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갑상선전절제술을 받은 환자에서 급성 Levothyroxine 중독 1예

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A Case of Massive Levothyroxine Intoxication in a Patient with Total Thyroidectomy

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The use of levothyroxine is increasingly widespread. There are relatively few reports of acute massive levothyroxine intoxication leading to emergencies in adults, and such intoxication has a wide range of presentations. Although thyroid gland activity is suppressed by thyroid stimulating hormone as a result of overdose exposure to exogenous thyroid hormone, it is unclear what symptoms are to be expected in acute levothyroxine intoxication in the absence of the thyroid gland. We report a case of massive acute levothyroxine intoxication in a patient with total thyroidectomy, along with observed changes over time in thyroid hormone levels and symptoms. To the best of our knowledge, this report presents the first description of acute massive levothyroxine intoxication in the absence of a thyroid gland. (Korean J Med 2015;88:313-317)

Keywords: Levothyroxine; Intoxication; Total thyroidectomy

INTRODUCTION

Levothyroxine is commonly prescribed, due to an increasing prevalence of thyroid disorders. Acute levothyroxine intoxication in adults has a wide range of toxicity presentations and a variable time to the onset of symptoms [1]. There are few reports of acute massive levothyroxine intoxication leading to emergencies in adults [2-5]. While thyroid gland activity is suppressed by thyroid stimulating hormone (TSH) with overdoses of exogenous thyroid hormone [6], it is unclear what symptoms and toxicity are expected with acute levothyroxine intoxication in the absence of a thyroid gland.

We report a case of massive acute levothyroxine intoxication in a patient with total thyroidectomy. We followed the serial

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changes in thyroid hormone levels and correlated these with the observed symptoms.

CASE REPORT

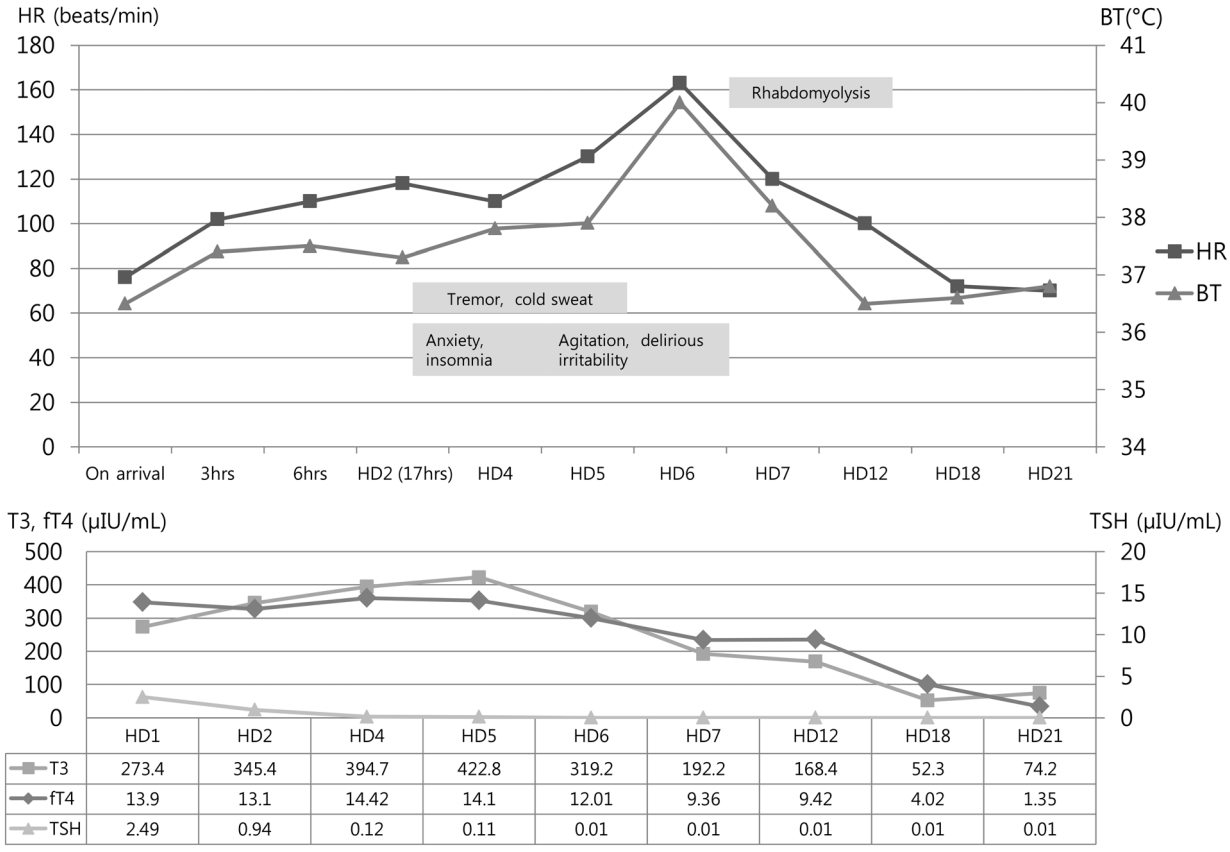
A 34-year-old woman was brought to the emergency room approximately four hours after a single ingestion of a large number of 0.1 mg levothyroxine tablets, in a suicide attempt. The family members had found the patient with an empty 200-tablet bottle of levothyroxine, and estimated that she had ingested all of them (total dose, 20 mg). She had been taking 0.15 mg levothyroxine daily since undergoing a total thyroidectomy and radioactive iodine therapy at another hospital three years previously, for papillary carcinoma. There were no distant metastases of the thyroid carcinoma.

