Subclinical hypothyroidism in lithium-treated psychiatric patients in Tehran, Islamic Republic of Iran

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قصور الدرقية الأدنى من السريري في المرضى النفسيين المعالجين بالليثيوم في طهران، جمهورية إيران الإسلامية

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الخلاصة: وقد قام الباحثون باستقصاء وظائف الغدة الدرقية لدى 46 مريضاً نفسياً (20 ذكراً و26 أنثى) ممن يُعالجون بالليثيوم، وذلك بقياس معدلات الثلاثي يودوثيرونين T3 والثيروكسين T4 والهرمون المنبه للدرقية TSH، كما تم كذلك تحرّي وجود أضداد الدرقية (البيروكسيداز المضادة للدرقية وأضداد الغلوبولين الدرقي). وقد تبين أن لدى ثمانية (17٪) من هؤلاء المرضى الستة والأربعين قصور درقية واضح. أما بقية المرضى، فقد كان هناك قصور درقي أدنى من السريري لدى 35٪ منهم، بينما كان المرضى الاثنان والعشرون الآخرون (48٪) أسْوِيَاءَ الدرقية. وكانت أضداد الدرقية موجودة لدى ستة مرضى ضمن مجموعة أسْوِيَاءَ الدرقية، وخمسة مرضى ضمن مجموعة القصور الدرقي. وتبيّن باستخدام معامل ناتج «بيرسون» وجود ترابط إيجابي بين معدل الهرمون المنبه للدرقية واستمرار استخدام الليثيوم وعمر المرضى الذين لديهم قصور درقي أدنى من السريري. وقد خلصت الدراسة إلى أن استمرار استخدام الليثيوم وعمر المريض، يمكن أن يمثلا مؤشراً معقولاً على ضرورة فحص المرضى الخالين من الأعراض وذلك لإمكانية إصابتهم بقصور درقي دون سريري بعد بدء علاجهم بالليثيوم.

ABSTRACT We investigated thyroid function in 46 (20 female & 26 male) psychiatric outpatients on lithium treatment by assessing triiodothyronine, thyroxine and thyroid stimulating hormone (TSH) levels. The presence of thyroid antibodies (anti-thyroid peroxidase and anti-thyroglobulin) was also assessed. Out of the 46 patients, 8 (17%) displayed overt hypothyroidism. Of the remaining patients, subclinical hypothyroidism was found in 16 patients (35%) and euthyroidism in 22 (48%). Thyroid antibodies were present in 6 patients in the euthyroid group and 5 patients in the hypothyroid group. The Pearson product-moment correlation results indicated positive association between TSH level and duration of lithium use and age of the patients with subclinical hypothyroidism. Duration of lithium use and age could be a reasonable indicator for screening asymptomatic patients for subclinical hypothyroidism after starting lithium treatment.

Hypothyroïdie infraclinique chez des patients psychiatriques traités au lithium à Téhéran (République islamique d'Iran)

RÉSUMÉ Nous avons examiné la fonction thyroïdienne chez 46 patients (20 femmes et 26 hommes) des consultations psychiatriques externes traités au lithium en évaluant le taux de triiodothyronine, de thyroxine et de thyréostimuline hypophysaire (TSH). La présence d'anticorps anti-thyroïde (anti-thyroperoxydase et anti-thyroglobuline) a également été évaluée. Huit (17 %) des 46 patients présentaient une hypothyroïdie patente. Parmi les patients restants, on a trouvé une hypothyroïdie infraclinique chez 16 d'entre eux (35 %) et une euthyroïdie chez 22 (48 %). Des anticorps anti-thyroïde étaient présents chez 6 patients dans le groupe de l'euthyroïdie et chez 5 patients dans le groupe de l'hypothyroïdie. Les résultats de la corrélation des moments mixtes de Pearson ont indiqué une association positive entre le taux de TSH, la durée de l'utilisation du lithium et l'âge des patients présentant une hypothyroïdie infraclinique. La durée de l'utilisation du lithium et l'âge pourraient servir d'indicateurs plausibles pour le dépistage de l'hypothyroïdie infraclinique chez des patients asymptomatiques après instauration d'un traitement au lithium.

