may be an important first step in recognizing and decreasing symptoms in families of children with ALL. Use of short screening questionnaires could be completed by mothers during their child's hospitalization or clinic visit. Several studies have tested interventions for parents of children with cancer. Two promising interventions are training in problem-solving skills (Sahler et al., 2005) and cognitive-behavioral therapy (Kazak et al., 2004). Studies were done either with parents of newly diagnosed children (Sahler et al., 2005) or with those of late in treatment children (Kazak et al., 2004), so further study on their effectiveness with parents of children with ALL is needed.

Mothers in this study were assessed only at one point in time when more than half of the children were in the first 6 months of maintenance. It would be informative to know if anxiety and depressive symptoms increased, decreased, or remained static from the time of diagnosis through maintenance, specifically in mothers of children with ALL. Further longitudinal research with larger ethnically diverse samples that included fathers would provide more information on the influence of socioeconomic status, ethnicity, and duration of treatment on anxiety, depressive symptoms, and emotional and physiological stress in both parents of children with ALL. In this study, mothers complete the short questionnaires without difficulty. Brief questionnaires could be completed at various time points during the ALL treatment trajectory.

We experienced difficulty collecting all cortisol samples from mothers of children with ALL. In addition, CAR is influenced by workday-weekend schedules, light exposure, and day-to-day emotional state that were not measured in this study (Schlotz, Hellhammer, Schultz, & Stone, 2004; Stalder, Evans, Hucklebridge, & Clow, 2010; Thorn, Hucklebridge, Esgate, Evans, & Chow, 2004). A better way to measure HPA functioning in this population may be to sample cortisol in hair. Hair cortisol is increasingly being used to measure chronic stress over several months (Stalder & Kirschbaum, 2012). A scenario could be to collect a few strands of hair at baseline and in 3-month increments by a member of the research team in the oncology clinic, eliminating the burden on mothers for collection.

ALL is a common form of cancer in children, and several features set it apart from other cancers diagnoses: Treatment for children with average risk of ALL generally follows a standardized treatment plan, and they have an excellent prognosis and a relatively low rate of relapse (Pieters & Carroll, 2008; Ries et al., 1999). Thus, research is needed that focuses only on ALL, as was done in this study. Findings of this study indicate that mothers of children with ALL experience anxiety and depressive symptoms months after treatment is initiated. Future research is needed that examines the emotional status of mothers of children with ALL longitudinally and explores the most effective ways to facilitate reduction of anxiety, depressive symptoms, and stress in these mothers.

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Table 1

Characteristics of Sample.

	ALL (n = 26), n (SD)	Control (n = 26), n (SD)	Unpaired <i>t</i> -test <i>P</i> value
Age of other (years)	32.4 (6.8)	36.0 (6.0)	.049
	ALL, n (%)	Control, n (%)	χ^2 <i>P</i> value
Married	21 (85)	19 (74)	.709
Ethnicity			
Caucasian	20 (77)	20 (77)	.123
Hispanic	6 (23)	4 (15)	
African American	0	1 (4)	
American Indian	0	1 (4)	
Education			.031
Graduate school	5 (19)	14 (54)	
College	7 (27)	6 (23)	
Technical school	6 (23)	1 (4)	
Completed high school	6 (23)	5 (19)	
Completed elementary school	2 (8)	0	
Employed (part-time and full-time)	12 (46)	18 (69)	.092

Note. ALL = acute lymphoblastic leukemia.

Table 2

Comparison of HADS, PSS, and Cortisol Analysis Between the ALL and Control Group.

	ALL (n = 26), Mean (SD)	Control (n = 26), Mean (SD)	ANOVA <i>P</i> value ^a
Cortisol			
AUC (nmol/L)	15.5 (7.9)	18.1 (6.7)	$F(3, 45) = 1.35, p = .25, \epsilon^2 = .03$
CAR (nmol/L) (diff wake to 30 minutes)	1.3 (5.0)	2.7 (3.7)	$F(1, 48) = 0.77, p = .39, \epsilon^2 = .01$
Slope	-0.3 (0.4)	-0.5 (0.5)	$F(1, 45) = 0.68, p = .42, \epsilon^2 = .01$
PSS	17.6 (6.3)	12.8 (8.8)	$F(1, 48) = 5.34, p = .025, \epsilon^2 = .03$
HADS			
Anxiety	7.7 (4.3)	5.3 (3.8)	$F(1, 45) = 2.83, p = .10, \epsilon^2 = .06$
Depression	5.0 (3.5)	2.2 (2.7)	$F(1, 45) = 9.53, p = .003, \epsilon^2 = .17$
HADS	n (%)	n (%)	χ^2 <i>P</i> value
Anxiety scores			
0–7	14 (54)	20 (77)	.048
8–10	7 (27)	3 (12)	
11–15	5 (19)	3 (12)	
Depression scores			
0–7	19 (73)	24 (92)	.040
8–10	6 (23)	2 (8)	
11–15	1 (4)	0 (0)	

Note. ALL = acute lymphoblastic leukemia; ANOVA = analysis of variance; AUC = area under the curve; CAR = cortisol awakening response; PSS = Perceived Stress Scale; HADS = Hospital Anxiety and Depression Scale.

^a. Maternal age and education level were included in all analysis as covariates.