Retrospective analysis of thyroid function in drug-free patients with bipolar disorder in China

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Research

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Abstract

Background

Bipolar disorder is a common mental illness with serious consequences. Clinical studies have found that thyroid function may have an impact on patients with bipolar disorder, but there are few relevant studies in China. So this study explores the characteristics of thyroid function in patients with bipolar disorder in China.

Methods

Using retrospective cohort study and a cross-sectional study, thyroid function tests were performed in inpatients from September 2015 to January 2018 in the Second Affiliated Hospital of Xinxiang Medical University, who were diagnosed with bipolar disorder and were not treated with medications for at least three months before hospitalization.

Results

We found that the triiodothyronine (T3) and free triiodothyronine (FT3) levels were significantly higher in bipolar mania than in bipolar depression ($P < 0.01$). The thyroid stimulating hormone (TSH) levels were significantly lower in male than female patients, while the FT3, free thyroxine (FT4) levels were higher in male than female patients ($P < 0.01$). Patients were divided into two groups: those who used lithium and those who did not. Both groups had a tendency of hypothyroidism after treatment. In addition, the T3 and FT3 levels were significantly higher in manic than in depressive status in those patients who had a transition between mania and depression in 28 patients compared with previous hospitalization ($P < 0.05$).

Conclusion

Patients with bipolar disorder may develop thyroid dysfunction at different stages and in male/female sexes.

Background

Bipolar disorder is a chronic mood disorder characterized by mania, hypo-mania, alternating depression or mixed episodes (Grande et al. 2016). Bipolar disorder is a relatively common disease that is prone to relapse, has a heavy disease burden and has a high risk of suicide (Mitchell and Malhi 2004; Müller-Oerlinghausen, Berghöfer, and Bauer 2002; Perry et al. 2019). Several studies have shown that the occurrence of bipolar disorder may be correlated with thyroid hormone metabolism disorder (Bauer et al. 2008; Lambert et al. 2016; Müller-Oerlinghausen, Berghöfer, and Bauer 2002; Wysokinski and Kloszewska 2014). Thyroid hormone plays an important role in the function and regulation of neural tissue activity. Therefore, any thyroid hormone synthesis, secretion, action and peripheral metabolic disorders can affect the normal function of nerve tissue (Bauer and Whybrow 2001). Patients with thyroid dysfunction are often associated with mood disorders. The most common psychiatric symptoms associated with thyroid dysfunction are mood disorders, cognitive dysfunction and anxiety (Bauer and Whybrow 2001). Gulseren et al. (Gulseren et al. 2006)found that patients had more severe symptoms of anxiety and depression during hypothyroidism, which recovered after thyroxine treatment. Another retrospective study of a large number of patients showed a higher incidence of bipolar disorder in patients diagnosed with hyperthyroidism (Hu et al. 2013). Schrekenberger et al. conducted a cross-sectional study and it was performed between untreated Graves' disease patients and the control group, and the differences between anxiety and depression levels and cerebral glucose metabolism were studied. They found that patients with hyperthyroidism had decreased glucose metabolism in the limbic system, activated foci in the posterior cingulate gyrus and inferior parietal lobe, and were associated with depression and anxiety (Schreckenberger et al. 2006). Bipolar disorder patients with thyroid dysfunction are often poorly treated when standardized treatment is used. Thyroid dysfunction increases the difficulty in the diagnosis and treatment of mood disorders (Bauer et al. 2014; Cole et al. 2002).

