Lithium therapy: an unusual cause of elevated and diffuse radioactive iodine uptake

Ebenezer A Nyenwe, MD[1]; Joseph N Fisher, MD[1]; Lester VanMiddlesworth, PhD, MD[2]

1 Division of Endocrinology, Diabetes and Metabolism, Department of Medicine, University of Tennessee Health Science Center, Memphis, TN 38163, USA

2 Department of Physiology and Division of Endocrinology, University of Tennessee Health Science Center, Memphis, TN 38163, USA

* **Correspondence:** *Ebenezer A Nyenwe, MD, Division of Endocrinology, Diabetes and Metabolism, University of Tennessee Health Science Center, 920 Madison Ave, Suite 909, Memphis, TN 38163, USA (eanyenwe@yahoo.com)*

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ABSTRACT

Lithium carbonate, a widely used treatment for bipolar disorders, is associated with goiter, hypothyroidism and thyrotoxicosis. However, the effect of lithium to increase radioactive iodine uptake has received little attention, thus, making Lithium a confounding factor in the interpretation of thyroid radionuclide studies. We herein report a case of misinterpreted high radioactive iodine uptake in a euthyroid, lithium-treated goitrous patient. We conclude that lithium therapy should be considered in the etiologic diagnoses of patients with goiter and homogenously elevated radioiodine uptake. It is pertinent to recognize this phenomenon in order to prevent unwarranted treatment with radioactive iodine or thionamides.

CASE REPORT

A 27-year-old woman was referred to our thyroid clinic for evaluation and treatment of hyperthyroidism, thought to be due to "Graves' disease". She had presented to her primary care provider for evaluation of goiter of two years duration. Ancillary investigations done by the referring physician included radioactive iodine (RAI) uptake and scan which showed diffuse uptake of 77.6%, reported as being consistent with Graves' disease. This report prompted her referral to our thyroid clinic. She complained of fatigue and dry skin but had no somnolence, change in weight or bowel habit. Her thyroid swelling was painless, stable in size and without associated dysphagia, dyspnoea or dysphonia. She was a vegetarian who used iodized salt. She gave history of bipolar disorder which had been treated with lithium carbonate for several years, but had no past history of thyroid disease. She was being maintained on 900mg of lithium carbonate daily. The patient was a nulliparous woman who had normal menstrual cycles.

Patient was well developed and well nourished with body mass index of 22 kg/m2 and blood pressure of 110/60 mmHg. Other vital signs were within normal limits. Her pupils were normal in size and symmetry and reacted appropriately to light and accommodation. She had no proptosis, lid retraction or lid lag, there was no ophthalmoplegia or conjuctival chemosis. Her physical examination was remarkable for firm, diffuse, non-tender, thyromegaly (about 3 times enlarged), without bruit. Patient had no cervical lymphadenopathy or carotid bruit. She was conscious and alert and had no focal neurological deficit. Her deep tendon reflexes were normal. She had no acropachy or pretibial edema. Examination of her chest, heart and abdomen was normal.

Laboratory and Imaging Studies

Her serum electrolytes and liver function tests were normal, and serum lithium level was 0.56 mmol/L (therapeutic range 0.6-1.4mmol/L). Thyroid function tests were normal (as were those done by the referring physician 2 months prior to our evaluation) with thyrotropin level of 0.89 mIU/L (0.5-5), free thyroxine level of 0.9 ng/dL (0.8-1.8) and free triiodothyronine level of 3.0 pg/mL (2.3-4.2). Anti-peroxidase antibody was undetectable (<10), urinary iodine excretion was

normal at 109 micrograms/day (100-460). Thyroid Ultrasonography confirmed diffuse goiter (Fig 1). Review of accompanying thyroid radionuclide uptake and scan with 631 μci of 123I sodium iodide, (requested by the referring physician for goiter) confirmed increased 24-hour uptake of 77.6% (reference range 10-30 %); and homogenous activity throughout both lobes of the thyroid gland (Fig. 2).

