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Risk factors of thyroid abnormalities in bipolar patients receiving lithium: a case control study

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Abstract

Background: Lithium-induced thyroid abnormalities have been documented in many studies. They may occur despite normal plasma lithium levels. The objectives of this study were: 1) to determine possible relationship between lithium ratio, defined as erythrocyte lithium concentrations divided by plasma lithium concentrations, and thyroid abnormalities in bipolar patients receiving lithium and 2) to find other possible risk factors for developing thyroid abnormalities in the subjects.

Methods: Sixty-eight bipolar patients receiving lithium therapy were enrolled in a cross-sectional evaluation of thyroid function test and thyroid size. Patients were divided into two groups based on their thyroid function tests and thyroid sizes. Erythrocyte and plasma lithium concentrations were determined by atomic absorption spectrometry for each patient. Lithium ratio was then calculated.

Results: No significant differences were found between age, positive family history of affective disorder, plasma lithium concentration, erythrocyte lithium concentration, and lithium ratio comparing the two groups. Thyroid abnormalities was significantly higher in women than in men ($p < 0.05$).

Conclusions: Lithium ratio does not appear to have a predictive role for thyroidal side effects of lithium therapy. Female gender was the main risk factor. We suggest more frequent thyroid evaluation of bipolar women who are treated with lithium.

Background

Lithium therapy is an established treatment in patients with bipolar disorders. This agent has a narrow therapeutic window. Additionally, lithium is known to cause alterations in various organ functions, thus it merits a regular monitoring. Among these, alteration in thyroid status induced by lithium treatment is important in the clinical evaluation of neuropsychiatric effects [1] including fatigue, memory impairment, and anhedonia.

The antithyroid effects of lithium were first observed in patients who received lithium carbonate and developed hypothyroidism and goiter. It was subsequently recognized that lithium increases intrathyroidal iodine content, inhibits the coupling of iodothyrosine residues to form iodothyronines [2–4] and prevents secretion of T4 and T3 [3–5]. The use of plasma level alone for monitoring could be misleading since the above side effects may occur even when lithium plasma levels are within the normal range.

It should be noted that in many respects erythrocyte membrane is similar to nerve cell and possibly some other cells. Therefore, erythrocytes have been useful for studying intracellular lithium ion, particularly due to its easy availability [6]. Lithium ratio (LR), the ratio of erythrocyte lithium concentration (ELC) to plasma lithium concentration (PLC), has been suggested for studying lithium side effects and may be a better indicator of toxicity than PLC [7,8].

To our knowledge, the relationship between LR and thyroid abnormalities in bipolar patients has not been studied. We performed this study to determine if LR may have a better correlation with lithium-induced thyroid abnormalities than PLC. This would result in fewer thyroid function tests (TFT), physical examinations and consequently reduce the cost of thyroid monitoring.

Since plasma lithium concentrations are being measured in patients receiving lithium, it would be easy to measure ELC simultaneously.

The study was designed to look at any possible relationship between lithium ratio (LR) and thyroid side effects. Also other possible risk factors for developing thyroid abnormalities were investigated.

Methods

Patient selection

Patients with bipolar disorder, admitted at Roozbeh Mental Health Hospital, who did not receive any drug(s) affecting thyroid or TFT were enrolled in the study. None of the subjects had a history of thyroid disorder before his/her first exposure to lithium. All the patients received equally similar doses of lithium. Additionally there was no significant difference in the number or the dose of other psychotropics (including benzodiazepines and haloperidol) among the patients. Pregnant women were excluded from the study. All participating subjects signed written informed consents prior to entering the study. Patients who fulfilled criteria for entry into the study were reassessed for diagnosis of bipolar disorder according to DSM IV criteria. The study protocol was approved by the Institutional Review Board.

Sampling

Blood samples for lithium determination were taken at 9 a.m. (12 ± 1 hours after the last dose), since lithium ratio and plasma lithium concentration change only minimally after this interval [9].

Data collection

Data regarding age of patients, number of hospital admission for psychiatric reasons, lithium dose, duration of lithium therapy, PLC, ELC, LR, family history for affective disorder, and sex are shown in table 1.

Thyroid evaluation

The thyroid size was evaluated by an experienced endocrinologist through palpation. Thyroid function tests (TFT) consisted of T3RU, TT4, FT3, and TSH determined by radioimmunoassay.

