Case report

Hungry bone syndrome after thyroidectomy for thyroid storm

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Accepted 22 September 2019

SUMMARY

A 39-year-old man was admitted to our hospital with the diagnosis of thyroid storm due to Graves' disease. Near-total thyroidectomy was performed after 1 month's pharmacological treatment, and he presented with tetany next morning. Serum corrected calcium value was 5.7 mg/dL. Procollagen type 1 N-terminal propeptide increased considerably, while tartrate-resistant acid phosphatase 5b decreased. These changes indicated that bone formation exceeded bone resorption in reverse after thyroidectomy. Calcium gluconate was administered intravenously for 14 days, before the patient was discharged. Oral administration of calcium and active forms of vitamin D was continued for 4 months. Rapid skeletal uptake of calcium from blood caused severe and persistent hypocalcaemia, which is called hungry bone syndrome. When patients with Graves' disease have severe thyrotoxicosis, high serum alkaline phosphatase levels and low bone mineral densities, they are at high risk for hungry bone syndrome after thyroidectomy, and should be educated for the symptoms of hypocalcaemia.

BACKGROUND

Hypocalcaemia often occurs after thyroidectomy for thyrotoxicosis, but most of the cases are transient, and the patients are easily treated with oral administration of calcium preparations and vitamin D supplementation. On the other hand, in a few cases, persistent hypocalcaemia could occur. Although patients with Graves' disease are usually discharged within a week after thyroidectomy, when hypocalcaemia is uncontrollable with oral administration of calcium preparations and vitamin D, hospitalisation should be prolonged until hypocalcaemia is subsided.

Clinicians have to be prepared for this unusual condition, because quite a large amount of calcium gluconate will be necessary for intravenous infusion. Here we report a case of a thyroid storm caused by Graves' disease, which showed a severe and persistent hypocalcaemia after near-total thyroidectomy.

CASE PRESENTATION

A 39-year-old man began to experience excessive sweating 1 year before coming to our hospital, and exertional dyspnoea and palpitations appeared 2 months before. His weight loss was pointed out by people around him. The breathing difficulty had been getting worse for 3 weeks and he was referred to our hospital. One of his cousins had undergone

thyroidectomy due to Graves' disease. He had been smoking one pack of cigarettes per day for 20 years. He worked at a yakiniku restaurant for more than 10 years and he had been healthy previously.

On admission, he was 169.5 cm tall and weighed 54.6 kg, with a body mass index of 19.0. He was alert, his body temperature was 37.3°C, his blood pressure was 144/80 mm Hg, his pulse rate was irregular at 136/min, his oxygen saturation level was 97% while breathing ambient air. He was sweating a lot, his enlarged thyroid gland was apparently visible, jugular venous distention was prominent. In addition, the patient had diarrhoea, tremor of the fingers and oedema of the lower thighs.

Laboratory data were as follows: alkaline phosphatase (ALP) 811 IU/L (normal range 104 to 338 IU/L), serum creatinine 0.36 mg/dL (0.60 to 1.10 mg/dL), thyroid stimulating hormone (TSH) 0.000 µIU/mL (0.350 to 4.940 µIU/mL), free thyroxine 5.47 ng/dL (0.70 to 1.48 ng/dL), free triiodothyronine >30.0 pg/mL (1.71 to 3.71 pg/mL), TSH receptor antibody 158 IU/L (<1.0 IU/L). Corrected calcium level was 9.1 mg/dL (8.8 to 10.1 mg/dL). The authors would like to add the following: all of the calcium values in this case report were displayed as corrected calcium by Payne's formula, that is to say, in case of low albuminemia (<4.0 g/dL), corrected calcium (mg/dL) is calculated by total calcium (mg/dL) + 4.0 - albumin (g/dL).¹

Chest radiography showed right dominant pleural effusion and heart enlargement. ECG showed atrial fibrillation with heart rate 131/min. A thyroid ultrasound showed diffuse large goitre and colour flow doppler sonography showed increased blood flow in the thyroid (figure 1). There were no apparent parathyroid glands. His Burch and Wartofsky scores were 60 points, which was highly suggestive of a thyroid storm. The patient was diagnosed as thyroid storm due to Graves' disease. After initiation of hydrocortisone, thiamazole, potassium iodine and bisoprolol, the patient's tachycardia and symptoms of exertional dyspnoea gradually improved. The patient was discharged on the 14th day of hospitalisation.

