LITHIUM INDUCED HYPERTHYROIDISM: CASE REPORT

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ABSTRACT
Introduction: Lithium is an integral drug used in the management of acute mania, unipolar and bipolar depression[1] and prophylaxis of bipolar disorders. Thyroid abnormalities associated with treatment lithium have been widely reported in medical literature to date.[2] These include goiter, hypothyroidism, hyperthyroidism and autoimmune thyroiditis. This current review explores the varied thyroid abnormalities frequently encountered among patients on lithium therapy and their management[3], since lithium is still a fundamental and widely drug used in psychiatry and Internal Medicine. Discussion: A 34-year-old woman with bipolar epilepsy disorder of 1-year duration was admitted for acute onset of amenorrhea, depression and polydipsia at admission, the patient was depressed and restless and loss of interest in surrounding. She is having the history of chronic liver disease. She had a coarse tremor in her upper limbs and brisk tendon reflexes but no ataxia. The patient had been prescribed a number of medications to treat recurrent auditory. These included multivitamins and B complex.). A urine toxicology screen was positive for benzodiazepine, as was expected (the patient had received lorazepam at another hospital). Conclusions: Thyroid function tests (serum thyroid stimulating hormone, free thyroid hormones-T3 and triiodothyronine [T3] concentrations and thyroid auto-antibodies) and More frequent assessment of thyroid function status and size during the course of therapy is recommended among middle aged females (≥50 years), patients with a family history of thyroid disease and those positive for thyroid auto-antibodies (anti-thyroid peroxidase and TSH receptor antibodies). By the withdrawal of the drug the condition of the patient was improved.

KEYWORDS: Thyroid abnormalities, Hyperthyroidism, Thyroid autoimmunity.

INTRODUCTION
Lithium remains an imperative drug in the long-term therapy of bipolar affective disorders.[1] It is also a proven prophylactic agent against relapses or recurrences of abnormal mood episodes in unipolar depression, hypomania and mania. It has also been shown to reduce suicidal risk and short term mortality.

Despite its proven efficaciousness, its use is associated with a myriad of clinical shortcomings. These include a narrow therapeutic window hence necessitating regular monitoring of therapeutic concentrations, cardiac toxicity, renal tubular dysfunction and endocrinopathies like thyroid abnormalities, hyperparathyroidism, transient hyperglycemia and nephrogenic diabetes insipidus.[4] This review will focus mainly on the effects of lithium on the normal physiological functioning of the thyroid gland and the frequently reported thyroid abnormalities associated with lithium therapy.[3]

General pharmacological features of lithium
Lithium is an alkali metal which is available mainly as lithium carbonate and citrate in immediate- and sustained-release preparations. It reaches peak plasma concentrations in 1–2 and 4–5 hours for the immediate and sustained release formulations respectively with an elimination half-life of 18–36 hours.[2] Its excretion is primarily via the kidneys and this renal clearance decreases with increasing age.[5]

The precise mechanisms by which lithium exerts its mood stabilizing effects[3] are still not very apparent. Its neurotropic effects are partially explained by the inhibitory effect on the N-methyl D-aspartate receptor that mediates cellular calcium influx and the suppression of activation of pro-apoptotic calcium dependent signaling pathways. Lithium also alters release of neurotransmitters and lessens glutaminergic activity.

Effects of lithium on the physiology of the thyroid gland
Multiple effects of lithium on the physiology[6] of the thyroid gland have been extensively studied. Lithium has been shown to be highly concentrated in thyroid cells. In-vivo and vitro studies in rats have shown that lithium reduces the uptake of radioiodine into rat thyroid and salivary glands. In humans, lithium administration may result in either reduced or increased thyroidal radioiodine uptake.[7] Several mechanisms are thought to explain this dual effect among humans. Low thyroid iodine uptake...
could be due to lithium induced iodide retention and competition for the iodide transport within the thyroid gland. An increase in the uptake could be mediated by the increased secretion of thyroid stimulating hormone (TSH) following lithium induced hypothyroidism.\(^\text{[8]}\)

Another key effect of lithium on thyroid gland functioning occurs at the level of hormone synthesis and release. Lithium inhibits synthesis and release of thyroid hormones. This inhibitory effect is due to the alteration in the tubulin polymerization and inhibition of the action of TSH on cyclic adenosine mono phosphate (c-AMP).\(^\text{[9]}\)

**Case Presentation**

A 34-year-old woman with bipolar epilepsy disorder of 1-year duration was admitted for acute onset of amenorrhea, depression and polydipsia on admission, the patient was depressed and restless and loss of interest in surrounding. Her skin was warm and sweaty, clinically dehydrated. She was tachycardic with a heart rate and 120/min. The rhythm was normal. She was afebrile... Her speech was pressured but not dysarthric. She had a coarse tremor in her upper limbs and brisk tendon reflexes but no ataxia.

The patient had been prescribed a number of medications to treat recurrent auditory. These included multivitamins and B complex. Her most recent medication was lithium 600 mg a day. According to her family, the patient’s ability to perform self-care had worsened over the previous year and she no longer took pride in her care. There was no family history of any psychiatric or thyroid illness. Patient’s thyroid function was normal 2 months prior, checked by her psychiatrist.