Assay of Lithium

The concentration of intracellular lithium was determined according to the direct method of Summerton [10]. Twice distilled water was added to the solutions of plasma and erythrocyte and the mixture was placed in the graphite furnace (GBC 932 AA, Australia). Conditions used by Decosterd et al were applied to provide reproducible results with acceptable sensitivity and accuracy [11]. Samples of RBC and plasma obtained from patients who were not treated with lithium were used for calibration, processed in a similar fashion and stored the same at -70°C. The latter samples were used to establish calibration curves and served as internal quality control samples during the assay. They were also analyzed whenever intra-assay variations were doubted and on the beginning of every working days. The instrument was allowed to warm up at least 30 minutes before each daily run.

All measurements were repeated twice to detect variability associated with the procedure.

Statistical analysis

Statistical analyses were performed using SPSS® for Windows™, release 10.0. Data were analyzed using unpaired student t-test and Fisher's exact test. A logistic regression analysis was performed to find out any relationship between covariates and the probability of thyroid abnormal-

Table 1: Comparing variables in normal thyroid with abnormal thyroid group.

Variables	Normal thyroid group		Abnormal thyroid group		p value
Age(yr[a])	33.78 ± 10.62		35.62 ± 12.86		p > 0.05
Admission[b] (n)	3.64 ± 3.40		3.30 ± 2.42		p > 0.05
Lithium carbonate dose (mg/d)	1114 ± 263		1157 ± 189		p > 0.05
Duration[c]	8.31 ± 8.34		13.35 ± 11.84		p = 0.188
PLC[d] (mmol/l)	0.50 ± 0.24		0.47 ± 0.19		p > 0.05
ELC[e] (mmol/l)	0.24 ± 0.17		0.15 ± 0.10		p = 0.021
LR[f]	0.51 ± 0.26		0.34 ± 0.18		p = 0.029
FH[h]	+	21	+	3	p = 0.037
	-	25	-	11	
Sex	Female	15	Female	10	p = 0.005
	Male	38	Male	4	

Plus-minus values are means ± SD a-yr = year b-admission = number of hospital admission for psychiatric problems c-Duration =Length of lithium therapy d-PLC = Plasma Lithium Concentration e-ELC = Erythrocyte Lithium Concentration f-LR = ELC/PLC h-FH = Family history of affective disorder in first degree relatives

ity occurrence. A 95% confidence limit was used as significance level.

Results

Sixty-eight patients with bipolar mood disorder (25 females, and 43 males with the mean age of 34 ± 11) entered the study. Fourteen patients were assigned to the group with abnormal thyroid function or/and size. The rate of each thyroid abnormality is demonstrated in figure 1.

The result of t-test analysis showed a significant decrease in the LR among patients with thyroid abnormality compared with those who had normal thyroid (table 1). Because data about duration of lithium therapy was not complete and reliable, therefore, it was omitted from the last analysis. Eligible variables (sex, FH, ELC, and LR) were selected for logistic regression analysis ($p < 0.1$). Sixty-one cases were included in the analysis. Thyroid abnormalities in females were 5.9 times as much as that in males (OR = 5.89, 95% CI = 1.57~22.00). There were no significant differences between the two groups with respect to FH, ELC, and LR in the ultimate analysis.

Discussion

When t-test was used to analyze the data, our study noted that patients with abnormal thyroid had lower LRs. However this was not confirmed in the final analysis when logistic regression model was used.

Inconsistencies were observed among different groups regarding the relationship between lithium side effects and LR.

There are reports of higher LRs in patients with lithium side effects [12,13]. In contrast, other reports show a higher LRs in those without lithium side effects [14,15]. Kamp did not find any correlation between the concentration of lithium in erythrocytes and the side effects of lithium [16].

With regard to thyroid function Rybakowski et al reported higher activity of lithium sodium counter-transport (LSC) in patients with higher TSH from a group of lithium-treated bipolar patients [17]. In the whole group and in female patients LSC was negatively correlated with LR [17]. Johnston et al found lower LRs in patients with side effects including hypothyroidism [14].

