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Hair cortisol in newly diagnosed bipolar disorder and unaffected first-degree relatives

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ABSTRACT

Objective: Hair cortisol is a promising new biomarker of retrospective systemic cortisol concentration. In this study, we compared hair cortisol concentrations in patients with newly diagnosed bipolar disorder (BD), their unaffected first-degree relatives and healthy individuals and identified potential predictors of hair cortisol concentrations in patients with BD.

Method: In a cross-sectional design, we compared hair cortisol concentrations in 181 patients with newly diagnosed/first episode BD, 42 of their unaffected first-degree relatives and 101 healthy age- and sex-matched individuals with no personal or first-degree family history of affective disorder. In patients with BD, we further investigated whether medication- and illness related variables, as well as measures of stressful life events in the preceding 12 months and childhood trauma, were associated with hair cortisol concentrations.

Results: Hair cortisol concentrations were 35.1% (95%CI: 13.0–61.5) higher in patients with BD ($P = 0.001$) compared with healthy individuals in models adjusted for age and sex. Hair cortisol concentrations in unaffected first-degree relatives did not differ from healthy individuals ($P = 0.8$). In patients, neither medication, illness duration nor stress related variables were associated with hair cortisol concentrations.

Conclusion: We found elevated hair cortisol concentrations in patients newly diagnosed with BD indicating the presence of physiological stress in early stages of BD.

1. Introduction

Stressful life events often precede the first major mood episode of bipolar disorder (BD) (Horesh et al., 2011) as well as subsequent mood episodes (Lex et al., 2017) and the tolerance for stressful life events seems to decrease with advanced illness burden (Kessing and Andersen, 2017). Further, BD seems associated with dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis (Belvederi Murri et al., 2016) including elevated concentrations of basal plasma and salivary cortisol concentrations although with large heterogeneity in findings (Belvederi Murri et al., 2016; Stalder and Kirschbaum, 2012). A major reason for the heterogeneous findings may be that plasma and saliva and also urine reflect circulating cortisol concentrations at the test moment that vary considerably with food intake, exercise, menstrual cycle, sleep and acute stress (Montero-Lopez et al., 2018; Stalder and Kirschbaum, 2012). In contrast, measurements of hair cortisol are indicators of systemic cortisol concentrations within the preceding months (Stalder and Kirschbaum, 2012), validly reflecting prolonged stress (Staufenbiel et al., 2013).

Assessment of hair cortisol concentration has several other benefits: first, it is a non-invasive procedure; second, the observed concentration is unaffected by sampling procedure and diurnal variations; and third, the measured concentration reflects an average concentration of free circulation cortisol in the months before the sample collection depending on the length of the hair sample (Russell et al., 2015; Stalder and Kirschbaum, 2012). A further advantage is that hair can be stored for years at room temperature while maintaining the same cortisol concentration over time (Russell et al., 2015). Toxicology and forensic science have integrated hair analysis for exogenous substances for more than 30 years (Pragst and Balikova, 2006) and international laboratories are collaborating toward standardization of hair cortisol measurements (Russell et al., 2015). Single hair cortisol concentration measurements include a strong trait component explaining 59–82% of the variance in contrast to state-related factors, which only explain a minor part of the variance (Stalder and Kirschbaum, 2012).

Only two studies have compared hair cortisol concentrations in

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patients with BD and healthy individuals. The first study did not find any difference in hair cortisol concentrations in 100 patients with BD and 195 healthy individuals, but found that patients with onset ≥30 years had elevated cortisol concentrations compared with patients with onset < 30 years in exploratory analyses (Manenschijn et al., 2012). The second study observed higher concentrations of hair cortisol in the 61 patients with BD type I compared with 82 healthy individuals (Streit et al., 2016). These two prior studies included patients with BD of an average age of 45–52 years (Manenschijn et al., 2012; Streit et al., 2016), hence patients with BD were supposedly in a later illness stage. Due to clinical progression of BD over time, it is relevant to study hair cortisol concentrations in earlier stages of BD and also in individuals predisposed to BD.

Higher salivary basal cortisol concentrations have been found in offspring of patients with BD than in offspring of individuals without mental illness (Ellenbogen et al., 2006, 2010). Another small prospective study of young offspring of patients with BD (n = 28) and offspring not predisposed to affective disorders (n = 31) found increased baseline salivary concentrations associated with onset of affective disorder within a 2.5-year follow-up period (Ellenbogen et al., 2011). In the present report, baseline hair cortisol concentrations were investigated. Moreover, in the same study, we currently collect hair cortisol samples from high-risk individuals over a 5-year period to investigate if hair cortisol may act as a risk predictor or later BD illness onset.