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Introduction

Lithium carbonate is widely used in the treatment of mood disorders such as bipolar disorder. It has been reported to induce gastrointestinal [*1*], neuromuscular [*2*] and endocrine adverse effects [*3*] in 35%–93% of patients taking it. To optimize its effect, therefore, it is important to be aware of these side-effects. Thyroid hypofunction is one of the most common endocrine side-effects associated with lithium treatment. In most cases lithium-induced hypothyroidism is subclinical [*4–6*].

The mechanism of the effect of lithium on the thyroid gland is not fully understood. However, it has been shown that lithium reduces iodine uptake into the gland, inhibits iodine addition to tyrosine, reduces triiodothyronine (T_3) and thyroxine (T_4) release and enhances thyroid stimulating hormone (TSH) release [*5–8*]. Furthermore, some studies have reported a higher incidence of thyroid antibodies in patients treated with lithium (24%) compared with those not taking lithium (12%) [*9,10*]. The risk of lithium-induced antibodies increases with the duration of therapy and is more common in women than in men [*9,10*].

It has been reported that up to 10%–20% of patients develop lithium-induced subclinical hypothyroidism [*11–13*]. The majority of these patients have few symptoms or none at all. However, it has been shown that conversion of subclinical hypothyroidism to overt hypothyroidism in the presence of circulating antibodies is high [*14*]. Therefore, routine screening of patients receiving lithium has been advocated. In this regard, TSH appears to be the most efficient parameter in revealing subclinical hypothyroidism in patients on lithium treatment [*11–13*].

In the present study we evaluated the possible effect of lithium on thyroid function tests (TSH, T_3 andT_4 levels) in 46 psychiatric outpatients at the Reference Laboratory of the Islamic Republic of Iran in Tehran.

Methods

Over the 2-year period 2001–2002, a total of 46 (20 female and 26 male) psychiatric outpatients attending the Reference Laboratory to check their serum lithium level were randomly selected for the study. A questionnaire was completed for each patient with the patient's age, any previous thyroid gland problems, time of possible onset and duration of lithium use. All the patients reported that before starting lithium treatment they had had their thyroid tested and the results were normal. Any patients with a previous thyroid disorder were excluded from the study. Thus 5 patients who had had their thyroid gland removed or had a thyroid disorder not associated with lithium use were excluded.

To investigate whether lithium is an important risk factor for the development of subclinical hypothyroidism, 95% confidence intervals (95% CI) were calculated. Then the Pearson product-moment correlation was performed to asses whether there was a correlation between pairs of variables such as TSH level, lithium concentration, duration of lithium use and age of patients with subclinical hypothryroidism.

Blood samples were drawn 8–10 hours after oral dose/s of lithium were given and sera were separated from the cells within 2 hours. Serum lithium concentration was determined using flame atomic absorption spectroscopy (Varian 20-plus) [*15,16*].

Sera were sent to the radioimmunoassay (RIA) laboratory for the determination of TSH (K1100To28202, Kavoshyar Iran Co.), T_3 (K1100To38203, Kavoshyar Iran Co.), T_4 (K1100To28203 Kavoshyar Iran

Co.) levels, as well as anti-thyroid peroxidase (anti-TPO) (Monobind, Inc. Product code: 1125-300, USA) and anti-thyroglobulin (anti-Tg) (Monobind, Inc. Product code:1025-300, USA).

Results

Table 1 gives the patient information. Duration of lithium use varied with a mean of 6 years (standard deviation 4.3) and range of 2–15 years. None of the patients had visible thyroid gland enlargement. Out of the 46 patients, 8 (17%) (4 females and 4 males) displayed overt hypothyroidism. Based on the completed questionnaires they were on levothyroxin and had normal TSH levels. Therefore, no further study was performed on this group of patients. Subclinical hypothyroidism, for which no thyroid supplementation was used, was observed in 16 patients (35%, 95% CI: 23.0%–54.0%) (6 female and 10 males) and euthyroidism was observed in 22 patients (48%) (14 females and 8 males). Of the16 subclinical cases, 5 had mildly elevated TSH levels (TSH 3.0–30 mU/L) and 11 had highly elevated TSH levels (TSH > 30 mU/L): normal TSH levels for adult are 0.5–3.0 mU/L. In both groups, free T_4 levels were normal.