There is evidence that except for the presence of hyperthyroidism and hypothyroidism, more patients with bipolar disorder exhibit subclinical thyroid dysfunction, with small changes in thyroid function levels (Bauer et al. 2008). Subclinical or clinical hypothyroidism, such as lower levels of thyroxine (Rybakowski and Sowinski 1973), and elevated levels of thyrotropin are more common in patients with bipolar disorder (Ezzaher et al. 2011; Valle et al. 1999). In addition, the increase of thyroid antibodies (anti-TPO) in patients with bipolar disorder was significantly higher than that in the normal population (Kupka et al. 2002). A study found that thyroid dysfunction may be associated with poor treatment outcomes and increased risk of relapse in some patients with bipolar disorder (Cole et al. 2002). There may also be a gender difference in thyroid dysfunction in patients with bipolar disorder. Some studies and reviews have found that there are also gender differences in thyroid function in the normal population (Shatynska-Mytsyk et al. 2016; Bauer et al. 2014), which may be related to the poor response of women with thyroid dysfunction to standardized treatment of bipolar disorder (Cole et al. 2002; Salloum et al. 2001). In the treatment of bipolar disorder, lithium salt is the drug of choice for long-term treatment of bipolar disorder, which can effectively prevent the occurrence of mania and depression, significantly reduce the risk of suicide, and reduce the number of recurrences (Cipriani et al. 2005; Geddes et al. 2004; investigators et al. 2010). Although lithium salt has a good effect on treatment, clinical doses are difficult to control, which often leads to thyroid function disorder (Kirov et al. 2005; McKnight et al. 2012).

Chinese studies have found that TSH levels in patients with bipolar II depression were lower than those in healthy controls, and there was no significant difference in FT3, T3, FT4, and T4 between the two groups (Zhong et al. 2019). In addition, some studies have found that the incidence of goiter and average TSH level in Chinese patients after lithium salt use are higher than those in the control group (Lee et al. 1992). At present, the results of thyroid function in patients with bipolar disorder are inconsistent, and few studies have been conducted on the characteristics of thyroid function level in Chinese patients with bipolar disorder. Therefore, we investigated: 1. Differences in thyroid function in patients with bipolar disorder in the manic or depressive state; 2. Differences in thyroid function between sexes in patients with bipolar disorder; 3. Changes of thyroid function in patients with bipolar disorder after combined treatment.

Materials And Methods

Subjects

This study is a retrospective cohort study and a cross-sectional study, which was approved by the Ethics Committee of The Second Affiliated Hospital of Xinxiang Medical University. Diagnosis of the patient's condition by two professional clinicians, and the inclusion criteria were as follows: 1. Meeting the bipolar disorder diagnosis by the International Statistical Classification of Diseases and Related Health Problems Diagnostic (ICD-10); 2. No medication for at least three months before admission; 3. No limit on age, sex. The following were exclusion criteria: 1. Alcohol or other substance dependence; 2. Have serious physical diseases; 3. Have a history of primary thyroid disease or other endocrine diseases; 4. Have other mental disorders other than bipolar disorder.

From September 2015 to January 2018, there were 20938 inpatients in the Second Affiliated Hospital of Xinxiang Medical University, including 3349 (15.99%) patients with bipolar disorder. Among these patients, we excluded 6 subjects with hyperthyroidism or hypothyroidism before treatment and 27 subjects whose bipolar disorder was not diagnosed clearly. Finally, 617 patients with bipolar disorder who were not treated for at least three months before admission and who underwent thyroid function test, were included in the sample study. There were 386 males (62.56%) and 231 females (37.44%). Including 74 patients with bipolar disorder received at least two thyroid function tests during hospitalization (two tests before treatment and after treatment for four weeks.). Among the 74 follow-up patients, the patients were treated with combination therapy, divided into two groups according to whether lithium salt was used or not. 34 cases were treated with lithium salt and 40 cases were not. There were no family history of bipolar disorder and other mental illness in groups, and gender, age, BMI, and thyroid function levels were matched before treatment. Patients mainly used mood stabilizer, anti-epileptic drugs, and second-generation antipsychotic treatment. The average lithium salt dosage was 0.6 g/day. In addition, there were 28 patients suffered from a shift in mood state between mania and depression during hospitalization (see Fig. 1).

Data collection and analysis

Demographic information was collected from patient records, such as gender, age, length of hospital stay, BMI, blood pressure, family history of mental illness. All patients had fasting phlebotomy measurements between 06:00 and 08:00 within 24 hours after admission. The laboratory test was performed by chemiluminescence immunoassay (Roche 411/Roche 601). The original reagents of Roche were used to determine the concentrations of TSH, T3, T4, FT3 and FT4 (TSH: thyroid stimulating hormone; T3: triiodothyronine; T4: thyroxine; FT3: free triiodothyronine; FT4: free thyroxine). The normal ranges of these measurements are: 0.27—4.20 mU/L for TSH, 1.30—3.10 nmol/L for T3, 66.00—181.00 nmol/L for T4, 3.10–6.80 pmol/L for FT3, and 12.00—22.00 pmol/L for FT4. Use Roche to control quality.

