Early Onset of Lithium-Associated Hypothyroidism

Annick Vincent, M.D., Philippe Baruch, M.D., Pierre Vincent, M.D.

Department of Psychiatry, Hôpital de l'Enfant-Jésus, Centre de recherche
Université Laval-Robert Giffard, Quebec, Quebec

Submitted: November 4, 1992
Accepted: January 18, 1993

In general practice, psychiatrists are confronted with the difficulty of structuring a rational design for the early detection of hypothyroidism. To determine the period during which a patient receiving lithium is most at risk of developing hypothyroidism, a retrospective study was conducted on the records of 154 patients at two general hospital lithium clinics from January 1980 to August 1991. Forty-two cases of hypothyroidism (clinical hypothyroidism and/or abnormally elevated levels of TSH) were detected. A significant difference was found between the onset of hypothyroidism and age (older patients developed more thyroid dysfunction), but no significant differences were found between thyroid abnormality and sex or diagnostic category and menopausal status, although trends were observed for the two former variables. This longitudinal study is the first to describe an outline of thyroid functioning in terms of the duration of treatment. Lithium-associated hypothyroidism develops most often during the first two years. Of the 42 cases of hypothyroidism, 16 were diagnosed within six months (38%), 23 within the first year (55%), and 31 two years (74%). Since thyroid functioning is an important parameter in the course of affective disorders, its close and frequent monitoring is mandatory during the first two years of treatment.

Key Words: lithium, hypothyroidism, bipolar disorders, major mood disorders

INTRODUCTION

In 1949, Cade introduced lithium as a specific treatment for manic disorder. It took 20 years for clinicians to notice a co-morbidity between lithium and a thyroid enlargement (Schou et al 1968) and between lithium and impaired functioning (Luby et al 1971). Männisto (1980) estimated that 3.28% of patients receiving lithium may develop clinical hypothyroidism (with a female:male ratio of 9:1) and that 34% had at least one abnormal thyroid test. Transböl et al (1978) found an elevated TSH (thyroid stimulating hormone) level in 23% of patients on lithium (39% of women) and a T3 (triiodothyronine) and T4 (thyroxine) decrease but within normal ranges. Bocchetta (1991) reported a prevalence rate of 19% subclinical hypothyroidism among 150 Sardinian outpatients at different stages of lithium treatment.

Few longitudinal studies have evaluated hypothyroidism in relation to the introduction of lithium therapy. The reported rates range from 7.8% with a mean duration of therapy of 3.4 years (Yassa et al 1988) to 19% with a mean duration of 6.8 years (Joffe et al 1988) and 42% with a mean duration of 15 years (Stancer and Forbath 1989). Other studies have found high levels of TSH and lower levels of T3 and T4 that

---

Partial results of this study were presented at a poster session at the 41st annual meeting of the Canadian Psychiatric Association, October 1991, Saskatoon, Saskatchewan.

The final results of this study were presented at the New Research (Young Investigators') Poster Session at the annual meeting of the American Psychiatric Association, May 1992, Washington, DC, and at the 61st annual meeting of the Royal College of Physicians and Surgeons of Canada, September 1992, Ottawa, Ontario.

Address reprint requests to: Dr. Annick Vincent, Department of Psychiatry, Hôpital de l'Enfant-Jésus, 1401, 18ème rue, Quebec (Quebec) Canada G1J 1Z4.

spontaneously reversed within less than 12 months (Maarbjerg et al 1987; Smigan et al 1984).

Lithium appears to exert its effect on the thyroid primarily by inhibiting thyroid hormone release, resulting in a compensatory elevation of TSH levels. Salata and Klein (1987) reviewed the mechanisms of action of lithium on the thyroid.

Hypothyroidism can mimic depressive symptoms (Gold et al 1982) and is associated with treatment-resistant depression (Gewirtz et al 1988) and rapid cycling (Bauer et al 1990). In general practice, psychiatrists are confronted with the difficulty of structuring a rational design to detect hypothyroidism early. The purpose of this retrospective study was to determine with greater precision the period during which a patient receiving lithium is most at risk of developing a thyroid dysfunction.

