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Lithium-associated clinical hypothyroidism

Prevalence and risk factors

ANN M. JOHNSTON and JOHN M. EAGLES

Background Rates of, and risk factors for, lithium-associated clinical hypothyroidism are uncertain.

Aims To determine prevalence of and risk factors for clinical hypothyroidism in patients treated with lithium carbonate.

Method Retrospective case-note review of 718 patients who had undergone serum lithium estimation during a 15-month period. Patients on thyroxine had a more detailed review.

Results The prevalence of clinical hypothyroidism during lithium treatment was 10.4%. The main risk factor was female gender (women 14% v. men 4.5%). Women were at highest risk during the first two years of lithium treatment, and women starting lithium aged 40–59 years had the greatest prevalence (>20%). No equivalent risk factors emerged in men, although, like women, their prevalence of hypothyroidism was substantially higher than community rates.

Conclusions The high rates of clinical hypothyroidism identified may call for a review of the drug information given to women, particularly to those starting lithium in middle age. Consideration should be given to screening for thyroid antibodies before treatment in high-risk cases. Monitoring of thyroid function should take into account gender, age and stage of lithium treatment.

Declaration of interest None.

The anti-thyroid effect of lithium has long been recognised (Schou *et al*, 1968; Luby *et al*, 1971), with lithium-associated clinical hypothyroidism said to occur in 2–5% of patients (Ferrier *et al*, 1995; Shelley, 1995). Although the existence of lithium-associated hypothyroidism is generally accepted, it is not undisputed; Bocchetta *et al* (1996) reported no excess of hypothyroidism in their lithium-treated cohort followed up for six years. Most prevalence studies have been limited by their sample size, usually of fewer than 200 subjects. Little is known of the factors that predispose to the development of hypothyroidism during treatment and, even for such a basic putative risk factor as gender, Leibenluft (1996) noted that it is not clear whether women are at higher risk than men. We set out to evaluate the prevalence of clinical hypothyroidism in a sample of 718 patients on lithium treatment and to identify the associated risk factors.

METHOD

Serum lithium estimations were carried out on 718 patients at the clinical biochemistry laboratory of Aberdeen Royal Infirmary between September 1994 and December 1995. Case notes were reviewed for the purpose of a regional lithium audit. A total of 103 patients received replacement thyroxine and were entered into a case-note review to detect biochemical thyroid parameters to support the diagnosis of clinical hypothyroidism and to establish the time-points at which lithium and thyroxine were commenced. Eighteen patients were excluded because their introduction of thyroxine treatment pre-dated lithium. Of the 85 remaining subjects on thyroxine, incomplete case-note information was supplemented by searching of the hospital laboratory results database and by contact with the patients' general practitioners. A further five subjects were excluded because the time relationship between lithium and thyroxine could not be established. In total 695 subjects were eligible for inclusion.

Validation of the diagnosis of clinical hypothyroidism

The following criteria were applied:

(a) Thyroid-stimulating hormone (TSH) above the laboratory reference limit of 3.3 mU/l. (Aberdeen Infirmary normal range=0.35–3.3 mU/l.)

(b) Plasma total thyroxine below the laboratory reference limit of 70 mmol/l. (Aberdeen Infirmary normal range=70–150 mmol/l.)

(c) Treating doctor's judgement that thyroxine treatment was indicated.

Using these criteria, a further eight patients were excluded from the clinically hypothyroid group: five cases where thyroxine was initiated on the basis of high TSH only; and three cases where thyroxine was being used as an adjunctive psychiatric treatment. In total, 72 cases were accepted as having clinical hypothyroidism, 61 of these (85%) having biochemical results available and fulfilling the above three criteria. The remaining 11 cases were accepted because although biochemical results at the time of starting thyroxine were not traceable, there was evidence in the case-note correspondence that starting thyroxine was based on unequivocal biochemical results and, in some cases, marked clinical features.

To find an approximation of the prevalence of hypothyroidism in the local population (Grampian Region), we used data from the Continuous Morbidity Recording Database. Accurate gender, age and repeat prescription data were available from 55 general practices, covering a total population of over 300 000 patients. Hypothyroid cases were identified as those being in receipt of a repeat prescription for thyroxine.

RESULTS

Description of the sample

The 695 patients eligible for inclusion comprised 430 women (62%) and 265 men (38%). The mean age of the women was 53 years (s.d.=15), with an average duration of lithium treatment of 7.5 years (s.d.=6.8). The mean age of the men was 48 years (s.d.=15), with an average duration of lithium treatment of 7 years (s.d.=5.9). The mean serum lithium level for the whole sample in 1995 was 0.64 mmol/l (s.d.=0.22), with 73% having

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levels between 0.4 and 0.8, 18% with levels above 0.8, and 9% with levels below 0.4 mmol/l.