Statistical analysis

All data was analyzed using SPSS 22.0 statistical software. We used Shapiro-wilk to test whether the data was normally distributed. Differences in demographic data were compared using Mann-whitney U and chi-square test. Chi-square test was used to compare the prevalence of mania and depression in different seasons. Mann-whitney U was used to analyze the differences in thyroid function between gender or mood states in patients with bipolar disorder. The differences in thyroid function before and after treatment was compared by the Wilcoxon Signed rank-test and the differences in thyroid function between the two treatment groups was compared by Mann-whitney U. Statistical significance was $P < 0.05$.

Results

Clinical, socio-demographic and biological parameters between mania and depression in patients with bipolar disorder

There were no differences in gender, age, length of hospital stay, BMI, family history of mental illness and thyroid dysfunction rate between mania and depression patients. The systolic/diastolic blood pressure in mania was significantly higher than that in depression patients, ($P < 0.01$) (see Table 1). Since we need to count the changes in different seasons, we choose a whole year as the observation unit. From November 1, 2015 to October 31, 2016, there were 2741 patients with bipolar disorder. There was no difference in the distribution of mania and depression in different seasons ($P > 0.05$) (Table 2).

Table 1. clinical, socio-demographic and biological parameters differences in mania and depression of patients with bipolar disorder.(n = 617)

Characteristics		Mania	Depression	X^2/Z	P
Gender,n(%)	Male	283(45.87)	103(16.69)	1.431	0.232
	Female	159(25.77)	72(11.67)		
Age(year)		31(24,47)	34(24,50)	-1.054	0.292
Inhospital stay duration,day		42.00(27.00,60.25)	40.00(22.00,55.00)	-1.522	0.128
BMI		23.74(21.28,26.78)	23.96(21.30,27.08)	-0.647	0.518
Blood pressure (mmHg)	Systolic blood pressure	126(119,135)	120(110,130)	-4.279	<0.001
	Diastolic blood pressure	80(75,89)	80(71,85)	-3.810	<0.001
Family history of mental illness, n(%)	Family history of psychosis	68(11.02)	25(4.05)	0.118	0.731
	No family history of psychosis	374(60.62)	150(24.31)		
Thyroid function ,n(%)	Normal	293(47.49)	128(20.75)	2.716	0.099
	Abnormal	149(24.15)	47(7.61)		
Note: denoted by median (first quartile, third quartile).					

Table 2. Distribution of mania and depression in patients with bipolar disorder in different seasons.(n = 2741)

	Spring	Summer	Autumn	Winter	X^2	P
Mania,n(%)	498(24.26)	571(27.81)	537(26.16)	447(21.77)	6.976	0.073
Depression,n(%)	155(22.53)	208(30.23)	201(29.22)	124(18.02)		
Note: spring is from February to April, summer is from May to July, autumn is from August to October, and winter is from November to January						

Thyroid function in patients with bipolar disorder in different mood states or genders

T3 and FT3 in mania were significantly higher than those in depression (P < 0.01).Further, the TSH of male patients was significantly lower than that of female patients, while the FT3 and FT4 of male patients were significantly higher than those of female patients (P < 0.01), as shown in Table 3.

Table 3. Comparison of thyroid function among patients with bipolar disorder in different clinical phases or genders.(n = 617)

	TSH(mU/L)	T3(nmol/L)	T4(nmol/L)	FT3(pmol/L)	FT4(pmol/L)
Mania	1.65(1.01,2.68)	1.84(1.58,2.09)	96.68(79.07,113,90)	4.93(4.37,5.58)	16.59(14.32,19.17)
Depression	1.80(1.03,3.00)	1.66(1.44,1.92)	93.16(79.87,108.20)	4.47(3.99,5.17)	16.51(14.50,18.14)
Z	-1.098	-4.434	-1.121	-5.009	-1.260
P	0.272	<0.001	0.262	<0.001	0.208
Male	1.51(0.98,2.59)	1.82(1.53,2.07)	95.91(78.84,111.80)	5.00(4.39,5.61)	16.76(14.68,19.03)
Female	2.02(1.09,3.15)	1.76(1.52,1.96)	96.28(80.43,116.40)	4.51(4.05,5.03)	16.10(13.72,18.58)
Z	-2.689	-1.658	-1.334	-5.777	-2.605
P	0.007	0.097	0.182	<0.001	0.009
Note: denoted by median (first quartile, third quartile).					
TSH: thyroid stimulating hormone					
T3: triiodothyronine					
T4: thyroxine					
FT3: free triiodothyronine					
FT4: free thyroxine					

