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Short Communication

Association between dehydroepiandrosterone-sulfate and attention in long-term survivors of childhood acute lymphoblastic leukemia treated with only chemotherapy

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ABSTRACT

Long-term survivors of childhood acute lymphoblastic leukemia (ALL) are at risk for neurocognitive impairment, as well as compromised hypothalamic-pituitary-adrenal (HPA) function. Dehydroepiandrosterone-sulfate (DHEAS) is an adrenal androgen commonly used as a marker of HPA function. In the general population, a low level of DHEAS has been associated with poorer cognition. At ≥2 years post-treatment, we examined the association of DHEAS with attention outcomes in 35 male and 34 female long-term survivors of childhood ALL (mean[standard deviation] age at evaluation 14.5[4.7] years; 7.5[1.9] years post-diagnosis) who were treated with only chemotherapy and without prophylactic cranial irradiation. Male survivors with low-normal levels of DHEAS had worse performance than male survivors with high levels of DHEAS on multiple measures of attention (all P's < 0.05). However, association between DHEAS and attention measures were not found in female survivors. Our results suggest that survivors of ALL who suffer from partial but persistent adrenal insufficiency may be at risk for neurocognitive deficits. This finding should be validated in a larger prospective study, with attention to sex differences in the potential impact of adrenal insufficiency on neurocognitive outcomes.

1. Introduction

Acute lymphoblastic leukemia (ALL) is the most common childhood malignancy. Despite the gradual omission of prophylactic central nervous system irradiation as a treatment modality (Pui et al., 2009), survivors of childhood ALL may still experience treatment-related late effects due to the exposure to multi-agent intravenous and intrathecal chemotherapy. Our research team has found that at more than 5 years post-diagnosis, long-term survivors of ALL who were treated with a contemporary chemotherapy protocol without cranial radiation demonstrated rates of attention problems higher than age-based normative data (Krull et al., 2016). Current research is now focused on the identification of the source and reduction of factors that contribute to these persistent neurocognitive deficits.

Survivors of childhood ALL are also at risk for endocrine disturbances, including precocious or delayed puberty, thyroid dysfunction, and metabolic disorders. Although these endocrine complications are predominantly associated with radiation, a recent report of 14,290 survivors from the Childhood Cancer Survivor Study indicated that, at 5 or more years post-diagnosis, survivors were significantly more likely to develop an endocrine disorder compared with siblings even when not treated with radiation (Mostoufi-Moab et al., 2016). Within the general population, memory and attention problems are common features of patients who suffer from inadequate hypothalamic-pituitary-adrenal (HPA) axis function (Schultebraucks et al., 2015).

Abbreviations: CPT, Conners' Continuous Performance Test; DHEAS, Dehydroepiandrosterone-sulfate.

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Dehydroepiandrosterone-sulfate (DHEAS) is one of the most abundant steriod hormones that is almost exclusively produced by the adrenal cortex; it is commonly used as a marker of HPA function in adults (Nasrallah and Arafah, 2003). Lower DHEAS levels have been found to predict accelerated global cognitive decline in elderly patients independent of age (Valenti et al., 2009). A blunted DHEAS response to stress has also been associated with poorer cognition, mood and sleep quality (Jackowska et al., 2013; Lennartsson et al., 2012). Even though there is evidence to support the presence of adrenal insufficiency in cancer survivors (Chemaitilly and Sklar, 2010), there is currently no study in the literature that focuses on the association of DHEAS levels with neurocognitive function.

In this study, we report the concurrent association between DHEAS and attention problems in long-term survivors of childhood ALL. We hypothesize that in adolescent and young adult long-term survivors of ALL, lower levels of DHEAS, which may be indicative of a partial but persistent impairment of adrenal function secondary to the cancer and/or its treatment, would be associated with poorer attention performance.

2. Methods

2.1. Participants

Long-term survivors treated on an institutional chemotherapy-only protocol (Pui et al., 2009), who were at least five years from diagnosis and over eight years of age, were eligible for this study. Survivors were excluded if they received cranial radiotherapy (CRT) for the treatment of central nervous system relapse or bone marrow transplantation, developed any relapse or a secondary cancer that required additional chemotherapy, had a pre-existing non-cancer-related neurodevelopmental or genetic disorder associated with cognitive impairment, had a subsequent brain injury unrelated to their cancer, or were not proficient in English. Of 85 survivors eligible for this study, 69 survivors (81%; 35 male and 34 female survivors) agreed to participate in the study and provided serum samples. This study was approved by the institutional review board at St. Jude Children's Research Hospital, and informed consent and assent were obtained as appropriately from the parents/guardians and/or patients.

