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Lower cortisol levels predict recurrence in remitted patients with recurrent depression: A 5.5 year prospective study ☆, ☆☆

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ABSTRACT

Major Depressive Disorder (MDD) is a highly recurrent disease. Stress-responsive system dysfunction seems to persist after remission. In patients with more chronic and recurrent depressive episodes, state related HPA-axis dysregulation might be a risk factor for prospective recurrence. This study examines the predictive effect of cortisol on consecutive episodes in remitted recurrently depressed patients.

Cortisol was assessed in saliva in remitted recurrently depressed patients ($n=55$) that were followed up prospectively for 5.5 years after remission. Recurrence was assessed using a well validated structured interview.

Lower mean morning cortisol levels predicted earlier time to recurrence over 5.5 year after correction for residual symptoms ($p=0.015$). Residual symptoms and childhood trauma slightly confounded the association between cortisol and recurrence. Lower cortisol levels were associated with having experienced traumatic childhood life events (42.3% in patients with lower cortisol versus 19.2% in patients with higher cortisol).

Our study provides further support for the predictive role over 5.5 year of HPA axis dysregulation, i.e. lower morning cortisol levels, of recurrence in recurrently depressed patients. Childhood trauma is associated to having lower cortisol levels. It might have long term consequences for dealing with stress and the HPA-axis.

1. Introduction

Major Depressive Disorder (MDD) is a highly recurrent disease. In the absence of prophylactic treatment, the rate of recurrence rises up to 80 percent (Frank et al.,1990). Therefore identifying predictors of recurrence and examining pathogenic mechanism of recurrence is essential. Stress has been considered as one of the cardinal pathogenic factors involved in MDD and its recurrence: childhood and recent life events, daily hassles, stress related to previous episodes and aberrant coping, all pose increased risks for MDD and its recurrences (Kessler, 1997; Kendler, Thornton, Gardner, 2001; Bockting et al., 2006a,b; Ten Doesschate et al. 2010; Nanni, Uher and Danese, 2012). Furthermore, stress reducing cognitive therapy (CT) has a benificial effect in preventing recurrence (Bockting et al., 2005, 2009; Vittengl et al., 2007; Guidi et al., 2011).

The hypothalamic pituitary adrenal (HPA) axis is the major neuroendocrine stress response system. Stress-responsive system dysfunction seems to persist after remission of acute depression. The dynamics associated with the course of the illness have not been thoroughly studied yet. Persistent dysregulation of the HPA axis after remission of depression may represent a trait-marker for the risk of recurrent depressive episodes (Modell et al., 1998, Goodyer et al., 2000; Zobel et al., 2001; Appelhof et al., 2006; Mannie et al., 2007).

Mixed findings have been reported for the role of cortisol. A previous finding of our group indicated that in remitted patients with major depression, higher posttreatment maximal cortisol levels on the DEX/CRH test were associated with relapse and with shorter relapse-free survival in a mixed outpatient group with the first and recurrent episodes (Appelhof et al., 2006). In addition, the proportion of remitted patients showing a persistent DST non-suppression were suggested to be more vulnerable to early relapse and recurrence, have poor outcome after discharge and suffer more often from persistent depression (Ribeiro et al., 1993; O'Toole and Johnson, 1997; Zobel et al., 1999). Hypercortisolism has also been reported by Zobel et al. (2001) as a marker for vulnerability for relapse and recurrence in previously depressed patients.

However, hypocortisolism has been reported as well; a phenomenon that is characterized by a hyporesponsiveness on different levels

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of the HPA axis in a number of stress-related states as Fries et al. (2005) stated in their overview. It was first reported in the eighties by using single-dose metyrapone test in depressed patients (Fava et al., 1984; Fava, 1994). Recently, Vreeburg (2010) studied in a longitudinal study including 837 patients with depressive and/or anxiety disorders, the association between salivary cortisol measures at baseline and the course of psychopathology. The patients with a lower cortisol awakening response were at a higher risk of developing a chronic course, compared to persons experiencing remission during the two-year follow up. Evening cortisol and cortisol suppression after dexamethasone intake were not associated with a chronic course. The association appeared to be similar across disorders (anxiety disorder, depressive disorder or co-morbid disorders). Another study found stable hyporeactivity of the HPA over one year in depressed women on job-stress-related long-term sick leave compared with controls (Wahlberg et al., 2009). Moreover, Sondeijker et al. (2008) reported over a study including young, not depressed adolescents, that low morning cortisol levels predicted future psychopathology.

In patients with more chronic or recurrent depressive episodes, state related HPA-axis dysregulation might be reflected in a cortisol hyposecretion when compared to non-depressed control-subjects (Oldehinkel et al., 2001). In a remitted recurrently depressed cohort of women, HPA system hypoactivity was found, both in the basal state and in response to a psychosocial stressor when compared to healthy subjects (Ahrens et al., 2008). In other disorders associated with chronic stress, such as posttraumatic stress disorder, cortisol hyposecretion has also been reported (Yehuda et al., 1990) and for a meta-analysis see (Meewisse et al., 2007). The impact of chronic stress in recurrent depression could explain why a low HPA-Axis activity could be a risk factor for recurrence.

