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CORTISOL LEVELS AND SUICIDE IN BIPOLAR I DISORDER

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Abstract

Context. Hypothalamic-pituitary-adrenal (HPA) axis irregularities have been described both in bipolar disorder and suicidal behaviour, but few studies have examined the relationship between suicidal behaviours and cortisol levels in bipolar disorder.

Objective. We compared HPA axis activity in bipolar I (BPD I) individuals with and without suicidal ideation and behaviour through multiple measurement of serum and salivary cortisol.

Design. Cross-sectional, observational study.

Subjects and Methods. 75 BPD I patients were assigned into 3 groups (no history of suicidal behaviour, history of suicidal ideation, history of suicide attempt), according to the C-SSRS. Socio-demographical and clinical data was obtained by using MINI 6.0 and a semi-structured questionnaire. Salivary samples were collected using Sarstedt Cortisol Salivette synthetic swab system for two consecutive days at 08:00, 16:00, 23:00 and salivary cortisol concentrations were determined by ELISA technique. A unique 1mg dose of dexamethasone was administered on the first day, at 23:00, after the collection of the saliva sample. Blood was collected on the first day at 8:00 AM and basal morning serum cortisol levels were determined by immunoassay with fluorescence detection.

Results. Cortisol parameters in our BPD I sample did not vary significantly in respect to suicidal history. However, patients with a history of suicidal ideation have significantly higher total cortisol outputs than patients with no history of suicidal behaviour in the 18 to 40 age category compared with the above 40 age category.

Conclusions. Total cortisol daily output varies significantly in an age-dependent manner in respect to suicidal thoughts in BPD I individuals.

Key words: cortisol, HPA, dexamethasone, suicide, bipolar, salivary cortisol, suicide risk.

INTRODUCTION

The hypothalamic-pituitary-adrenal axis (HPA) regulates the peripheral functions of the organism related to metabolism and immunity and exerts important cerebral effects over neuronal survival and neurogenesis in structures such as the hippocampus and amygdala (1). While acute stress stimulates the medullar adrenal sympathetic system, triggering responses such as "fight or flight" and activates the catecholamine pathway, chronic stress produces a series of physiological modifications and behavioural adaptations along the HPA axis, which lead to an increase of cortisol release, among other corticosteroids (2). Mood disorders are considered to have a close relationship with stress. In the case of bipolar disorder, acute episodes can be triggered by stress, especially when these episodes occur right after the disease onset (3). It has been about 40 years since the dysregulation of the HPA axis was recognized as being part of the pathophysiological mechanism of bipolar disorder, and, since then, it has been determined that this dysregulation occurs due to a combination of genetic predisposition and environmental factors (4). Patients with bipolar disorder present a hyperactive HPA axis, higher levels of systemic cortisol, they are non-responders to the dexamethasone (DXM) and the DXM/corticotrophin release hormone (DXM/CRH) dynamic tests (5). Moreover, it has been proven that including first-generation offspring of patients that suffer from bipolar disorder have higher basal cortisol levels and are also non-responders to the DXM/CRH suppression test (6).

On the other hand, the stress-diathesis theory of suicide posits that predisposing (i.e. genetic vulnerability and childhood adversities) and precipitating (i.e. psycho-social, psychiatric disorders) risk factors (7), manifest

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through the non-suppression of cortisol following the DST, which is associated with an increased risk for future suicide (8-10). This is supported, in turn, by data which reports suicide as a major cause of death in patients with Cushing Syndrome (11). However, other studies did not reach the same outcomes regarding the aforementioned link between suicide and the HPA axis dysregulation (12, 13). Low plasma cortisol levels have been considered to be a predicting factor for suicide, and were reported among the relatives of those who died by suicide (14, 15). Increases in baseline cortisol and reduced glucocorticoid receptor responsiveness were reported among those with a high suicide risk (16-19). Specifically, higher levels of bedtime salivary cortisol have been associated with a higher suicide risk among individuals with bipolar disorder (20). Plausible explanations that may account for the discrepancies in results regarding the HPA axis in suicidal behaviour may be explained by the allostatic load theory of age-dependent exposure to stress overtime (21).

