A retrospective study of pituitary-thyroid interaction in patients with first-episode of bipolar disorder type I in Mania State

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Abstract

Bipolar disorder (BD)-mania is related to the dysfunction of anterior pituitary gland, but the pituitary-thyroid interaction on the acute stage of BD has been controversial. In order to rule out the effects of drugs, we aimed to determine the upstream interaction of first-episode of BD type I in mania state, and tried to find the relationship between thyroid-stimulating-hormone (TSH) and Prolactin (PRL).

This study included 70 real-world patients diagnosed with first-episode BD-mania recruited and 70 healthy controls (HC) matched for age and sex from 2016 to 2017 in the same district of Shanghai. We compared the levels of thyroid hormones and prolactin between the two groups, and linear regression and curve estimation were used for the correlation analysis of TSH and PRL.

There were differences in triiodothyronine (TT3), total thyroxin (TT4), and free thyroxine (FT4) concentrations between the groups (P< .05). After being grouped by sex, higher PRL in the male and female BD-mania subgroup were observed compared to each isosexual HC (P< .01, Cohen’s d = 0.82/1.08, 95%CI (0.33, 1.31)/(0.58, 1.58)). Higher FT4 in the male BD-mania group was observed compared to the HC males (P< .01, Cohen’s d = 0.90, 95%CI (0.41, 1.39)) while the female BD-mania group showed lower TT3 and TT4 compared to the HC females (P< .01, Cohen’s d = 0.93/0.88, 95%CI (0.43, 1.42)/(0.39, 1.37]). In the female BD-mania group, correlation analysis established an inverse relationship between PRL and TSH (r = 0.25, F = 11.11, P< .01).

The findings demonstrate that sex impacts the concentration of hormones secreted by the anterior pituitary of patients with first-episode BD-mania. The increased PRL may be a putative mechanism that underlies the onset in female patients with a moderate inverse relationship between TSH and PRL. Thyroid hormones and prolactin levels may be developed as potential markers for identifying BD-manic.

Abbreviations: BD = bipolar disorder, BDNF = brain-derived neurotrophic factor, BSDS = Bipolar Spectrum Diagnostic Scale, FT3 = free triiodothyronine, FT4 = free thyroxine, HPTA = hypothalamus-pituitary-thyroid axis, ICD-10 = the International Statistical Classification of Diseases and Related Health Problems, the Tenth Revision, M.I.N.I = the Mini-International Neuropsychiatric Interview, PRL = prolactin, SCMHC = Shanghai Changning Mental Health Center, TSH = Thyroid hormones, TSH = thyroid-stimulating-hormone, TT3 = triiodothyronine, TT4 = total thyroxine, YMRS = Young manic rating scale.

Keywords: bipolar disorder, manic state, negative feedback, prolactin, thyroid gland function tests

1. Introduction

Bipolar disorder (BD) is a complex, recurrent, and severe illness characterized by one authenticated and one current affective episode (hympanic, manic, depressive or mixed). Because of mood-congruent psychotic symptoms, the disease increases the risk of having self harmed and attempted suicide with high lethal intent. Common polygenic variation contributes to risk of schizophrenia and BD. Schizophrenia has been reported an increased prevalence of thyroid autoimmunity (adjusted incidence rate ratios ranging from 2.3 to 3.3) while there is no evidence showing a definite relationship between BD and specific autoimmune thyroid diseases. Thyroid autoimmunity has been
suggested to be an independent risk factor for BD with no clear association with lithium exposure and it might serve as an endophenotype for BD.

