

Cortisol-a Key Factor to the Understanding of the Adjustment to Childhood Cancer

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Abstract

Background: Malignancy and its treatments could cause disturbance in homeostasis of body such as cortisol secretion. The present study has investigated the effects of cortisol level imbalance in behavioral and emotional adjustments.

Methods: Seventy-eight children with Acute Lymphoblastic Leukemia (ALL) have involved in this study. Their salivary cortisol level, which were sensitive to pain and disruptive behaviors, have measured.

Results: Cortisol level effect in different periods: within duration of reaction to pain, sensitivity to pain and disruptive behaviors have evaluated. In addition abnormal regulation of cortisol levels have shown a very strong relationship between sensitivity to pain and the disruptive behaviors. Cortisol suppression was responsible for adjustment by the participants to stressful conditions.

Conclusion: Previous investigations have shown that there is a low reaction to stressor which decreases the vitality as well as impairing a negative memory in low cortisol levels. The findings of the present study demonstrated a nonlinear relation between cortisol level and sensitivity to pain as well as disruptive behaviors. Therefore, regulation of cortisol- up and down- is predisposed to maladjustment.

Keywords: Child; Cancer; Cortisol; Pain; Disruptive behavior disorder

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Introduction

The sympathetic nervous system activity is a suitable standard for the study of the biological foundation of emotions. One of the investigating ways for system activity could be the cortisol level measuring [1]. For instance, when anxiety is heightened, the cortisol level increases correspondingly [2]. Salivary cortisol has emerged as a non-invasive technique as well as a potential biological stress measurement, in different researches, then involving children because the linear relation between salivary cortisol and serum cortisol [3].

Some previous studies have examined the effects of changes in the salivary and blood cortisol level from a developmental perspective. Cortisol patterns are generally established at early infancy [4, 5]; despite this, the activity of the Hypothalamic-Pituitary-Adrenal (HPA) axis is almost intense in young children [6]; while it develops a downward trend until puberty [7]. Researchers believe that

children initially respond to new and threatening stimuli equally; however, over time, they learn to distinguish between novelty and unfriendly stimuli; therefore, they learn how to respond biologically according to the situation [8, 9]. Gradually, when children are more exposed to environmental changes, they demonstrate more regulation of activity in the HPA axis [10]. A number of studies have indicated that children with HPA hyperactive or other dysfunctions in this system are emotionally negative and socially isolated [11].

In addition, the activity of the HPA axis has been investigated in patients with cancer. Radiation therapy is the common cause of irreversible thalamic and pituitary dysfunctions in cancer patients [12]. Chemotherapy as part of standard treatment for ALL could cause adrenal suppression in children even after tapering the dose for over 9 days [13]. A study of leukemic children with lumbar punctures has shown variability in children's salivary cortisol response. Investigators have found that children with

lower levels of pain tolerance have shown elevations in cortisol after experiencing lumbar puncture [14].

The important question in this study is how cortisol level could affect an adjustment in children with cancer. For this reason, we have investigated the relation between cortisol level with respect to sensitivity to pain and disruptive behaviors.

Children with cancer have often suffered from unpredictable and out of control pains. This usually drives such children and their family to desperation and distress [15]. A wide variety of diagnostic but painful methods and aggressive treatments are administered on children with Acute Lymphoblastic Leukemia (ALL) [16]. But the most painful treatment such as injection and specially bone marrow transplantation provoke anxiety and unavoidable reactions in pediatric oncology cases [17]. Painful medical processes induce a wide variety of reactions in children, from unavoidable reactions to loud cries of pain [18]. The first experience of pain might create a vicious cycle for subsequent painful experiences. The pain is accompanied by a high sense of anxiety and anticipation of terrible experience in similar situations [19]. Moreover, laboratory studies have shown that there are obviously individual differences in reactions to pain [20]. It has great importance to note such individual differences for reacting pain, but tend to remain constant over time [21]. A change in the cortisol level constitutes a crucial factor in pain sensitivity. Studies have revealed that the cortisol levels of children have been increased after aggressive treatments [22]. In sum, according to studies, treatment of cancer leads to variation of cortisol secretion. On one hand, cortisol suppression due to chemotherapy and in the other hand invasive treatment such as painful injection disrupts cortisol rhythm in children with cancer. The main question of present study is how cortisol level could change the effect on adjustment.