Suicide constitutes a major public health problem, considering that approximately 1 million people die each year by taking their own lives (22). One of the latest challenges in assessing suicide risk among patients has been determining a model that correctly expresses the importance of psychosocial and neuropsychiatric biochemical influences, in order to further elaborate methods for preventing suicide (23-26). A systematic review of the data presented in the literature from 1980 until 2014, placed about 3.4 – 14% of suicide deaths among those with bipolar disorder, and, moreover, 23–26% of people with bipolar disorder were found to have attempted suicide (27). Furthermore, among the psychosocial factors mentioned above, gender, age, marital status, and social integration can greatly affect one's desire to live, especially if s/he suffers from bipolar disorder (27). Among those with bipolar disorder, it has been shown that men are more likely to die by suicide, while women register a higher number of suicide attempts (27) . As far as age is concerned, bipolar disorder patients, contrary to the general population, attempt suicide much earlier in life (27) . Those with no significant other are more at risk for suicide, which partly relates to findings that those with poor support from a social network are at risk, as well (27). Lastly, another important risk factor for suicidal crises in BPD is represented by drug or alcohol abuse (27).

The present study aims to examine HPA axis activity by determining the levels of morning serum and salivary cortisol, midnight salivary cortisol, total daily salivary cortisol output, and total daily cortisol output decrease post-DST in a BPD I cohort, with respect to past suicide attempts, past suicidal ideation and individuals with no history of suicidal thoughts or behaviour. To address the discrepancies mentioned above we further examine the potential moderating role of age, taking into account a recent meta-analysis of cortisol levels and suicidal behaviour, that draws on the notion of allostatic load theory (28), which reports that cortisol was associated with suicide attempts in an age-dependent manner (21).

MATERIALS AND METHODS

The study protocol followed the practice of the Declaration of Helsinki and was approved by the Ethics Committee of the "Prof. Dr. Alexandru Obregia" Clinical Psychiatry Hospital.

Participants

All the BPD I patients admitted in the "Prof. Dr. Alexandru Obregia Clinical Psychiatry Hospital" in Bucharest, Romania, between June 2015 and March 2016 were asked to partake in the current study. The inclusion criteria were: documented diagnosis of bipolar I disorder, confirmed by application of the Mini-International Neuropsychiatric Interview (29) with ages between 18 and 65. The exclusion criteria were: the presence of any psychiatric disorder that, in the opinion of the investigators, could interfere with the clinical or biological assessments (e.g. organic mental disorders, mental retardation, etc.), any significant physical disability, severe or uncontrolled medical conditions, pregnancy or postpartum. The seventy-five patients ultimately included in the present study signed the written informed consent form before any clinical or biological procedures were conducted.

Clinical assessments

The Romanian translated version 6.0.0 of the Mini-International Neuropsychiatric Interview (M.I.N.I.), a structured diagnostic interview based on the Diagnostic and Statistical Manual for Mental Disorders (DSM-IV), (30) was administered in order to confirm the positive diagnosis of BPD I for the participants included in the study (31).

The Romanian version of the Columbia Suicide Severity Rating Scale (C-SSRS), a semi-structured interview, was used for assessing suicide ideation and behaviour (32). The first subscale, the suicidal ideation scale is a 5-point ordinal scale, ranging from 1 (wish

to be dead) to 5 (active suicidal ideation with specific plan and intent). Patients who denied suicidal ideation received a zero score. Suicidal ideation intensity assessment is comprised of five items (i.e., frequency, duration, controllability, deterrents, reasons for suicidal thoughts), each rated on an ordinal scale. This subscale uses two different assessment periods (i.e. lifetime, past month). The second subscale, measuring suicidal behaviour investigates interrupted, aborted, and actual suicide attempts, as well as preparatory behaviour for a suicide attempt and non-suicidal self-injurious behaviour. Furthermore, actual suicide attempts (most recent/most lethal/initial) are assessed by an ordinal lethality subscale, which categorizes the medical consequences of actual suicide attempts on a scale from 0 (no physical damage) to 5 (death). The subscale additionally registers the number of attempts (actual, interrupted and aborted) and uses two distinctive assessment periods (lifetime and past year).

