Case report

Lithium-induced hyperthyroidism, thyrotoxicosis and mania: a case report

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Case

A 46-year-old woman with bipolar affective disorder of 4 year’s duration was admitted for acute onset of agitation, delirium and confusion. She had been placed in 4-point restraints during transfer from another hospital. On admission, the patient was agitated and restless and was verbally abusive to the hospital staff. Her skin was warm and sweaty, clinically dehydrated. She was tachycardic with a heart rate ranging between 97 and 120/min. The rhythm was normal. She had mild bilateral pedal edema and was afebrile. She was oriented to place but not to time or person. She appeared to be experiencing visual and auditory hallucinations and had racing thoughts. 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 (hears her dead fathers voice) and visual hallucinations (seeing angels) as well as paranoid delusions. These included ziprasidone and risperidone. 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) and liver panel admission results were: 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 (Table 1).

In addition, her lithium level was 3.6 mEq/l (0.6–1.2), which led us to diagnose lithium toxicity. In view of her neuropsychiatric symptoms, hemodialysis was initiated, which brought her lithium level down to 0.5 mEq/l within 24 h. Hemodialysis was continued for two additional days. To treat the hyperthyroidism, the patient received intravenous propylthiouracil and propranolol. Her mental status returned to normal after 1 week of treatment after which the propylthiouracil was stopped but propranolol was continued. Her thyroid function continued to be normal after discharge.

Discussion

Lithium is concentrated in the thyroid gland three to four times more than plasma.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.2 The prevalence of goiter associated with lithium treatment ranges from 30 to 55%.3–5 Hypothyroidism is a well-known effect of lithium use, with prevalence ranging between 6 and 52% in various studies.6 Because of its ability to inhibit thyroid secretion, lithium has been used to treat
hyperthyroidism. Given this goitrogenic effect of lithium, lithium-associated thyrotoxicosis is intriguing indeed.

The first case of thyrotoxicosis with lithium was reported in 1974.5 Because it is so rare, the incidence is difficult to estimate. Kirov et al.6 followed prospectively 33 females with bipolar affective disorder who were taking lithium—only one developed hyperthyroidism over 146 patient-years. Bocchetta and Loviselli7 estimated the annual incidence to be 0.1% by observing women for the equivalent of 680 patient-years. Other studies estimate prevalence of thyrotoxicosis with lithium use to range between 1.7 and 1%.8,9

Etiologies of hyperthyroidism in lithium-treated patients include diffuse goiter, toxic multinodular goiter and ‘painless thyroiditis’.10 Lithium therapy has also been reported to induce antibody formation and auto-immunity 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.12 Lithium induced or exacerbated auto-immune phenomenon is a likely reason of high prevalence of ‘silent thyroiditis’ in lithium-treated patients. Miller and Daniels10 calculated the odds of lithium exposure to be 4.7-fold higher in patients with thyroiditis. Kontozoglou and Mambo13 noted histopathological features of immunological phenomenon—lymphoid follicles with fibrosis in affected thyroid glands. However, other prospective studies failed to detect any difference in prevalence of autoimmunity, pre- and post-lithium treatment.14,15 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.

Scanelle16 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.17 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, hyperreflexic and had hand tremor. She did not have a palpable goiter/thyroid nodule. She also did not have any ophthalmic 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.18,19 In our case, there may be an overlap of clinical picture with lithium toxicity.

Burch and Wartofsky 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 Burch and Wartofsky criteria score was 40.20 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, Oakley et al.21 explained the relationship of lithium toxicity and thyrotoxicosis. His study postulates that thyrotoxicosis itself may contribute to development of lithium toxicity. 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. Owada et al.22 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. High thyroid hormone level, in turn, may have

Table 1 Thyroid function tests

<table>
<thead>
<tr>
<th>TSH (0.40–5.5 μU/ml)</th>
<th>Free T3 (1.6–4.4 pg/ml)</th>
<th>Free T4 (0.7–1.8 ng/dl)</th>
<th>Total T3 (94–170 ng/dl)</th>
<th>Total T4 (5.5–11 mcg/dl)</th>
<th>% T3 uptake (21–40.5%)</th>
<th>T3 uptake (10–26 mcg/dl)</th>
<th>Thyroglobulin (0.8–49 ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outside hospital</td>
<td>&lt;0.015</td>
<td>7.5</td>
<td>3.0</td>
<td>236</td>
<td>42</td>
<td>218</td>
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</tr>
<tr>
<td>Cleveland Clinic</td>
<td>0.016</td>
<td>1.8</td>
<td>1.8</td>
<td>12.4</td>
<td>35%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 week F/U</td>
<td>&lt;0.015</td>
<td></td>
<td></td>
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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 hypothyroidism but rarely leads to thyrotoxicosis. Thyrotoxicosis itself can precipitate or worsen mania. This case substantiates that it is important to keep this particular association in mind when caring for lithium-treated patients.

Conflict of interest: None declared.

References


