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Differences in hypothyroidism between lithium-free and -treated patients with bipolar disorders

Zhang-Jin Zhang [a,*], Qiang Li [a], Wan-Hu Kang [a], Qing-Rong Tan [b], Cheng-Ge Gao [a], Feng-Gang Zhang [b], Huai-Hai Wang [b], Xian-Cang Ma [a], Ce Chen [a], Wei Wang [a], Li Guo [b], Ya-Hong Zhang [b], Xiao-Bo Yang [a], Rui-Guo Zhang [b]

[a] *Department of Psychiatry, The First Hospital, Xi'an Jiaotong University College of Medicine, Xi'an, Shannxi 710061, China*
[b] *Department of Psychiatry, Xijing Hospital, The Fourth Military Medical University, Xi'an, Shannxi 710032, China*

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Abstract

The majority of the previous studies of thyroid abnormalities in bipolar patients was conducted in populations containing various proportions of lithium-treated subjects. In the present study, we sought to determine whether there exist differences in hypothyroid profile between lithium-free and -treated bipolar patients. Bipolar patients never treated with lithium and carbamazepine ($n=78$) and those currently in lithium therapy ($n=53$) were included in this study. Serum concentrations of total thyroxine (T_4), total triiodothyronine (T_3), and thyroid-stimulating hormone (TSH) were compared between lithium-free and -treated patients. The rate of hypothyroidism in lithium-free patients was significantly lower than those treated with lithium (6.3%–10.8% vs. 28.0%–32.1%). Significant changes in the three thyroid indices indicative of hypothyroidism were consistently associated with longer illness duration in lithium-free manic patients, but with greater severity of mania and more mood episodes in their lithium-treated counterparts. In lithium-free depressed patients, more episodes were associated with lower T_4 levels; whereas in their lithium-treated counterparts, longer illness duration was associated with higher TSH levels and females with lower T_3 levels. These results suggest that bipolar patients with and without lithium exposure differ in prevalence and association of hypothyroidism and may have different response to thyroid hormone therapy.

Keywords: Bipolar disorder; Thyroid hormone; Thyroid-stimulating hormone; Hypothyroidism; Lithium; Mania; Bipolar depression

Introduction

Over the past three decades, the relationship between thyroid axis abnormalities and affective disorders has been well documented (Bauer et al., 2003; Joffe and Sokolov, 1994; Kleiner et al., 1999). Most investigations focused on the prevalence and association of thyroid hypofunction with diagnostic subtypes, demographic and clinical characteristics in bipolar patients (Kupka et al., 2003). It is generally accepted that a higher prevalence of thyroid hypofunction occurs in female patients and those with rapid cycling (Kupka et al., 2003). Long-term evaluation of thyroid function has also been suggested to predict stages of illness development, clinical outcomes, and treatment response in certain types of affective illnesses (Baumgartner et al., 1995; Cole et al., 2002; Frye et al., 1999a,b; Kusalic and Engelsmann, 1998; Marangell et al., 1997). Nevertheless, many studies have reported results that conflict with these views (Ahmadi-Abhari et al., 2003; Cassidy et al., 2002; Frye et al., 1999a,b; Joffe et al., 1988; Kupka et al., 2002; Post et al., 1997; Sack et al., 1988; Wehr et al., 1988). These inconsistencies are thought to be partially related to the differing proportions of subjects with lithium and/or carbamazepine therapy (Valle et al., 1999).

It is well known that lithium therapy can cause alternations in thyroid status by blocking iodothyronine formation and inhibiting thyroid hormone release with a compensatory increase in thyroid-stimulating hormone (TSH) levels (Baumgartner et al., 1997; Lazarus, 1996; Lombardi et al., 1993). The anticonvulsant mood stabilizer carbamazepine has also been

* Corresponding author. Department of Psychiatry, Uniformed Services University of the Health Sciences, 4301 Jones Bridge Road, Bethesda, MD, 20814, USA. Tel.: +1 301 295 1591; fax: +1 301 295 1042.
E-mail address: zhangz68@yahoo.com (Z.-J. Zhang).

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reported to induce a reduction in serum thyroid hormone levels and hypothalamic–pituitary–thyroid axis function (Baumgartner et al., 1997; Herman et al., 1991). This decreased thyroid function, which is manifested primarily as a low level of thyroxine (T_4) and triiodothyronine (T_3) and elevated thyroid-stimulating hormone (TSH) level, can be classified as either overt or subclinical hypothyroidism (Wenzel et al., 1974). It has been reported that the antithyroid effects of lithium therapy accounted for 3%–5% of overt hypothyroidism and 21% of subclinical hypothyroidism observed in affective disorder patients (Kleiner et al., 1999; Perrild et al., 1990). This has led to the hypothesis that there may be differences in thyroid profile between bipolar patients with and without lithium exposure.

