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Case Report

Lithium as an alternative option in thionamide-resistant Graves' disease

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Highlights

- Lithium is a potentially effective adjunct for thionamide-resistant Graves' disease.
- Lithium was shown to improve the efficacy of RAI and reduce the subsequent increase in thyroid hormone levels after RAI in our patient.
- A "start low and go slow" initiation of lithium may reduce the severity of its adverse effects.

Abstract. Conventional treatments for Graves' disease include thionamides, radioactive iodine therapy (RAI), and thyroidectomy. Occasionally, patients may develop resistance to thionamides and may require additional treatment. We present the case of an adolescent girl with thionamide-resistant Graves' disease who was successfully treated with lithium and subsequent RAI after stabilizing her thyroid hormone levels. Following RAI, the patient developed hypothyroidism, and thyroxine replacement therapy was initiated. This case highlights the potential of lithium as a safe and effective alternative for controlling hyperthyroidism in Graves' disease and its role in preparing patients for more definitive treatment.

Key words: Graves' disease, lithium, thionamide, thyroid

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Introduction

Graves' disease (GD) is the most common cause of thyrotoxicosis in children and adolescents (1). Conventional treatments for Graves' disease include thionamides, radioactive iodine therapy (RAI), and thyroidectomy. Adjunctive therapies, including beta-blockers, corticosteroids, inorganic iodides (e.g. potassium iodide, Lugol's solution, iopanoic acid), and cholestyramine, have been reported to offer more rapid control of hyperthyroidism (2–4). Despite these interventions, some patients may require additional treatment to achieve a euthyroid state. Here, we present a case of Graves' disease relapse in a patient who was resistant to high doses of thionamides but responded effectively to lithium before undergoing RAI.

Case Report

A 15-yr-old girl presented to a general practitioner with increased appetite and goiter. The patient was diagnosed with thyrotoxicosis and received carbimazole (CBZ) for 18 months. She was in remission but developed her first relapse of hyperthyroidism 6 months after stopping treatment, presenting with an enlarging goiter, palpitations, and tremors. The patient resumed CBZ (25 mg/d) and was referred to our institution.

Graves' disease was diagnosed based on elevated free T_4, suppressed TSH levels, and positivity for anti-TSH receptor, anti-thyroglobulin, and anti-thyroid peroxidase antibodies (**Table 1**). Neck ultrasonography revealed a diffuse goiter with heterogeneous parenchymal echogenicity and increased glandular vascularity. Despite gradually increasing the dosage of CBZ to 40 mg daily and adding oral propranolol (10 mg three times daily), the patient remained thyrotoxic, both clinically and biochemically (**Fig. 1**).

Poor drug compliance was initially suspected as a possible explanation for the suboptimal response to CBZ. However, despite hospitalization for direct supervision of drug intake, the patient's serum free T_4 levels did not improve, and the hospital staff confirmed the patient's adherence to the prescribed drug regimen. As the patient had previously responded to CBZ, genetic factors were less likely to be the underlying cause of thionamide resistance. Drug interactions were excluded because the patient was not consuming any medications other than propranolol.

The patient's hyperthyroidism remained resistant to CBZ, prompting the consideration of alternative treatment options. Both RAI and thyroidectomy are definitive treatments for refractory Graves' disease. The patient and her family opted for RAI because of concerns regarding the anesthetic risk and surgical scarring associated with thyroidectomy. To stabilize the patient's thyroid hormone levels before RAI, oral lithium carbonate was initiated, as lithium carbonate is known to be an effective adjunct for RAI, and other options, such as Lugol's solution, may affect RAI administration. Following initiation of lithium carbonate at a dose of 400 mg twice daily, the patient reported mild polydipsia and polyuria, with urine output up to 1.8 L per m^2 per day, but was clinically not dehydrated. Her serum sodium level was 137 mmol/L (reference range,

Table 1. Laboratory findings of the patient during the first relapse of Graves' disease

Parameters	Results	Reference range
Thyroid hormone		
TSH (mIU/L)	<0.01	0.67–3.72
Free T_4 (pmol/L)	35.6	8.5–15.7
Thyroid autoantibodies		
Anti-TSH receptor antibody (IU/L)	12.3	<1
Anti-thyroglobulin antibody (IU/mL)	568.8	<100
Anti-thyroid peroxidase antibody (IU/mL)	350	<50
Blood cell count		
White cell count ($\times 10^9$ per L)	6.7	3.9–10.7
Neutrophil ($\times 10^9$ per L)	3.9	2.1–7.8
Renal function test		
Serum sodium (mmol/L)	138	138–145
Serum potassium (mmol/L)	3.9	3.4–4.7
Serum urea (mmol/L)	5	2.6–6.8
Serum creatinine (μmol/L)	50	50–71
Liver function test		
Total bilirubin (μmol/L)	8	2–12
ALP (U/L)	161	62–280
ALT (U/L)	31	8–24

ALP, alkaline phosphatase; ALT, alanine aminotransferase.

