A SURVEY OF MENTAL DISORDERS USING HAIR CORTISOL CONCENTRATION

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ABSTRACT:

Depression is a severe, treatable disorder which continues to remain under-detected in the primary care settings and is associated with symptoms such as melancholy, loss of pleasure, loss of energy, difficulty in concentrating, and suicidal thoughts. Stressful life events are one of common precedents in the first episode of depression, and may leave a person more vulnerable to develop subsequent episodes. Various techniques such as psychological questionnaires, measuring cortisol concentration, MRI scanning have been employed to measure the severity of depression. The conventional sources to measure cortisol levels are plasma, urine or saliva, which provide only acute cortisol exposure. Measuring cortisol concentration in hair has emerged over recent years as it provides a long-term, month-by-month systematic cortisol exposure. The purpose of this paper is to survey the promising results of correlation between HCC and mental disorders. A review of statistical techniques and machine learning algorithms used in previous work is included.

Keywords: Depression, Hair Cortisol Concentration, Mental disorder

[1] INTRODUCTION

According to WHO, Depression is a common mental disorder and one of the main causes of disability worldwide. This disorder is of major public health importance, in terms of its prevalence and the suffering, dysfunction, morbidity, and economic burden. Symptoms of depressions range widely from less severe ones such as difficulty concentrating and fatigue, to more serious indications such as persistent aches, feeling of anxiety and “emptiness.” It can cause severe consequences to humans since it is different from simple mood fluctuations or temporary emotional responses. In extreme cases, depression can lead to suicidal attempts and in fact, Centers for Disease Control and Prevention reports depression as one of the
leading causes of suicides [1]. The report on Global Burden of Disease estimates the point prevalence of unipolar depressive episodes to be 1.9% for men and 3.2% for women, and the one-year prevalence has been estimated to be 5.8% for men and 9.5% for women. It is estimated that by the year 2020 if current trends for demographic and epidemiological transition continue, the burden of depression will increase to 5.7% of the total burden of disease and it would be the second leading cause of disability-adjusted life years (DALYs), second only to ischemic heart disease [2]. It is now widely accepted that psychological stress may alter the internal homeostatic state of an individual. During acute stress, adaptive biochemical responses occur, which include increased adrenocortical secretion of hormones, primarily cortisol [3]. These responses help an individual cope up with the stressor, but may be detrimental when stressful experiences are extreme or chronic, particularly when these experiences occur early in life [4].

The most common biological marker to measure stress response is cortisol, which is released by the hypothalamic-pituitary-adrenal (HPA) axis. The HPA axis is one of the stress response systems of the body which consists of the hypothalamus, the pituitary gland and the adrenal gland. The HPA axis activates and co-ordinates the stress response by receiving and interpreting information from other areas of the brain as well as from the autonomic nervous system [5]. A hormonal cascade is initiated in response to the stressor with the release of corticotrophin releasing hormone (CRH) from the hypothalamus, which simulates the release of ACTH from the pituitary gland. ACTH then triggers the breakdown pregnenolone within the adrenal cortex into the glucocorticoid, cortisol which is subsequently secreted into the blood circulation. Until a few years ago, cortisol has solely been analyzed from blood serum, saliva or urine. These analyses offer the possibility to explore the dynamics and the concentration of acute (serum, saliva) or short-term (urine) circulating cortisol concentrations [6]. Hair cortisol measures are considered to reflect free cortisol levels.

Hair grows at an average rate of 1 cm per month. Therefore, the first centimeter of hair at the scalp follicle indicates last month’s cortisol production; the second 1-cm segment indicates the cortisol production of the month before, and so on [7]. Hair cortisol is not affected by sex, hair treatments (i.e., dyes or permanents), pharmaceutical intake, or self-reported health. Hair cortisol analyses have also been validated [7] and correlated with repeated salivary cortisol [8] and 24-hour urinary cortisol measures [9]; therefore, this assessment is an accurate biomarker for cortisol measurement. In particular, hair cortisol levels are positively associated with the number of self-reported serious life events; thus, this measure could serve as a retrospective biomarker of increased cortisol production that reflects exposure to major life stressors [10]. Long term changes to the secretion of the cortisol, such as under conditions of chronic stress, are well known to be associated with a range of mental disorders. Dysregulation of the HPA-axis is known to occur in several psychiatric disorders, such as anxiety disorder (e.g. post-traumatic stress disorder) [11] and mood disorders including bipolar disorder (BD) [12]. In addition, depression and mania are common psychiatric symptoms seen in patients treated with corticosteroids or suffering from Cushing's Syndrome, a disorder caused by cortisol excess [13].
There are various mental disorders such as Generalized Anxiety Disorder (GAD), Major Depression (MD), Bipolar Disorder (BD) and Post-Traumatic Stress Disorder (PTSD). We are describing the relationship between HCC and these disorders. Previous research on cortisol secretion in PTSD however has produced inconsistent results. The majority of findings suggest a generally lower cortisol levels in PTSD patients; e.g. cortisol levels in 24 h urine [14], saliva [15] and blood [16] have been found to be reduced in PTSD patients in comparison to healthy controls. In contrast, a number of studies have also provided evidence for increased cortisol levels in 24 h urine [17] and cerebrospinal fluid [18] in PTSD patients compared to non-traumatized controls. Similar results of elevated salivary [19] as well as 24 h-urinary [20] cortisol levels in PTSD patients have also been reported when PTSD patients were compared with traumatized controls. Finally, some studies have failed to observe significant differences between salivary cortisol levels of PTSD patients and traumatized controls [21] as well as between urinary cortisol levels of PTSD patients and healthy controls [22]. Stuedte used the novel method of hair cortisol analysis to examine cumulative long-term cortisol secretion in a severely traumatized PTSD sample. The results revealed that hair samples of PTSD participants contained higher cortisol levels than those of traumatized controls. Furthermore, a positive association was found between hair cortisol levels and the number of lifetime traumatic events. The hair cortisol findings suggest that PTSD in severely traumatized individuals who continue to live under stressful conditions might be associated with general hypercortisolism [23].