Treatment and Outcome

She was reassured that her thyroid function was normal and that her goiter and elevated RAI uptake were most likely due to effect of lithium on the thyroid gland. She was advised to continue lithium therapy, to follow up with her psychiatrist, and to return to the clinic in 6 months for re-evaluation. However, Lithium was replaced with carbamazipine by her psychiatrist. Re-evaluation two months after discontinuing lithium therapy revealed her lithium level was undetectable (< 0.3 mmol/L). Repeat 24-hour RAI uptake with 15 μci of 131I was 31.2%, thyroid scan with 99mTc-pertechnetate showed slight thyromegaly with homogenous uptake and mild hyperperfusion of the thyroid gland (Fig. 3).

DISCUSSION

Lithium carbonate was introduced into clinical medicine for the treatment of bipolar disorders in 1949 (1,2). About two decades after its introduction, Schou et al reported the occurrence of goiter in 4% of lithium treated patients (3). Subsequent studies have shown that thyroid disorders are common in patients undergoing lithium therapy, with goiter and hypothyroidism occurring in 50% and 20% respectively (4). Long-term lithium therapy is also associated with increased risk of thyrotoxicosis (5-8). The incidence of thyrotoxicosis was 2 – 3 fold higher in lithium-treated patients compared to the general population (5,6). Thyrotoxicosis due to silent thyroiditis (with reduced radionuclide scitigraphic pattern) is fairly well reported (5-7), although hyperthyroidism (with increased radionuclide scintigraphic pattern) due to toxic diffuse goiter, toxic multinodular goiter or toxic solitary nodule has been reported as well (5). Lithium increases intra-thyroidal iodine content (2,9), a property which has been exploited clinically in the treatment of thyrotoxic crisis, thyroid cancer and Graves' hyperthyroidism (9). However, little attention has been drawn to the effect of lithium to increase radioiodine uptake in thyroid radionuclide studies.

We have presented a young woman with background history of bipolar disorder, who developed diffuse goiter while being treated with lithium. Initial evaluation with radionuclide uptake and scan showed elevated and diffuse uptake which was interpreted as "consistent with Graves' disease" by the reporting radiologist. Diffuse thyromegaly with elevated radioactive iodine uptake in the absence of iodine deficiency, prior thionamide therapy, thyrotropinoma or thyroiditis may lead to a mistaken diagnosis of Graves' disease if due attention is not paid to thyroid function tests; and as in this patient, history of lithium therapy. Although, elevated radioiodine uptake in this patient can be explained by lithium induced intra-thyroidal retention of iodine, it is also possible that this patient might have been at the recovery phase of lithium induced silent thyroiditis when the first radioactive iodine study was done. However, the absence of thyrotoxic symptoms and consistently normal thyroid function tests argue against this diagnosis. Hyperthyroidism, with elevated radionuclide uptake has been reported in patients treated with lithium carbonate (5); but given the lack of thyrotoxic symptoms and normal levels of thyrotropin and thyroid hormones, the likelihood of this in our patient is quite remote. The other possibilities in this case include thyrotropinoma and autoimmune thyroid disease which are effectively excluded by normal thyroid function and absence of thyroid autoantibodies.

Given the increased incidence of thyrotoxicosis in patients treated with lithium, this effect of lithium to increase radioiodine uptake could be a confounding factor in the interpretation of thyroid radionuclide studies as was the case in our patient. Misinterpretation in cases like this could prove harmful as such patients may be treated with radioactive iodine or thionamides. The main lesson from this case therefore, is that lithium therapy should be considered in the differential diagnoses of patients with goiter and high radioiodine uptake. We estimate that this effect of lithium may be more common than is recognized, since lithium is widely used in the treatment of bipolar disorders and up to half of these patients may have goiter. Lastly, the clinical course of this patient suggests that the effect of lithium on radioiodine uptake is transient; just as long-term follow up of lithium-treated patients has shown that lithium induced goiter and hypothyroidism are reversible (10).