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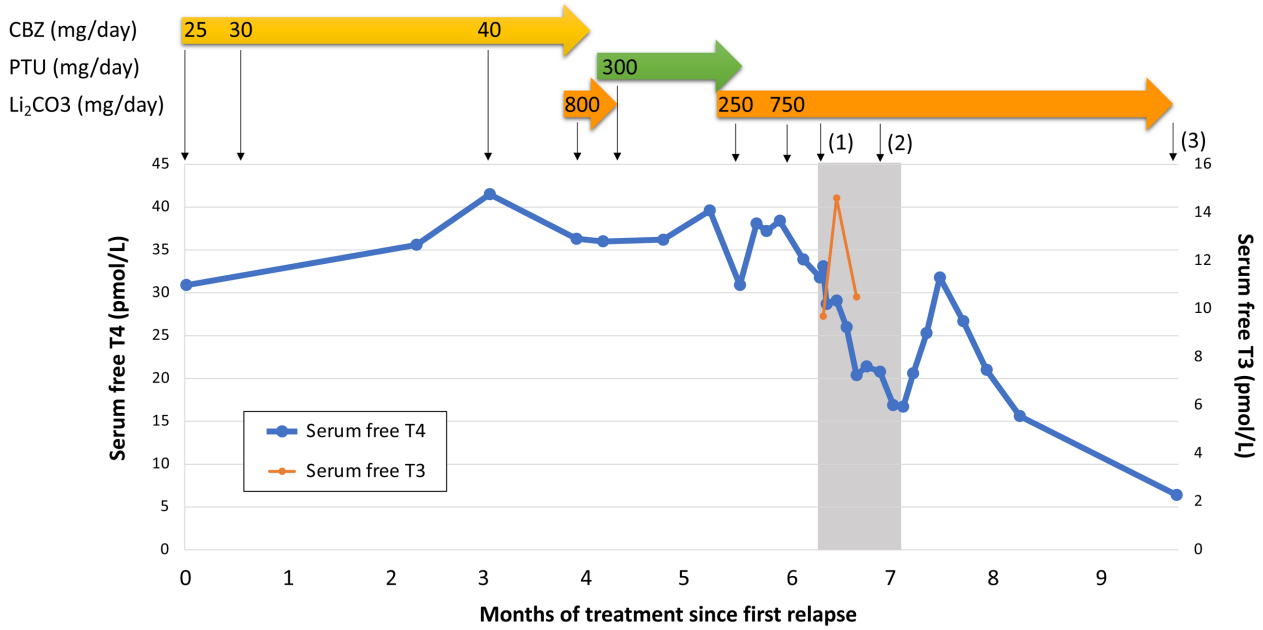

Fig. 1. An overview of the clinical course of the patient. Changes in antithyroid drug dosages and choices are indicated by arrows. The dark gray area indicates the duration of hospitalization for worsening thyroid symptoms until RAI administration. At time point 1, intravenous hydrocortisone, oral methimazole, Lugol's solution, and oral propranolol were added for two days. At time point 2, 10 mCi of RAI was administered. At time point 3, lithium carbonate was discontinued, and thyroxine replacement was initiated. RAI, radioactive iodine therapy; CBZ, carbimazole; PTU, propylthiouracil; Li_2CO3, lithium carbonate.

138–145 mmol/L), serum urea level was 5.2 mmol/L (reference range, 2.6–6.8 mmol/L), and serum creatinine level was 47 μmol/L (reference range, 50–71 μmol/L). Trough serum lithium level was normal at 0.26 mmol/L (reference range, 0.60–1.20 mmol/L). Serum osmolality was 282 mOsm/kg (reference range, 275–295 mOsm/kg) and paired urine osmolality was 341 mOsm/kg. Owing to concerns about the potentially evolving nephrogenic diabetes insipidus related to lithium use, lithium carbonate was discontinued nine days after its initiation and replaced with propylthiouracil (PTU) at a dosage of 100 mg three times daily. However, her serum free T_4 level remained elevated at 39.6 pmol/L one month after the initiation of PTU. Subsequently, lithium carbonate was reintroduced, starting at a lower dose (125 mg twice daily) and gradually increasing to 250 mg thrice daily for three weeks. During the second trial, the patient did not experience polydipsia or polyuria and her serum sodium, urea, and creatinine levels remained normal. Her serum free T_4 level decreased slightly to 31.8 pmol/L after one week.