Prevalence of clinical hypothyroidism

Seventy-two patients (60 female, 12 male) had developed clinical hypothyroidism since starting lithium, giving an overall prevalence of 10.4%. The prevalence was significantly higher in women at 14% compared to 4.5% in men ($\chi^2=15.7$, d.f.=1, $P<0.0001$). In women, the median time between the start of lithium treatment and the development of hypothyroidism was 24 months, and in men it was 59 months.

Comparison with approximate local prevalence

The overall prevalence of hypothyroidism in the Grampian area, approximated through the number of patients receiving repeat prescriptions for thyroxine, was 3.2% in women aged 20–79 years (3224/98 050) and 0.66% in men aged 20–79 years (586/88 964). The rate of hypothyroidism on lithium was significantly higher in women, with a relative risk of 4.8 for women (95% CI=3.6–6.3; $\chi^2=151$, d.f.=1, $P<0.000001$) and 7.2 for men (95% CI=4–12.8; $\chi^2=59$, $P<0.000001$). The rates were examined further by age group (see Table 1).

Survival analysis

Subjects receiving continuous lithium treatment were subjected to survival analysis. Continuous lithium was defined as those having no lithium-free periods since lithium commenced, or one lithium-free interval of less than three months if in the first three years of treatment, or less than six months if in the fourth and subsequent years of treatment. By these criteria 79% of the women (341/430) and 78% of the men (207/265) were included. Time to hypothyroidism was compared using survival curves obtained from the Kaplan–Meier method (Bland & Altman, 1998). Differences between the curves were evaluated with the log rank test. Men and women were compared in Fig. 1. Women were separated into three groups according to their age on starting continuous lithium treatment, and compared in Fig. 2.

The difference between the male and female ten-year survival curves was significant at $P=0.0003$. The sharpest decline in survival was in the first two years in women, with 91% surviving hypothyroidism, with rates of 86% and 80% at the end of years 5 and 10, respectively. In men the survival was much flatter, with corresponding rates of 97%, 96.5% and 94%.

Figure 2 shows women subdivided according to age at the time they commenced lithium. The lowest survival was in the group aged 40–59 years; their survival of hypothyroidism was 87%, 81% and 72% at the end of years 2, 5 and 10. Their survival was significantly less than that of the younger age group ($P=0.044$, $\chi^2=4.06$, d.f.=1), although not significantly different from that of the older age group ($P=0.01$, $\chi^2=2.68$, d.f.=1). When the middle-aged sample was compared to the rest of the sample, the difference was significant ($P<0.02$, $\chi^2=5.78$, d.f.=1).

Incidence per 100 years of lithium exposure

The total duration of lithium exposure was calculated for the whole male and female samples; in the hypothyroid cases the duration of lithium until the diagnosis of hypothyroidism was calculated. The overall incidence in the women was 2.17 cases, and in the men it was 0.68 cases per 100 years of lithium treatment. Rates in the first two years were then compared to the overall rates in the subsequent years of treatment, as in Table 2.

Table 1 Prevalence of hypothyroidism: rates on lithium *v.* community rates

Age (years)	Prevalence of hypothyroidism on lithium (no. hypothyroid/total no.)		Approximate community prevalence (no. hypothyroid/total no.)		Relative risk (95% CI)	
Women						
20–39	9.8%	(9/91)	1%	(320/33 324)	11.3	(5.6–22.7)
40–59	13.4%	(25/186)	2.7%	(1220/45 645)	5.65	(3.7–8.7)
60–79	16%	(22/137)	8.8%	(1684/19 081)	1.98	(1.24–3.13)
Men						
20–39	0%	(0/89)	0.13%	(53/41 614)	–	–
40–59	6.5%	(7/107)	0.7%	(228/31 235)	9.5	(4.38–20.7)
60–79	7.5%	(5/66)	1.9%	(305/16 115)	4.25	(1.69–10.6)

