Associations between psychiatric symptoms and cortisol levels in Nicaraguan young school-age children

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ABSTRACT

The regulation of the Hypothalamus-Pituitary-Adrenal axis (HPA-axis) with its end product cortisol seems to be affected in several psychiatric disorders. Although findings are not conclusive, internalizing symptoms have primarily been associated with higher diurnal cortisol levels and externalizing symptoms with lower cortisol levels. In this study on nine-year-olds in Nicaragua ($n=111$), we investigated associations between child psychiatric symptoms, using the Child Behavior Check List (CBCL), and saliva cortisol levels collected in the morning and afternoon, also adjusting for potential confounders. In line with previous findings, internalizing symptoms were significantly associated with higher morning, but not afternoon cortisol levels. Surprisingly, externalizing symptoms were also significantly associated with higher morning cortisol levels. Possibly, this association between externalizing symptoms and cortisol levels may be characteristic of early ages, representing a higher exposure to external stressors. The study highlights the need for prospective studies, following the development of the HPA-axis and its association with psychiatric symptoms.

1. Introduction

The Hypothalamus-Pituitary-Adrenal axis (HPA-axis) with its end product cortisol is an important part of the neuroendocrine system, mediating the response to psychosocial, physiological and chemical challenges, thereby promoting homeostasis (Ulrich-Lai and Herman, 2009). The characteristic diurnal rhythm of the axis is typically established during the first months of life (de Weerth et al., 2003). According to the theory of allostatic load, exposure to repeated or chronic stressors may lead to a dysregulation of central physiological systems as the HPA-axis, resulting in an increased susceptibility for stress related diseases such as metabolic (diabetes, obesity), cardio-vascular, and immunological disorders as well as disorders related to the central nervous system (Juster et al., 2010). Maternal exposure to stressors during pregnancy may result in sensitization to subsequent stressors in the child. For instance, Essex et al. (2002) found higher cortisol levels than in controls in concurrently stressed preschoolers who had been exposed to maternal stress during the fetal period. Exposure to only

fetal or concurrent stressors was not related to cortisol levels. Individual differences concerning perception of and reactions to stressors, may also increase the allostatic load, by inducing behavioral and physiological responses that in the long run may lead to ill-health (Juster et al., 2010). A constitutional over-reactivity of the HPA-axis and high diurnal cortisol levels are two examples.

An increasing amount of research has focused on the regulation of the HPA-axis in psychiatric disorders, especially in depression. The vast majority of studies on adult depression report findings indicating a disturbed diurnal rhythm and in major depression disorder this seems to be occurring in about half of the cases (Herbert, 2013). In a review of studies on the association between adult depression and HPA responses to psychological stressors, clinically depressed individuals, compared to non-affected controls, also had a blunted stress reactivity. Furthermore, they had an impaired stress recovery with higher cortisol levels even when baseline levels were included as co-variates in the analyses (Burke et al., 2005). Previously it has been questioned if HPA-axis changes are also related to pediatric depression (Kaufman et al., 2001). One meta-analytic (Lopez-Duran et al., 2009) and one narrative (Guerry and Hastings, 2011) review support the hypothesis that HPA-axis dysfunction is involved in depression during childhood. First, children with depression have moderately high cortisol levels throughout the day. Second, they have an atypical response to

dexamethasone suppression test with higher cortisol production – indicating reduced suppression - compared to non-depressed peers (Lopez-Duran et al., 2009). There are fewer studies on reactions to psychological stressors but the findings so far suggest that this type of reactivity may also be dysfunctional. As to developmental aspects, there seems to be a stronger association between HPA-axis dysfunction and depression with increasing age (Guerry and Hastings, 2011). Moreover, HPA-axis dysfunction seems to precede depression during adolescence and early adulthood (Guerry and Hastings, 2011).

For anxiety disorders most studies point towards higher basal levels and hyper-responsiveness at exposure to stressors (Vreeburg et al., 2010; Faravelli et al., 2012). However, results may vary depending on the type of disorder. Thus, post-traumatic stress disorder has been associated mainly with lower cortisol levels, whereas panic disorder, agoraphobia, obsessive–compulsive disorder and generalized anxiety disorder have been associated with higher cortisol levels (Faravelli et al., 2012; Heim et al., 2000). Social phobia has been associated with hyper-responsiveness to a stressor, but with lower baseline levels (Faravelli et al., 2012). It has been argued that hypo-arousal in anxiety disorders, may correspond to counter-regulative adaptation with downregulation of the HPA axis due to a high stress load (Faravelli et al., 2012).

