Hypothyroidism Revealed During General Anesthesia in a Patient With Treatment-Resistant Depression: A Case Report

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General anesthesia in patients with undiagnosed hypothyroidism can lead to neurological, pulmonary, and cardiovascular complications. We report a case of hypothyroidism in a patient with treatment-resistant depression detected intraoperatively based on multiple clinical findings. A 49-year-old woman was scheduled for orthognathic surgery for mandibular prognathism. She had depression since the age of 36 and was taking multiple psychotropic medications. After induction, she had persistent hypotension, bradycardia, low bispectral index, and hypothermia that were resistant to treatment. After ruling out common causes and reducing the anesthetic agents, blood tests were performed intraoperatively to examine thyroid function which revealed hypothyroidism. No delayed recovery or postoperative abnormalities were observed. Lithium carbonate was identified as the most likely cause of hypothyroidism by an endocrinologist. Given the overlap in signs and symptoms, hypothyroidism may be overlooked in a patient with depression. The possibility of hypothyroidism should be considered especially noted in patients taking lithium carbonate. Furthermore, suspicion of hypothyroidism based on clinical findings during anesthesia may prompt the need for further evaluation.

Key Words: General anesthesia; Depression; Hypothyroidism; Lithium carbonate.

Anesthesia and surgery in patients with undiagnosed or untreated hypothyroidism may lead to complications such as delayed anesthetic recovery, respiratory insufficiency, hyponatremia, congestive heart failure, and even coma.[1] Additionally, patients with depression can have signs and symptoms that overlap with hypothyroidism, making its detection difficult. Overall, 60% to 70% of patients with major depressive disorder (MDD) experience either a response without complete remission or no response at all despite adequate treatment[2]; this condition is referred to as treatment-resistant depression (TRD). In patients with TRD, similarities between the signs and symptoms of depression and hypothyroidism, such as depressed mood or easy fatigue, can lead to delayed detection of hypothyroidism.

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We report a case of a patient with TRD who was determined to be in a hypothyroid state intraoperatively based on biological reactions after the induction of general anesthesia. The patient provided written informed consent for the publication of this report.

CASE PRESENTATION

A 49-year-old woman (height, 161.3 cm; weight, 44.6 kg; and body mass index [BMI], 16.1 kg/m^2) was scheduled to undergo orthognathic surgery (bilateral sagittal split osteotomy) under general anesthesia for skeletal mandibular prognathism. The patient was diagnosed with MDD at the age of 36 years and was hospitalized for approximately 2 months at the age of 40 years. Thereafter, she was treated as an outpatient with biperiden (2 mg), lurasidone (60 mg), mirtazapine (15 mg), quetiapine (300 mg), ramelteon (8 mg), flunitrazepam (2 mg), and lithium carbonate (500 mg). Despite taking multiple medications, the patient continued to have a depressed mood and decreased motivation, was unable to work, and performed only minimal basic activities

Table 1. Preoperative Blood Testing.

	Value	*Normal range*
White blood cell count, $10^3/\mu L$	6.1	3.3–8.6
Red blood cell count, $10^6/\mu L$	3.73↓	3.86–4.92
Hemoglobin, g/dL	12.2	11.6–14.8
Hematocrit, %	36.5	35.1–44.4
Blood platelet, $10^4/\mu L$	241	158–348
Total protein, g/dL	6.6	6.6–8.1
Serum albumin, g/dL	4.3	4.1–5.1
Aspartate aminotransferase, IU/L	71↑	13–30
Alanine aminotransferase, IU/L	99↑	7–23
Gamma-glutamyl transferase, IU/L	37↑	9–32
Blood urea nitrogen, mg/dL	5	8–20
Creatinine, mg/dL	0.82↑	0.46–0.79
Estimated glomerular filtration rate, mL/min	58.3↓	
Creatine phosphokinase, IU/L	101	41–153
Total cholesterol, mg/dL	250↑	142–248

of daily living. Her mother also suffered from depression. Her attending psychiatrist suggested that although oral surgery under general anesthesia was possible, it would be better to avoid interrupting her regular medications. There was no specific comment on thyroid function from the attending psychiatrist.

Given the risk of coronavirus and the associated restrictions on surgical cases at the time, the patient's surgery was postponed for 3 months. Urine tests and blood tests including complete blood count, serum chemistry, coagulation ability, blood glucose level analyses performed 22 days before surgery revealed hepatic and renal dysfunction and a marginal increase in total cholesterol level (Table 1). Notably, no preoperative thyroid function tests were conducted. At the time of preoperative examination, the patient's heart rate (HR) was 73 bpm, blood pressure was 99/61 mm Hg, SpO_2 was 98%, and axillary temperature was 36.3°C.