METHOD

The charts of patients at two general hospital lithium clinics (Hôpital de l'Enfant-Jésus and Hôpital du Saint-Sacrement) from January 1980 to February 1991 were reviewed. Patients who stated that they took their medication regularly and who had normal thyroid levels prior to lithium treatment were included in the sample. Each patient's age, sex and menopausal status were recorded. Other medication being taken and the diagnosis made by the patient's psychiatrist (according to DSM-III and DSM-III-R criteria) were registered. Blood levels of lithium, creatinine and thyroid function parameters (TSH, T3, T4 and thyroid antibodies) were recorded.

Most patients' TSH levels were measured every two to three months. Hypothyroidism was considered to be present when a frank clinical disorder was diagnosed or/and when TSH levels were above normal levels more than once (normal levels: TSH between 1980 and 1986 – 2 mU/l to 10 mU/l, and TSH between 1987 and 1991 – 0.4 mU/l to 6.0 mU/l). This spectrum includes the three grades of hypothyroidism described by Wenzel et al (1974) (grade I – frank clinical hypothyroidism, grade II – higher TSH level with few signs of symptoms, grade III – subclinical).

To compare the data, we used the Student's t-test or ANOVA for quantitative variables, followed by the Newman-Keuls test for post-hoc comparisons and chi-square analysis or Fisher's exact test (2×2) for qualitative data. A value of $p < 0.05$ was considered statistically significant.

RESULTS

One hundred and fifty-four patients (107 women, 47 men) were included in the study. The mean age was 47 ± 14 years (range = 22 to 87 years). The mean duration of lithium therapy was 59 ± 31 months (range = 2 to 136 months). Forty of the women (37%) had reached menopause. There was no significant difference in age between the men and women ($p = 0.15$). The duration of lithium therapy was significantly greater for the men than for the women ($p = 0.0151$). Most of the patients received at least one concomitant medication (benzodiazepine, tricyclic, antipsychotic and/or antiparkinsonian). One patient was also taking carbamazepine. The sample consisted of 111 patients with bipolar disorder (type I with mania and type II with hypomania), 25 patients with recurrent unipolar depression and 18 with schizoaffective disorder.

Nine of the men and 33 of the women (42 of the 154 patients (27%)) developed lithium-associated hypothyroidism. None of the patients had toxic levels of lithium or significantly high levels of creatinine.

Thirty-three (30%) of the bipolar patients developed lithium-associated hypothyroidism, compared with seven (28%) of the patients with recurrent unipolar depression and two (11%) of the patients with schizoaffective disorder. This difference was not statistically significant, possibly because the sample of patients with schizoaffective disorder was too small (chi-square = 2.715, $p = 0.257$).

There was a significant difference between the mean age of the patients who developed a thyroid hypofunction associated with lithium and the mean age of the patients who remained euthryoid. The mean age of the 42 patients with hypothyroidism was 51 ± 11 years, and the mean age of the 112 patients who were euthyroid while taking lithium was 45 ± 14 years (two-factor ANOVA, $p = 0.004$). There was no significant difference between hypothyroidism onset and sex (Fisher's exact test, $p = 0.170$) or whether or not the subjects had reached menopause (16 of the 40 menopausal women and 17 of the 67 non-menopausal women developed hypothyroidism; Fisher's exact test, $p = 0.133$). Other studies have found a higher rate of hypothyroidism among women on lithium (Männisto 1980; Transböl et al 1978). In our sample, the difference between the onset of hypothyroidism and sex was statistically significant only when the patients under 50 years of age were considered (one of the 24 males and 18 of the 70 females developed hypothyroidism; Fisher's exact test, $p = 0.036$).

Fig. 1 illustrates the number of cases of hypothyroidism as a function of the duration of treatment with lithium. Of the 42 cases of lithium-associated hypothyroidism, 16 (38%) were diagnosed within six months, 23 (55%) within the first year, and 31 (74%) within two years. Three patients discontinued lithium therapy: two because of rapid and markedly symptomatic hypothyroidism, and one who was planning a pregnancy. Twenty-five of the 42 patients who developed hypothyroidism received hormonal therapy (sodium levothyroxine). Thyroid antibodies were not measured before lithium was started for the majority of patients before 1986, or for the patients with normal thyroid functioning. These parameters could therefore not be compared.

