HORMONES 2014, 13(2):286-289

Case report

Hypocalcaemia following thyroidectomy unresponsive to oral therapy

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ABSTRACT

Hypocalcaemia due to hypoparathyroidism following thyroidectomy is a relatively common occurrence. Standard treatment is with oral calcium and vitamin D replacement therapy; lack of response to oral therapy is rare. Herein we describe a case of hypoparathyroidism following thyroidectomy unresponsive to oral therapy in a patient with a complex medical history. We consider the potential causes in the context of calcium metabolism including: poor adherence, hungry bone syndrome, malabsorption, vitamin D resistance, bisphosphonate use and functional hypoparathyroidism secondary to magnesium deficiency. Malabsorption due to intestinal hurry was likely to be a contributory factor in this case and very large doses of oral therapy were required to avoid symptomatic hypocalcaemia.

Key words: Hypocalcaemia, Hypoparathyroidism, Thyroidectomy, Unresponsive

INTRODUCTION

Hypoparathyroidism, due to accidental gland removal or ischaemia, is the most common complication of thyroid surgery, occurring transiently in 8.3% of cases and permanently in 1.7% of cases.[1] It occurs more commonly following total thyroidectomy, especially for Graves' disease. In common with other causes of hypoparathyroidism, standard treatment involves oral calcium and vitamin D supplementation, titrated to relieve symptoms but avoid side effects such as nephrocalcinosis and nephrolithiasis. Intravenous supplementation of calcium may be required for the first 72 hours following thyroidectomy until oral therapy takes effect, but lack of response to oral therapy thereafter has rarely been reported. In this paper, we report a case of post-thyroidectomy hypocalcaemia unresponsive to large doses of oral therapy. We consider the potential causes for lack of response to treatment, alongside a review of previous case reports.

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Received 21-11-2012, Accepted 10-04-2013

CASE

A 27-year old woman had a complex medical and psychiatric history. She suffered from depression and anxiety disorder and had been managed by psychiatric

services for a number of years. A coccygectomy had been performed for chronic coccyx pain, and due to complications arising from this, the patient had undergone panproctocolectomy, with ileostomy and PEG formation. Multiple episodes of septicaemia occurred during one admission. These were postulated to be due to deliberate infection of central venous catheters by the patient using her stoma contents: an identical strain of vancomycin resistant enterococcus was isolated on each occasion, with no abdominal source of infection.

Several months prior to ileostomy formation, the patient was referred to the endocrinology clinic complaining of symptoms of hyperthyroidism. On the basis of clinical features and positive thyroid antibodies, she was diagnosed with Graves' disease and treatment was started with carbimazole. Symptoms of hyperthyroidism were poorly controlled and thyroid function tests remained deranged. Poor compliance was thought to be a contributory factor, a suggestion strongly denied by the patient.

18 months after diagnosis of Graves' disease, the patient was admitted to hospital with fever, tachycardia, decreased consciousness and high stoma output. She was treated for thyroid storm with beta-blockers, steroids and propylthiouracil, subsequently rendered euthyroid with sodium ipodate and referred for emergency total thyroidectomy. The surgeon's contemporaneous notes stated that "the recurrent laryngeal nerve was displayed and carefully avoided along with all parathyroid glands". She was discharged two days later with a serum calcium level of 2.06 mmol/L (normal range: 2.2-2.6 mmol/L).

Two days after discharge following thyroidectomy the patient presented with cramps and peri-oral tingling. Medication included a proton pump inhibitor, selective serotonin uptake inhibitor, analgesia and oral calcium supplementation. Initial investigations were as follows: Ca^{2+} 1.81 mmol/L, Mg^{2+} 0.63 mmol/L (normal range: 0.7-1.0), PO_4^{3-} 2.39 mmol/L (normal range: 0.8-1.45 mmol/L), PTH 14 ng/L (normal range: 14-72 ng/L). Treatment was started with intravenous calcium gluconate and oral magnesium glycerophosphate, calcitriol and calcium carbonate. Over the subsequent weeks, cessation of intravenous calcium therapy proved impossible, each attempt resulting in a rapid and symptomatic fall in serum calcium. PTH concentration was below the normal range, but thyroid function was well controlled on oral thyroxine. Serum alkaline phosphatase levels were in the normal range.

Intravenous magnesium infusion to increase serum magnesium concentration to 1.08mmol/L did not result in any detectable increase in serum PTH or calcium. Bendroflumethiazide at a dose of 5mg per day was commenced to increase renal calcium reabsorption. The urinary calcium excretion was 0.021mmol/L (using the formula urine calcium x serum creatinine/urine creatinine), indicating excessive excretion relative to serum calcium concentration,[2] an expected result in hypoparathyroidism.