All regular medications were continued orally until the morning of the surgery. The axillary temperature before entering the operation room on the day of surgery was 36.5°C. Before anesthesia induction, the patient's HR was 51 bpm, blood pressure was 102/64 mm Hg, and SpO_2 was 98%. General anesthesia was induced with 100 μg of fentanyl, continuous propofol administration using a target-controlled infusion (TCI) pump (initial TCI rate set at 5 μg/mL), 0.15 μg/kg/min infusion of remifentanil, and 30 mg bolus of rocuronium. For specific propofol induction doses, a bolus dose of 52 mg was given in 15 seconds, followed by continuous infusion at 306 μg/kg/min. The continuous infusion rate was then automatically changed to maintain the target blood concentration at 5 μg/mL. General anesthesia was induced with the patient falling asleep when the effect site concentration of propofol was 2.1 μg/mL. Despite lowering the TCI of propofol to 3.8 μg/mL after nasal intubation, her systolic blood pressure decreased to below 80 mm Hg. Ephedrine boluses (total, 12 mg) were administered without response. While maintaining anesthesia with a TCI of 2.8 μg/mL of propofol and a 0.1 μg/kg/min continuous infusion of remifentanil, administration of 50 to 100 μg of phenylephrine increased the systolic pressure to 80 to 90 mm Hg. However, the duration of the phenylephrine was only a few minutes, much less than the 5 to 10 minutes commonly expected, and the patient's blood pressure decreased to 55/30 mm Hg at the lowest reading. No erythema, skin rashes, or respiratory abnormalities, which can be considered as signs or symptoms of anaphylaxis, were seen. It was also visually confirmed that there were no overdoses of propofol or remifentanil due to infusion pump malfunctions. The propofol TCI was lowered to 2.6 μg/mL, continuous administration of phenylephrine at 0.15 μg/kg/min was started, and 500 mL of hydroxyethyl starch was rapidly administered, enabling maintenance of her systolic pressure above 80 mm Hg approximately 90 minutes after the induction.

While maintaining general anesthesia with as small a target blood concentration as 2.6 μg/mL of propofol (the recommended concentration is 3.1–3.6 μg/mL, calculated from 1.0–1.5 μg/mL above the effect site concentration upon induction) and 0.1 μg/kg/min of remifentanil, the bispectral index (BIS) was low (between 22 and 33). Before the start of surgery (1 hour 7 minutes after the start of anesthesia), infiltration anesthesia with 5.4 mL of 3% prilocaine (total, 108 mg) containing felypressin 0.03 IU/mL (total, 0.108 IU) was used for local anesthesia. After the start of surgery, the BIS remained between 32 and 40 with surgical stimulation and between 21 and 28 without. The patient had persistent sinus bradycardia (40–44 bpm). Her bladder temperature, which was 36°C at the start of the measurement (32 minutes after the start of anesthesia), decreased to 35.2°C within 50 minutes (1 hour and 23 minutes after the start of anesthesia) despite using a warming blanket. Considering the possibility of a malfunctioning thermometer, her rectal temperature was also measured, which was also 35.3°C, and did not deviate from her bladder temperature (1 hour and 30 minutes after the start of anesthesia).

Given the lack of response to vasopressors and clinical signs such as dehydration, drug overdose, monitoring equipment failure, and anaphylaxis, we opted to obtain a blood test to assess for hypothyroidism (1 hour and 40 minutes after the start of anesthesia). The results showed that the thyroid-stimulating hormone level was 47.23 μIU/mL (reference value: 0.34–4.22 μIU/mL), free thyroxine (FT4) level was less than 0.25 ng/dL (reference value: 0.77–1.59 ng/dL), and free triiodothyronine (FT3) level was 1.07 ng/mL (reference value: 2.24–3.5 ng/mL). By the time the blood analysis was completed and the results received, 100 minutes had passed since the start of surgery (2 hours and 54 minutes after the start of anesthesia). The left ramus and

body of the mandible had already been split and the patient's blood pressure was generally stable due to the continuous infusion of phenylephrine, so the surgery continued. Anesthesia was maintained with the lowest possible doses of propofol (TCI of 2.5–2.8 μg/mL) and remifentanil (0.1 μg/kg/min); no additional fentanyl doses were administered. Both bladder and rectal temperatures increased gradually to 36.0°C with the continuous use of a warm-air heating device. Blood pressure during maintenance was relatively stable (85–100/45–50 mm Hg), and the BIS remained at 30 to 40. Blood glucose levels were measured 4 times intraoperatively and ranged from 80 to 112 mg/dL.