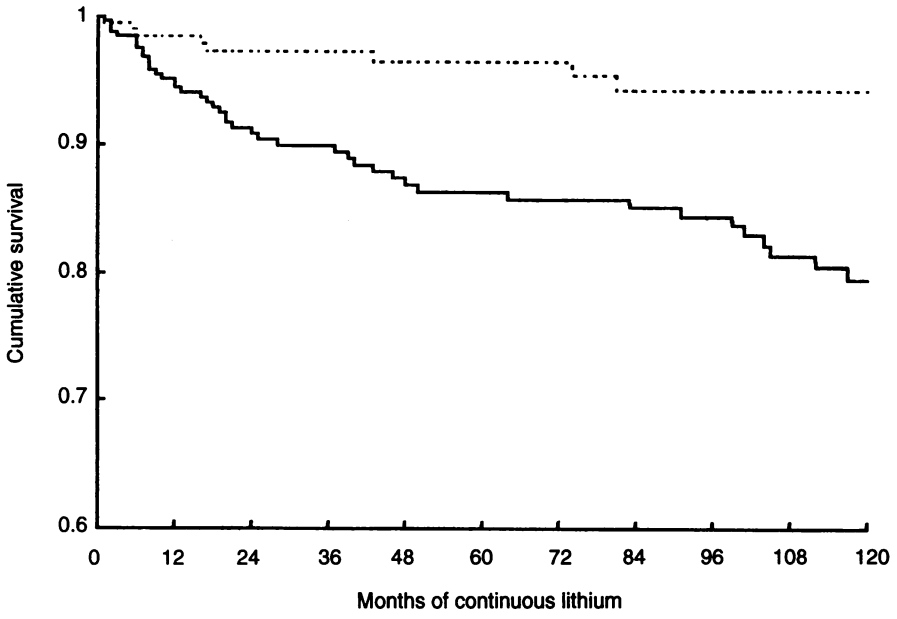


Fig. 1 Ten-year survival for 'time to hypothyroidism' in women *v.* men: (·····) men, *n*=207 at start; (——) women, *n*=341 at start.

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The incidence of hypothyroidism was increased significantly in the first two years of lithium treatment in women, but in men the difference was not statistically significant.

DISCUSSION

In this study the overall prevalence of clinical hypothyroidism in patients receiving lithium was 10.4%. The prevalence in women was significantly higher at 13.8% than in men at 4.5%. High rates were found in women who started lithium between the ages of 40 and 60 years, whose eventual rates were over 20%. In females, the incidence of hypothyroidism was three times higher in the first two years of lithium treatment compared with the rate thereafter. Although risk factors in men were less clear, the prevalence and incidence of clinical hypothyroidism, as in women, were significantly higher in lithium-treated subjects than in the general population.

Comparison with other studies

Although studies vary widely in reported rates of lithium-associated hypothyroidism (see Goodwin, 1990) recent reviews quote figures of 2–5% (Ferrier *et al*, 1995; Shelley, 1995). It is well-established that minor and transient thyroid abnormalities can be induced by lithium (Maarbjerg *et al*, 1987), so we confined our study to those with clinical hypothyroidism. Our findings are similar to those found by Yassa *et al* (1988), who reported clinical hypothyroidism in 7.8% of 116 patients studied. There is nothing about our sample that would explain the higher than expected rates; there is, for example, no tertiary referral service that could lead to an over-representation of people with rapid-cycling illness or resistant depression, in whom hypothyroidism is more common (Cowdry *et al*, 1983; Hickie *et al*, 1996). It is possible that hypothyroid patients on lithium are somehow selected to remain on both treatments, thus increasing the prevalence figures. If this is the case, it would be interesting to know why they are selected.

Our cohort of 695 patients constitutes, to our knowledge, the largest prevalence study to date and it would seem appropriate that generally quoted figures for lithium-associated hypothyroidism are revised significantly upwards. It would not seem justifiable to quote rates of 3–5% to middle-aged women starting on lithium when their eventual rates are in excess of 20%.