Approximately 10 days after receiving this dose of lithium, the patient developed an episode of pharyngitis with a sore throat, fever, and palpitations. The evaluation revealed sinus tachycardia with a heart rate of up to 146 beats per minute and a normal blood pressure of 118/86 mmHg. Her serum free triiodothyronine (fT3) level was elevated up to 14.6 pmol/L (reference range, 3.4–6.5 pmol/L), and her free T_4 level was 33.1 pmol/L. The patient was hospitalized in the general ward for close monitoring. In addition to oral lithium carbonate, intravenous hydrocortisone (100 mg, three times daily), oral methimazole (20 mg, four times daily), Lugol's solution (2 drops, three times daily), and oral propranolol (10 mg, three times daily) were added as adjuncts due to an initial concern regarding thyroid storm. Additional test results over the subsequent days showed no significant rebound in her thyroid hormone levels; further, the patient did not exhibit other characteristics of a thyroid storm, such as altered sensorium or diarrhea. Therefore, thyroid storm treatments were discontinued two days later and oral lithium carbonate was continued at the same dose. Gradual improvement in her symptoms was observed, and her heart rate normalized. After two weeks of hospitalization, the serum free T_4 level decreased to 20.8 pmol/L. Subsequently, RAI (10 mCi) was administered and the patient remained stable after receiving RAI, without any evidence of a thyrotoxic crisis. A transient rise in the serum free T_4 level was noted, up to 31.8 pmol/L two weeks after RAI, but she remained asymptomatic. Serum free T_4 levels gradually normalized 2 months after RAI. Another repeated measurement three months after RAI showed a low free T_4 level of 6.4 pmol/L, which was compatible with post-RAI hypothyroidism. Lithium carbonate was discontinued, and thyroxine replacement was initiated. The patient remained euthyroid for four months after RAI.

Ethical statement

This study was approved by the New Territories

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West Cluster Research Ethics Committee (NTWC/REC/22009). Informed consent was obtained from the parents.

Discussion

Thionamides, such as methimazole, CBZ, and PTU, are the mainstay of treatment for most patients with Graves' disease. They prevent the iodination of tyrosine residues in thyroglobulin by thyroid peroxidase, thereby inhibiting thyroid hormone synthesis (5). Although most patients with Graves' disease respond to thionamides, thionamide resistance has been reported (6–11). Resistance to two different thionamides was evident in our patient. Escalating the thionamide dose beyond the standard range may help control hyperthyroidism (7). However, this strategy may be associated with a higher risk of adverse effects, including allergies, skin rashes, and agranulocytosis.

Possible mechanisms of thionamide resistance include drug malabsorption, rapid drug metabolism, anti-drug antibodies, and impaired intrathyroidal drug accumulation or action (6). In this case, the absence of gastrointestinal symptoms suggested that drug malabsorption was unlikely. Measurements of thionamide levels and anti-drug antibodies might be useful but are not widely available in local laboratories. A perchlorate discharge test may be performed to confirm resistance to antithyroid drugs, with a negative result indicating drug resistance due to inadequate blockade of iodide organification, and a positive result indicating a certain extent of iodide organification and potential lack of compliance (7). Excess iodine reduces the absorption and oxidation of thionamide in the thyroid gland and may thus alter the response of the thyroid gland to thionamide (12). Excess iodine can be diagnosed by measuring urinary iodine excretion. However, this test is not readily available, and there is no relevant drug or food history suggestive of excess iodine intake.

Different approaches, including RAI and thyroidectomy, have been used to manage thionamide-resistant thyrotoxicosis (13). However, it is prudent to control hyperthyroidism before definitive treatment to reduce the risk of a thyrotoxic crisis. Beta-blockers and corticosteroids may alleviate symptoms or restore euthyroidism more rapidly; however, they do not treat the underlying causes of thyrotoxicosis. Inorganic iodides such as potassium iodide, Lugol's solution, and iopanoic acid have been used as adjunct treatments in patients with Graves' disease, especially in those scheduled for thyroidectomy (14). The use of iodide leads to the loading of intrathyroidal iodine and a subsequent decrease in thyroid hormone synthesis, known as the Wolff–Chaikoff effect (10). Although iodide may be effective in suppressing thyroid hormone levels in the short term, relapse of thyrotoxicosis eventually occurs because of the escape phenomenon (10). Moreover, the prolonged use of iodide renders RAI unfeasible for at least a few weeks (15). Cholestyramine is a bile acid sequestrant that binds to thyroid hormones in the gastrointestinal tract, preventing them from being reabsorbed by the enterohepatic circulation (11). It has been shown to cause a more rapid decline in serum thyroid hormone levels when added to antithyroid drugs in patients with Graves' disease (3, 4), but its long-term efficacy remains unclear.

