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Prolactin and thyroid hormone levels are associated with suicide attempts in psychiatric patients

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ABSTRACT

The aim of this study is to evaluate biological factors associated with recent suicidal attempts in a naturalistic sample. A total of 439 patients suffering from major depression disorder (MDD), bipolar disorder (BD) and psychotic disorders (schizophrenia, schizoaffective disorder and psychosis not otherwise specified), who were consecutively assessed in the Emergency Department of an Italian Hospital (January 2008–December 2009), were included. In the whole sample, suicide attempters and non-attempters differed with regard to free triiodothyronine (FT3) and prolactin values only. A univariate general linear model indicated significant effects of sex ($F_{1;379}=9.29$; $P=0.002$), suicidal status ($F_{1;379}=4.49$; $P=0.04$) and the interaction between sex and suicidal status ($F_{1;379}=5.17$; $P=0.02$) on prolactin levels. A multinomial logistic regression model indicated that suicidal attempters were 2.27 times (odds ratio (OR)=0.44; 95% confidence interval (95%CI): 0.23/0.82; $P=0.01$) less likely to have higher FT3 values than non-attempters; while prolactin values failed to reach statistical significance (OR=0.99; 95%CI: 0.98/1.00; $P=0.051$). Both prolactin and thyroid hormones may be involved in a complex compensatory mechanism to correct reduced central serotonin activity. Further studies may help in understanding how these findings can be used by clinicians in assessing suicide risk.

1. Introduction

Suicide is a complex issue involving a number of psychological, social, cultural and biological factors. Most theories propose a diathesis stress model in which certain psychological and biologic factors predispose a person to suicidal behaviour, which may be triggered by stressful life events. The presence of a psychiatric disorder was reported among the most consistently reported risk factors for suicidal behaviour – more than 90% of people who die by suicide are psychiatrically ill at the time of death (Cavanagh et al., 2003) – as well as for suicide attempts (Beautrais et al., 1996), although recent reports challenged this assumption and proposed a comprehensive phenomenologically oriented approach to suicide assessment (Pompili, 2010a; Pompili, 2010b).

So far, investigations into the relationship between suicidality and the hypothalamic–pituitary–thyroid (HPT) axis activity are scarce and have yielded conflicting results. Some investigators have found that depressed patients with a suicidal behaviour or intent exhibited a reduced thyroid stimulating hormone (TSH) response to morning administration of protirelin (thyrotropin-releasing hormone, TRH) (Linkowski et al., 1983; Linkowski et al., 1984; Corrigan et al., 1992), while others did not (Banki et al., 1984; Kavoussi et al., 1993; Jokinen et al., 2008).

However, the normal results of the TRH test performed in the morning (when the TSH circadian pattern approaches its nadir)

Abbreviations: HPT, hypothalamic–pituitary–thyroid; TSH, thyroid stimulating hormone; TRH, thyrotropin-releasing hormone; PRL, prolactin; d-FEN, d-fenfluramine test; 5-HT, 5-hydroxytryptamine; HPA, hypothalamic–pituitary–adrenal; ED, Emergency Department; DSM-IV TR, Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision; MDD, major depression disorder; BD, bipolar disorder; MINI, Mini International Neuropsychiatric Interview; DSM-III-R, Diagnostic and Statistical Manual of Mental Disorders, third edition, revised; SIDP-IV, Structured Interview for DSM-IV Personality; AST, aspartate transaminase; ALT, alanine transaminase; BUN, blood urea nitrogen; GGT, gamma-glutamyltransferase; FT3, free triiodothyronine; FT4, free thyroxine; CLIA, chemiluminescent immunoassay; BIC, Schwarz's Bayesian information criterion; OR, odds ratio; CI, confidence interval.

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do not necessarily mean that the HPT axis function is normal. We have previously shown that pituitary TSH secretion is more sensitive to TRH stimulation in the evening (at 2300 h) than in the morning (at 0800 h) and that the difference in TSH response between 2300 and 0800 h TRH tests is an even more sensitive measure in detecting HPT-system changes: this chronobiological index is reduced in about three-quarters of major depressed inpatients (Duval et al., 1990; Duval et al., 1996).

Retrospective studies, using a prolactin response to the d-fenfluramine test (d-FEN; a presynaptic serotonin (5-hydroxytryptamine, 5-HT)-releasing and -uptake-inhibiting agent), have suggested that reduced serotonergic functioning may be a marker of increased suicide risk in patients with major depression (Correa et al., 2000) and schizophrenia (Correa et al., 2002). The aetiology of this abnormality remains unknown, but it has been suggested (Dinan, 1994) that overactivation of the hypothalamic–pituitary–adrenal (HPA) axis by chronic stress, and the associated hypercortisolism, could induce changes in 5-HT pathways. Consequently, it has been hypothesised that 5-HT abnormality in patients with a history of suicidal behaviour could be secondary to hyperactivity of the HPA axis.

1.1. Study aims

Therefore, the purpose of this study was to investigate whether psychiatric patients who attempted suicide were different from those who did not with regard to routinely collected biochemical and endocrine parameters, such as prolactin and thyroid hormones. To reach this goal, we focussed our attention on patients suffering from affective or psychotic disorders who were assessed in an Italian Emergency Department (ED) and then admitted in a Psychiatry Department. Specifically, the study addressed three major issues: (1) To what extent can suicide attempters be different from non-attempters based on the analysis of blood markers?; (2) To what extent do two diagnostic groups of suicide attempters differ when analysing blood markers?; and (3) to what extent can biological markers associated with suicide attempts be used as predictors?