Her abnormal blood count (CBC) white blood cells (WBC) of 11.76 k/ul (3.5–11), hemoglobin 10.8 g/dl (11.5–15.5), platelet 88 k/ul (150–400) and alanine aminotransferase (ALT) 54 U/l (8–20). A urine toxicology screen was positive for benzodiazepine, as was expected (the patient had received lorazepam at another hospital). Electrolyte levels, renal function and urine analysis were within normal limits. Her thyroid function, on admission, was consistent with hyperthyroidism.

**DISCUSSION**

Lithium is concentrated in the thyroid gland three to four times more than plasma.\(^\text{[1]}\) An important action of lithium is to inhibit thyroid hormone release by altering tubulin polymerization and inhibiting action of thyroid-stimulating hormone on the cAMP pathway.\(^\text{[2]}\) The prevalence of goiter associated with lithium treatment ranges from 30 to 55%. Hypothyroidism is a well-known effect of lithium use, with prevalence ranging between 6 and 52% in various studies. Because of its ability to inhibit thyroid secretion, lithium has been used to treat hyperthyroidism.

The first case of thyrotoxicosis with lithium was reported in 1974. Because it is so rare, the incidence is difficult to estimate. Borchetta and Loviselli estimated the annual incidence to be 0.1% by observing women for the equivalent of 680 patient-years.\(^\text{[17]}\)\(^\text{[18]}\)\(^\text{[19]}\) Other studies estimate prevalence of thyrotoxicosis with lithium use to range between 1.7 and 1%.

Etiologies of hyperthyroidism in lithium-treated patients include diffuse goiter\(^\text{[15]}\), toxic multinodular goiter and ‘painless thyroiditis’. Lithium is also implicated in granulomatous thyroiditis. Lithium therapy has also been reported to induce antibody formation and autoimmunity in susceptible individuals. Wilson reported that 20% of lithium-treated patients had antithyroid antibodies compared with 7.5% without lithium treatment. He also described increased B-cell activity and decreased ratio of suppressor to cytotoxic T cells. Lithium induced or exacerbated auto-immune phenomenon is a likely reason of high prevalence of ‘silent thyroiditis’ in lithium-treated patients. Miller and Daniel\(^\text{[10]}\) calculated the odds of lithium exposure to be 4.7-fold higher in patients with thyroiditis. Hershman noted histopathological features of immunological phenomenon—lymphoid follicles with fibrosis in affected thyroid glands.\(^\text{[13]}\) However, other prospective studies failed to detect any difference in prevalence of autoimmunity, pre- and post-lithium treatment. In our patient, the thyroid antibodies, C-reactive protein (CRP) and sedimentation rate (ESR) were normal, suggesting that an inflammatory process was probably not the cause of the hyperthyroidism.

Jope R postulated that an ‘escape’ mechanism following hormonal release inhibition favored by lithium can explain the development of hyperthyroidism. Another potential mechanism is direct toxic effect of lithium on thyroid gland similar to amiodarone—non-inflammatory ultra-structural lysosomal and mitochondrial damage.\(^\text{[10]}\) We believe that thyroid destruction by a direct toxic effect led to thyroglobulin and thyroid hormone release in our patient. It also substantiates her thyroid problem as primary rather than factitious.

Given our patient’s altered mental status, we could not elicit a complete history of thyrotoxic symptoms. She was tachycardic, hyperreflexia and had hand tremor. She did not have a palpable goiter/thyroid nodule. She also did not have any ophthalmologic signs of thyroid disease such as exophthalmos. Ophthalmopathy has been described in lithium associated thyrotoxicosis in a couple of studies although they did not have accurate eye measurement. In our case, there may be an overlap of clinical picture with lithium toxicity.\(^\text{[7]}\)

Mossa P quantified precise scoring system for diagnosis of thyroid storm, based on clinical signs and symptoms—temperature, cardiovascular dysfunction, central nervous system effect and gastrointestinal symptoms. Our patient’s he criteria score was 40.\(^\text{[18]}\) In the setting of hyperthyroidism, a score between 25 and 44
suggests impending thyroid storm or severe thyrotoxicosis. We do not know how much her delirium and psychosis were contributed by lithium toxicity. Her blood lithium level was normal within 24 h and hemodialysis was continued to prevent rebound. Her confusion persisted for a week, correlating well with her thyroid function.

Interestingly, Adida M et al explained the relationship of lithium toxicity and thyrotoxicosis. His study postulates that thyrotoxicosis itself may contribute to development of lithium toxicity.[7] Seventy percent of filtered load of Lithium is reabsorbed in proximal tubule by sodium-hydrogen antiporter. It appears thyroid hormone can induce this cotransport mechanism, increasing lithium reabsorption and reducing fractional excretion of lithium.[8] He reported 10 hyperthyroid patients in whom fractional excretions of lithium were well below the normal controls.

We believe that in our patient, thyroid destruction, a direct toxic effect of lithium, led to thyroglobulin and thyroid hormone release.[9] High thyroid hormone level, in turn, may have potentiated lithium toxicity by above-mentioned mechanism and was primarily responsible for her mental status changes. In conclusion, lithium treatment for mania is well known to cause her mental status changes. In conclusion, lithium toxicity and thyrotoxicosis. His study postulates that it is important to keep this particular association in mind when caring for lithium-treated patients.

CONCLUSION
Lithium being an effective and pivotal drug in the management of affective disorders, concomitant thyroid dysfunction remains a pertinent clinical subject to address. Significant proportions of patients treated with lithium develop clinically hyperthyroidism. Lithium increases the risk of thyroid autoimmunity in susceptible individuals. Lithium induced hyperthyroidism is infrequent.

REFERENCE