J Anesth (2012) 26:595–597
DOI 10.1007/s00540-012-1365-y

CLINICAL REPORT

Perioperative management of a patient with thyroid hormone resistance who underwent total thyroidectomy for thyroid cancer

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Received: 17 July 2010 / Accepted: 15 February 2012 / Published online: 3 March 2012

Abstract Resistance to thyroid hormone (RTH) is a rare, predominantly inherited syndrome that involves impaired tissue responsiveness to thyroid hormones. We describe the perioperative management of a patient with RTH who underwent total thyroidectomy. Although surgery performed under general anesthesia was uneventful, after the surgery the patient developed difficult-to-treat hypocalcemia that lasted until postoperative day 4. Moreover, thyroid function even after discharge remained unstable despite replacement therapy. We suggest that the parathyroid and thyroid function of patients with RTH be followed very closely and that nociceptive stimulus of the surgery and postoperative pain be reduced as much as possible.

Keywords Resistance to thyroid hormone · Thyroidectomy · Thyroid cancer · Hypocalcemia

Introduction

Patients with resistance to thyroid hormone (RTH) syndrome have elevated serum thyroid hormone (TH) concentrations, inappropriately normal or elevated thyrotropin (TSH) concentrations, and decreased sensitivity to TH. In other words, RTH is a dominantly inherited condition characterized by impaired tissue responsiveness to thyroid hormone [1–4]. With a few exceptions, the genetic basis of RTH is a mutation of one of the two thyroid hormone receptor β (TRβ) alleles [5, 6]. We report a case of RTH in which the patient underwent a total thyroidectomy for thyroid cancer.

Case report

A 26-year-old woman, 166 cm in height, weighing 59 kg, was diagnosed with thyroid papillary carcinoma and was scheduled for a total thyroidectomy and right radical neck dissection. Her thyroid hormone concentrations suggested hyperthyroidism [TSH, 2.06 mIU/ml (normal range, 0.6–4.6 mIU/ml); free triiodothyronine (free T_3), 4.75 pg/ml (1.71–3.71 pg/ml); free thyroxine (free T_4), 1.89 ng/dl (0.70–1.48 ng/dl)], and she was treated with thiamazole for control of hyperthyroidism. However, as her thyroid hormone concentrations remained high, the scheduled thyroidectomy was therefore postponed, and attempts were made to normalize the patient's thyroid hormone concentrations. One month later, the patient suddenly experienced chills and severe fatigue, indicative of hypothyroidism. After a T_3-loading test was performed, the free T_3 concentration was found to have increased to 19.22 ng/ml, but no lowering of TSH concentration was observed. T_3 loading did not induce symptoms of hyperthyroidism, and the patient's general fatigue was alleviated. Magnetic resonance imaging did not show a pituitary adenoma. On the basis of these data, a diagnosis of systemic RTH was suggested, and the thyroidectomy was rescheduled.

The patient was premedicated with intramuscular midazolam (3 mg) and oral thiamazole (50 μg). General

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anesthesia was induced with fentanyl (0.1 mg), propofol (120 mg), and vecuronium (5 mg), and a tracheal tube was inserted orotracheally. General anesthesia was maintained with 2.0–3.5% sevoflurane, nitrous oxide, and oxygen. During the intraoperative period, slight hypercapnia ($PaCO_2$, 50 mmHg) and spontaneous breathing were observed despite adequate mechanical ventilation (volume control ventilation: tidal volume 600 ml, frequency 12–14/min). At the end of the surgery, a slight elevation in body temperature (maximum rectal temperature, 38.0°C) and tachycardia (90/min) were observed. Oxygenation and blood pressure were mostly stable. The patient's parathyroid gland was transplanted to the sternocleidomastoid muscle. At the end of the operation, the ionized Ca concentration was revealed to be 0.99 mmol/l (1.13–1.32). Once anesthesia was terminated, the patient awakened smoothly and the tracheal tube was removed. For postoperative pain, fentanyl (0.35 mg) and diclofenac sodium (50 mg) were administered. The durations of operation and anesthesia were 8.5 and 9.5 h, respectively.