The propofol, remifentanil, and phenylephrine infusions were discontinued at the same time once surgery was complete, and 100 mg of sugammadex was administered. Twenty minutes after stopping the anesthetic agents, the patient's eyes opened, and she exhibited return of a cough reflex. The patient was extubated after sufficient spontaneous respiration and a stable respiratory rate was confirmed. The total operation time was 3 hours 33 minutes, anesthesia time was 5 hours 17 minutes, infusion volume was 1600 mL, blood loss was 200 mL, and urine volume was 600 mL. Her vital signs before leaving the operation room were as follows: HR, 56 bpm; blood pressure, 130/67 mm Hg; and bladder temperature, 36.3°C.

On the first postoperative day, a diagnosis of hypothyroidism was confirmed by an endocrinologist, and the patient was started on 50 μg of levothyroxine and 15 mg of hydrocortisone. Hashimoto disease was ruled out based on the results of the anti-thyroid peroxidase antibody (reference value: 0–5.6 IU/mL) and anti-thyroglobulin antibody (reference value: 0–4.11 IU/mL) levels being less than the detection threshold. Thus, drug-induced hypothyroidism due to lithium carbonate was suspected based on her medical history.

Discussions between the endocrinologist and attending psychiatrist revealed 1) that the lithium was started 1 year and 3 months prior to her visit to our hospital and that 500 mg per day had been taken for the past 8 months; 2) thyroid function tests had been performed every 6 months at the attending psychiatrist's hospital; and 3) thyroid function tests had been performed 3 months before the preoperative examination at our department during which her euthyroid state was observed. After consultation with the endocrinologist and psychiatrist in charge, her daily dose of lithium carbonate was reduced. However, the drug was not discontinued due to concerns about worsening her psychiatric symptoms.

DISCUSSION

We report a case wherein hypotension, low BIS, and hypothermia were observed during general anesthesia in a patient with TRD, subsequently revealing thyroid gland hypofunction attributed to the patient's daily lithium carbonate.

Factors leading to low BIS values during general anesthesia include hypotension, anesthetic overdose, muscle relaxant effects, cerebral ischemia, severe hypoxia, and hypothermia. As for muscle relaxants, a previous study has reported that muscle relaxants alone can decrease BIS.[3] Further, a 1°C reduction in body temperature can reportedly result in a 1.1 to 1.8 decrease in BIS.[4,5] Considering these reports, it is unlikely that the low BIS noted in our patient was caused by hypothermia alone. In addition, cerebral ischemia and severe hypoxia were ruled out based on the perioperative course. Therefore, it is likely the low BIS was mainly due to an overdose of anesthetics for this patient who had hypothyroidism.

Hypothermia during general anesthesia results from a combination of impaired thermoregulation by anesthetic agents and exposure to a cold environment.[6] In particular, thin patients are more susceptible to losing body heat to the outside environment. In this case, our patient had a BMI of 16.1 kg/m^2, which corresponded to moderate thinness according to the World Health Organization criteria.[7] However, we have not previously noted cases of central temperatures as low as nearly 35°C despite using a warming blanket in our hospital. Therefore, we decided to perform intraoperative thyroid function tests in consideration of the other possible factors contributing to hypothermia besides being thin.

Hypotension, bradycardia, low BIS, and hypothermia may often be singularly present during general anesthesia. However, the findings of this case suggest that when these signs occur simultaneously with hypothermia despite warming therapies and that the major reasons such as excessive anesthesia, hypoglycemia, and anaphylaxis can be ruled out, hypothyroidism should be considered and thyroid function tests performed as early as possible. We recognize that tests for thyroid function are not always available at all dental facilities.