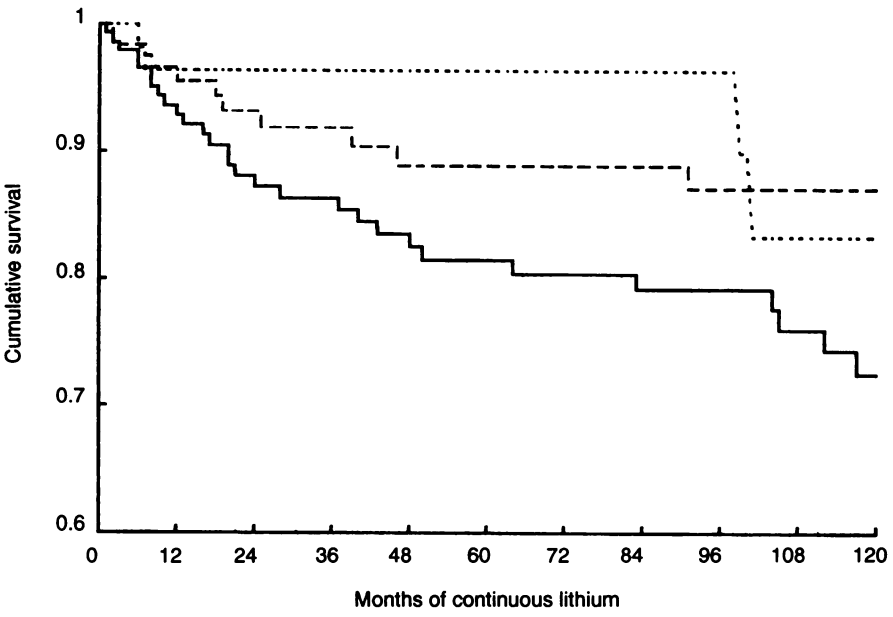


Fig. 2 Ten-year survival for 'time to hypothyroidism' in women: (- - - -) age <40 years, *n*=128 at start; (——) age 40–59 years, *n*=149 at start; (·····) age >60 years, *n*=64 at start.

Table 2 Hypothyroid cases per 100 years of lithium exposure

Years of lithium treatment	Total years of lithium exposure	No. hypothyroid	Cases per 100 years	*P*
Women				
0–2	705.22	30	4.25	
>2	2060	30	1.46	<0.0001[1]
Men				
0–2	465.88	5	1.07	
>2	1295	7	0.54	0.38 (NS)[2]

1. χ^2=19.37.
2. Yates' corrected χ^2=0.75.

Although there are problems in obtaining accurate incidence figures retrospectively, our annual incidences of clinical hypothyroidism (2.17% in women and 0.68% in men) are substantially higher than the community incidences (0.41% and 0.06%) found by Vanderpump *et al* (1995). Our community prevalence figures are also rather high compared to prevalences found in the Whickham community study (Tunbridge *et al*, 1977). Our community figures were not backed up by biochemical validation of the hypothyroid diagnosis, but were used to give a reasonable approximation of the rates of clinical hypothyroidism in the local population. The relatively high community rates could simply reflect modern thinking on hypothyroidism, that mild or 'subclinical' disorders are worthy of treatment (Weetman, 1997). Because we specifically excluded the cases on lithium with subclinical disorder, then arguably the relative risks that we cited in the comparison of lithium-treated and community rates could be underestimates.

The anti-thyroid effect of lithium

Lithium's anti-thyroid effect involves several mechanisms: its main effect seems to be an inhibition of thyroid hormone release (Jefferson, 1990). It can also promote thyroid autoimmunity, possibly by causing shifts in T-lymphocyte populations (Calabrese *et al*, 1985). The risk factors that we identified may be due partly to the acknowledged higher frequency of positive thyroid

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antibodies titres found in women, particularly in those of middle age and beyond. Unfortunately, in this study, very few subjects had their thyroid autoimmunity titres checked before starting lithium. However, of the 60 women who developed hypothyroidism, 15 were screened for at the time of the hypothyroid diagnosis and 13 of them were found to be antibody-positive.

Does it matter?

The psychiatric relevance of clinical hypothyroidism is well-known and there are some indications that even subclinical abnormalities have psychiatric consequences (Monzani *et al*, 1991). It is not clear whether patients who develop clinical hypothyroidism during the course of lithium treatment fare any differently from their counterparts who remain euthyroid. Because there may be a delay before the diagnosis is made and thyroxine treatment is started, then for the untreated period, at least, lithium could be adding to the symptoms that it was prescribed to treat. It is important that clinical observation and laboratory tests are used appropriately to reduce this risk. It is not impossible that the pharmacological combination of lithium and thyroxine might be particularly effective, although we are not aware of any studies in this area. More research is needed into the psychiatric and physical effects of clinical and subclinical hypothyroidism during lithium treatment.

CLINICAL IMPLICATIONS

- The drug information given to women starting lithium should be reviewed, particularly to those starting the drug in middle age.
- Consideration should be given to screening for thyroid antibodies in high-risk cases before the institution of lithium therapy.
- Monitoring of thyroid function should take account of gender, age and stage of lithium treatment in addition to careful clinical observation.

LIMITATIONS

- The retrospective nature of the data may have led to inaccuracies in the determination of the incidence of hypothyroidism.
- The relatively small number of hypothyroid men on lithium made it unlikely that specific risk factors would be identified in men.
- The contribution of serum lithium concentrations at the time of the diagnosis of hypothyroidism could not be investigated.

ANN M. JOHNSTON, MRCPsych, Psychiatric Unit, Hairmyres Hospital, East Kilbride, Lanarkshire; JOHN M. EAGLES, FRCPsych, Royal Cornhill Hospital, Aberdeen

Correspondence: Ann M. Johnston, Consultant Psychiatrist, Psychiatric Unit, Hairmyres Hospital, Eaglesham Road, East Kilbride, Lanarkshire G75 8RG

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