The mechanism of lithium induced thyroid disease is not known with certainty. However, it has been shown that lithium increases intra-thyroidal iodine content by stimulating thyroidal iodide uptake while blocking the release of organic iodine; it also inhibits thyroid hormonogenesis. (2,9). Berens et al demonstrated that lithium-treated rats fed with low iodine diets had significantly higher 131I uptake compared to non lithium-treated animals. The effects of lithium may be mediated through inhibition of thyroid adenyl cyclase which is the second messenger in the thyrotopin signal transduction pathway (11). However, it is noteworthy that chronic administration of lithium in rats produced both stimulatory (increased iodide trapping) and inhibitory (decreased iodine release) effects (2), suggesting that lithium may be acting, at least in part, by another mechanism other than inhibition of adenyl cyclase. Lithium-treated patients show a small early rise in serum thyrotropin level which normalizes as treatment is continued. Therefore, goiter may result from compensatory increase in thyrotropin level, in an attempt to maintain normal thyroid function. Hypothyroidism, which is often subclinical, supervenes when this adaptive mechanism fails.

TEACHING POINT

This case report demonstrates that lithium therapy should be considered in the differential diagnoses of patients with goiter and high radioiodine uptake. All homogenously increased radioactive iodine uptake is not due to Graves' disease, particularly in patients treated with lithium. Recognition of this phenomenon would prevent misdiagnosis of Graves' disease and unwarranted treatment with radioactive iodine or thionamides.