Should other more common causes be ruled out and hypothyroidism strongly suspected during the intraoperative period, steps can be taken to mitigate risks. First, immediate countermeasures like reducing the dosing of anesthetic agents and anesthetic depth, including propofol or fentanyl, can be adopted to avoid overdose and delayed awakening which may result in patients with hypothyroidism. In addition, the surgeon could be advised to stop or shorten the surgery time if feasible depending on the stability of the patient. If the patient's condition is unstable, the option of discontinuing the procedure due to explicit indications of hypothyroidism can be considered. Second, preparations can be made for delayed awakening or prolonged apnea, such as the use of ventilators in recovery. Third, the possibility of myxedema coma, a serious

Table 2. Mechanisms and Examples of Drugs That Can Cause Hypothyroidism.[10]

Mechanism	*Drug examples*
Inhibits synthesis and secretion of thyroid hormones	Antithyroid drugs, iodine, iodine-containing drugs (amiodarone, radiographic contrast agents), lithium, interferon-α (molecular-targeted agents)
Decreases TSH secretion	Dopamine, dobutamine, glucocorticoids, somatostatin, amiodarone
Increases thyroxine-binding globulin binding	Estrogen, 5-fluorouracil, tamoxifen
Promotes thyroid hormone metabolism	Carbamazepine, phenytoin, phenobarbital, rifampicin
Decreases absorption of thyroid hormone	Calcium carbonate, ferrous sucralfate, cholestyramine, calcium polycarbophil, aluminum hydroxide gel

Abbreviation: TSH, thyroid-stimulating hormone.

complication of hypothyroidism, should also be considered. The incidence of myxedema coma is rare, but the fatality rate is high and reportedly approximates 29.5% in a large-scale database study in Japan.[8] Myxedema coma is also known to be induced by stress from general anesthesia and surgery.[9] Fourth, prompt collaboration with an endocrinologist allows for earlier postoperative initiation of appropriate treatment like starting the patient on hormone replacement therapy.

Recognize that even healthy patients may feel depressed after oral surgery due to postoperative pain and eating restrictions. Moreover, if the patient had been diagnosed with depression, the attending surgeon is likely to conclude that such a depressive mood is due to the aforementioned causes or the effects of depression. However, if the reason for a depressed mood is attributed to hypothyroidism, the detection of hypothyroidism based on intraoperative signs may contribute to helping the patient avoid or shorten the duration of exacerbations of depressed mood due to hypothyroidism.

Hypothyroidism is also known to be induced by several medications (Table 2).[10,11] Lithium is one of the effective drugs used in patients with TRD to enhance the effect of antidepressant drugs.[12,13] However, lithium carbonate has the side effect of inhibiting thyroid hormone release and is one of the causative agents of drug-induced hypothyroidism. A retrospective analysis reported that the risk of hypothyroidism is increased by using lithium (hazard ratio, 2.31; 95% confidence interval, 2.05–2.60; $P < .0001$).[14] The prevalence of overt hypothyroidism in patients taking lithium carbonate is reported to be approximately 8% to 30%.[15,16]

If signs and symptoms of hypothyroidism occur as a side effect of lithium use, they may not be recognized in patients with TRD as findings attributed to hypothyroidism, such as depression or easy fatigue, may overlap with those of TRD. In this case, our patient's attending psychiatrist had judged that the patient's depressed mood and low motivation were caused by depression because 1) thyroid function tests were performed regularly and had always confirmed a euthyroid state, 2) the symptoms had continued over a long period, and 3) there were no subjective changes since the previous thyroid function tests. Information from the psychiatrist regarding thyroid function was not provided before surgery, and thyroid function tests were not performed during preoperative screening.

Most dental anesthesiologists do not perform thyroid function tests on patients taking lithium who have no obvious signs or symptoms of hypothyroidism. Previous reports have revealed that women during the first several years of lithium treatment and women aged 40 to 59 years who take lithium are at the highest risk of developing lithium-derived hypothyroidism.[17,18] Interestingly, our patient fulfilled all these criteria. Therefore, particular attention should be paid to patients with TRD taking lithium who fulfill the above-mentioned conditions and confirmation of the patient's thyroid status should be considered before surgery regardless of changes in signs or symptoms.

CONCLUSION

Because symptoms such as a depressed mood or fatigue can overlap between hypothyroidism and MDD/TRD, poorly optimized hypothyroidism may be overlooked. Thus, attention should be paid to perioperative thyroid function in depressed patients, especially when taking oral lithium carbonate. Clinical findings like hypotension, bradycardia, hypothermia, and low BIS during general anesthesia may lead to suspicion of hypothyroidism, especially if other common causes are ruled out. Further steps may include reducing anesthetic dosing to prevent inadvertent overdose or delayed awakening and prompt consultation with an endocrinologist.

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