Biological analysis

Saliva samples were collected using Sarstedt Cortisol Salivette synthetic swab systems (Sarstedt AG & Co, Germany) at 08:00, 16:00 and 23:00 the day after signing the informed consent form. A unique 1mg dose of dexamethasone was administered at 23:00, after the collection of the saliva sample. Further saliva samples were collected at 08:00, 16:00 and 23:00 on the next day. Detailed written and verbal instructions were given for the collection process, and to avoid eating, drinking anything other than water, smoking or brushing their teeth at least 30 min prior to collecting the samples. Saliva samples were refrigerated immediately after collection at a temperature between 2°C and 8°C for a maximum of 48 hours. The samples were then centrifuged for 2 minutes at 1000 g and stored at a temperature below -20°C until analysed. Salivary cortisol concentrations were determined by ELISA using the Euroimmun kit system (Medizinische Labordiagnostika AG, Germany). Total cortisol output was estimated by calculating the "area under the curve with respect to ground (AUCG)" as described by Pruessner and collaborators (33). The calculations were performed separately for the two days, and the nominal decrease in cortisol output was calculated as a marker for the dexamethasone-induced suppression of cortisol secretion. Saliva cortisol levels are expressed in μg/dL.

Venous blood was collected after fasting, at 8:00, on the first day. Serum was used for the determination of basal cortisol by immunoassay with fluorescence detection, using the TS AIA-PACK CORT system (Tosoh Bioscience, USA), as per manufacturer's protocol. The assay range is up to 60 μg/dL with a sensitivity of 0.2 μg/dL. The total precision coefficient of variation (CV) is 3.9%, 4.3% and 4.6% for low, medium and high levels, respectively. The manufacturer reference ranges are 8-25 μg/dL for morning cortisol (08:00-10:00). Serum cortisol levels are expressed in μg/dL throughout this article.

Statistical analysis

The Kolmogorov-Smirnov test was used to test for the normality of data distributions. Spearman and Pearson correlation coefficients were calculated, as appropriate. We used the Student's t test and Mann-Whitney U test to compare the distribution of quantitative data across pairs of two samples; analysis of variance (ANOVA) and the Kruskal-Wallis test to compare the distribution of quantitative data across more than two samples; and the $\chi 2$ test for that of qualitative data, using Fisher's Exact where needed. The Levene statistic was used to test for the equality of variances. Tukey's and Tamhane's post hoc tests were used to test for pairwise differences between the groups as appropriate. We used the IBM Statistical Pack for Social Sciences (SPSS) version 22.0.0.0 for statistical analysis.

RESULTS

Demographical and clinical characteristics of the sample

Seventy-five patients were ultimately included in the study, with a mean age of 44.28 ± 11.38 years. Of the total number of participants 41.3% were males. According to the M.I.N.I 6.0 and DSM IV-TR diagnostic criteria, most of our patients presented in a manic episode (N = 39, 52.0%), 21.3 % in a depressive episode (N=16), 6.7% in a mixed episode (N=5) and 20.0% were in remission (N=15).

According to the C-SSRS criteria, of the 75 BPD I participants included in the analysis, 25.33% (N = 19) had no history of suicidal thoughts or behaviours, 44.0% (N = 33) reported suicidal ideation in the past, while 30.66% (N= 23) recounted for past suicide attempts.