Previously prescribed proton pump inhibitor therapy was stopped, oral replacement therapy was changed to calcium citrate and alfacalcidol liquid to improve absorption and therapy was given via the PEG tube to ensure compliance. Testing for coeliac disease was negative. Four days of continuous intravenous calcium therapy in order to reduce intestinal transit time and hence aid gastrointestinal absorption was instituted but did not lead to a more permanent rise in serum calcium. Serum 1, 25 Vitamin D, measured seven weeks post-operatively, was found to be 32 pmol/L (normal range: 20-120 pmol/L).

After a period of nine weeks and sequential increases in oral therapy to 6g daily of calcium as calcium citrate and 3μg alfacalcidol twice daily, a relatively stable serum calcium of 1.9 mmol/L was attained without intravenous therapy. The patient remained free of symptoms of hypocalcaemia and was discharged from hospital. The patient continued to suffer occasional symptoms of hypocalcaemia with fluctuations in serum calcium concentration. Further dose adjustment of oral therapy had little effect on serum calcium concentration, but intravenous infusions were rarely required.

DISCUSSION

Lack of response to oral therapy in treatment of hypoparathyroidism following thyroidectomy has rarely been reported. With knowledge of previous reports, we postulated and attempted to exclude six potential causes.

Poor adherence or interference with therapy was a potential contributor to persisting hypocalcaemia, and supervised administration of liquid therapy, given via the PEG tube, was instituted. A urinary laxative screen was negative. The patient was assessed by a psychiatrist and diagnosed with anxiety and depression, but was not thought to be suffering from a factitious disorder.

Hungry bone syndrome, a rapid influx of calcium into the bones due to high bone turnover, is a recognised cause of hypocalcaemia following thyroidectomy for thyrotoxicosis.[3] In this patient, serum markers of bone turnover were in the normal range throughout, and serum PTH remained suppressed throughout the admission and beyond discharge.

Magnesium is required both for the release and the peripheral action of PTH. This patient was mildly hypomagnesaemic following thyroidectomy, in spite of oral magnesium supplementation. In order to ensure there was no element of functional hypoparathyroidism due to hypomagnesaemia, intravenous magnesium sulphate was infused, resulting in a serum concentration just above the normal range. Serum PTH level was unchanged, with no improvement in serum calcium concentration. In functional hypoparathyroidism, PTH rises rapidly following intravenous magnesium infusion.[4]

Vitamin D resistance has been postulated to be a cause of oral treatment failure for hypoparathyroidism following thyroidectomy.[5] In our patient this seemed unlikely given normal calcium, phosphate and PTH levels prior to thyroidectomy.

In the kidney, 75-80% of filtered calcium is reabsorbed in the proximal tubules passively, with around 20% being absorbed under the control of PTH. Bendroflumethiazide was commenced to improve renal calcium absorption, with no discernable change in serum calcium. Fractional urinary excretion of calcium was subsequently measured and found to be excessive relative to serum calcium, an expected result, but unlikely to be the sole cause of ongoing hypocalcaemia given the large doses of oral calcium.

To our knowledge, there have been five case reports of failure of oral therapy for hypoparathyroidism due to malabsorption. Marcondes et al have reported a case of coeliac disease first uncovered when oral treatment for hypoparathyroidism failed.[6] Testing for coeliac disease was negative in this patient. In a case reported by Komindr et al, treatment with vitamin D and calcium carbonate failed to correct hypocalcaemia following thyroidectomy due to achlorhydria; calcium chloride was successfully employed instead.[7] In this patient, a previously prescribed proton pump inhibitor was stopped early during the course of treatment and therapy changed from calcium carbonate to calcium citrate, the absorption of which is not affected by achlorhydria.

Three cases of poor response to treatment of hypoparathyroidism following thyroidectomy have been reported as due to malabsorption as a result of abdominal surgery. Pietras et al reported a case resulting from formation of a Roux-en-Y gastric bypass,[8] and Hylander et al reported a case due to short bowel syndrome following extensive resection of the small bowel.[9] Seki et al have reported a case of hypoparathyroidism post-thyroidectomy in a woman who had previously undergone gastrectomy.[10]

Richmond has described a case of refractory hypocalcaemia following thyroidectomy due to long-term bisphosphonate use.[11] In that case, the patient required six days of intravenous calcium therapy followed by six weeks of oral therapy but then remained normocalcaemic without any therapy. The patient in this report had never used bisphosphonate therapy.

The patient reported in this case had an entirely intact small bowel but had previously presented numerous times complaining of excess stoma output. These symptoms may have been related to hyperthyroidism, or may have been fictitious, but we believe that lack of response to oral therapy in this patient may have been due to malabsorption, possibly as a result of intestinal hurry. Symptoms of hypocalcaemia were eventually controlled using very large doses of alfacalcidol and calcium citrate orally, with occasional return of symptoms; further dose adjustments had little effect on serum calcium concentration.

In conclusion, we have described a case of post-thyroidectomy hypoparathyroidism unresponsive to oral therapy. We investigated and excluded potential causes, attempted to control intestinal transit time and accounted for lack of adherence. We eventually

achieved a low but generally stable serum calcium concentration with large doses of oral therapy.

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