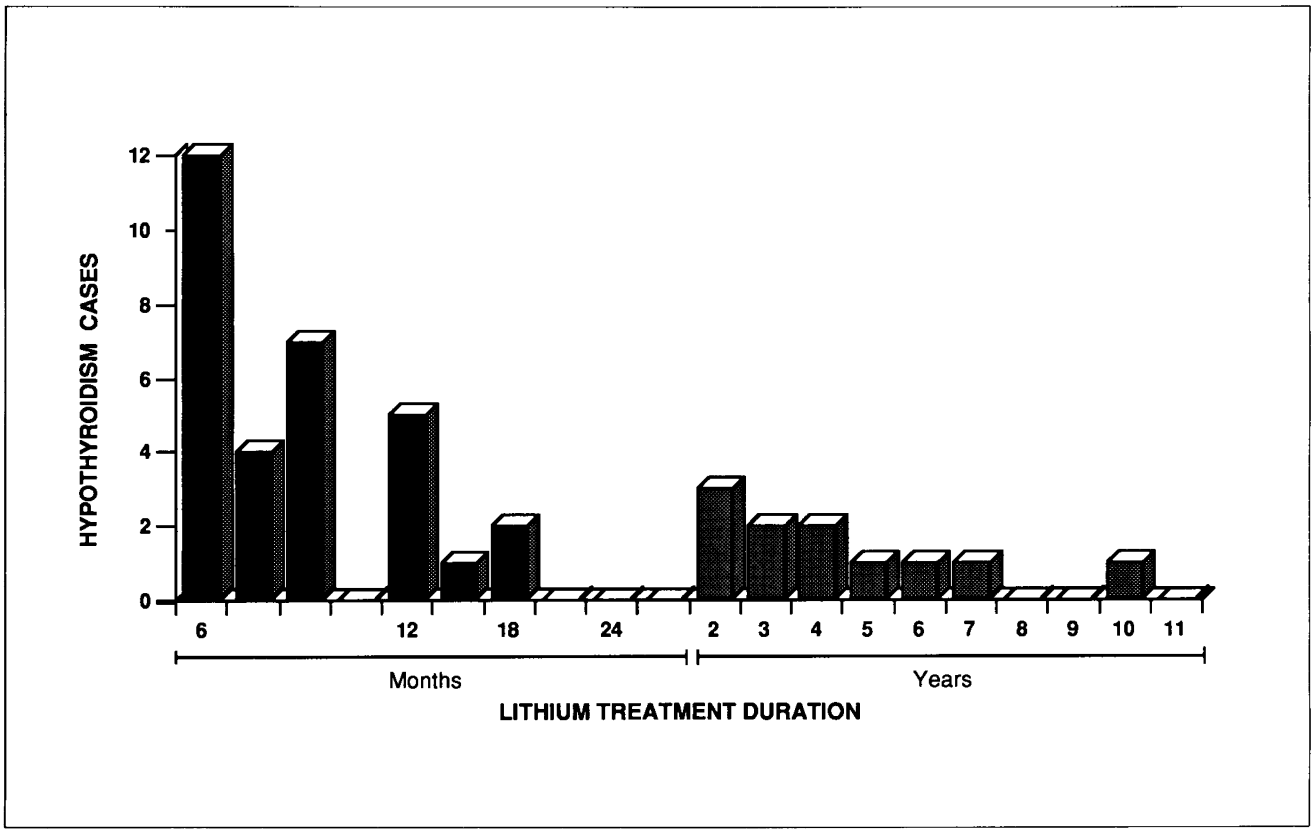

Fig. 1. Occurrence of hypothyroidism as a function of the duration of treatment with lithium.

DISCUSSION

A 27% rate of hypothyroidism was found after a mean duration of lithium therapy of 4.9 years, which is within the range found in the literature. Some researchers (Männisto 1980; Transböl et al 1978) have reported a higher rate of iatrogenic hypothyroidism among women taking lithium. The data from this study confirm this difference only for the group under 50 years of age. A statistically significant difference was also found between the age of patients who developed hypothyroidism and the age of patients who remained euthyroid but no difference between the onset of hypothyroidism and menopausal status. In this study, the onset of hypothyroidism appears to become more frequent with age for males but is more equally distributed among age groups among women. Future studies are needed to explore the relationships between lithium-associated hypothyroidism and age or sex.