Lithium, a drug used to treat the bipolar affective disorder, has shown a favorable response in thyrotoxicosis. Lithium is concentrated in thyroid follicular cells and its effects on thyroid hormone secretion are similar to those of iodide (16). It inhibits iodine uptake, interferes with tyrosine iodination, changes thyroglobulin structure, and interferes with iodotyrosine synthesis (17). Lithium blocks the release of thyroid hormones from thyroglobulin, which, in turn, inhibits adenylate cyclase and prevents the activation of thyroid hormone receptors by TSH or thyroid-stimulating antibodies (16). Lithium has been used as a standalone treatment or in combination with other antithyroid drugs, such as methimazole (18) and iodide (19). Its efficacy as a standalone treatment for Graves' disease was demonstrated in a study in which lithium was administered to 11 patients with Graves' disease who relapsed after conventional treatment. Eight patients became clinically euthyroid within two weeks after the start of lithium therapy, and their thyroid hormone levels decreased by 35% (20).

Lithium has also been used as an effective adjunct to RAI (21, 22). Lithium has been shown to minimize the increase in thyroid hormone levels after RAI administration by preventing the release of preformed thyroid hormones from the thyroid gland, without affecting thyroidal radioactive iodine uptake. A randomized controlled trial demonstrated that adjunct lithium administration at the time of RAI prevented the increase in thyroid hormone levels associated with antithyroid drug withdrawal and RAI administration (22). Furthermore, lithium improves the efficacy of RAI by prolonging radioiodine retention in the thyroid, leading to an increase in the total radiation dose delivered to the thyroid (23). A recent meta-analysis including six randomized controlled trials showed a higher cure rate for hyperthyroidism when lithium was used as an adjunct to RAI. In the subgroup analysis, the addition of lithium to RAI for Graves' disease was associated with a 15% higher cure rate than RAI alone (24).

Following the gradual escalation of the lithium carbonate dose to 750 mg/d during the patient's second trial, her thyroid hormone levels decreased significantly. This dose falls within the reported effective range of lithium dosages, which typically ranges from 600 to 1,000 mg/d. Notably, the exacerbation of the patient's symptoms during a subsequent febrile episode was not associated with a concomitant rebound in free T_4 levels. In retrospect, this observation suggests that her symptoms may have been due to the natural course of her acute illness, occurring against the background of her long-standing thyrotoxic state, rather than a genuine exacerbation of her thyrotoxicosis. While the two-day short course of adjunctive treatments may have

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contributed to the initial improvement of thyrotoxicosis during the hospitalization period, the subsequent sustained fall in free T_4 levels over the next two weeks, following cessation of these adjuncts demonstrated the therapeutic effect of lithium. This effect not only made the subsequent administration of RAI safer but also enhanced its efficacy.

Potential adverse effects of lithium include neurological disturbances, gastrointestinal upset, cardiac arrhythmia, hypercalcemia, and hypermagnesemia (16). Nephrogenic diabetes insipidus may result from interference with the action of antidiuretic hormone, particularly in cases of long-term treatment or lithium toxicity. Despite the initial polydipsia and polyuria, our patient tolerated the slower reintroduction of a lower dose of lithium. Therefore, a "start low and go slow" initiation of lithium is preferable. The therapeutic serum lithium concentration ranges between 0.6 and 1.2 mmol/L, with toxicity occurring at concentrations greater than 1.5 mmol/L (16). Since lithium has a narrow therapeutic index, serum lithium levels should be monitored even in the absence of risk factors for toxicity (16). Interestingly, our patient's serum lithium levels during treatment were below the reference therapeutic range, ranging from 0.26 to 0.65 mmol/L. A lower therapeutic level of lithium may be adequate to suppress hyperthyroidism without causing toxicity (25).

In conclusion, lithium is an effective adjunct for thionamide-resistant Graves' disease. Our case demonstrates its possible role, when used in conjunction with RAI, to improve the efficacy of RAI and reduce subsequent increases in thyroid hormone levels. A "start low and go slow" initiation and close monitoring of serum lithium levels may reduce the severity of its adverse effects.

Conflict of interests: The authors declare no conflicts of interest.

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