Table 1 summarizes the socio-demographic and clinical characteristics of the bipolar I individuals categorized by suicide history. As expected, several characteristics varied significantly across types of suicide ideation/attempt history. Overall, bipolar

individuals differed in age, gender, illness duration and number of past depressive episodes in respect to suicide history groups within our BPD I sample. Marital and employment status, age of onset, past manic episodes, current medication (i.e. mood-stabilizers, antidepressants, antipsychotics), alcohol intake, and smoking habits did not differ significantly across our BPD I subgroups. None of the BPD I participants was on oral corticosteroids.

HPA axis examination

Levels of morning serum and salivary cortisol, midnight salivary cortisol, total daily salivary cortisol output, and total daily cortisol output decrease post-DST in our BPD I sample did not vary significantly across the "past suicide attempts", "past suicidal ideation" and "individuals with no history of suicidal thoughts or behaviour" subgroups (see Table 2).

However, since cortisol secretion and suppression have been hypothesized to be different in suicidal individuals younger than 40 years of age vs. patients 40 years of age and older (34), we performed a stratified analysis of our data to test this hypothesis. Indeed, our results show that total cortisol output varies significantly across the three groups (see Table 3) in patients under 40 years of age, as patients with a history of suicidal ideation have significantly higher total cortisol outputs than patients with no history of suicidal behaviour (p = 0,009 – Tamhane's test), and these results were not found in patients 40 years of age and older (see Table 4).

DISCUSSION

To the best of our knowledge, this is the first study that examines the functionality of the HPA axis in suicidal bipolar I individuals by determining the levels of morning serum and salivary cortisol, midnight

Table 1. Socio-demographic and clinical characteristics of patients with no history of suicidal behaviour *vs.* patients with a history of suicidal ideation *vs.* patients with a history of suicide attempts

Socio-demographical and clinical parameters	No history of suicidal behaviour (N=19)	History of suicidal ideation (N=33)	History of suicide attempts (N=23)	p
Age (years)	38.90 ± 11.64	47.85 ± 11.25	43.61 ± 9.79	0.026[1]
Gender				
Male	12 (38.7%)	14 (45.2%)	5 (16.1%)	0.025[2]
Female	7 (15.9%)	19 (43.2%)	18 (40.9%)	
Marital status				
Married	8 (29.6%)	11 (40.7%)	8 (29.6%)	
In a relationship	4 (26.7%)	4 (26.7%)	7 (46.7%)	NS[3]
Single	7 (21.2%)	18 (54.5%)	8 (24.2%)	
Employment status				
Employed	8 (32.0%)	10 (40.0%)	7 (28.0%)	NS[3]
Unemployed	11 (68.0%)	23 (60.0%)	15 (72.0%)	
Age at onset (years)	28.95 ± 9.06	31.21 ± 9.38	29.26 ± 9.05	NS[4]
Illness duration (years)	9.95 ± 7.34	16.64 ± 10.95	14.35 ± 8.18	0.005[4]
Total number of episodes, of which	10.74 ± 6.14	15.88 ± 10.24	17.00 ± 9.70	NS[1]
Manic	4.79 ± 2.70	5.76 ± 5.05	5.44 ± 5.43	NS[1]
Depressive	2.90 ± 2.90	5.79 ± 4.12	7.65 ± 6.92	0.002[1]
Current treatment with mood stabilizers				
Yes	18 (26.9%)	28 (41.8%)	21 (31.3%)	
No	1 (12.5%)	5 (62.5%)	2 (25.0%)	NS[3]
Current treatment with antipsychotics				
Yes	19 (28.4%)	30 (44.8%)	18 (26.9%)	
No	0 (0.0%)	3 (37.5%)	5 (62.5%)	NS[3]
Current treatment with antidepressants				
Yes	2 (11.8%)	6 (25.3%)	9 (52.9%)	
No	17 (29.3%)	27 (46.6%)	14 (24.1%)	NS[3]
Current smoking				
Yes	7 (15.9%)	21 (47.7%)	16 (36.4%)	NS[2]
No	12 (38.7%)	12 (38.7%)	7 (22.6%)	
Current alcohol abuse				
Yes	5 (41.7%)	5 (41.7%)	2 (16.7%)	NS[3]
No	14 (22.2%)	28 (44.4%)	21 (33.3%)	

Data presented as average ± standard deviation or number (% in category of the parameter), 1 Kruskal-Wallis test, 2 c2 test, 3 Fisher's Exact test, 4 ANOVA.