In spite of this, therefore, there has long been a debate between the interactive change of the pathophysiology in the hypothalamus-pituitary-thyroid axis (HPTA)\textsuperscript{6-8} and prolactin (PRL)\textsuperscript{9,10} during the treatment and maintenance of mood. BD is strongly associated with immune dysfunction\textsuperscript{11} that may impact the function of the anterior pituitary, however, the reference range of the anterior pituitary hormone levels which are related to recurrent BD’s have yet to be defined. Metabolic dysregulation of the axis at any part of the storage, secretion, activity, or bypass can affect the function of normal neural connections resulting in a psychotic symptom cluster. Thyroid hormones (THs) can strongly affect mood and behavior through phenotypic symptom clusters related to the illness. Thus, THs can modulate intrinsic neuronal activity to lower thresholds, which play permissive roles in the expression of affective “pacemakers”, and potentially impact vulnerability set points to switch between over-activity (BD-mania) and under-activity (BD-depression).\textsuperscript{12}

Moreover, THs and PRL could impact the expression of abnormal neuronal activity within the affective circuits. BD is interrelated with many neuroendocrine diseases and biologic studies have suggested that the relationship between mood disorder and medical illness is bidirectional in nature. This provides support for the multiplayer of shared and specific etiologic factors interlinking these clinical conditions.\textsuperscript{13} On the other hand, clinical manifestation, course, and prognosis of neuroendocrine disease are closely associated with affective symptoms.\textsuperscript{14}

The pituitary and the hypothalamus serve as a functional unit in controlling the secretion of various hormones. BD-related symptoms could be either worsened by an acute change in thyroid hormones, or compensated for by the maintenance of stable levels below a critical threshold, through regulation by the anterior pituitary. The function of the HPTA plays an important role in neuropsychiatric disorders, for example, hyperthyroidism (Graves’ disease) is characterized by typical emotional irritability, increased activity, and sleep deprivation,\textsuperscript{15} similar to mania syndrome.

Varying from traditional biomedicine, the theory of the classical neuroendocrine feedback states that physiological feedback systems are mostly modulated by negative feedback and self-protection. The self-regulatory mechanism of BD-mania is aimed at relieving symptoms through the hyposecretion of and self-protection. The self-regulatory mechanism of BD-mania feedback systems are mostly modulated by negative feedback classical neuroendocrine feedback states that physiological syndrome.\textsuperscript{14}

2. Methods

2.1. Study design

The diagnosis of BD-mania was ascertained through the International Statistical Classification of Diseases and Related Health Problems, the Tenth Revision (ICD-10). Universal diagnostic agreement was good for mood disorders between the Diagnostic and statistical manual of mental disorders (DSM) and ICD nosology\textsuperscript{10,21} while the ICD-10 system is now officially used in China. Three-level ward rounds were rigorously operated and diagnosed by two experienced psychiatrists independently.

2.2. Setting

This study was reviewed and approved on 11/01/2016 by the Institutional Ethical Committee for clinical research of the corresponding institutes from the Changning District (2016001). Data of the patients with BD-mania were collected at the psychiatric departments of Shanghai Changhai Mental Health Center (SCMHC) from November 2016 to October 2017. Written informed consent was obtained from participants or their next of kin after a complete description of the study was given.

2.3. Participants

For this study, we analyzed medicine-naïve patients at reproductive age with discrimination of anterior pituitary function between sex.\textsuperscript{22} Inclusion criteria were: Chinese Han; aged from 16 to 40 with secondary sex characteristic; medicine-naïve first-episode BD-mania including the diagnostic code (F31.0, F31.1 or F31.2) without comorbid diagnosis; Bipolar Spectrum Diagnostic Scale (BDS) ≥ 12.\textsuperscript{23} Exclusion criteria were: History of central nervous system disease; central nervous system disease; confirmed nervous system disease through MRI examination; history of thyroid diseases, adrenal diseases, or gonad diseases tested from B-ultrasonography or immunoserology; taking levothyroxine, antithyroid, glucocorticoid, estrogen, progestin, oral contraceptive, bromocriptine, or other medicine related to pituitary diseases in the past six months; alcohol or tobacco abuse; history of antipsychotic medications; pregnant or in postpartum period; estrus cycle in women (luteinizing hormone ≥ 14IU/L according to the People's Republic of health industry standards– www.nhc.gov.cn/); taking antipsychotic or mood stabilizer within two weeks.