There have been at least 361 studies performed that compared HPA axis function between depressed and non-depressed individuals, however few studies examined the predictive value of the HPA activity on course in recurrent and chronic depression (for a meta-analysis see Stetler and Miller, 2011). The current longitudinal study examined the role of the HPA axis on prospective recurrence over 5.5 years in remitted patients with recurrent depression (i.e. having at least 2 previous episodes). All patients ($N=172$) achieved a good remission state at entry of the study (i.e. not meeting criteria of a depressive episode according to the DSM-IV-TR criteria and a HRSD score less than 10), though residual symptoms are common after remission in depression (Beshai et al., 2011; Fava, 1999). Since cortisol levels are considered as rather state dependent, controlling for residual depressive symptoms in these remitted patients is necessary (Ribeiro et al., 1993). We aimed to determine (I) whether HPA-axis measures predict time to recurrence in remitted recurrently depressed patients corrected for residual depressive symptoms. In line with the previous studies on chronic recurrent depression we expect that in this *highly recurrent remitted* MDD group lower cortisol levels predict prospective recurrence over 5.5 year. Stress and childhood trauma might affect the predictive value of the HPA-axis on recurrence (Ormel et al., 2001; Carpenter et al., 2009). Therefore, (II) we will examine the role of stress (current daily hassles) and childhood trauma on the predictive value of the HPA-axis on recurrence.

2. Methods

2.1. Participants and procedure

For this study we included patients from a clinical trial in which the effect of regular care (including no care at all) on recurrence was compared to regular care with additional preventive cognitive therapy (Bockting et al., 2005). To be eligible for the trial, subjects had to meet the following criteria: (a) at least two Major Depressive Episodes (MDEs) in the last five years, as defined according to DSM-IV (1994) and assessed by the Structured Clinical Interview for DSM-IV (SCID, First et al., 1996) by trained evaluators; (b) current remission status according to DSM-IV criteria, for longer than 10 weeks and no longer than two years ago; (c) Hamilton Rating Scale for Depression (Hamilton, 1960) of <10 (as is common in relapse/recurrence prevention studies). Exclusion criteria were current mania or hypomania or a history of bipolar illness, any psychotic disorder (current and previous), organic brain damage, alcohol or drug misuse, predominant anxiety disorder, recent ECT, recent Cognitive Therapy (CT) or receiving CT at the start of the study, or current psychotherapy with a frequency of more than two times a month. Co-morbidity on axis I was assessed using the SCID (First et al., 1996). There was no restriction in using pharmacotherapy (the effect of use will be examined). Participants were recruited at psychiatric centers and through media announcement. They provided informed consent to enter the protocol. The protocol was approved by the institutional ethics review committees. We were able to collect HPA-axis baseline data from 55 patients in the control group ($N=84$; regular care only). More detail about participants, recruitment, inclusion and exclusion criteria are available in Bockting et al. (2005).

2.2. Study measures

2.2.1. Inclusion criteria and primary outcome measure

Participants were screened on inclusion and exclusion criteria via the telephone version of the Structured Clinical Interview for DSM-IV (SCID-I, APA, 1994; First et al., 1996). Kappa for interrater agreement between the interviewers (psychologist/research assistants), based on audiotaped interviews, for inclusion or exclusion was 0.77, which is indicative of good/excellent agreement. Time to recurrence was also assessed with the SCID-I (First et al., 1996). At baseline and at five follow-up assessments (3, 12, 24, 36 and 66 months), current and past depressive episodes (covering the prior months) were checked from the start of the study. All interviews were audiotaped. Two independent experienced psychiatrists who were blind to treatment condition evaluated all participants meeting the DSM-IV criteria for major depression. In cases of disagreement, the ratings of the psychiatrists were used for further analyses. The kappa for interrater agreement between the interviewers and psychiatrist on categorization of a recurrence versus no recurrence was 0.96, indicating high agreement.

2.2.2. Prediction variables

2.2.2.1. Cortisol. Salivary cortisol. Subjects were asked at baseline to provide saliva in neutral cotton salivettes (Sarstedt AG and Co, Nümbrecht, Germany) at home at three time points on two consecutive days (08:00 and 22:00, day 1, 08:00 day 2). Saliva reliably reflects the blood cortisol concentrations, in a relatively stress-free and minimally intrusive way (Kirschbaum and Hellhammer, 1994). They were instructed to rinse their mouth with water, not to brush their teeth and remain in the fasting state before collecting the sample, and to keep the samples in the refrigerator until sending the samples back to the clinic. Storage took place at −20 °C on day 3. Smoking, age, the use of antidepressants, benzodiazepines, oral contraceptives, and bodymass index were recorded. Salivary cortisol was determined by radioimmunoassay (RIA) designed for saliva samples (IBL Hamburg). The intra-assay variation for cortisol was intra- and inter-assay variations were 5.1% and 6.5%, respectively of a subsample (55 of 84 patients) hormone measures that was collected. No significant differences on any of the patient characteristics and time to recurrence were detected between this sample and the complete sample ($N=84$; all p's >0.10). The following hormone continued variables were calculated: (1) mean morning cortisol and (2) evening cortisol. Since the distributions of these measures were skewed transformed variables (by taking the natural logarithm) were used in the survival analyses.

2.2.2.2. Severity of depressive residual symptoms. The 17-item Hamilton Rating Scale for Depression (HRSD, Hamilton, 1960) was used to assess participants' baseline levels of depressive symptomatology (of <10). The HRSD, administered by psychologist/research assistants who were blind to treatment condition, is a widely used semi-structured clinical interview that covers a range of affective, behavioral and biological symptoms and has acceptable psychometric properties (Rabkin and Klein, 1987). Scores can range from 0 to 52. Our four interviewers second rated 17 interviews. The Intraclass Correlation (ICC) was 0.94, indicating high agreement. Since the distributions of these measures were skewed transformed variables (by taking the natural logarithm) were used in the survival analyses.

2.2.2.3. Stress: daily hassles en childhood trauma. To measure baseline daily hassles, the 114-item Everyday Problem Checklist was used (EPCL). The items of the EPCL refer to stressors of daily living, particularly those in the domains of work, parenthood, relationship, and household activities (continuous score). The EPCL