A down-regulation of the HPA-axis with lower cortisol levels, hyposensitivity to stressors and a high threshold to arousal has been described in relation to externalizing disorders and disruptive behaviors (Alink et al., 2008; Dietrich et al., 2013). Such a pattern has been hypothesized to underlie sensational seeking behavior, which is a common symptom in disruptive disorders (Hirshfeld-Becker et al., 2003). Along the same line, low baseline salivary cortisol concentrations have been suggested as a potential biomarker for attention deficit/hyperactivity disorder (ADHD) (Scassellati et al., 2012). However, this relation between low cortisol levels and externalizing symptoms does not seem to be valid for young children. A review concluded that pre-school children with externalizing symptoms had higher basal cortisol levels than comparisons, a finding that contrasts the lower levels found in school-aged peers with externalizing symptoms (Alink et al., 2008). Along the same line, in a study on school age children with ADHD, lower diurnal cortisol levels than in comparisons were only present in children above 10 years of age (Isaksson et al., 2012). One hypothetical explanation of this age discrepancy is that externalizing disorders may be associated with a higher stress load, which can be illustrated by the higher exposure to punishments and inconsistent discipline in children with conduct problems (Alink et al., 2008). Early high levels reflecting continuous exposure to stressors may thus as a consequence of exhaustion turn into low levels in a similar way that has been hypothesized for anxiety disorders with low cortisol levels, see above (Faravelli et al., 2012).

The HPA-axis may be influenced by a large variety of factors during childhood, which need to be taken into consideration when trying to assess the relation between psychiatric symptoms and cortisol levels. Particularly the qualities of the psychosocial environment have been in focus in previous studies. In the study referred to above about concurrently stressed preschoolers who had been exposed to maternal stress during the fetal period, maternal depression, beginning in infancy, was the strongest predictor of child cortisol (Essex et al., 2002). Exposure to marital conflict has been associated with both a negative appraisal of self-blame in adolescents, age 10–17, and a blunted cortisol slope (Lucas-Thompson et al., 2015). Interestingly, self-blame predicted less robust cortisol decreases over the day. Findings concerning the influence of socioeconomic status (SES) in the family are not conclusive with reports both on higher diurnal levels (Clearfield et al., 2014) and lower morning cortisol levels (Zalewski et al., 2012).

Studies from settings outside Northern America and Europe are scarce in this field. Nicaragua is one of the poorest countries in Latin America. Half a million of the people lives in extreme poverty, on less than 1.25 US dollars/day (World bank, 2015). We need to know if previous results concerning psychiatric symptoms and cortisol levels are valid in such an environment. Within the design of a larger prospective research program, following a Nicaraguan birth cohort, we discovered a possibility to approach these issues using follow up data at child age of nine years. The sample intends to represent young children from the poor population in a developing country.

Thus, the aim of this study was to investigate associations between psychiatric symptoms and diurnal cortisol levels in nine-year-olds in Nicaragua, adjusting for potential confounders. We hypothesized that higher ratings on internalizing symptoms would be associated with higher diurnal cortisol levels, whereas externalizing symptoms would be associated with lower cortisol levels.

2. Methods

2.1. Participants and procedure

As part of a longitudinal study (Valladares et al., 2009; Isaksson et al., 2015), following pregnant women identified in the community demographic surveillance site of UNAN-León, Nicaragua and their offspring, 111 women were interviewed by a trained female assistant using questionnaires regarding maternal distress, partner abuse, maternal social support and child psychiatric symptoms (for details see below). All questionnaires were reviewed by a field supervisor and the main researcher (EV). The children (mean age: 8.6 years, SD: 0.52; 60 girls, 50 boys, one without information about gender) also collected saliva samples for cortisol analysis in the morning and in the afternoon.

2.2. Questionnaires on maternal psychosocial factors

2.2.1. Maternal education
Self-reported maternal level of education was used as a proxy of socioeconomic status. The variable was dichotomized into low (up to primary school) or high (secondary school or university).

2.2.2. Maternal emotional distress
The Self-Reporting Questionnaire (SRQ-20) was used to measure emotional distress during the last four weeks. It includes 20 questions (yes/no) on depression, insecurity, anxiety, fear and defenselessness. The scale is used by the national mental health program of the ministry of health, which recommends a cut off at ≥ 6 points (MINSA, 1998), which was applied in this study.

2.2.3. Abuse against women
Violence was measured through the Spanish version of the questionnaire developed by the WHO Multi-Country Study on Women's Health and Domestic Violence against Women (Garcia-Moreno et al., 2006) that includes different dimensions of partner violence (emotional, physical and sexual), in total 10 questions (yes/no). The women were asked if they had been exposed to partner violence during the last year. Any report of exposure to violence (emotional and/or physical and/or sexual) was categorized as "exposure to abuse".

2.2.4. Social support
Maternal social support was measured using a questionnaire developed by Hanson and colleagues (Hanson et al., 1997). Social