OUTCOME AND FOLLOW-UP

As it was unlikely to improve his Graves' disease with drug treatment alone, thyroidectomy was indicated. Two weeks after the discharge, he was readmitted to surgical ward in our hospital. Before surgery, the surgeon explained the risk of hypocalcaemia and the possibility of tetany symptoms, and

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To cite: Kusuki K, Mizuno Y. *BMJ Case Rep* 2019;**12**:e231411. doi:10.1136/bcr-2019-231411

Figure 1 Thyroid ultrasonography. Right lobe, 40 (wide) ×38 (depth) ×81 (length) mm; left lobe, 30×39×81 mm; depth of isthmus, 12 mm. Colour flow Doppler sonography showed moderate intraparenchymal vascularity.

in case of hypocalcaemia, drip infusion and oral administration of calcium preparations would be performed. The day after the admission, he underwent near-total thyroidectomy leaving 1.5 g of thyroid remnant. The operation was successful, and one parathyroid gland was in the resected thyroid gland. The other three glands were not identified in the operation. Intact parathyroid hormone (PTH) was 135 pg/mL immediately after surgery (when calcium value was 7.5 mg/dL). Hospitalisation was continued and the next morning after surgery, he presented with tetany. Serum calcium values decreased and calcium gluconate was administered intravenously each time when there was a complaint of tetany (total 550 mg of elemental calcium for 3 days). But tetany symptom got worse day by day. He was transferred to the endocrine department on the 5th day from the operation.

As for laboratory findings at this point, ALP further increased to 1106 IU/L, and the corrected serum calcium value was 5.7 mg/dL. Serum potassium level was 4.4 mmol/L (normal range 3.3 to 4.8 mmol/L), magnesium level was 1.9 mg/dL (1.8 to 2.4 mg/dL). Urinary calcium was also as low as 19 mg/gCr. Procollagen type 1 N-terminal propeptide significantly increased to 750 µg/L, from preoperative value of 52.4 µg/L (18.1 to 74.1 µg/L), while tartrate-resistant acid phosphatase 5b decreased significantly. (figure 2) Oral administration of precipitated calcium carbonate 3 g/day, calcium lactate 9 g/day and alfacalcidol 1.5 µg/day, 11

days of intravenous drip infusion of calcium gluconate (6800 mg of calcium gluconate hydrate per day, equivalent to 628 mg of elemental calcium per day), the serum calcium level and the tetany symptom improved, and he was discharged. Calcium level at the discharge was 8.1 mg/dL. Calcium level increased to 9.3 mg/dL 3 days after the discharge. After that, serum ALP was still high and oral administration of calcium and alfacalcidol was required for next 4 months. (figure 3) Bone mineral density (BMD) prior to thyroidectomy was not measured, but 1 month and 7 months later, BMD was measured by dual energy X-ray absorptiometry. BMD of the lumbar spine L2-L4 increased from 1.008 to 1.135 g/cm² (young adult mean: from 85% to 95%), that of femoral neck increased from 0.610 to 0.712 g/cm² (young adult mean: from 64% to 75%). Parathyroid function was normal with intact PTH 58 pg/mL (normal range 10 to 65 pg/mL) 9 months after the surgery when calcium level was normal and stable.

DISCUSSION

Thyrotoxicosis often causes bone mineral loss.² Several subtypes of thyroid hormone receptors including thyroid hormone receptor $\alpha 1$ are in the nucleus of osteoclasts and osteoblasts, and triiodothyronine (T3) can activate both of the cells. Mainly T3 exerts anabolic actions on developing skeleton, and catabolic effects on adult bone.³ In thyrotoxicosis, bone turnover increases, showing increased bone resorption and bone formation. Before treatment, resorption is much greater than formation, causing reduced BMD, which is referred to as thyrotoxic osteodystrophy.⁴ After thyroidectomy, thyrotoxic state was suddenly removed, bone formation exceeds bone resorption in reverse and rapid skeletal uptake of calcium from blood causes severe and persistent hypocalcaemia, which is called hungry bone syndrome.⁵ After total thyroidectomy for hyperthyroidism, transient hypocalcaemia is not rare, occurring in 27 per cent of patients, and if the patients have Graves' disease, the percentage increases to 47 per cent. Permanent hypocalcaemia is uncommon, occurring in approximately 1 per cent of patients.⁶

Figure 2 Transition of bone metabolic marker. P1NP, procollagen type 1 N-terminal propeptide; TRACP-5b, tartrate-resistant acid phosphatase 5b.