Hair cortisol concentrations have not previously been investigated in newly diagnosed patients with BD. Further, hair cortisol concentrations have neither been investigated in unaffected first-degree relatives of patients with BD.

1.1. Aim and hypotheses

The aims of the present study were: (I) to compare the cumulative hair cortisol concentrations over the preceding three months in patients with newly diagnosed/first episode BD and their unaffected first-degree relatives with healthy individuals. (II) to determine whether illness- and medication variables as well as measures of stressful life events and childhood trauma in patients with BD were associated with hair cortisol concentrations.

We hypothesized that concentrations of hair cortisol would be elevated in patients with BD and - to a lesser degree - in their unaffected first-degree relatives compared with healthy individuals without a family history of psychiatric disorders. Further, we hypothesized that higher hair cortisol concentrations would be associated with longer illness duration, stressful life events and childhood trauma.

2. Materials and methods

2.1. Study design

The recruitment for the current study took place from June 2015 to September 2017. The present report is a cross-sectional investigation of baseline data from the ongoing longitudinal Bipolar Illness Onset Study (BIO), which aims to identify biomarkers for BD (Kessing et al., 2017). The study protocol was approved by the Committee on Health Research Ethics of the Capital region of Denmark (protocol No. H-7-2014-007) and the Danish Data Protection Agency, Capital Region of Copenhagen (RHP-2015-023). All participants provided written informed consent. The study complied with the Declaration of Helsinki principles (Seoul, October 2008).

2.2. Participants

2.2.1. Patients with bipolar disorder

Patients were recruited from the Copenhagen Affective Disorder Clinic that covers the Copenhagen catchment area of 1.6 million inhabitants (Region Hovedstaden) and offers service for patients newly diagnosed with BD. All patients referred to the Copenhagen Affective Disorder Clinic as newly diagnosed with BD or having a first episode of mania or hypomania were routinely invited to participate in the BIO study. Inclusion criteria were an ICD-10 diagnosis of BD or a single manic episode and age 15–70 years. Exclusion criterion was having an organic BD secondary to brain injury. Patients with BD received treatment as usual in the Copenhagen Affective Disorder Clinic without interference from study investigators.

2.2.2. Unaffected first-degree relatives

Siblings and children of the included patients with BD were invited to participate upon consent by the participating patient. Inclusion criteria were being a first-degree relative of an included patient with BD and aged 15–40 years. Exclusion criteria were an ICD-10 diagnosis lower than F34 including substance abuse, psychotic illnesses and a diagnosis of unipolar disorder or BD. We did not restrict the number of unaffected first-degree relatives included per patient with BD; however, we adjusted our analysis for the familial relationship.

2.2.3. Healthy individuals

Age- and sex matched healthy individuals were recruited among blood donors from the Blood Bank at Rigshospitalet, Copenhagen, Denmark by contacting blood donors in the waiting room at the Blood Bank on random days. Inclusion criterion was age 15–70 years. Exclusion criteria were a personal or first-degree family history of psychiatric disorders that had required treatment.

2.3. Clinical assessments

The initial diagnostic assessment of patients was held by a specialist in psychiatry, in the Copenhagen Affective Disorder Clinic, diagnosing patients with BD according to ICD-10 and classifying patients with BD as type I or type II according to DSM-5 criteria as part of daily practice. Following informed consent, the initial clinical diagnosis of BD was confirmed in a semi-structured research based interview using the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) (Wing et al., 1990). Diagnosis of the current affective state was based on ICD-10 criteria. Severity of depressive and manic symptoms was assessed using the Hamilton Depression Rating Scale-17 items (HAMD-17) (Hamilton, 1960) and the Young Mania Rating Scale (YMRS) (Young et al., 1978), respectively. The Childhood Trauma Questionnaire (CTQ) (Bernstein et al., 1994), Stressful Life Events (SLE) (Kendler et al., 1998) and the Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989) were administered at the day of assessment. We used the PSQI global score, where a score > 5 indicates sleep disturbance (Buysse et al., 1989).

Absence of lifetime psychiatric morbidity defined by ICD-10 was confirmed for healthy individuals whereas psychiatric morbidity of F34 and higher according to ICD-10 were registered for unaffected first-degree relatives. Current medication was recorded for all participants.

2.4. Anthropometric assessment

After a 10-minutes rest blood pressure was measured using a calibrated automatic sphygmanometer (Microlife BP A3 plus). Lightly dressed and without shoes, height was measured to the nearest millimetre on a rigid stadiometer and weight was measured to the nearest 0.1 kg using a calibrated floor scale (Kern MPE PM). Waist circumference was measured as the midpoint between the lowest rib and the iliac crest in an upright position to the nearest millimetre as described in the World Health Organisations guidelines (Cornier et al., 2011).