Discrepancies observed may be due to different methods of assay used, different designs of studies, definitions of thyroid disorder, and methods of patient selection. In this study, a direct method of lithium determination in erythrocytes was used. This method is much more accurate and less variable compared to the indirect method of lithium determination [15]. It has been observed that LR is different in various types of psychiatric disorders [18–20]; LR may also differ during episode and during maintenance therapy [21–23]. It should be noted that our study only included hospitalized bipolar patients, however other studies included patients in different stages of the bipolar disorder or patients with other types of psychiatric diseas-

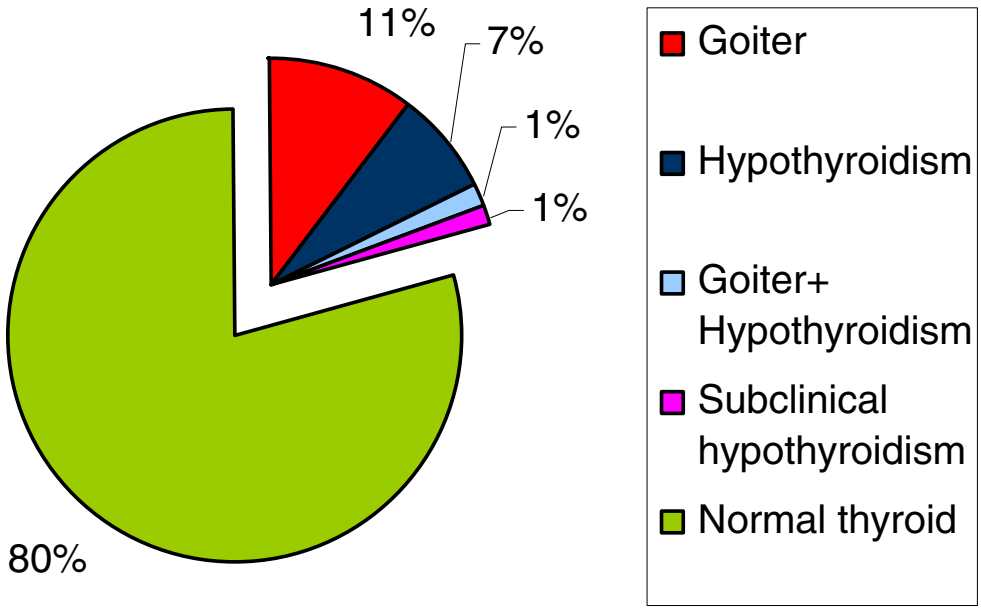

Figure 1
Rate of thyroid abnormalities in the study.

es. [12,13,16]. Among potential sources of discrepancies regarding LR and side effects, possible ethnic differences may exist as reported by Strickland et al [24].

The conflicting results might also be partially due to different methods of analysis applied. Absence of significant difference between PLCs in the two groups demonstrates its inability to detect lithium-induced thyroid side effects.

Unless all the factors that govern the concentration of lithium in RBC are introduced, it remains unclear whether or not LR could be used as a diagnostic tool or as a predictor for developing lithium-induced thyroid disorders.

Although Perrild et al reported no gender difference with regard to goiter and thyroid volume [25], several investigators showed higher incidences of lithium-induced thyroid abnormalities in women [26–29] which is in agreement with our findings. For instance, Johnston and Eagles reported a higher prevalence of clinical hypothyroidism in women [30].

Bocchetta et al reported female gender and presence of thyroid autoimmunity as risk factors for developing lithium-induced thyroid abnormalities in a cohort study [31].

Environmental (iodine deficiency) or intrinsic (autoimmunity) risk factors may inhibit compensatory mechanisms that operate in most patients and lead to thyroid dysfunction [31].

Probably, iodine deficiency does not play a significant role in thyroid abnormalities in Iran due to universal salt iodization since 1989 [32]. According to the report of Heydarian et al who conducted Tehran Thyroid Study, the frequencies of AbTPO+ and AbTG+ (antithyroid antibod-

ies) were 15.9% in women versus 8.3% in men ($p < 0.001$) and 21.5% in women versus 11% in men ($p < 0.001$), respectively [33]. The higher rate of thyroid abnormalities in females observed in this study may be due to the autoimmunity effects.

Conclusions

This study showed that LR could not be used as an indicator or a diagnostic tool for thyroid abnormalities. We suggest that monitoring thyroid size and function should take into account patient's gender, since being a female may be a risk factor to develop lithium-induced thyroid abnormalities. Further studies are needed to confirm our findings.

Authors' contributions

SAAB carried out the psychological assessment and patient selection , PG participated in its coordination and manuscript performance (main supervisor), FF participated in most part of the study as a PhD student for PhD thesis (main performer), FE carried out thyroid function assessment, HF supervised the instrumental analysis, ARD designed the study (main supervisor), IJ assisted in instrumental analysis, ZNH performed the statistical analysis, SD participated in lithium level determination. All authors read and approved the final manuscript.

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