Figure 3 Overall clinical course, and transition of serum corrected calcium and ALP. ALP, alkaline phosphatase; Ca, calcium.

Patient's perspective

I had felt tiredness several months before hospitalisation, but I was nearly 40 years old and I thought it was probably because of my hard work and age. But 1 week before hospitalisation, I became short of breath even with a small movement, and I felt my carotid artery beat. I went to a nearby clinic, and I had a pleural effusion by X-ray. I received a letter of introduction to go to a large hospital.

Once I was discharged from the hospital, my physical condition was good. But my hands began to feel numb after the surgery. Before surgery I had heard from a surgical doctor that these symptoms could be possible, but then my hands became increasingly immobile and breathing became more difficult. After moving to the internal medicine department and calcium infusion started in earnest, I think the symptoms have improved considerably.

Learning points

- Hungry bone syndrome is rare, but cannot be missed in thyrotoxic patients who underwent thyroidectomy. Thyrotoxic state is suddenly removed after the operation, bone formation exceeds bone resorption in reverse and rapid skeletal uptake of calcium from blood causes severe and persistent hypocalcaemia.
- Severe thyrotoxicosis, low bone mineral density and high serum alkaline phosphatase predict the severity of hypocalcaemia after total thyroidectomy.
- When hypocalcaemia is uncontrollable with oral administration of calcium preparations and active forms of vitamin D, hospitalisation should continue to settle down the hypocalcaemia by intravenous calcium infusion.
- Patient education and frequent postoperative serum calcium monitoring are essential for the patients at high risk for hungry bone syndrome after thyroidectomy.

According to a prospective study with 40 thyrotoxic subjects and 40 euthyroid controls undergoing total thyroidectomy, thyrotoxic osteodystrophy was an important predisposing factor for postoperative hungry bone syndrome and baseline BMD reflects the severity of hypocalcaemia.⁷ This study also described elevated serum ALP correlated strongly with postoperative hypocalcaemia, which reflects the increased activity of the osteoblast.⁴ Measuring BMD before thyroidectomy is not common in routine practice. However, in cases with a high risk of hungry bone syndrome, such as cases with severe hyperthyroidism and/or with high ALP, measuring BMD beforehand should be considered to predict the risk of hungry bone syndrome. When a patient with Graves' disease is at high risk for hungry bone syndrome after thyroidectomy, frequent monitoring of serum calcium is required. It is extremely important to educate the patients at high risk, for the symptoms of hypocalcaemia.

Hypoparathyroidism due to surgical damage could be also a possible cause of hypocalcaemia. However, in this case, postoperative parathyroid function was maintained at a considerable level, according to intact PTH level after the surgery, thus hypoparathyroidism can be ruled out. In addition, Michie *et al* stated that postoperative hypocalcaemia in thyrotoxic patients could not be explained solely by parathyroid damage, according to the investigation of 266 thyrotoxic patients who had undergone thyroidectomy and other patients who had undergone other forms of surgeries in the neck.⁴

Severe and prolonged hypocalcaemia in our case was caused by marked enhancement of bone formation and rapid calcium uptake into bone, in view of further serum ALP elevations and changes in bone metabolic markers after surgery.

Here are brief introductions of three case reports of hungry bone syndrome after the treatment of thyrotoxicosis. One patient was a 29-year-old Hawaiian pregnant woman with Graves' disease who presented with severe hypocalcaemia after thyroidectomy.⁸ After delivery her serum calcium level became stable and she could withdraw from intravenous calcium infusion. Foetal calcium requirements would be the secondary cause of hypocalcaemia in this case. The second patient was a 25-year-old Japanese woman with Graves' disease and insulin-dependent

diabetes mellitus who presented with severe hypocalcaemia after thyroidectomy.⁹ The third patient is a 54-year-old Chinese woman with Graves' disease who had treated previously by thyroidectomy and later by radioactive iodine, subsequently presented with severe hypocalcaemia.⁵ In common, all of them had severe thyrotoxicosis before thyroidectomy with high serum ALP levels.

In conclusion, we experienced a case of thyroid storm caused by Graves' disease, which showed a rapid and prolonged hypocalcaemia after thyroidectomy. When the patients with Graves' disease have severe thyrotoxicosis, high serum ALP levels and low BMD, they are at high risk for hungry bone syndrome after thyroidectomy. When hungry bone syndrome occurs, hospitalisation and intravenous calcium infusion should be continued until hypocalcaemia settles.

Contributors KK was the patient's doctor and had a central role in writing this manuscript. YM advised for patient care and corrected this manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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