Two hours after surgery, the patient reported numbness in her arms and feet. Therefore, calcium gluconate (0.3 g/h) was administered. The next morning, the patient lost consciousness, her eyeballs tended to roll, and she did not respond to auditory stimuli. Symptoms of tetany continued despite calcium gluconate supplementation, and serum calcium concentrations decreased to 6.8 mg/dl (8.3–10.5). Sinus tachycardia (100 bpm), tachypnea (30 breaths/min), and fever (temperature 38.0°C) were observed concurrently. Hypothyroidism and hypoparathyroidism were suspected: calcium gluconate (4.0 g/day), liothyronine sodium (200 μg/day), and hydrocortisone sodium succinate (50 mg) were also administered. On postoperative day 2, the patient slowly regained consciousness and she was able to respond via eye movements, but tetany persisted. On postoperative day 4, her calcium concentration was in recovery trend (7.6 mg/dl), she was alert again, and the tetanic symptoms resolved. Her parathyroid hormone (PTH) concentration remained low [4 pg/ml (10–65 pg/ml)], and the thyroid hormone level was still unstable (free T_3, 5.1 pg/ml; free T_4, 0.9 ng/dl; TSH, 0.2 mIU/ml) despite replacement therapy (liothyronine sodium 75 μg/day, levothyroxine sodium 25 μg/day). On postoperative day 30, her calcium concentration increased to a level within the normal range. Her thyroid hormone level was still unstable (free T_3, 3.42 pg/ml; free T_4, 1.74 ng/dl; TSH, 18.85 mIU/ml) under thyroid hormone administration (liothyronine sodium 25 μg/day, levothyroxine sodium 250 μg/day). The patient was discharged 48 days after surgery, but her symptoms, including paroxysmal sinus tachycardia, abnormal sweating, diarrhea, general fatigue, and chills continued even after discharge. Eight years past the operation now, she still needs Ca replacement (calcium L-asparate, 1,200 mg; alfacalcidol, 4 μg), and her thyroid hormone status is unstable (liothyronine sodium, 500 μg/day; levothyroxine sodium, 30 μg/day; free T_3, 5.60 pg/ml; free T_4, 2.34 ng/dl; TSH, 8.97 mIU/ml).

TR mutation analysis identified a Pro447Leu mutation in the TRβ gene. The patient's mother also had high concentrations of TSH, T_3, and T_4; therefore, it was suspected that the patient had inherited this disease from her mother.

Discussion

Resistance to thyroid hormone is an inherited syndrome that involves reduced tissue sensitivity to thyroid hormone. The hallmark of RTH is an elevated serum thyroid hormone concentration associated with nonsuppressible TSH. Other clinical signs include goiter, short stature, decreased weight, tachycardia, hearing loss, attention-deficit hyperactivity disorder, decreased IQ (intelligence quotient), and dyslexia [7, 8].

We present a case of RTH in a woman who had undergone total thyroidectomy for thyroid cancer. There is no description in the literature of anesthetic management of a patient with RTH, and the appropriate line of management in such cases has not yet been established. We were not sure whether the patient's thyroid function would remain stable during the perioperative period. The important anesthetic implications of RTH are that intraoperative stress should be avoided and that an optimal level of anesthesia be maintained. We premedicated the patient with thiamazole to prevent possible hyperthyroid crisis during operation. In this case, the patient's reaction to the anesthetics including propofol, fentanyl, and sevoflurane was almost normal, but we are not sure that these anesthetics were sufficient to suppress surgical stress and postoperative pain. After the patient returned to the ward on completion of the surgery, she experienced tetany and lost consciousness, which continued for 4 days. The possible causes of these symptoms included (1) hypocalcemia, (2) thyroid function disorder, and (3) adrenal gland dysfunction; other complicating factors may be related. Postoperative hypocalcemia is one of the major complications of total thyroidectomy. It seems that a low PTH, despite a parathyroid transplantation, is caused by parathyroid dysfunction. McLeod et al. reported that 7 of 60 patients (11.7%) who underwent thyroidectomy developed asymptomatic hypocalcemia, whereas 8 patients (13.3%) developed symptomatic hypocalcemia [9]. However, there is no evidence so far that RTH is related to hypoparathyroidism. With regard to thyroid function, the patient suffered hyper- and hypothyroid symptoms despite thyroid hormone supplementation in the postoperative period, and these symptoms continued even after discharge. The therapeutic

management of RTH for the total thyroidectomy patient should be done by following the clinical status and mimicking as much as possible the preoperative hormonal pattern for serum T_4 and T_3, even if optimal TSH suppression cannot be achieved [10]. Recently, four case reports of patients with RTH who underwent total thyroidectomy were published [10–12]. These cases also revealed unstable thyroid function, but severe hypocalcemia was not described.