Thyroid function in bipolar disorder patients treated with lithium

Patients with bipolar disorder were divided into groups according to whether they used lithium. Compared with those before treatment, TSH were significantly increased, but T3, T4, FT3, FT4 were significantly decreased after treatment in two groups (all P < 0.01). However, there was no significant differences in thyroid function between the two groups (all P > 0.05) (See Table 4).

Table 4
Comparison of thyroid function among patients with bipolar disorder unused lithium salt and use lithium salt

	△TSH(mU/L)	Z	P	△T3(nmol/L)	Z	P	△T4(nmol/L)	Z	P	△FT3(pmol/L)	Z
Unused lithium salt (n = 40)	2.07(0.34,3.50)	-3.387	< 0.001	-0.27(-0.54,-0.003)	-4.368	< 0.001	-22.47(-39.63,-5.13)	-3.858	< 0.001	-0.95(-1.43,-0.03)	-4.207
Use lithium salt (n = 34)	1.97(0.74,3.81)	-3.868	< 0.001	-0.23(-0.55,-0.05)	-4.503	< 0.001	-24.77(-38.15,-4.68)	-4.590	< 0.001	-0.65(-0.98,-0.39)	-4.899
Z	-0.743			-0.038			-0.206			-0.575	
P	0.457			0.970			0.837			0.565	
Note: denoted by median (first quartile, third quartile); △=after 4 weeks of treatment - before treatment											
TSH: thyroid stimulating hormone											
T3: triiodothyronine											
T4: thyroxine											
FT3: free triiodothyronine											
FT4: free thyroxine											

Thyroid function in bipolar disorder patients with states transition between mania and depression compared with previous hospitalization

There was a shift in mood state between mania and depression in 28 patients compared with previous hospitalization. Table 5 showed that the T3 and FT3 of the manic patients were significantly higher than that of the depressed patients (both $P < 0.05$).

Table 5. Comparison of thyroid function in 28 patients with bipolar disorder had a mood states transition.

Thyroid function	Mania	Depression	△(Mean,95% CI)	t/Z	P
TSH(mU/L)	2.91 ± 2.69	2.20 ± 1.48	0.71(-0.28~1.70)	-0.991	0.322
T3(nmol/L)	1.75 ± 0.34	1.52 ± 0.33	0.23(0.03~0.44)	2.345	0.027
T4(nmol/L)	97.76 ± 24.98	96.55 ± 24.94	1.22(-11.65~14.09)	0.194	0.847
FT3(pmol/L)	4.69 ± 0.80	4.29 ± 0.86	0.40(0.04~0.76)	2.303	0.029
FT4(pmol/L)	16.17 ± 3.54	16.62 ± 3.87	-0.45(-2.14~1.23)	-0.552	0.586
Note: denoted by Mean ± SD; △=manic thyroid function - depressed thyroid function					
TSH: thyroid stimulating hormone					
T3: triiodothyronine					
T4: thyroxine					
FT3: free triiodothyronine					
FT4: free thyroxine					

Discussion

In this study, 617 patients with bipolar disorder who had not been treated with drugs for at least three months before hospitalization were taken as the study objects, of which 442 were patients with manic episodes and 175 were with depressive episodes. There were no differences in general information such as gender, age, length of hospital stay, BMI, family history of mental illness and abnormal thyroid function rate among manic and depression patients who did not take drugs three months before hospitalization. Also, there was no difference in the distribution of emotional transition in different seasons. Only systolic/diastolic blood pressure in mania was higher than that in depression systolic/diastolic blood pressure. It is speculated that this may be related to the risk of irritability and high mood in patients with bipolar mania.