The patient had a history of major depressive disorder. Twenty days before admission, she had taken approximately 20 antidepressant tablets with suicidal intention, and was treated at another hospital.

On admission, the patient was alert and in no distress. On initial evaluation, she was asymptomatic, and had stable vital signs as follows: blood pressure, 130/90 mmHg; heart rate, 76 beats/min; temperature, 36.5℃; respiratory rate, 16 breaths/min. Electrocardiography (ECG) revealed a normal sinus rhythm.

Laboratory blood work on admission showed the following values: hemoglobin, 11 g/L (reference range, 12-16); white cell count, 10,320/mL (4,000-8,000); platelet count, 360,000/mL (150,000-400,000); sodium, 139 mmol/L (136-146); potassium, 3.9 mmol/L (3.5-5.0); total calcium, 9.13 mg/dL (8.4-10.2); aspartate transaminase (AST), 13 U/L (5-40); alanine aminotransferase (ALT), 37 U/L (5-40); and alkaline phosphatase, 69 U/L (35-123). A thyroid function test revealed elevated serum levels of free T4 at 13.99 ng/dL (0.7-1.8) and T3 at 273 ng/dL (60-190), with a reference level of TSH at 2.49 μIU/mL (0.25-4). The thyroglobulin level was < 0.1 ng/mL (0-70) and thyroglobulin antibody was present at < 20 U/mL (0-60). Gastric lavage followed by administration of activated charcoal was performed as the initial therapy, and the patient was admitted to the intensive care unit, where she was monitored and rehydrated.

At three hours after admission, her heart rate had increased to 102 beats/min; it continued to exceed 100 beats/min, and increased to 118 beats/min on the second hospital day (17 hours after admission). Oral propranolol at a dose of 20 mg was initiated, and the dosage was titrated to 140 mg over the next three days, based on her heart rate. On hospital day (HD) 2, her serum free T4 was 13.1 ng/dL, T3 was 345.4 ng/dL, and TSH was 0.94 μIU/mL. Figure 1 illustrates the serial levels of free T4 and T3, together with heart rate and other symptoms. On HD 3, she complained of cold sweating, tremor, anxiety, and insomnia. On HD 4, the levels of free T4 and T3 were further increased to 14.42 ng/dL and 394.7 ng/dL, respectively, with suppressed TSH at 0.12 μIU/mL. On HD 5, her heart rate increased to 130 beats/min and ECG showed sinus tachycardia. Body temperature also increased to 38.0℃. The patient showed episodes of agitation, delirium, and irritability, which increased progressively. Rapid-acting benzodiazepine (lorazepam) treatment was initiated, but the symptoms persisted. Serum free T4 was 14.1 ng/dL, T3 was 422.8 ng/dL, and TSH was 0.11 μIU/mL. The next day (HD 6), her body temperature had increased to 40℃ and acetaminophen was prescribed. The patient's heart rate was also increased to 163 beats/min, with sinus tachycardia by ECG, and oral propranolol was changed to intravenous esmolol. The levels of creatine phosphokinase (CPK), myoglobin, AST, and ALT, which were normal at the time of admission, were increased to 10,500 U/L (26-200), 1,535 ng/mL (25-58), 225 U/L, and 80.5 U/L, respectively. We considered rhabdomyolysis, and the patient was treated with increasing hydration and urine alkalinization. Fortunately, the serum free T4 and T3 decreased to 12.01 ng/dL and 319.2 ng/dL, respectively, and the TSH suppression continued. On HD 7, the patient regained consciousness. Serum free T4 and T3 levels were further decreased to 9.36 ng/dL and 192.2 ng/dL, respectively. Over the next four days, intravenous esmolol was continued, and the patient's heart rate was reduced gradually to below 100 beats/min. On HD 9, her levels of CPK, myoglobin, AST, and ALT were 10,872 U/L, 534 ng/mL, 208 U/L, and 126 U/L, respectively. By HD 11, CPK, myoglobin, AST, and ALT had been gradually reduced to 2,770 U/L, 385 ng/mL, 71 U/L, and 94 U/L, respectively. On HD 12,