There appears to be a trend, which is not statistically significant, toward patients with bipolar and unipolar disorders developing hypothyroidism more frequently than patients with schizoaffective disorder who are receiving lithium therapy. A larger sample with more unipolar patients and particularly more schizoaffective patients would be necessary to confirm that difference.

This is the first study in which the onset of lithium-associated hypothyroidism is clearly time-delineated in a large group of patients followed for a long period. Since a thyroid dysfunction can influence the course of all depressive disorders and may induce rapid cycling, and given the high rate of early onset hypothyroidism — 38%, 55% and 74% of thyroid dysfunction appearing within six, 12 and 24 months respectively — early serial follow-up of thyroid parameters is important for patients treated with lithium.

Based on these data, a determination of TSH every two to three months for the first two years is recommended, after which TSH could be measured biannually. This type of follow-up could be easily done in a general hospital lithium clinic.

Because of the retrospective design of this study, hypothyroidism could not be further categorized into the three grades described by Wenzel et al (1974). With this design, it was possible to establish more quickly than with a prospective study the critical time during which a patient on lithium is most at risk of developing a thyroid dysfunction. Based on these data, future research could focus on the first two years of lithium treatment and include a systematic follow-up of

the clinical and subclinical manifestations of lithium-induced hypothyroidism.

REFERENCES

Bauer MS, Whybrow PC, Winokur A (1990) Rapid cycling bipolar affective disorder, I. Association with grade I hypothyroidism. Arch Gen Psychiatry 47:427-432.

Bocchetta A, Bemardi F, Pedditzi M, Loviselli A, Velluzzi F, Martino E, Del Zompo M (1991) Thyroid abnormalities during lithium treatment. Acta Psychiatr Scand 83:193-198.

Gewirtz GR, Malaspina P, Hatterer JA, Feureisen RN, Klein D, Gorman JM (1988) Occult thyroid dysfunction in patients with refractory depression. Am J Psychiatry 145:1012-1014.

Gold MS, Pottash ALC, Extein I (1982) "Symptomless" autoimmune thyroiditis in depression. Psychiatr Res 6:261-269.

Joffe RT, Kutcher S, MacDonald C (1988) Thyroid function and bipolar affective disorder. Psychiatr Res 25:117-121.

Luby E, Schwartz D, Rossenbaum H (1971) Lithium carbonate-induced myxedema. JAMA 218:1298

Maarbjerg K, Vestergaard P, Schou M (1987) Changes in serum thyroxine (T4) and serum thyroid stimulating hormone (TSH) during prolonged lithium treatment. Acta Psychiatr Scand 75:217-221.

Männisto PT (1980) Endocrine side-effects of lithium. In: Handbook of Lithium Therapy. Johnson FN (ed). Baltimore, MD: University Park Press, pp 310-322.

Salata R, Klein I (1987) Effects of lithium on the endocrine system: a review. J Lab Clin Med 110:130-136.

Schou M, Amdisen A, Eskjer JS, Olsen T (1968) Occurence of goiter during lithium treatment. Br Med J 3:710-713.

Smigan L, Wahlin A, Jacobsson L, Von Knorring L (1984) Lithium therapy and thyroid function tests, a prospective study. Neuropsychobiology 11:39-43.

Stancer HC, Forbath N (1989) Hyperparathyroidism, hypothyroidism and impaired renal function after 10 to 20 years of lithium treatment. Arch Intern Med 149:1042-1045.

Transböl I, Christiansen C, Baastrup PC (1978) Endocrine effects of lithium I. Hypothyroidism, its prevalence in long term treated patients. Acta Endocrinol (Copenh) 87:759-767.

Yassa R, Saunders A, Nastase C, Camille Y (1988) Lithium-induced thyroid disorders: a prevalence study. J Clin Psychiatry 49:14-16.

Wenzel KW, Meinhold H, Raffenberg M, Adlkofer F, Schleusener H (1974) Classification of hypothyroidism in evaluating patients after radioiodine therapy by serum cholesterol, T3 uptake, total T4, FT4-index, total T3, basal TSH and TRH test. Eur J Clin Invest 4:141-148.