The samples of healthy controls (HC) were selected randomly from a name list of approximately 500 individuals screened in the Physical Examination Center of Tongren Hospital Affiliated to Shanghai Jiaotong University School of Medicine. All the data was gathered by the SCMHC Information Department. The patients’ personally identifiable information was redacted in order to protect patient privacy and anonymity before being provided for analysis. In order to understanding the research content, education needed to be above high school. Exclusion criteria were the same as those of the BD patients, in addition, with BDS ≥ 6. Seventy patients (35 male and 35 female) were enrolled in the BD-mania group and 70 healthy records (35/35) were collected in HC group (see Fig. 1 for a flow diagram of
sample selection). The samples were pre-screened by the Mini-
International Neuropsychiatric Interview (M.I.N.I.).[24]

Our study was based on approval by the Institutional Ethical
Committee for clinical research of Shanghai Changning Mental
Health Center, Shanghai, China. Written informed consent was
provided according to the Declaration of Helsinki.

2.4. Variables
2.4.1. General self-made questionnaire. The general self-made
questionnaire contained questions on age, sex, ethnicity, course
of disease, level of education, menstrual history, family history,
alcohol or tobacco abuse, medication history, and review of
recent drug use.

2.4.2. Young manic rating scale (YMRS). The YMRS symptom
rating scale has been shown to be a reliable and valid instrument
in the assessment of the severity of psychopathology of manic
symptoms.[25] The scale is divided into two parts. The first part
consists of 7 items, each rated using a 4-point scale while the other
4 items are rated on an 8-point scale. The higher the score, the
more severe the manic state is likely to be.

2.5. Bipolar spectrum diagnostic scale (BSDS)
The Chinese version of the BSDS has reached a high standard of
reliability and validity in BD patients.[23] The scale is divided into
two parts. The first part is a description of 19 BD symptoms
(answering by yes (score 1) or no (score 0)) and the second part is a
general assessment, which provides a scale rating from 0 to 6 for
the total compliance of symptoms, with a combined total of 0 to
25. The higher the score, the more likely BD is to be diagnosed.
The diagnosis of BD was almost excluded with results less than 6.

2.6. Hemoconcentration of neuroendocrine test
The evaluation of THs and PRL included TSH, free triiodothy-
ronine (FT3), free thyroxine (FT4), triiodothyronine (TT3), total
thyroxin (TT4), and PRL. We collected venous blood from
patients meeting the above criteria at 7:00 in the next morning.
An electrochemical luminescence immunoassay was carried out
by the Roche Cobas e601 automatic electrochemiluminescence
immunoassay system, which was provided by Shanghai lanwei
clinical testing co., LTD. The above analysis system was
measured as TSH (range, 0.27–4.20 mIU/L), TT3 (range, 1.3–
3.1 nmol/L), TT4 (range, 66–181 nmol/L), FT3 (range, 2.8–7.1
pmol/L), FT4 (range, 12–22 pmol/L), and PRL (range, male: 86–
390; female: 72–511 mIU/L).

2.7. Bias
All measurement data were inspected for normality by
Kolmogorov-Smirnov tests. Recruited volunteers may have their
selective bias. They were matched to a group based on age, sex, ethnicity and without diagnosis recognized by the M.I.N.I.

2.8. Study size

The sample size of this study was relatively modest.

2.9. Quantitative variables

Normal distribution metering data was represented as mean (standard deviation (SD)) while skewed distribution measured data was represented as medians and quartiles.

2.10. Statistical methods

All statistical computations were performed using IBM SPSS Statistics Version 18.0 for windows (Chicago Inc, USA). A Chi-square test was conducted to analyze demographic data. An independent sample T-tests was used for age, BSDs, and YMRS evaluation. Excluding TSH, covariance analysis was used for THs, with age set as the covariance. Two sample rank sum tests were used for TSH and PRL between groups. Linear regression and curve estimation were conducted to make correlation analysis of TSH and PRL in each group. All statistical analyses were defined as two-tailed P values, significance level of 5% (α = 0.05). Bonferroni corrections for multiple comparisons were applied, and the level was α = α/c, c (number of pairwise comparisons) = (k(k−1))/2. The effect sizes were employed by the Cohen’s d and its confidence intervals (CI).