Our study found that T3 and FT3 in patients with mania were significantly higher than those in patients with depression, which was similar to the results of previous studies (Gordon et al. 1999; Weatherman 2007). Thyroid hormones (especially T3) are structurally similar to norepinephrine (NE) (Weatherman 2007). T3 is mainly concentrated in the nucleus and projection sites of the central NE energy system (Rozanov and Dratman 1996), which may be transmitted from the locus to its NE target through axonal transport (Gordon et al. 1999), thus increasing the activity of postsynaptic adrenergic activity (Whybrow and Prange 1981). NE plays an important role in the regulation of emotions, and excessive NE can lead to restlessness in patients. Thyroid hormone may also induce mania by enhancing the neurotransmission of 5-HT, especially by reducing the sensitivity of 5-HT_{1A} autoreceptor in the nucleus raphe and increasing

the sensitivity of 5-HT_2 receptors (Bauer, Heinz, and Whybrow 2002). In conclusion, the hypothalamic-pituitary-thyroid axis and the neurotransmitter system share a common biosynthetic precursor, tyrosine (Weatherman 2007). At the same time, they all exist in key areas of the brain, and thyroid hormone receptors are widely distributed in the limbic system of the brain, which is related to the pathogenesis of emotional disorders, and the neurotransmitter system regulates emotions by regulating the activities of the limbic area and cortex (Bauer, Heinz, and Whybrow 2002). Therefore, thyroid hormone itself may act as a neurotransmitter or interact with the primary neurotransmitter system to influence the mood of patients (Bauer et al. 2008; Chakrabarti 2011; Zhang et al. 2015).

The results of this study showed that the TSH of male patients was significantly lower than that of female patients, and the FT3 and FT4 of male patients were significantly higher than those of female patients. The level of thyroid function in patients with bipolar disorder was different between genders, indicating gender differences in bipolar disorder. A number of related studies support this view (Arnold 2003; Barnes and Mitchell 2005; Bauer et al. 2014). It has been found that estrogen receptors and thyroid hormone receptors have associated DNA binding domain. Therefore, estrogen and thyroid receptors may bind competitively to specific DNA targets (DiPippo, Lindsay, and Powers 1995; Gantus et al. 2011), which may be the reason for gender differences in thyroid dysfunction in patients with bipolar disorder.

In this study, thyroid function was compared in patients with bipolar disorder before and after treatment. The patients were divided into lithium salt group and non-use lithium salt group. The results showed that after treatment, TSH was increased but T3, T4, FT3 and FT4 were decreased in both groups. There was a trend of hypothyroidism, which was similar to the results of the previous study (Frye et al. 2009). It is speculated that both lithium salt and antipsychotics may affect thyroid function. Some clinical studies support this view (Park et al. 2011; Suppes et al. 2009; Vedal et al. 2018). The possible mechanisms of lithium-induced hypothyroidism include: 1) lithium may inhibit TSH-induced iodine uptake, thereby reducing iodine biosynthesis and neonatal thyroid hormone formation (Urabe et al. 1991). 2) Lithium can stabilize thyroid microtubules, and thus affects the release of thyroid hormone (Bhattacharyya and Wolff 1976). 3) Lithium inhibits the conversion of thyroxine to nitrous oxide in peripheral and neuronal cells (Bagchi, Brown, and Mack 1978). 4) Lithium accumulates in the thyroid at a concentration three to four times its plasma concentration. The most common thyroid side effects of long-term lithium salt therapy are goiter and hypothyroidism (Kraszewska et al. 2014). Therefore, it is recommended to regularly detect thyroid function levels in the clinical treatment of bipolar disorder.

This study has the following limitations: 1. Since it is an observational study, the reason cannot be explained. 2. In this study, we did not have the control group with lithium salt monotherapy for bipolar disorder patients. Thus, it was not possible to determine whether lithium salt would affect thyroid function itself. 3. The sample size in this study was limited. Moreover, due to the small number of patients with bipolar mixing, they were not included in the study. 4. In this natural real-world study, the choice of laboratory testing and treatment was based on the doctor's decision in clinical practice, which may have the follow-up bias and treatment drug selection bias.