Thyroid hormones have been used as replacement therapy for the treatment of lithium-induced hypothyroidism (Bauer et al., 2003). Adjunctive thyroid hormones have also been of therapeutic value in treatment-resistant affective patients (Bauer et al., 2003). However, these studies have not yet addressed the therapeutic effects of thyroid hormone therapy in subjects never exposed to lithium and carbamazepine.

There is a large population of patients in China with bipolar disorders who have been ill for years but have never received appropriate medication. This has provided the possibility for determining whether there are differences in thyroid profile between bipolar patients with and without lithium exposure. We report here the results obtained from comparisons of serum concentrations of total T_4, total T_3, and TSH between lithium-free and -treated patients with bipolar disorders.

Methods and materials

Subjects

The study was conducted in two teaching hospitals in Xi'an, Shaanxi Province of China from September 2002 to October 2004. The protocol was approved by the Medical Ethical Committee of the First Hospital of Xi'an Jiaotong University. All patients signed an informed consent document before entering the trial.

Both males and females aged 18 to 65 years who met the following eligibility criteria were included in the study: (1) a primary diagnosis of bipolar disorders and currently experiencing a manic or major depressive episode based on DSM-IV definition (American Psychiatric Association, 1994); (2) never received treatment with lithium and carbamazepine before entry into the trial (defined as lithium-free patients), or currently under lithium therapy for at least 3 months (defined as lithium-treated patients); and (3) no previous diagnoses of clinical thyroid abnormalities and other endocrinological diseases. The severity of manic and depressive symptoms was assessed using the 11-item Young Mania Rating Scale (YMRS, Young et al., 1978) and the 17-item Hamilton Rating Scale for Depression (HAMD, Hamilton, 1960), respectively.

Thyroid evaluation

On the day the patients were screened, blood samples for the analyses of total T_4, total T_3, and TSH were obtained from eligible patients in morning time (07:00–09:00) following an overnight fast. Five milliliters of whole blood were drawn through elbow veins and collected into tubes. Sera were separated and stored at −70 °C until assayed.

The serum concentration of T_4 and T_3 was measured using microparticle radioimmunoassay (Isotope Research Institute, the Academy of Nuclear Energy of China, Beijing, China). The serum concentration of TSH was determined using double-antibody radioimmunoassay (Union Medical and Pharmaceutical Technology Tianjin Ltd., Tianjin, China). The sensitivity, intra- and inter-assay coefficients of variation were 5.1 nmol/L, <10%, and <15% for T_4, 0.3 nmol/L, <5.3% and <6.7% for T_3, and 0.25 μIU/mL, <10% and 15% for TSH, respectively. Normal ranges in the First Hospital Laboratory were: T_4: 54.2–174.2 nmol/L; T_3: 1.2–3.4 nmol/L; and TSH: 0–10 μIU/mL.

Data analysis

Data of continuous variables are expressed as mean± standard deviation (SD). Comparisons of thyroid indices were conducted using two-way analysis of variance (ANOVA) across lithium-free and -treated groups with a covariate of diagnostic subtypes, gender, duration of illness, number of mood episodes, and severity of symptoms, followed by Bonferroni's *t*-test to further determine differences between

Table 1
Demographic and clinical characteristics of manic and bipolar depressive patients

	Mania		Bipolar depression	
	Li^- (n=32)	Li^+ (n=25)	Li^- (n=46)	Li^+ (n=28)
Male, *N* (%)	19 (59.4)	13 (52.0)	26 (56.5)	11 (39.3)
Age (y)	32.1±12.0	31.6±14.3	30.2±10.0	31.7±9.1
Duration of illness (m)	38.4±54.0	58.8±45.6	51.6±55.2	82.8±78.0[a]
Number of mood episodes	2.6±1.8	3.7±1.6[b]	3.7±3.4	4.6±3.5
YMRS or HAMD scores[c]	29.3±8.0	28.9±7.8	23.1±4.5	25.9±4.3
Use of psychotropic drugs other than Li and CBZ, *N* (%)[d]	4 (12.5)	2 (8.0)	10 (21.7)	3 (10.7)

[a] Student's *t*-test: t=2.045, p=0.045.
[b] Student's *t*-test: t=2.021, p=0.049.
[c] Young Mania Rating Scale (YMRS) on mania and Hamilton Rating Scale for Depression (HAMD) on bipolar depression.
[d] Psychotropic drugs mainly included antipsychotics and antidepressants. Li: lithium; CBZ: carbamazepine.