Table 2. Differences in cortisol secretion parameters between patients with no history of suicidal behaviour *vs*. patients with a history of suicidal ideation *vs*. patients with a history of suicide attempts

Cortisol secretion parameter	No history of suicidal behaviour (N=19)	History of suicidal ideation (N=33)	History of suicide attempts (N=23)	p
08:00 morning cortisol (blood)	16.95 ± 4.54	18.48 ± 4.86	16.83 ± 4.77	NS[1]
08:00 morning cortisol (saliva)	3.77 ± 1.91	4.85 ± 3.36	3.64 ± 2.69	NS[2]
23:00 evening cortisol (saliva)	1.62 ± 2.99	1.20 ± 1.14	1.44 ± 1.96	NS[2]
Total cortisol output (saliva)	30.03 ± 17.45	40.44 ± 25.65	41.20 ± 38.74	NS[2]
Total cortisol output decrease post-DST[3]	23.94 ± 18.52	25.25 ± 21.52	29.40 ± 33.20	NS[2]

[1]ANOVA, 2 Kruskal-Wallis test, 3 Dexamethasone suppression test.

Table 3. Differences in cortisol secretion parameters between patients with no history of suicidal behaviour *vs*. patients with a history of suicidal ideation *vs*. patients with a history of suicide attempts, in the less than 40 years old group

Cortisol secretion parameter	No history of suicidal behaviour (N=19)	History of suicidal ideation (N=33)	History of suicide attempts (N=23)	p
08:00 morning cortisol (blood)	17.87 ± 4.62	20.80 ± 4.96	16.99 ± 5.28	NS[1]
08:00 morning cortisol (saliva)	3.68 ± 1.37	6.48 ± 4.51	4.27 ± 2.50	NS[2]
23:00 evening cortisol (saliva)	0.58 ± 0.35	1.87 ± 1.36	1.50 ± 2.07	NS[2]
Total cortisol output (saliva)	25.41 ± 6.51	59.96 ± 29.25	35.18 ± 29.13	0.009[1]
Total cortisol output decrease post-DST[3]	16.11 ± 2.54	32.95 ± 31.16	29.35 ± 23.84	NS[1]

[1]ANOVA, 2 Kruskal-Wallis test, 3 Dexamethasone suppression test.

Table 4. Differences in cortisol secretion parameters between patients with no history of suicidal behaviour *vs*. patients with a history of suicidal ideation *vs*. patients with a history of suicide attempts, in the 40 years of age or older group

Cortisol secretion parameter	No history of suicidal behaviour (N=19)	History of suicidal ideation (N=33)	History of suicide attempts (N=23)	p
08:00 morning cortisol (blood)	15.69 ± 4.40	17.32 ± 4.48	16.77 ± 4.75	NS[1]
08:00 morning cortisol (saliva)	3.85 ± 2.44	3.91 ± 2.08	3.40 ± 2.80	NS[2]
23:00 evening cortisol (saliva)	2.51 ± 3.98	0.80 ± 0.76	1.41 ± 1.98	NS[2]
Total cortisol output (saliva)	33.99 ± 23.10	28.51 ± 13.53	43.45 ± 42.41	NS[2]
Total cortisol output decrease post-DST[3]	31.76 ± 24.75	20.72 ± 12.15	29.42 ± 37.31	NS[2]

[1]ANOVA, 2 Kruskal-Wallis test, 3 Dexamethasone suppression test.

salivary cortisol, total daily salivary cortisol output, and total daily cortisol output decrease after DST.