Conclusions

In summary, we studied the level of thyroid function in patients with bipolar disorder in China. Thyroid hormones may play an important role in bipolar disorder. Patients with bipolar disorder had thyroid dysfunction in both mania and depression, and the change in thyroid function may also be related to gender and medication. Therefore, it is necessary to conduct a comprehensive thyroid assessment in patients with bipolar disorder. All patients should be regularly examined for thyroid function to prevent adverse reactions of hormonal imbalance.

Declarations

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Authors' contributions

RLZ, XYZ and XSG were responsible for study design. XSG, BY, YZL, QW and FJ were responsible for data collection. YZ, QW and BY participated in the statistical analysis of the data. BY and YZL participated in the preparation and writing of the thesis. XYZ participated in the editing and revision of the manuscript. RLZ was responsible for the critical revision of the manuscript. All authors contributed and approved the final manuscript.

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Availability of data and materials

The data that support findings of this study are available from the corresponding author. The data are not publicly available due to in the need to safeguard the privacy of the participants.

Ethics approval and consent to participate

This research has been approved by the Ethics Committee of the Second Affiliated Hospital of Xinxiang Medical University. Informed consent was obtained from all patients.

Consent for publication

Not applicable.

Competing interests

The authors declare no conflicts of interest in the research related to this manuscript.

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Figures

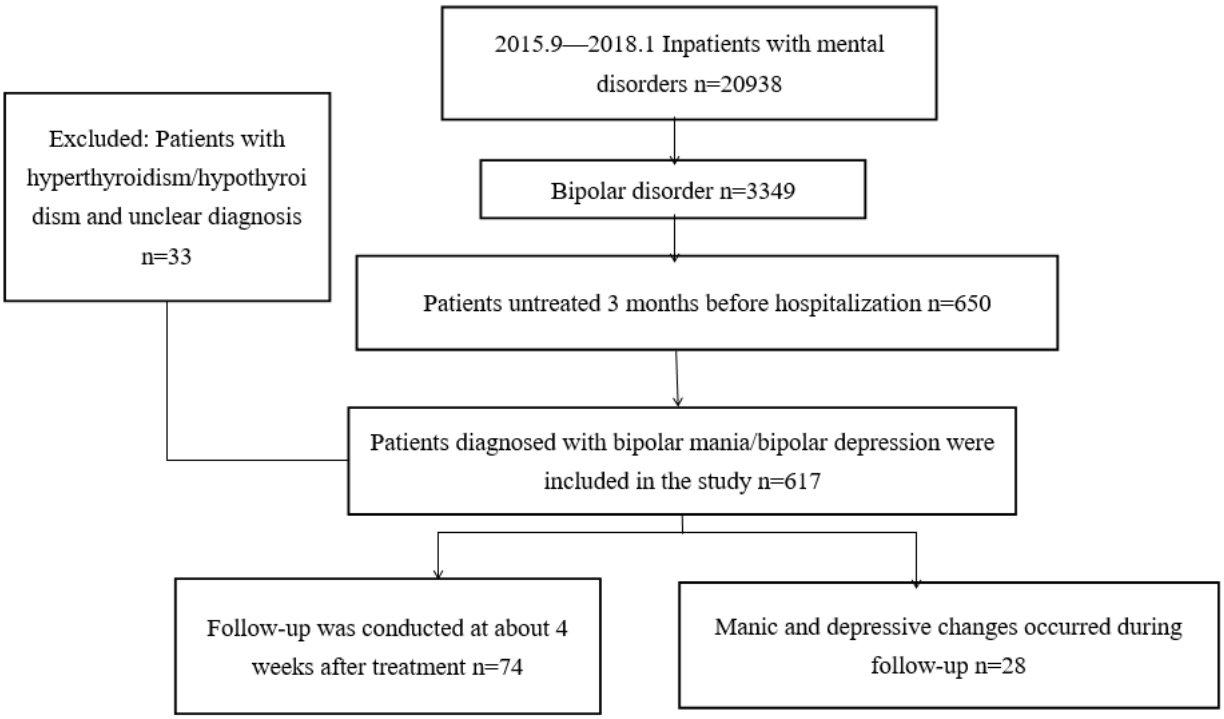

Figure 1

Study design and sample selection