Materials and Methods

Participants

Seventy-eight (33 females, 44 males) children with Acute Lymphoblastic Leukemia (ALL) have involved in this study. Potential participants have identified from the list of Outpatient Chemotherapy Room and have selected randomly. The eligibility criteria for inclusion in the original study were for different children groups as below: (1) Between 3 and 12 years; (2) Suffered from Acute Lymphoblastic Leukemia (ALL) (3) Cured by chemotherapy. From the initial list of the potential participants, three children have not taken part in the research. All the patients have received standard induction chemotherapy according

to the NOPHO-92-ALL protocol. Data gathering carried out exactly before taking chemotherapy drugs. The prednisolone dosage was 60mg/m² per day for 5 weeks, tapering over 9 days.

Measures

Cortisol

The measurement of cortisol in saliva, reliably reflects physiologically active free cortisol levels in blood, since unbound plasma cortisol diffuses easily from blood to saliva. Salivary samples have collected using the Salivate system from Sarstedt, and then centrifuged. Cortisol kits have refrigerated until retrieve and radioimmunoassay; employing commercial reagents from Diagnostic Systems Laboratories, Inc. Samples has stored at 5°C until using EIA kits from Salimetrics, Inc. The intra-assay coefficients of variation were 3.1 and 0.7%, while the inter-assay values were 3.04 and 1.6%, respectively for low and high controls. The value of 12 nmole/l for the lower limit of a normal stimulated cortisol in saliva has chosen as all tested patients at baseline had a normal stimulated s-cortisol > 500 nmole/l, then a stimulated cortisol in saliva > 12 mol/l.

Disruptive Behavior Disorder (DBD)

The Disruptive Behavior Disorder rating scale (DBD) is a 42-item inventory that assesses all symptoms of externalizing behavior disorders as described in the DSM-IV [23]. The questionnaire could be completed by caregivers. Higher scores have indicated greater severity of problems. Scores above the 95% represented the clinical range. Adequate psychometric properties have been established.

Before using DBD in this study, we have revised the test based on mothers interview, and ALL children interview. According to the results of the interviews, ten of forty-two items of DBD have selected and 5 items included the following have added: s/he all the time is nagging, s/he stops playing, s/he stops regular eating, s/he is crying nonstop and s/he is requesting unusual things. Kendall's coefficient of concordance (W) has computed to assess whether there was significant agreement on the rank order among three practitioners, four nurses and four mothers in the pediatric oncology ward.

The Face Legs Activity Cry and Consolability (FLACC)

The FLACC observational pain assessment tool has been widely used to measure pain intensity in young children [24]. This tool provides a reliable and a

Table 1. Descriptive data based on disease characteristics

Variables	%	M	SD
Age in year		7 years	4.22
Sex			
Male	53		
Female	47		
Months since diagnosis		28 month	0.34
Age of diagnosis			
Early childhood	36.2		
School age	63.8		
Stage of illness			
Newly diagnosed	56.8		
Relapsed	43.20		
Cortisol Level			
Low	41.65		
Normal	47.31		
High	11.04		

Table 2. Participants characteristics based on variable study

Variables	95%Confidence Interval for Mean	M	SD
Cortisol	3.8-5.008	4.40	0.30
Pain reaction duration	43.77-47.99	45.88	1.05
Sensitive to pain	5.37-6.21	5.79	0.21
Disruptive behaviors	42.49-49.53	46.01	1.76

Table 3. Statistics model for the effect of cortisol level on pain reaction duration, sensitivity to pain and disruptive behaviors

Variables	R ²	F	df ₁	df ₂	P
Cortisol					
Pain reaction duration	0.80	101.05	3	74	0.001
Sensitivity to pain	0.79	93.08	3	74	0.001
Disruptive behaviors	0.83	122.84	3	74	0.001

valid framework for assessment of pain in children. This simple tool contains five categories (face, legs, activity, cry and consolability), each of them is scored from 0 to 2 to provide a total score ranging from 0 to 10. FLACC scale is a measurement used to assess pain for children between the ages of 2 months–7 years or individuals that are unable to communicate their pain. The scale is scored between a range of 0–10 with 0 representing no pain. The scale has 5 criteria which are each assigned a score of 0, 1 or 2.

The FLACC scale has also been found to be accurate for use with adults in Intensive-Care Units (ICU) who are unable to speak due to intubation. The FLACC scale offered the same evaluation of pain as did the Checklist of Nonverbal Pain Indicators (CNPI) scale which is used in ICUs.