3. Results

3.1. Demographic characteristics

There was no difference in age between the two groups (t=0.52, P > .05). Higher BSDs in BD-mania was observed compared to HC, as well as gender subgroups (t=44.71/34.13/29.59, P < .01, df’s=138), Cohen’s d for total, male, and female were 10.69, 8.16, and 7.07, respectively. See Table 1.

Within the BD-mania group, we recruited 49 patients with BD-mania without psychotic symptoms, and 21 with BD-mania with psychotic symptoms. There was no significant difference in the subtypes of BD, age, length of illness, BSDs, or YMRS between the gender subgroup of BD-mania (t=0.96/0.90/0.46/1.47, P > .05, df’s=138). See Table 2.

3.2. Hormone hemococoncentrations of the thyroid and PRL

Bonferroni correction for multiple comparisons was applied, the level was 0.05/3 = 0.0167. There were significant differences in TT3 (t=3.86, P < .01, Cohen’s d = 0.65, 95%CI (0.31, 0.99), df=138), TT4 (t=2.43, P = 0.014, Cohen’s d = 0.41, 95%CI (0.08, 0.75), df=138) and FT4 (t=2.89, P < .01, Cohen’s d = 0.49, 95%CI (0.15, 0.82), df=138) between the BD-mania and HC groups. After being grouped by sex, higher PRL in the male and female BD-mania subgroup were observed compared to each sex HC [(male/female) = 3.43/4.52, P < .01, Cohen’s d = 0.82/1.08, 95%CI (0.33, 1.31/0.58, 1.58), df’s=68]. Higher FT4 in the male BD-mania group was observed compared to the HC males [(male/female) = 3.78, P < .01, Cohen’s d = 0.90, 95%CI (0.41, 1.39), df=68] while the female BD-mania group showed lower TT3 and TT4 compared to the HC females [(t=3.87/3.68, P < .01, Cohen’s d = 0.93/0.88, 95%CI (0.43, 1.42)/0.39, 1.37), df’s=68]. See Table 3.

3.3. Linear regression and curve estimation for PRL and TSH in BD-mania

Linear regression was used to determine the relationship between PRL and TSH. There was no linear relationship in the male BD-

| Table 1 | Demographic characteristics of patients with BD-mania and HC. |
|-----------------|-----------------|-----------------|-----------------|-----------------|
|                | BD-mania (n=70) | HC (n=70) | t value | P |
| Age (yr)       | 24.3 (5.1)      | 24.7 (4.3)  | 0.52   | .60 |
| Male           | 24.9 (5.5)      | 25.3 (4.7)  | 0.38   | .71 |
| Female         | 23.7 (4.7)      | 24.1 (4.8)  | 0.36   | .72 |
| Length of illness (m) | 8.3 (3.9) | /         | /     | /   |
| BSDS total     | 17.9 (2.6)      | 2.3 (1.3)   | 44.71  | <.01 |
| Male           | 17.8 (2.3)      | 2.5 (1.2)   | 34.13  | <.01 |
| Female         | 18.1 (2.9)      | 2.1 (1.4)   | 29.59  | <.01 |
| YMRS total     | 28.2 (3.4)      | /         | /     | /   |
|                |                  |            |  | |
| BD-mania       |                  |            |  | |
|                | = Bipolar disorder in mania state, BSDS = Bipolar Spectrum Diagnostic Scale, HC = Healthy control, SD = standard deviation, YMRS = Young Manic Rating Scale. |

| Table 2 | Demographic comparison between genders in the BD-mania group. |
|-----------------|-----------------|-----------------|-----------------|-----------------|
|                | Male (n=35) | Female (n=35) | χ2/ t value | P |
| Subtypes (n,%) |                  |                  |                | |
| Mania without PS | 25 (71.4%) | 24 (68.6%) | 0.07 | .79 |
| Mania with PS | 10 (28.6%) | 11 (31.4%) | 0.38 | .71 |
| Age (yr)       | 24.9 (5.5)      | 23.7 (4.7) | 0.96    | .34 |
| Length of illness (m) | 8.7 (3.5) | 7.9 (4.2) | 0.90 | .39 |
| BSDS total     | 17.8 (2.3)      | 18.1 (2.9) | 0.46    | .65 |
| YMRS total     | 28.8 (3.8)      | 27.6 (2.8) | 1.47    | .147 | 0.15 (0.41, 3.10) |

