Psychoneuroendocrinology (2008) 33, 1387—1393

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/psyneuen

HPA axis hyperactivity as suicide predictor in elderly mood disorder inpatients

Jussi Jokinen *, Peter Nordström

Department of Clinical Neuroscience/Psychiatry, Karolinska Institutet, Karolinska University Hospital, Solna, SE-171 76 Stockholm, Sweden

Received 2 July 2008; received in revised form 30 July 2008; accepted 31 July 2008

KEYWORDS
HPA axis;
Cortisol;
DST;
Suicide;
Suicide attempt;
Depression;
Elderly

Summary Dysregulation of the hypothalamic—pituitary—adrenal (HPA) axis function is associated with suicidal behaviour and age-associated alterations in HPA axis functioning may render elderly individuals more susceptible to HPA dysregulation related to mood disorders. Research on HPA axis function in suicide prediction in elderly mood disorder patients is sparse. The study sample consisted of 99 depressed elderly inpatients 65 years of age or older admitted to the department of Psychiatry at the Karolinska University Hospital between 1980 and 2000. The hypothesis was that elderly mood disorder inpatients who fail to suppress cortisol in the dexamethasone suppression test (DST) are at higher risk of suicide. The DST non-suppression distinguished between suicides and survivors in elderly depressed inpatients and the suicide attempt at the index episode was a strong predictor for suicide. Additionally, the DST non-suppression showed higher specificity and predictive value in the suicide attempter group. Due to age-associated alterations in HPA axis functioning, the optimal cut-off for DST non-suppression in suicide prediction may be higher in elderly mood disorder inpatients. These data demonstrate the importance of attempted suicide and DST non-suppression as predictors of suicide risk in late-life depression and suggest the use for neuroendocrine testing of HPA axis functioning as a complementary tool in suicide prevention.

1. Introduction

Suicide is a major public health concern and old age is an important moderating variable for suicide risk. Suicide rates in elderly persons over 65 differ markedly from country to country but there is a general trend towards increasing rates with increasing age. The absolute number of suicides in the elderly is expected to rise and more precise ways to identify potential risk factors including biomarkers for elderly suicides are needed.

Prospective biological studies suggest that dysfunctions in the hypothalamic—pituitary—adrenal (HPA) axis have some predictive power for suicide in mood disorders (Mann et al., 2006; Jokinen et al., 2007). Disturbances in the HPA system measured with the dexamethasone test (DST) (non-suppression) have been associated with increased risk of suicide in depressed patients in several prospective studies (Coryell and Schlesser, 1981, 2001; Targum et al., 1983; Roy et al.,

* Corresponding author. Tel.: +46 8 51776759; fax: +46 8 303706.
E-mail address: jussi.jokinen@ki.se (J. Jokinen).

0306-4530/$ — see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.psyneuen.2008.07.012

1986; Boza et al., 1988; Norman et al., 1990; Yerevanian et al., 1983, 2004). A recent meta-analysis (Mann et al., 2006) concluded that non-suppressors have 4.6-fold increased risk of suicide compared with suppressors. There is though increasing evidence that DST non-suppression may not be a useful predictor for mood disorder outpatients (Coryell et al., 2006) or for those without a clinical history of suicide attempt (Jokinen et al., 2007). The optimal threshold for post DST cortisol to define the non-suppressor status in suicide prediction was lower than the reference threshold and may be different for men and women (Jokinen et al., 2008).

Aging increases the cortisol response to pharmacological challenge with corticotropin-releasing-hormone (CRH) and increasing insensitivity of the HPA axis to the feedback of cortisol may be another factor involved in the activation of the HPA axis during aging (Heuser et al., 1994). Aging is associated with increasing non-suppression rates to DST (Keitner et al., 1992). In a recent meta-analysis of 45 studies (including both pharmacological and non-pharmacological challenges, e.g. psychosocial stress and both challenge and suppression procedures), an increased cortisol response to challenge in older compared to young subjects was demonstrated as well as a 3-fold stronger effect of aging on cortisol responses to challenge in women compared with men (Otte et al., 2005). Heuser et al. (1994) demonstrated higher peak cortisol at baseline and after DST in females compared with males and suggested that age-associated alterations in HPA function in healthy volunteers are more prominent in women. Many diseases that increase in prevalence with aging have been associated with an exaggerated cortisol response to pharmacological challenge, including depression (Holsboer, 2001; Gold and Chrousos, 2002), metabolic syndrome (Rosmond et al., 1998; Reynolds et al., 2003) and Alzheimer's disease (de Leon et al., 1988; Lupien et al., 1999). Higher posttreatment maximal cortisol levels on the dexamethasone-corticotropin releasing hormone test (DEX/CRH test) were associated with relapse of major depression (Appelhof et al., 2006) and hyperactivity of the HPA axis predicted worse treatment outcome (Brouwer et al., 2006).