	HD1	HD2	HD4	HD5	HD6	HD7	HD12	HD18	HD21
T3	273.4	345.4	394.7	422.8	319.2	192.2	168.4	52.3	74.2
fT4	13.9	13.1	14.42	14.1	12.01	9.36	9.42	4.02	1.35
TSH	2.49	0.94	0.12	0.11	0.01	0.01	0.01	0.01	0.01

Figure 1. Free T4 (fT4), T3, and TSH level, heart rate (HR), body temperature (BT), and other symptoms were monitored over time. TSH, thyroid stimulating hormone; HD, hospital day.

intravenous esmolol was changed to oral propranolol at 160 mg, which was titrated over the next six days to 40 mg, based on the patient's heart rate. Her serum free T4 was 9.42 ng/dL, T3 was 168.4 ng/dL, and TSH was 0.01 μIU/mL. On HD 15, CPK, myoglobin, AST, and ALT levels were normalized to 183 U/L, 21 ng/mL, 20 U/L, and 31 U/L, respectively. The serum levels of free T4 and T3 were gradually reduced, and on HD 18, T4 was 4.02 ng/dL, T3 was 52.3 ng/dL, and TSH was 0.01 μIU/mL. The patient's heart rate stabilized at 72-82 beats/min, and she was clinically asymptomatic. On HD 21, free T4 and T3 were within the reference range at 1.35 ng/dL and 74.2 ng/dL, respectively, and TSH was still suppressed. On HD 26, 0.05 mg levothyroxine was initiated, and the dosage was titrated to 0.15 mg as a suppressive treatment for thyroid papillary carcinoma. The patient was transferred to a psychiatric unit for treatment of her depression, and discharged at HD 57.

DISCUSSION

The present case documents the serial changes in thyroid hormones and symptoms after acute massive levothyroxine intoxication in a patient with total thyroidectomy. To the best of our knowledge, this report presents the first description of acute massive levothyroxine intoxication in the absence of a thyroid gland.

The use of levothyroxine has increased. It is the preferred thyroid hormone preparation because of its low immunogenicity, approximately 7-day half-life, and easy to follow treatment regimen [1]. Levothyroxine intoxication may arise from intentional or accidental ingestion of excessive doses of the hormone. Acute levothyroxine intoxication has a wider range of toxicity presentations in adults than is seen in children, because the amount ingested is usually relatively larger, and its metabolism is slower

[2,3]. The long half-life of levothyroxine also represents an additional potential risk for intoxication [1].

An excess of thyroid hormones has important repercussions for all systems, in particular the cardiovascular and sympathetic nervous systems. Thus, sinus tachycardia or dysrhythmia and emotional lability are characteristic of thyrotoxicosis, and occur frequently. Hyperthermia can occur secondary to the thermogenic effects of thyroid hormone and of psychomotor agitation [7]. Although severe sequelae are rare, respiratory failure, myocardial infarction, hemiparesis, and coma have been reported. Severe agitation, muscle weakness, focal myocarditis, rhabdomyolysis, and delayed palmar desquamation have also been reported [8].

The onset time of symptoms is varied. Most patients can be asymptomatic immediately after ingestion of a levothyroxine overdose, or even hours or days after ingestion; the onset of symptoms can be delayed for as much as 6-11 days [2]. In our case, tachycardia occurred at 17 h after levothyroxine ingestion; adrenergic symptoms, including tremor, anxiety, and insomnia, appeared on the third HD, and psychiatric symptoms, including agitation and delirium, occurred on the fifth HD. The most severe symptoms, including rhabdomyolysis and extreme hyperthermia, reached a peak on the sixth HD. Thyroid hormone levels increased gradually, and began to decline at night on the sixth HD. At HD 21, we observed a decline in thyroid hormone to within the reference range.