BD-mania = Bipolar disorder in mania state, BSDS = Bipolar Spectrum Diagnostic Scale, HC = Healthy control, PS = psychotic symptoms, SD = standard deviation, YMRS = Young Manic Rating Scale.
mania group [F=0.42, P=.52, 95% CI (-58.5, 112.8), df=1] (Fig. 2A) whereas PRL and TSH were linearly dependent in the female BD-mania group with weak correlation [r²=0.13, F=4.71, P=0.037, 95% CI (-273.8, 8.8), df=1]. Using a scatter diagram for correlation (TSH set as independent variable on the x-axis and PRL as the dependent variable on the y-axis), further curve estimation showed an inverse relationship between PRL and TSH in the female BD-mania group with a moderate correlation [r²=0.25, F=11.11, P=.002], the inverse function equation [27]: \( y=b_0+b_1x \) (\( b_0=294.5, b_1=772.0 \)). (Fig. 2B).

### 4. Discussion

#### 4.1. Key results

At the endocrine glandular level, we found that patients with BD-mania had overall lower TT3 and T4 and higher FT4 levels. After comparing the subgroups, we found that sex may be responsible for the differences. Male patients had higher FT4 levels, while female patients had lowest TT3 and T4. The increase in peripheral secreted THs leads to high risk of hyperthyromia, irritability, and distractibility, thus, the increase of FT4 in the male BD-mania group was consistent with symptoms of a mania-like state [28]. The hypothyroidism theory in BD is usually explained by the compensatory mechanism of the thyroid [29]. It is important to note that the results of the female BD-mania group were inconsistent with the biological peripheral roles of T3 and T4. Although there were no differences between men and women shown in the BSDS and YMRS for the clinical diagnosis of BD [30], our data of the female BD-mania group supported the compensatory hyposecretion of TT4 in BD-mania. In addition, the decreased TT3 level may result from the simultaneous decrease in TT4 as high-functioning T3 mainly originates from the deiodination of T4. Thus both may reduce the long term TSH secretion in the anterior pituitary. This trend was seen in the female patient subgroup (1.95 mIU/L VS. 1.77 mIU/L), however it was not significant in the acute first-episode BD. In the disease condition, BD-mania neuroendocrine regulation may differ among genders [31].

At the anterior pituitary level, there is no evident difference of TSH level in BD-mania, on the other hand, the negative feedback regulation of the anterior pituitary gland might not be established so soon in the onset of BD-mania. Özerdem et al [17] found that TSH increased more frequently in female patients and that self-regulation triggers the compensation mechanism of the thyroid gland in the disease.

In order to discuss the relationship between the differences of sex in thyroid disease and hyperprolactinemia, we needed to know whether they both significantly correlated to sex [17, 33]. We thus recruited patients aged 16 to 40 with sexual characteristics as a confounding factor. Due to the physiological effects of PRL, sex differences were evident. Post-pubertally, the expression of growth hormone and PRL is sexually dimorphic with males exhibiting higher growth hormone levels and females higher PRL levels. The aberrant increase of PRL causes side effects on the pathological lactation and menstruation of women. Additionally, TSH level might be sensitive to changes in circulating estrogen in women and increases after an induced acute increase of estradiol with PRL, which is a classic estradiol-upregulated pituitary hormone. Previous studies have indicated that women with BD are at a higher risk for mood episodes during periods of intense hormonal fluctuation (e.g., postpartum, premenstrual, perimenopause) [34].

Furthermore, TSH has been reported to stimulate the release of PRL under psychological stress. The TSH acts on the pituitary PRL cells to stimulate the expression of PRL mRNA [35] thus promoting its synthesis and secretion, which may explain the correlation between TSH and PRL in females with BD-mania. Bromocriptine, a dopamine agonist widely used in the treatment of hyperprolactinemia may further explain elevated PRL as it blocks the dopamine channel in the tubero-infundibular system and the dopamine antagonist effects of antipsychotic drugs [36]. Studies have shown that BD does not change the sensitivity of dopamine neurons in the hypothalamus-pituitary system anomalies [37]. In our study, there might be a correlation between the increased PRL in BD-mania and the onset of manic symptoms. Therefore, a correlation study of the hormones secreted by PRL and the pituitary is expected to be a potential biomarker for clinicians to use in medical treatment.