**Figure: 1.** Mean (±SEM) hair cortisol concentrations of PTSD patients and traumatized controls[23].

Cobbs examined participants (8-15 years of age) which were hospitalized for traumatic brain injury (TBI; n=55; M age =13.9 yrs; 40 males) or extra cranial injury (EI; n=29; M age 12.3 yrs, 20 males). Six months post-injury, saliva was collected before and after the Trier Social Stress Test and later assayed for cortisol and sAA. Compared to participants with EI, children with TBI had elevated cortisol and adolescents had elevated salivary Alpha Amylase (sAA) [25].

Generalized anxiety disorder (GAD) is characterized by chronic excessive, uncontrollable anxious worrying about various life circumstances accompanied by multiple somatic and cognitive symptoms. These features may constitute a substantial source of subjective distress, potentially leading to dysregulations of the body’s stress response systems, particularly the hypothalamic-pituitary-adrenal (HPA) axis regulating the secretion
of cortisol. Yet, research investigating the potential role of HPA axis dysregulation in GAD is limited and the few available studies have reported mixed findings [26]. Specifically, elevated basal cortisol levels have been observed in GAD patients compared with healthy controls in diurnal salivary [27] and plasma [28] assessments. Further, cortisol levels of affected patients were found to decrease in response to cognitive therapy and pharmacological treatment [29]. These findings further combine well with earlier studies suggesting reduced HPA axis negative feedback sensitivity in GAD patients [30]. Hilbert classified the participants as GAD, GAD comorbid with MD and MD without GAD. In case classification, GAD and MD groups showed significantly higher scores compared to the healthy comparison group in all clinical questionnaires. And in disorder classification, applying the cortisol data to the classification problem resulted in good balanced accuracy (74.60%, p = .0088, sensitivity: 77.78%, specificity: 71.43%) [32].

Bipolar disorder (BD) is a severe mental illness characterized by recurrent mood episodes with a global prevalence of around 2.4% [33]. In BD patient, research has demonstrated altered cortisol levels [34] and increased cortisol secretion has been reported [35]. Manenschijn found significantly elevated hair cortisol levels in the group of patients with their first depression or mania ≥ 30 years of age compared to the group of patients with their first depression or mania before 30 years of age (p=0.004) [36].

![Figure: 2. HCC in healthy controls, bipolar disorder patients with younger and older age of onset. HC, healthy controls; p-values are adjusted for age, gender, use of hair products, hair treatment and frequency of hair wash [36].](image)

Streit found that perceived stress in BD and SCZ patients was higher than healthy controls (p<0.02).HCC was higher in BD patients compared to SCZ patients and healthy controls [47]. Dettenborn included 23 depressed patients (8 men and 15 women) and 64 age- and gender matched control participants in his research. They took 2 hair segments from all the participants (segment 1: first 3 cm segment most proximal to scalp and segment 2: next 3cm segment of hair). Their findings represent that depressed patients had higher HCC than controls in both hair segments [39].
Figure: 3. HCC in depressed and healthy control participants in near scalp (segment 1, 23 depressed vs 64 controls) and adjacent (segment 2, 19 depressed vs 50 controls) 3 cm segment [39].

Ksenia Pochigaeva determined that Hair cortisol levels differed significantly between groups, with lower levels in the Major Depressive Disorder (MDD) group, as compared to controls (p = 0.007) [40].

[3] MATERIALS AND METHODS

Until now, research has been done on the correlation between hair cortisol concentration and specific mental disorders. As of now, we can compare the cortisol levels in patients having multiple different mental disorders. HCC varies according to the type of mental disorder, ranging from extremely high values to low values. Various studies have been done on various mental disorders and the results are quite interesting as shown in table 1.