On initial presentation, we expected a less severe course and a rapid recovery because the patient did not have a thyroid gland and there was no ongoing production of endogenous thyroid hormone (although thyroid gland activity is suppressed by TSH under conditions of exogenous thyroid hormone overdose). However, the patient experienced severe thyrotoxic episodes, and it took 21 days for the thyroid hormone levels to return to normal. There are some limitations to our ability to compare this case with other cases of patients with thyroid glands because of variability in ingested doses, duration, treatment, and individual characteristics. Nevertheless, our case was not milder in either clinical course or recovery time than previously reported cases of patients with functioning thyroids, who ingested comparable doses and were treated with supportive care [3,4]. Previous reports have demonstrated that clinical symptoms, onset time, and recovery period are not correlated with the initial plasma levels of T4 and T3 in massive accidental or intentional levothyroxine intoxication in adults. The severity of toxicity is not predicted by the dose ingested or by initial plasma levels of T4 and T3 [9]. This supports the hypothesis that levothyroxine toxicity may depend upon individual variation in peripheral hormone action on target organs, in addition to the level of exogenously ingested or endogenously secreted thyroid hormone. The cellular activities of thyroid hormone are mediated by T3, the active form. T3 binds to nuclear receptor proteins that function as transcription factors to regulate the expression of many genes. In our case, symptoms and signs were correlated with changes in T3 rather than in free T4. Individual differences in the action of type II deiodinase, which converts T4 to T3 or reverse T3, and which is inhibited by the peripheral conversion of T4 to the metabolically active T3, may also affect toxicity [1].

The most appropriate treatment after levothyroxine intoxication has not yet been established. Supportive therapy, including beta-blockers for tachycardia, acetaminophen for fever, and sedation for agitation, can be useful once symptoms appear. The potential benefits of administration of an antithyroid drug or glucocorticoid or of invasive procedures, such as charcoal hemoperfusion or plasmapheresis, must be balanced against the potential risks [2,8]. We did not treat the present case with antithyroid drugs because she had no thyroid gland, and we believed that an antithyroid drug would have no effect. In addition, we did not perform invasive procedures because our patient made a satisfactory clinical recovery with the aid of support and symptomatic management. However, there remains the possibility that invasive procedures such as charcoal hemoperfusion of plasmapheresis could have led to a more rapid recovery.

This case provides an illustration of the clinical course and consequences of massive levothyroxine intoxication in the absence of a thyroid gland. Under these conditions, the clinical course is similar to that observed in the presence of a thyroid gland and, thus, should be managed as carefully.

중심 단어: Levothyroxin; 중독; 갑상선전절제술

REFERENCES

1. Garber JR, Cobin RH, Gharib H, et al. Clinical practice guidelines for hypothyroidism in adults: consponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. Thyroid 2012;22:1200-1235.
2. Kreisner E, Lutzky M, Gross JL. Charcoal hemoperfusion in the treatment of levothyroxine intoxication. Thyroid 2010; 20:209-212.
3. Yoon SJ, Kim DM, Kim JU, et al. A case of thyroid storm due to thyrotoxicosis factitia. Yonsei Med J 2003;44:351-354.
4. Hack JB, Leviss JA, Nelson LS, Hoffman RS. Severe symptoms following a massive intentional L-thyroxine ingestion. Vet Hum Toxicol 1999;41:323-326.
5. Bhasin S, Wallace W, Lawrence JB, Lesch M. Sudden death associated with thyroid hormone abuse. Am J Med 1981;71: 887-890.
6. Nayak B, Burman K. Thyrotoxicosis and thyroid storm. Endocrinol Metab Clin North Am 2006;35:663-686.
7. Silva JE. The thermogenic effect of thyroid hormone and its clinical implications. Ann Intern Med 2003;139:205-213.
8. Gerard P, Malvaux P, De Visscher M. Accidental poisoning with thyroid extract treated by exchange transfusion. Arch Dis Child 1972;47:980-982.
9. Gorman RL, Chamberlain JM, Rose SR, Oderda GM. Massive levothyroxine overdose: high anxiety-low toxicity. Pediatrics 1988;82:666-669.