The DST has been commonly employed to assess HPA axis dysregulation and failure to suppress cortisol has consistently been found to predict completed suicide in patients with mood disorder (8-10). However, the present study did not show any significant variations in total daily cortisol output decrease after DST in our BPD I sample in respect to suicidal history, therefore, our outcomes are in line with other studies that did not replicate the aforementioned link between suicide and the HPA axis dysregulation (12, 13). Furthermore, our results did not yield any significant associations between serum or salivary cortisol levels and suicide risk among BPD I patients, unlike other studies with reports regarding low plasmatic cortisol levels as a predicting factor for suicide (14, 15) or increased plasmatic baseline cortisol among those at risk for suicide (16-19) in various population samples. Particularly for BPD, increased levels of bedtime salivary cortisol have been associated with a higher suicide risk (20), outcomes that could not be replicated in our study. One plausible explanation for this discrepancy might be the difference in sampling, our population being comprised of only BPD I individuals, while the aforementioned study used the wider, bipolar spectrum diagnoses as inclusion criteria.

However, when controlling for age, our results showed that the total daily cortisol output varied significantly across the BPD I sample in relation to suicidal risk (see Table 3). As seen in table 4, patients with a history of suicidal ideation had significantly higher total daily cortisol outputs than patients with no history of suicidal behaviour, in the sample with a up to 40 years of age. Conversely, no negative or other association was found between total daily cortisol output and suicidal ideation when the average age was at least 40 years in the BPD I sample. These findings are in line with the allostatic load theory that postulates age-dependent maladaptive responses of the HPA axis to

stress exposure overtime (28) and with recent scientific literature which correlates high suicide risk with a hyperactive HPA axis in younger individuals, that later down-regulates with age, after chronic exposure (21). Results of the association between suicidal behaviour, platelet serotonin (35), or cortisol levels were also highlighted in other research studies (36). Even though our research did not reveal any significant correlations between suicide attempts and cortisol levels in BPD I, the data shows trends that reflect a relationship that should be further explored with larger samples size.

Given the effect of medication (37) and smoking (38) on cortisol levels, we analysed the distribution of these confounding factors within the three BPD I subgroups and no significant variance was observed. In our analysis we included antipsychotics, mood-stabilizers and antidepressants, as these were the pharmacological treatments among our BPD I sample. None of the patients included in the study were on oral corticosteroids. As the types of medications utilized and the smoking habits among our three bipolar subgroup were uniformly distributed, and due to the limited sample size, we did not proceed to further control for their influence on cortisol levels with respect to suicide risk in BPD I individuals.

The main limitation of this study is the relatively small sample size. However, the very low mean differences in cortisol secretion parameters are similar to those described by other authors (21). Considering this and the high variability of cortisol secretion in time, in our opinion, these parameters would be practically impossible to use in clinical settings for the evaluation of suicide risk in BPD I individuals. Other several limitations of the current study need to be considered. Clinical and biological assessments were performed just once, thus, longitudinal data for completed suicide attempts is not available. Moreover, our suicide attempter's sample size was too small in order to properly test for specific BPD I suicide confounders on serum and salivary cortisol levels.

In conclusion, the results of the present study did not show any significant differences in morning serum/salivary cortisol, midnight salivary cortisol, total daily salivary cortisol output, and total daily cortisol output decrease post-DST levels in respect to "past suicide attempts", "past suicidal ideation" and "individuals with no history of suicidal thoughts or behaviour" subgroups in our BPD I sample. However, when controlling for age, significantly higher total daily cortisol outputs were found in BPD I individuals with a history of suicidal ideation, compared with patients with no history of suicidal behaviour, in the sample with age under 40.

Our results are in line with current research findings that support higher cortisol levels in individuals with suicidal ideation (35, 36) and submit to the allostatic hypothesis age-dependent maladaptive responses of the HPA axis to stress exposure overtime (28) and with recent scientific literature which correlates high suicide risk with a hyperactive HPA axis in younger individuals, that later downregulates with age, after chronic exposure (21).

Conflict of interest

The authors declare that they have no conflict of interest concerning this article.

Conflict of interest

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