Duration of reaction to pain

Duration of reaction to pain is a behavioral checklist comprises of four items on its rating scale [25]. These four points would consider the first reaction he/she makes, these reactions might fear induced ones; then where and when exactly have the reaction to pain begun; considering the last reactions exhibited before the restoration of calm, for instance when a baby stops crying and goes back playing or being active again. These points indicate duration of reactions and the time that response to pain ends. Kendall's coefficient of concordance has calculated from the points that given by the physician's assistant, the psychologist in the ward, three of the mothers and the experimenter. The value of Kendall's ω

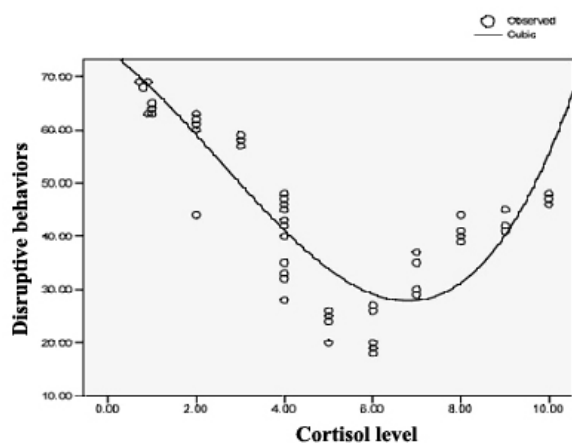


Figure 1. Relation between cortisol level and disruptive behaviors

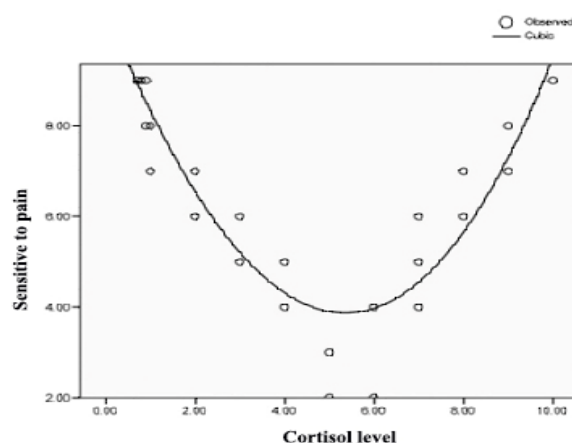


Figure 2. Relation between cortisol level and sensitivity to pain

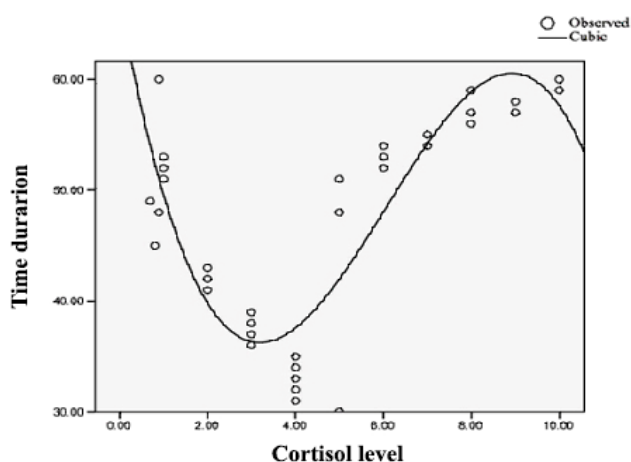


Figure 3. Relation between cortisol level and time duration

in this scale was 0.88 which was significant at $p < 0.001$. After chemotherapy treatment, the average time for reaction to pain was ($M=12\text{sec}$; $SD=0.86$).

Results

Table 1 has shown descriptive data according to disease characteristics. Average of participant's age was about 7 years old. Fifty-three percent of them were boys and 47% were girls. About thirty-six percent of them have diagnosed in the early childhood. According to laboratory report, 41.65% have shown lower and 11.04% higher cortisol level than standard. Table 2 demonstrates range and mean of study variety.

To evaluate the effect of cortisol level on pain reaction duration, sensitivity to pain and disruptive behaviors (Table 3), nonlinear regression has used to estimate parameters of a best-fit pattern function to data. A cubic curve has fitted through all data to obtain parameter estimation. The analyses has revealed that the nonlinear effect of salivary cortisol is highly predictive of pain reaction duration. This duration has shown a high regression coefficient. Based on Figure 1, participants could not react to pain when either cortisol level is low ($b_1 = -22.04$) or is high ($b_3 = -22.58$) then in the normal rate of cortisol, they relatively react pain much sooner ($b_2 = 4.69$).

The analyses revealed that the nonlinear effect of salivary cortisol is highly predictive of

the duration of reaction to pain (Figure 1), sensitivity to pain (Figure 2) and disruptive behaviors (Figure 3).