To our knowledge none of the prospective biological studies of DST non-suppression in suicide prediction has focused on the elderly mood disorder patients. We hypothesized that the HPA axis dysfunction may be a biomarker of suicide risk in elderly mood disorder inpatients and that age adjusted threshold of DST non-suppression might offer better predictive value and optimise the use of the DST in suicide prediction.

The aim of the study was to investigate the predictive potential of one biological marker: the DST non-suppression and one clinical risk factor: a previous suicide attempt in suicide prediction in elderly mood disorder inpatients.

2. Methods

2.1. Subjects

The Regional Ethical Review Board in Stockholm approved the study protocol (Dnr. 2005/1152-31/1).

The larger cohort has been previously described (Jokinen et al., 2007). This study involved 99 elderly (65 years or older) psychiatric inpatients (25 men and 74 women, mean age 73 years, S.D. = 5.8) admitted to the psychiatric wards at the Karolinska University Hospital between 1980 and 2000 with a DSM diagnosis of mood disorder (unipolar, major depressive disorder, single episode or recurrent, bipolar disorder, depressed or dysthymic disorder); 24 patients had attempted suicide just before admission, 5 patients had used a violent suicide attempt method (definition according to Traskman et al., 1981).

Patients with a medical condition or taking medication known to interfere with the results at the time of the DST were excluded.

2.2. Neuroendocrine testing

All DST were performed during the depressive episode. One mg of dexamethasone was given orally at 23:00 h, and plasma cortisol levels were determined from blood samples drawn the following day at 08:00 h, 16:00 h and 23:00 h using a commercial radioimmunoassay. The predictive value of non-suppressor status (cortisol level 5 μg/dl or above in any sample following day) for suicide was analysed.

2.3. Causes of death

All patients were followed up for the cause of death. All deaths that occurred between study enrolment (from February 15, 1980 to September 9, 2000) and November 15, 2005 were included. The patients who died within the follow-up period were identified and the causes of death were obtained from Statistics Sweden which keeps the National Swedish Cause of death register for the National Board of Health and Welfare. During a mean follow-up time of 17 years (range 5.8—25.5 years), six suicides were identified from the death certificates. The subsequent analysis concerns the patients who committed suicide.

The suicide method was drowning in three cases, two patients jumped and one died of self-poisoning, i.e. 5 patients had used a violent suicide method. Five patients committed suicide within 2 years from DST (median 324 days, range between 4 and 639 days), one patient died of suicide after more than 5 years from entering to the study.

2.4. Data analysis

Group differences were assessed with Fisher's Exact test in categorical variables and with Kruskal—Wallis' test in continuous variables.

DST non-suppression and suicide attempt as predictors for suicide were analysed using Fisher's exact test. Statistical analysis (with JMP V software, SAS Institute Inc., Cary, NC, USA) was conducted to analyse post DST plasma cortisol levels in suicides and survivors using Kruskal-Wallis' test. The p-value was set at $<.05$. All tests were 2-tailed.

An ad hoc ROC analysis was used to find optimal thresholds for non-suppressor status to best predict suicide. Receiver-operating characteristic (ROC) curves and tables were created for post DST cortisol levels at 16:00 h to establish the optimal cut-off values. ROC areas under the curves (AUCs) were calculated as a measure of the diagnostic performance, and differences were calculated and tested according to the methods of Hanley and McNeil (1983). The cut-off point that optimised sensitivity (proportion of patients correctly