We carried out the Pearson product-moment correlation between the TSH level of the 16 patients with subclinical hypothyroidism and lithium concentration, duration of lithium use and age. Significant differences were observed for patient's age (r = 0.71, $P < 0.01$) and duration of lithium use ($r = 0.76$, $P < 0.001$); lithium concentration was not significantly correlated ($P > 0.05$) (Table 2). Furthermore, using the Fisher exact test there was no significant difference for sex and occurrence of subclinical hypothyroidism ($P > 0.05$).

Thyroid antibodies (anti-TPO and anti-Tg) were present in 6 patients (27%) (5 females and 1 male) in the euthyroid group (n = 22). In addition, 5 patients (31%) (3 females and 2 males) in the subclinical group tested positive for these antibodies (Table 3).

Discussion

Subclinical hypothyroidism is defined as elevated concentration of TSH and normal level of serum T_4. This disorder in lithium-treated patients may be present without symptoms [*6,11,12,17,18*]

In the present study thyroid function was evaluated in 46 psychiatric (20 female and 26 male) outpatients with different duration of lithium treatment (2–15 years) and 16 (35%) patients displayed subclinical hypothyroidism after starting lithium treatment. They appeared to be symptom-free and did not complain of any side-effects.

Table 1 **Patient information**

Sex	Total number of patients	Mean (SD) duration of lithium use (years)	No. of patients with overt hypothyroidism	Mean (SD) age (years)	No. of patients with subclinical hypothyroidism	Previous thyroid gland disorder
Female	20	5.4 (4.3)	4	53 (3)	6	No
Male	26	6.3 (4.0)	4	45 (5)	10	No

SD = standard deviation.

Table 2 **Pearson product-moment correlations between variables and thyroid stimulating hormone (TSH) level in the 16 subclinical patients**

Variable	*r*	*P*-value
TSH & age	0.71	0.01
TSH & lithium concentration	0.29	0.28
TSH & lithium duration	0.76	0.001

Since in the normal population the prevalence of subclinical hypothyroidism ranges from 1% to12% [*19,20*], our results indicate lithium is an important risk factor for the development of subclinical hypothyroidism.

Studies have reported the incidence of lithium-induced hypothyroidism increases with the duration of treatment [*21*]. The mean duration of lithium treatment for our subclinical hypothyroid patients was relatively long at 6 years. Duration of lithium treatment was significantly associated with the risk of increased TSH levels and the development of subclinical hypothyroidism ($P < 0.001$). In addition, researchers have shown that the incidence of subclinical hypothyroidism increases with age, especially in women [*22*]. Our preliminary data indicate a correlation ($P < 0.01$) between TSH level in subclinical hypothyroid patients and age, but sex was not a significant factor ($P > 0.05$).

Table 3 **Positivity of thyroid autoantibodies in lithium-induced subclinical hypothyroidism and euthyroid cases**

Thyroid autoantibodies in [a]	Euthyroid (*n* = 22)	Subclinical (*n* = 16)
Females	5	3
Males	1	2
Total (%)	6 (27)	5 (31)

[a] ***Anti-thyroid peroxidase & anti-thyroglobulin.***

Previous studies have indicated the presence of thyroid autoantibodies (24%) in patients receiving lithium is high [*9,10*]. Furthermore, it has been shown that lithium may accelerate the production of the thyroid autoantibodies that may be present prior to lithium treatment [*9*]. Singer reported that overt hypothyroidism develops in a high proportion of subclinical cases who have positive thyroid autoantibodies [*14*]. In our study, 5 subclinical patients (31%) displayed high thyroid autoantibody titres. Our data also indicate that lithium-induced subclinical hypothyroidism may occur in the absence of thyroid autoantibodies (11 patients) although subclinical patients are at higher risk of developing overt hypothyroidism. Because of our small sample size, antibody positivity by itself was not a good marker for predicting conversion of subclinical hypothyroidism to overt hypothyroidism.

Our results indicate that duration of lithium use and age regardless of sex could be a reasonable indicator for screening asymptomatic patients for subclinical hypothyroidism after starting lithium treatment. In addition, TSH appears to be a more suitable parameter for assessing subclinical hypothyroidism than the presence of positive thyroid autoantibodies.

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