



SHORT COMMUNICATION

Adequate endocrine and cardiovascular response to social stress in survivors of childhood acute lymphoblastic leukemia



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Received 7 June 2013; received in revised form 21 July 2013; accepted 22 July 2013

KEYWORDS

HPA axis;
Cardiovascular stress
response;
Trier Social Stress Test;
Acute lymphoblastic
leukemia;
Child

Summary Survivors of childhood ALL have been demonstrated to have increased morning cortisol levels compared to healthy controls. Information regarding the response of the HPA axis and the sympathetic nervous system to stress in childhood ALL survivors is not available. The present study aimed at assessing the endocrine and cardiovascular stress response in childhood ALL survivors and healthy controls by evaluating perceived stress on visual analog scales, by determining saliva cortisol, blood pressure and heart rate in response to the Trier Social Stress Test for Children (TSST-C). Fifty survivors who had completed their treatment for childhood ALL 57 (IQR 47.0–72.3) months before and 50 healthy age and sex matched controls were included. Exposure to the TSST-C induced a significant response of perceived stress, saliva cortisol and cardiovascular outcome variables in the total study group. These responses did not significantly differ between survivors of childhood ALL and healthy controls. We conclude that the endocrine and cardiovascular response to social stress are intact in survivors of childhood ALL.

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1. Introduction

Acute lymphoblastic leukemia (ALL) is the most common malignancy in childhood. Significant alterations in HPA axis function of survivors of childhood ALL have been identified. We have shown before that survivors of ALL have higher morning cortisol levels and enhanced cortisol suppression in response to oral dexamethasone compared to healthy controls (Gordijn et al., 2012). In addition, a recent study demonstrated higher plasma cortisol levels as well as a higher cortisol amplitude in the response to the Trier Social Stress Test (TSST) in adult survivors of childhood cancer in comparison to healthy controls (Laufer et al., 2012). Since stressful life events early in life may result in long-term dysregulation of the HPA axis (De Bellis et al., 1999; Engert et al., 2011), it is conceivable that the experience of a life-threatening disease such as cancer and the intensive treatment with chemotherapy may account for a stressful life event as well. Studies in trauma exposed children have not only shown enhanced cortisol levels, but also increased sympathetic nervous system activity (Saltzman et al., 2005; Pervanidou and Chrousos, 2007). Increased sympathetic outflow may have clinical implications, since it is associated with development of metabolic syndrome (Lambert et al., 2010). In addition, an altered cardiovascular response to stress is an early predictor of an increased risk for cardiovascular disease in later life (Treiber et al., 2003). To date, no studies have investigated sympathetic nervous system activity in survivors of childhood ALL. Therefore, we now assessed the endocrine and cardiovascular response to a psychosocial stressor in survivors of childhood ALL by the TSST for children (TSST-C). Referring to previous studies regarding the stress response in traumatized subjects (Heim et al., 2000; Armbruster et al., 2011), we hypothesized that survivors of childhood ALL show an enhanced endocrine and cardiovascular response in comparison to healthy controls.

2. Methods

2.1. Participants

As this concerns a follow-up study, all 45 survivors of childhood ALL who participated in our previous study on HPA axis function in childhood ALL survivors (Gordijn et al., 2012) were invited to participate in the present study and 6 of them declined. Eleven additional patients who initially responded positively to our previous study but ultimately refused to participate were invited for the present study and agreed to participate. The study population consisted of children that had been treated according to the Dutch Childhood Oncology Group (DCOG) ALL-9 or ALL-10 protocol between May 1997 and February 2008 in the VU University Medical Center Amsterdam, the University Medical Center Utrecht and the Radboud University Nijmegen Medical Center in the Netherlands. The control group consisted of age (in years) and sex matched friends of the ALL survivors. Exclusion criteria were treatment with glucocorticoids at the time of the study, dysfunction of the hypothalamus, the pituitary and/or the adrenals and being under treatment for relapsed ALL. This study was approved by our institutional review board and written informed consent was obtained from the children and their caregivers.

2.2. Procedure

For stress induction children were exposed to the TSST-C which was described in detail by Buske-Kirschbaum et al. (1997). After a clinical interview and a physical examination of 30 min, the TSST-C was performed which consisted of a 30-min relaxation period watching a video, a 10-min preparation period, a 5-min public speech task, and a 5-min age-appropriate mental arithmetic task. The latter two tasks were carried out in front of a "jury" judging the child's performance. This was followed by a 10-min debriefing period, during which the child was praised for his/her excellent performance, and by another 50-min relaxation period watching a video (Fig. 1). All TSST-C sessions started at 1300 h and were performed by the same research nurse.

The perceived stress of the TSST-C was analyzed by a visual analog scale (VAS). At repeated time intervals ($t = 0$, $t = 60$, $t = 70$, $t = 80$, $t = 90$ and $t = 140$ min) (Fig. 1), participants indicated their perceived stress, by placing a mark on a 10-cm horizontal line, the left end of the line being labeled "not at all" (0) and the right end "extremely" (10). In order to evaluate the endocrine stress response to the TSST-C, saliva samples for cortisol were collected at repeated time intervals ($t = 60$, $t = 70$, $t = 80$, $t = 90$ and $t = 140$ min) (Fig. 1). Cardiovascular determinants were continuously monitored by the Nexfin (BMEYE B.V., Amsterdam, the Netherlands). The Nexfin device non-invasively registers the pressure waveform in the finger, and provides measurements of the beat-to-beat brachial blood pressure and heart rate and the pulse contour analysis-based estimated stroke volume, cardiac output and systemic vascular resistance. The Nexfin monitor has been validated clinically and is considered to be a reliable method for noninvasive blood pressure measurement (Eeftink Schattenkerk et al., 2009).

2.3. Cortisol assessment and analysis

Saliva cortisol samples were stored at -20°C until analysis with a commercially available competitive luminescence immunoassay (IBL-International, Hamburg, Germany) of all samples in one batch (Westermann et al., 2004). The intra- and inter-assay coefficients of variance were both below 8%.

2.4. Statistical analysis

Within-group differences were assessed by t-tests for continuous variables, and by chi-square test for categorical variables. For analysis of the effect of the stressor on the VAS scores and the endocrine and cardiovascular outcome variables, repeated-measurement analysis of variance (ANOVA) was used. VAS scores, cortisol data and cardiovascular outcome variables were log-transformed before statistical analysis to obtain normal distribution, whilst untransformed values are presented in Fig. 2. Data regarding cortisol levels were also analyzed by area under the curve with respect to the ground (AUCg), which is a measure of the total cortisol secretion, and with respect to the increase (AUCi), which is a measure of the dynamics of cortisol secretion (Pruessner et al., 2003). In addition, the stress-induced cortisol increase was assessed by peak level minus nadir level, peak level minus baseline level and peak level

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