ABBREVIATIONS

RAI = radioiodine uptake

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FIGURES

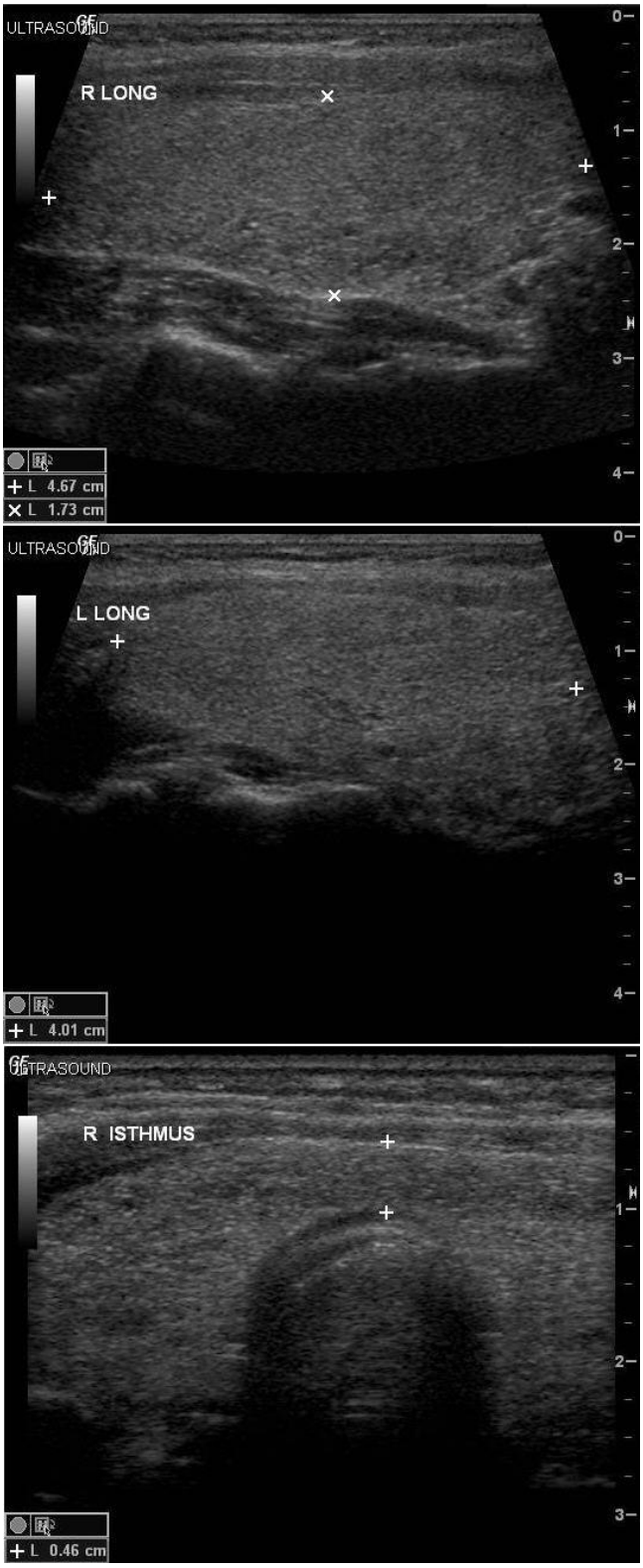

Figure 1: Grayscale thyroid ultrasonography of the patient while being treated with lithium showing diffuse thyromegaly

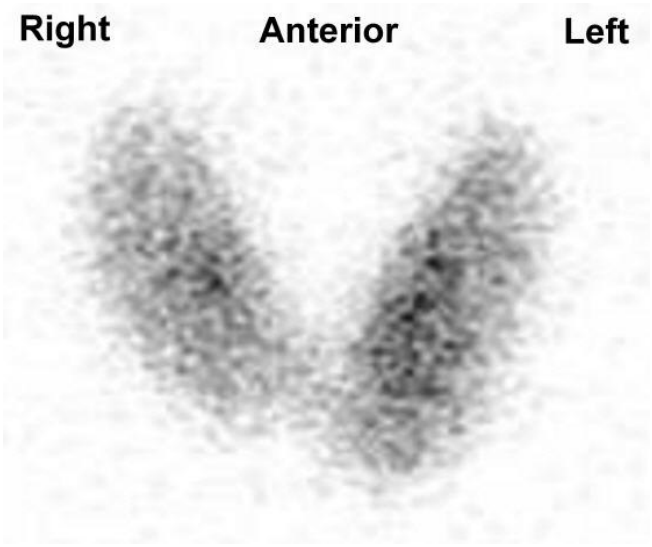

Figure 2: Thyroid Scintigraphy with 631 µci of I23I sodium iodide, showing increased 24-hour uptake of 77.6% and homogenous activity throughout both lobes of the thyroid gland while on treatment with lithium.

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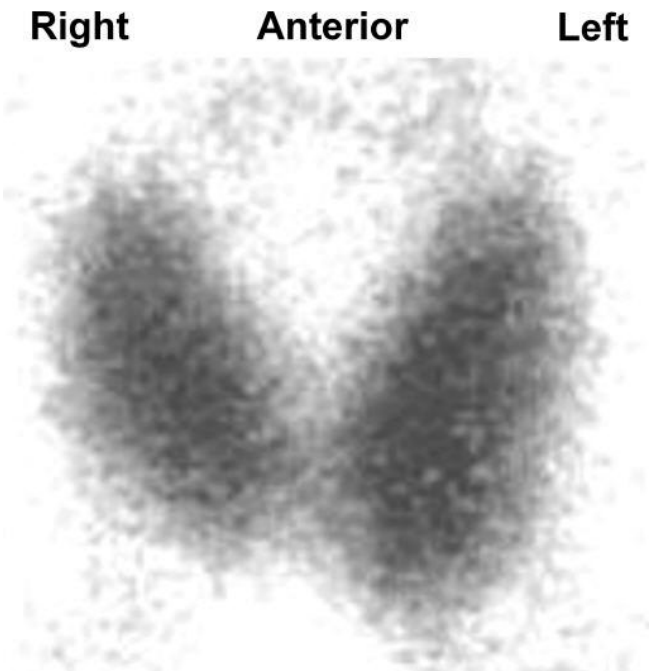

Figure 3: 99mTc-pertechnetate scentigraphy of the thyroid after lithium was discontinued showing diffuse uptake; 24 hour RAI uptake with 15 µci of 131I was 31.2%.