2.2. Attention outcomes

Survivors completed the Conners' Continuous Performance Test – 2nd Ed. (CPT-II), a computerized sustained attention measure that yields scores for detectability, omissions, commissions, variability, perseverations, hit reaction time, vigilance and risk taking (Conners, 2001). Tests were administered by a master's-level psychological examiner, under the supervision of a board-certified licensed neuropsychologist.

2.3. Biomarker assay

A total of 5 mL of blood was drawn from all participants according to standard procedures within 24 h of attention testing. Samples were processed and the serum was removed, aliquoted and stored at −80 °C until assay. The serum was assayed in duplicate using standardized immunoassays for DHEAS.

2.4. Statistical analysis

Attention measures were transformed into age-adjusted Z-scores using national normative data and presented for descriptive purposes. As there is evidence in the literature that highlights a sex effect in the relationship between sex hormones and health outcomes (Goldman and Glei, 2007; Jackowska et al., 2013), all analyses were conducted separately in male and female survivors. Based on existing literature, we did not expect DHEAS to fall below clinical ranges in the majority of these survivors, though we did expect there to be a threshold effect between DHEAS and health outcomes. DHEAS levels were rank-ordered into tertiles by sex and the CPT raw scores were compared between survivors falling in the bottom tertile *vs* other tertiles using general linear modeling, adjusting for Tanner Stage (pre-pubescent Stage I *vs* pubescent Stages II to IV *vs* post-pubescent Stage IV), age at attention evaluation and time since diagnosis. A higher raw score is indicative of greater attention problems. This approach has been adopted by other studies in the literature that looked at the effect of physiological biomarkers on health outcomes (Cheung et al., 2016; Goldman and Glei, 2007).

3. Results

Survivors' demographic and clinical characteristics, as well as DHEAS values for each reference group, are presented in Table 1. As in the general population, male survivors had overall higher DHEAS levels than female survivors. A majority of the survivors had DHEAS levels that were within the normal reference range, though 8/35 (22%) male and 4/34 (12%) female survivors had DHEAS levels that were below age-, sex- and Tanner Stage-based clinical reference for healthy children and adolescents (Elmlinger et al., 2002; Guran et al., 2015). Age was positively correlated with DHEAS level in both male ($r_{sp} = 0.81$, $P < 0.0001$) and female ($r_{sp} = 0.61$, $P < 0.0001$) survivors. Body mass index was positively correlated with DHEAS in male ($r_{sp} = 0.67$, $P < 0.0001$), but not in female survivors ($r_{sp} = 0.22$, $P = 0.20$). Tanner Stage (Stage I *vs* Stage II–IV *vs* Stage V) is associated with DHEAS levels in both male (median[IQR] ug/dL 25.2 [7.9–69.1] *vs* 101.8 [69.2–123.8] *vs* 144.1 [127.5–245.1]; $P < 0.0001$) and female (39.9 [18.3–52.4] *vs* 82.7 [64.2–139.9] *vs* 108.0 [83.9–153.1]; $P = 0.003$) survivors.

Survivors scored below normative reference on multiple measures of attention (Table 1). After adjusting for Tanner Stage, age at evaluation and time since diagnosis, male survivors in the bottom tertile of DHEAS level demonstrated worse attention performance than those in other tertiles (omissions mean Z-score −1.24 vs. −0.62, $P = 0.03$; variability −1.38 vs. −0.50, $P = 0.008$; perseverations −1.47 vs. −0.67, $P = 0.01$; vigilance −1.38 vs. −0.32, $P = 0.04$; Fig. 1). Association between DHEAS and attention measures were not found in female survivors.

4. Discussion

To our knowledge this is one of the first studies to explore the potential contribution of HPA axis function to neurocognitive outcomes among cancer survivors. Sex differences were observed in the association between DHEAS and neurocognitive function. Male survivors with low-normal DHEAS levels demonstrated worse attention than male survivors with higher DHEAS.

The majority of the survivors had DHEAS levels that were within the normal range. This population of ALL survivors was not expected to have major adrenal complications as they were not treated with CRT or neurosurgery, which are significant predictors of HPA dysfunction in cancer survivors (Chemaitilly and Sklar, 2010). However, survivors within the bottom DHEAS tertile demonstrated low-normal DHEAS levels based on their age groups, which may imply some partial form of persistent adrenal insufficiency that may be induced by alkylating agents and glucocorticoids (Chemaitilly and Sklar, 2010). Our preliminary results suggest that in survivors of childhood ALL who are already at-risk for cancer treatment-related neurotoxicity, subclinical disruption in the HPA axis during long-term cancer survivorship may be associated with