In order to discuss the interactions of pituitary hormones, we needed to know whether anterior pituitary dysfunction affected only certain kinds of anterior pituitary cells or several kinds [38]. Theoretically, in the condition that hyposecretion of peripheral glands occurs, feedback information is transmitted to the hypothalamus, then positive or negative feedback of the
hypothalamus secretes hormone releasing factors that stimulate both peripheral glands and the hypersecretion of PRL.\textsuperscript{[39]} Neuroimmunology research has found that TSH interacts with PRL through tumor necrosis factor-\textalpha and interleukin-1\textbeta to affect the neural immune system.\textsuperscript{[40]} Although female neural diseases of the immune system are more common, the relationship is not clear yet. A recently published systematic literature search indicated that most of the previous studies ignored the complexity and timeliness of the effects of medicine on the neuroendocrine of BD-mania.\textsuperscript{[41]} Benvenga S et al.\textsuperscript{[34]} found that women with an estradiol-dependent increase in TSH do however exist, as do PRL-dependent increases. Based on the above theory, we attempted to make a related analysis of TSH and PRL in first-episode BD type I-mania. We found that PRL in female patients with BD-mania might have a weak negative and a moderate inverse relationship with TSH even when TSH secretion did not increase. Thus, we assume that the increase in both is not easily synchronized, with the loss of synchrony previously found during

Figure 2. A. The scatter plot of TSH and PRL in male patients with BD-mania. B. The linear regression and curve estimation for TSH and PRL in female patients with BD-mania.
prolonged critical illness. Aromatase expression in TSH and PRL may have a regulatory role on the synthesis and secretion of these hormones.\textsuperscript{42} Capozzi et al.\textsuperscript{43} indicated that BD-mania, as an acute stress reaction, together with hypothyroidism, are other frequent conditions of hyperprolactinemia.

4.2. Limitations, interpretation, and generalisability

Neuroendocrine diseases are closely associated with mental disorders. It enlightens us that future work on BD should not be limited to dual variable regression analysis,\textsuperscript{44} but to multivariate regression analysis. Targeting pituitary dysfunctions might be a novel strategy to improve the outcomes of BD. There are several limitations in the current study. The medicine-naive design was the highlight of our research. Therefore, a large sample study was guaranteed to ensure the homogeneity of samples. The conclusions can thus only be applied to a first-episode patient. Some confounding factors are difficult to eliminate, for instance, most clinical researches can not exclude lithium, which is a strong confounding factor of thyroid dysregulation, while the menstrual cycle may be related to PRL levels.

4.3. Perspective

As previously mentioned, the classic negative feedback regulation is in contrast to the traditional biomedical model that states hyperthyroidism can lead to clinical manifestations of mania symptoms. A higher prevalence of thyroid dysfunction was found in BD, with 11.4–24.5% being above or below the risk ratio of TSH considered for BD-mania.\textsuperscript{145} Therefore, the current explanation hardly fits both theories. If these theories are not accepted simultaneously, then according to the monism analysis of the disease, abnormal thyroid function and BD-mania are not due to comorbidity. Profound interactions between the immune system and the HPTA exist and both immune and endocrine factors mediate neuroplastic effects.\textsuperscript{46}

Female BD patients are more likely to develop thyroid autoimmunity.\textsuperscript{15} Gender difference and the relationship between TSH and PRL deserve further study. A previous study found that the compensatory feedback of the HPTA may decline with chronic deferment of the disease. Thus, increased FT4 and TSH becomes a comparatively steady state under chronic psychiatric stress, and the sex differences may disappear.\textsuperscript{159} This also indicates that the long-term follow-up cohort study will be an important point worth noting in future research ideas.

Acknowledgments

The authors thank Min Zhu for English language editing.

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