Discussion

According to the results, cortisol levels dramatically have decreased in children with Acute Lymphoblastic Leukemia (ALL). Consequences of cortisol suppression could be permanent and dangerous. For example, abnormal regulation of cortisol rhythm has associated with various negative outcomes, including: tumor growth, early mortality, and increasing pain [26, 27]. Chronic cortisol abnormal regulation causes hippocampal dysfunction, hence resulting in memory impairment and other cognitive problems [28]. Studies in physically healthy individuals have shown relations between disruption of HPA axis rhythms and affective mental illness as well as chronic stress [29, 30]. Despite the negative consequences of decreasing cortisol, it could be an important determinant for adjustment in childhood cancer.

Reaction to stressors

Cortisol level characterizes intensity of response to perceive stress [31]. Emotional reaction to stressors declines, while chemotherapy or malignancy progress caused decrease in cortisol level. This evidence confirms some previous findings that despite stressful situations, survivors of childhood cancer demonstrate a good adjustment, even better than healthy children [32]. Survivors react to stressful stimuli with less intensity and this made researchers to conclude that this group could adapt very well. Therefore, perhaps it could be a better adjustment if only a smaller emotional response, has replied to stress because cortisol level failure; but this conclusion has simply stated that cortisol plays a complex role in adjustment to childhood cancer.

Liveliness

There are some evidences that declining cortisol level could associate with abnormality in glucose metabolism and the subsequent loss of energy [33]. In some previous studies, children with cancer have shown less liveliness in comparison to healthy children [34]. Nevertheless, less liveliness and happiness in children with cancer might be related to cortisol suppression.

Impaired negative memory

Glucocorticoids such as cortisol could affect memory retrieval; they are also important information of new memories [35]. Depressing

cortisol levels before memory recall has long-lasting effects [36]. Recently, an interesting phenomenon has been discovered in young women who have received a double dose of metyrapone, a drug that inhibits cortisol secretion, then they have reported impaired recall of the negative parts of a story [37]. In another study, it has observed that children with cancer, compared with healthy children, could recognize more positive images [38]. Probably, positive bias or repressed negative memories in such cases could be the outcomes of cortisol diminishing.

Sensitivity to pain

Numerous environmental and genetic factors have found as responsible for individual variability in pain response [39]. In addition, different brain regions have been related with sensitivity to pain [40]. In the present study, cortisol level is introduced as an important hormonal factor for different individual pain sensitivity.

Disruptive behaviors

Interview with participants' mothers has revealed that disruptive behaviors in children with cancer have shown differences with healthy children. For instance, when a number of red blood cells decrease in leukemic children, they demonstrate a behavioral syndrome which includes nagging, refusal to play, refusing to eat, continuous crying and requesting unusual things. Unfortunately, there is no standard checklist about disruptive behaviors of children in hospitals. The results of this study show that this syndrome is also related to cortisol suppression. This syndrome is important then its relation to cortisol level is critical. For example, it could be an important alarm for the practitioner when a patient shows bad condition.

The findings of the present study have reported a nonlinear relation between cortisol level and pain sensitivity as well as disruptive behaviors. In other words, the rate of pain sensitivity and disruptive behaviors have ascended with cortisol level increase. When cortisol has reduced, pain sensitivity and disruptive behaviors have both subsided. Dramatically, it has also found out that pain sensitivity and disruptive behaviors have suddenly increased with cortisol suppression. Therefore, abnormal regulation of cortisol- up and down- is prone to maladjustment. Children with suppressed cortisol might more likely die because of debilitated immune system. Usually, researchers have ignored investigating disruptive behaviors in these patients, because the children with critical situation have not prepared to participate in psychological research;

instead, they think about survival instincts. It is possible that survivor cortisol remain constant over time (regulate in lower rate). This phenomenon could be explained by the scoop theory. The "scoop" model as a developmental perspective in the reaction to pain has posed that not only the genetic elements determine the reaction of neurons to pain [41], but also, environmental elements such as chemotherapy drugs directly have effects on reactions to painful conditions. Neuron system has changed through environmental conditions during certain critical periods of development might have a more lasting effect that could even continue till adulthood. Nevertheless, further studies should be designed to compare cortisol level in children with cancer after chemotherapy.

Conflict of Interest

No conflict of interest to disclose.

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Authors' Contribution

Manijeh Firoozi and Mohammad Ali Besharat have designed the study. Manijeh Firoozi has collected the data and written the paper. Mohammad Ali Besharat has contributed to data gathering.

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