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CSF 5-HIAA and DST non-suppression — Orthogonal biologic risk factors for suicide in male mood disorder inpatients

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Abstract

Two biomarkers of suicide risk; non-suppression in the dexamethasone suppression test (DST) and low 5-hydroxyindoleacetic acid (5-HIAA) in the cerebrospinal fluid (CSF) have been reported to be predictors of suicide in mood disorders. The interrelation of the two systems seems to be different in suicide attempters compared with depressed inpatients who have not made a suicide attempt, indicating that the two biomarkers may be seen as independent. This investigation examined the interrelation of low CSF 5-HIAA and DST non-suppression in suicide victims with mood disorder. Fifty-eight mood disorder inpatients not receiving any treatment with antidepressants underwent lumbar puncture and the DST. Plasma cortisol levels at 8:00 a.m., 4:00 p.m. and 11:00 p.m. were analysed in relation to CSF 5-HIAA. All patients were followed up for causes of death and suicides were verified with death certificates. During follow-up (mean 21 years), 11 (19%) patients had committed suicide. In male suicide victims ($n=6$), the serum cortisol level at 4:00 p.m. showed a significant positive correlation with CSF 5-HIAA. Low CSF 5-HIAA predicted all early suicides (within 1 year), whereas all males who committed suicide after 1 year were DST non-suppressors. In female suicide victims ($n=5$), the post-DST serum cortisol did not correlate with CSF 5-HIAA. Low CSF 5-HIAA and DST non-suppression are orthogonal biologic risk factors for suicide in male mood disorder inpatients. CSF 5-HIAA is associated with short-term suicide risk; dysregulation of the hypothalamic-pituitary-adrenal axis seems to be a long-term suicide predictor.

Keywords: Suicide; CSF 5-HIAA; Serotonin; HPA axis; Dexamethasone suppression test; Depressive disorder; Prediction

1. Introduction

The stress diathesis model of suicidal behaviour has focused on two candidate biomarkers for suicidal behaviour: low 5-hydroxyindoleacetic acid in cerebrospinal fluid (CSF 5-HIAA) and non-suppression in the dexamethasone suppression test (DST) as a marker of hypothalamic–pituitary–adrenal (HPA) axis dysfunction (Mann, 2003). A meta-analysis of 27 reports, both prospective and retrospective, found that suicide attempters, particularly those who use violent methods, had low CSF 5-HIAA compared with psychiatric controls (Lester, 1995). Prospective studies of the serotonergic system and suicide uniformly report that low CSF 5-HIAA levels predict an elevated risk for suicide (for review, see Mann and Currier, 2007). The DST, frequently abnormal in mood disorder patients,

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is considered to measure glucocorticoid receptor-mediated negative feedback (Pariante and Miller, 2001). Both low CSF 5-HIAA and DST non-suppression contribute to a more than 4-fold increased suicide risk in a recent meta-analysis (Mann et al., 2006). However, there is new evidence that DST results may not be a useful predictor for mood disorder patients with no clinical history of suicidality (Coryell et al., 2006; Jokinen et al., 2007). Post-DST serum cortisol levels at 4:00 p.m. correlated significantly with suicide in male suicide attempters (Jokinen et al., 2008a).

The serotonin (5-HT) system and the HPA axis have complex interrelationships (Porter et al., 2004). Disturbances in serotonin neuroregulation and in HPA-axis activity are both likely, and possibly independent, factors in the genesis of suicidal behaviour (Fawcett et al., 1997). Patients with non-suppression of cortisol may be at high risk for future suicide regardless of CSF-5-HIAA levels and DSM diagnoses (Westrin and Nimeus, 2003). The interrelationship between post-DST serum cortisol and CSF 5-HIAA levels was significantly different in depressed inpatients with and without an index suicide attempt, indicating that these two biomarkers may be seen as independent biomarkers in suicide attempters (Jokinen et al., 2008b). However, interactions between the serotonin system and the HPA axis in suicide victims with a mood disorder have not been extensively elucidated.

The purpose of the present study was to investigate the interrelation of CSF 5-HIAA and the cortisol response in the DST in mood disorder inpatients who committed suicide during follow-up.

2. Methods

The Regional Ethical Review Board in Stockholm approved the study protocol.

2.1. Subjects

This is a retrospective cohort study involving 58 psychiatric inpatients (23 men and 35 women, mean age 47 years, S.D. = 14) admitted to the psychiatric clinic at the Karolinska University Hospital with a diagnosis of mood disorder: unipolar, major depressive disorder, single episode or recurrent, bipolar disorder, depressed or dysthymic disorder. Patients with substance abuse or psychotic disorder (schizophrenia spectrum) were excluded. Twenty-five patients had attempted suicide just before admission. Patients with a medical condition (or taking medication) known to interfere with the results at the time of the DST and lumbar punctures were not included.

2.2. CSF monoamine metabolites and the dexamethasone test

Lumbar punctures were performed in a standardized manner between 8 and 9 a.m. after patients had been fasting in bed since midnight. CSF (12 ml) was drawn with the patient in a sitting position, the needle being inserted between lumbar vertebrae IV and V. The CSF was immediately centrifuged and stored at −80 C. CSF 5-HIAA was analysed by using mass fragmentography (GC-MS) according to methods developed by Bertilsson (1981). The coefficient of variation of the analytical method is less than 5%.

At admission 1 mg of dexamethasone was given orally at 11:00 p.m., and plasma cortisol levels were determined from blood samples drawn the following day at 8:00 a.m., 4:00 p.m. and 11:00 p.m. Non-suppressor status was defined as a cortisol level of 138 mol/l = 5 μg/dl) or above in any sample on the following day. There were no significant differences in CSF-5-HIAA or plasma cortisol levels between patients who had the lumbar puncture and DST done within 8 days after admission, between 9 and 14 days or above 14 days.

2.3. Causes of death

All patients were followed up for cause of death. The patients who died within the follow-up period were identified and the causes of deaths were obtained from Statistics Sweden, which maintains the National Swedish Cause of Death Register for the National Board of Health and Welfare. During a mean follow-up time of 21 years, 30 patients had died, and 11 suicides (6 men and 5 women) were identified from the death certificates. Nineteen patients (6 men and 13 women) had died of natural causes or in accidents. The subsequent analysis concerns the patients who committed suicide.

2.4. Data analysis

Post-dexamethasone plasma cortisol levels at 8:00 a.m., 4:00 p.m. and 11:00 p.m. were analysed in relation to the CSF 5-HIAA levels separately. Median split subgrouping for further analysis of CSF 5-HIAA levels in suicide victims and survivors was applied. Statistical analysis (with JMP V software, SAS Institute inc., Cary, NC, USA) was conducted with regression analysis (Pearson product