2. Methods

2.1. Design

This is a cross-sectional study of patients suffering from mood disorders and psychosis consecutively admitted to the ED of Sant'Andrea Hospital (Rome) between January 2008 and December 2009 and then hospitalised in the Department of Psychiatry of the same Hospital. Inclusion criteria were a Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision (DSM-IV TR) diagnosis of a mood disorder, namely major depression disorder (MDD; single episode or recurrent) and bipolar disorder (BD; both type I and II), or a psychotic disorder (including schizophrenia, schizoaffective disorder, psychosis not otherwise specified). Exclusion criteria were having a clinically significant unstable illness (e.g., hepatic or renal insufficiency, cardiovascular, pulmonary, gastrointestinal, endocrine, neurological, infectious and neoplastic disease), metabolic disturbance (including thyroid hormonal and prolactin disease) or intellectual disability and not completing screening blood examination.

Subjects participated voluntarily in the study, and each subject provided written informed consent. The study protocol received ethics approval from the local research ethics review board.

2.2. Participants

Participants were 439 consecutive patients (207 men and 232 women). The mean age of the patients was 41.62 ± 13.43 years (Min./Max.: 19/79 years). Twenty per cent of the patients were diagnosed with MDD, 53.1% with BD and 26.9% with psychosis. More than 57% of the BD patients presented mixed episodes, above 35% only (hypo)-maniac symptoms and around 8% only depressive symptoms. Eighteen per cent of the sample was admitted for a suicidal attempt committed in the last 24/48 h. All the suicide attempters had some physical injuries associated with the attempt. According to the revised nomenclature (Silverman et al., 2007a, 2007b), these acts should be labelled suicide attempts type II, that is, a self-destructive act with some degree of intent to end one's life and some identifiable injuries.

2.3. Diagnosis and mental-status assessment

All patients admitted to the ED suffering from psychiatric disorders or having attempted suicide are referred to a psychiatrist while in the ED, where an interview is performed. During such interviews, a complete mental examination is performed. Clinicians performing mental examinations relied on the Mini International Neuropsychiatric Interview (MINI). The MINI is a short structured interview developed in France and the United States to explore 17 disorders according to Diagnostic and Statistical Manual of Mental Disorders, third edition, revised (DSM-III-R) (American Psychiatric Association, 1987). It has undergone many reliability and validity studies (Amorim et al., 1998), and one section of this instrument is dedicated to the assessment of suicidal risk, with questions about past and current suicidality. In our patients, MINI diagnoses were confirmed by clinical diagnoses based on the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision (DSM-IV-TR) criteria. Clinical diagnoses were assigned by a staff psychologists and the attending psychiatrist. Personality disorders (PDs) were assessed by the Structured Interview for DSM-IV Personality (SIDP-IV) (Pfohl et al., 1997).

Cognitive function was assessed using the Mini Mental State Examination (Folstein et al., 1975). The Mini Mental State Examination is a brief questionnaire test that is used to screen for cognitive impairment.

Suicide methods were collapsed into a dichotomous variable: violent methods (e.g., hanging, jumping, shooting or stabbing, drowning and burning) and non-violent methods (e.g., poisoning and gassing).

2.4. Blood biochemical analyses

On acceptance in the ED, all subjects were seen by a physician and a blood work was performed. The following tests were done: glucose (mg dl^{-1}; DS), total cholesterol (mg dl^{-1}), triglycerides (mg dl^{-1}), aspartate transaminase (AST; U l^{-1}), alanine transaminase (ALT; U l^{-1}), blood urea nitrogen (BUN); mg dl^{-1}), gamma-glutamyltransferase (GGT); U l^{-1}), free triiodothyronine (FT3; pg ml^{-1}), free thyroxine (FT4; ng dl^{-1}), TSH (μU l^{-1}), and prolactin (ng ml^{-1}). Venipucture was performed on a forearm vein. Blood samples were sent to a centralised laboratory that performed analysis following standard procedures. A competitive chemiluminescent immunoassay (CLIA) was used to determine FT3 concentrations, sequential CLIA for FT4 concentrations and a two-site (sandwich) CLIA was used for TSH dosing. For prolactin assessment, a one-step (sandwich) CLIA has been used. All these tests were performed using a Beckman Coulter UniCel® DxI 800 Access® Immunoassay System.

2.5. Statistical analysis

t-tests for independent samples were performed to identify differences in biochemical and sociodemographic variables measured on the dimensional scale, one-way Fisher exact tests and chi-squared tests (χ^2) were performed to identify associations between variables measured on nominal scales. Benjamini and Hochberg's correction was used for multiple testing (Benjamini and Hochberg, 1995). Because prolactin may be associated with sex, we performed a univariate general linear model with prolactin levels as a dependent variable and diagnosis, sex and the interaction of sex × diagnosis as independent variables. Variables significant at the bivariate analyses were entered as predictors in two logistic regression models. The likelihood-ratio chi-square difference was used to select the best model. We report Schwarz's Bayesian information criterion (BIC). This is a criterion for choosing between different models with different numbers of parameters, to determine which is the 'best fit' to the observed data, while balancing goodness-of-fit and parsimony. The BIC introduces a penalty term for the number of parameters in the model. The -2 log likelihood was also used as a criterion for the nested models. We report associations between variables as odds ratios (ORs) and their 95% confidence intervals (95%CIs).

Our analysis could identify difference with a α level set at 0.05 and power at 0.80 (*t*-test analysis, two tailed). We could detect overall small mean effect sizes ($d=0.375$) in the comparison of FT3 and FT4 as examples. All the analyses were performed with the Statistical Package for Social Sciences (SPSS) for Windows 17.0, except for power analysis calculations, which were performed with Systat 11.0.

3. Results

3.1. Differences between diagnostic groups

To assess whether laboratory (biochemical and endocrinologic) values were associated with diagnosis, we performed bivariate