<table>
<thead>
<tr>
<th>Sr No</th>
<th>Authors</th>
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<th>Samples</th>
<th>Methods</th>
<th>Results</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Ksenia Pochigaeva et al. (2017) [40]</td>
<td>Major Depressive Disorder (MDD)</td>
<td>21 female patients with MDD and 22 female age-matched controls</td>
<td>17-item Hamilton Depression Rating Scale (HAMD-17), Beck Depression Inventory (BDI) and the Spielberger state trait anxiety inventory (STAI), StatSoft Statistica 10</td>
<td>The levels of hair cortisol were significantly lower in the MDD group, while serum cortisol levels were significantly higher in patients, as compared with controls.</td>
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<td>2</td>
<td>Linda Ewing-Cobbs et al. (2017) [25]</td>
<td>PTSD</td>
<td>Participants with Traumatic brain injury (TBI) (n=55, 40 males) and Extracranial injury (EI) (n=29, 20 males)</td>
<td>Preinjury questionnaire and Statistical approach</td>
<td>Relative to a healthy non-injured group, Injured children had high cortisol level</td>
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<td>3</td>
<td>Kevin Hilbert</td>
<td>Separating Subjects with</td>
<td>Penn State Worry</td>
<td>Classification of</td>
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<tr>
<td>Study (Year)</td>
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<td>Shamla Mantri et al. (2016) [32]</td>
<td>GAD (n = 19), MD without GAD (n = 14), and healthy comparison subjects (n = 24)</td>
<td>Questionnaire (PSWQ), Beck Depression Inventory-II (BDI), SVM classification</td>
<td>GAD verses MD was significantly affected by cortisol values than questionnaires.</td>
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<td>Susann Steutel-Schmiedgen et al. (2016) [31]</td>
<td>17 GAD patients (12 females), 12 MD patients (10 females), 21 age- and gender matched healthy control individuals (15 females)</td>
<td>Penn State Worry Questionnaire (PSWQ), Beck Depression Inventory (BDI), Perceived Stress Scale (PSS), Screening Scale of Chronic Stress of the Trier Inventory for the Assessment of Chronic Stress (SSCS-TICS), SPSS, ANOVA</td>
<td>MD patients exhibited lower HCC than controls and GAD patients (both p’s &lt; .05), with no differences between GAD patients and controls (p = .936).</td>
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<td>Streit et al. (2016) [38]</td>
<td>159 SCZ patients, 61 BD patients and 82 healthy controls</td>
<td>Screening scale for chronic stress (SSCS), Genetic analysis, SPSS 20.0</td>
<td>BD patients had higher HCC (5.07 pg/mg ± 7.15) compared to controls (3.51 pg/mg ± 5.67).</td>
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<td>Staufenbiel et al. (2014) [37]</td>
<td>71 BD patients</td>
<td>Paykel’s self-report questionnaire, Social Support List, Young Mania Rating Scale, SPSS 20.0</td>
<td>The number of negative life events was associated with increased HCC.</td>
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<td>Hinkelmann et al. (2013) [41]</td>
<td>27 women and 16 men with a diagnosis of major depressive disorder and healthy 26 women, 15 men</td>
<td>Salivary cortisol analysis, hair cortisol analysis</td>
<td>significant association of childhood trauma with lower long-term cortisol secretion.</td>
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<td>Susann et al. (2013) [24]</td>
<td>28 PTSD patients, 27 traumatized and 32 nontraumatized healthy control subjects</td>
<td>ANOVA</td>
<td>Posttraumatic stress disorder patients and traumatized control subjects exhibited 59% and 51% lower HCC than non-traumatized control subjects.</td>
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<td>LUCIA DETTENBORN et al. (2012) [39]</td>
<td>Participants were 23 depressed patients (8 men and 15)</td>
<td>Beck Depression Inventory, ANOVA</td>
<td>Depressed patients had approximately 50% higher hair cortisol concentration</td>
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<td>10</td>
<td>Manenschijn et al. (2012) [36]</td>
<td>100 BD patients and 195 healthy controls</td>
<td>The Questionnaire for Bipolar Illness, SPSS 17.0</td>
<td>Patients with co-morbid panic disorder (n = 14) hair cortisol levels were significantly lower than in BD patients without panic disorder (22.13 versus 34.67 pg/mg hair, p = 0.019)</td>
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<td>11</td>
<td>Susann Steudte et al. (2011) [23]</td>
<td>10 PTSD patients (mean age 19.2) and 17 traumatized controls (mean age 20.1)</td>
<td>Ball mill method</td>
<td>PTSD patients had higher hair cortisol than traumatized controls</td>
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[6] DISCUSSION AND FUTURE WORK

The main aim of this review was to describe the relationship between hair cortisol, Stress. The chronic stress as measured in hair cortisol shows a more pronounced effect. Therefore Hair cortisol research is a viable option to shed light onto the etiology of stress-related pathology. The use of hair in research on cortisol is a very recent trend. Longitudinal studies with large samples are needed to establish the relationship between the different psychopathological diagnoses and the longterm HPA axis activity as measured in hair cortisol concentration. The analysis of hair cortisol concentrations attracts the protective factors, personality aspects and their psychological effects on the physiological stress response [42].

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