TRs are encoded by the TRα and TRβ genes, which are located on different chromosomes. Mutation of TRβ causes the human genetic disease RTH. The TRβ mutant proteins identified in RTH have reduced or no T_3-binding affinity or transcriptional capacity [13]. A close correlation was discovered between members of a family who were affected by RTH and the TRβ gene [14]. The identification of a Pro453His mutation in the TRβ gene of one kindred established that RTH is caused by mutations of this gene [15]. To date, approximately 137 different mutations in the TRβ gene have been reported [16] in more than 500 individuals [7, 10]. TR$\beta^{PV/PV}$ mice with a C-terminal 14-amino-acid frameshift mutation spontaneously develop follicular thyroid carcinoma [17]. TRβ^{PV} might play a role independently or in cooperation with other pathways, directly or indirectly, in the transformation of TSH-stimulated proliferative thyroid cells to cancer cells [13]. It is not clear so far whether a mutation of TRβ is related to the abnormal regulation of calcium.

In conclusion, we report a case of RTH in a patient who had undergone total thyroidectomy for thyroid cancer. During the postoperative period, the patient suffered disordered consciousness and severe hypocalcemia, and her thyroid function remained unstable. The therapeutic management of RTH with a total thyroidectomy patient should be done by following the clinical status and mimicking as much as possible the preoperative hormonal pattern for serum T_4 and T_3, even if optimal TSH suppression cannot be achieved. We suggest that the parathyroid and thyroid function of patients with RTH be followed very closely and that nociceptive stimulus of the surgery and postoperative pain be reduced as much as possible.

References

1. Refetoff S, DeWind LT, DeGroot LJ. Familial syndrome combining deaf-mutism, stuppled epiphyses, goiter and abnormally high PBI: possible target organ refractoriness to thyroid hormone. J Clin Endocrinol Metab. 1967;27:279–94.
2. Cooper DS, Ladenson PW, Nisula BC, Dunn JF, Chapman EM, Ridgway EC. Familial thyroid hormone resistance. Metabolism. 1982;31:504–9.
3. Refetoff S, Weiss RE, Usala SJ. The syndromes of resistance to thyroid hormone. Endocr Rev. 1993;14:348–99.
4. McDermott MT, Ridgway EC. Thyroid hormone resistance syndromes. Am J Med. 1993;94:424–32.
5. Weiss RE, Balzano S, Scherberg NH, Refetoff S. Neonatal detection of generalized resistance to thyroid hormone. JAMA. 1990;264:2245–50.
6. Asteria C, Rajanayagam O, Collingwood TN, Persani L, Romoli R, Mannavola D, Zamperini P, Buzi F, Ciralli F, Chatterjee VK, Beck-Peccoz P. Prenatal diagnosis of thyroid hormone resistance. J Clin Endocrinol Metab. 1999;84:405–10.
7. Weiss RE, Refetoff S. Resistance to thyroid hormone. Rev Endocr Metab Disord. 2000;1:97–108.
8. Brucker-Davis F, Skarulis MC, Grace MB, Benichou J, Hauser P, Wiggs E, Weintraub BD. Genetic and clinical features of 42 kindreds with resistance to thyroid hormone. The National Institutes of Health Prospective Study. Ann Intern Med. 1995; 123:572–83.
9. McLeod IK, Arciero C, Noordzil P, Stojadinovic A, Peoples G, Melder PC, Langley R, Bernet V, Shriver CD. The use of rapid parathyroid hormone assay in predicting postoperative hypocalcemia after total or completion thyroidectomy. Thyroid. 2006; 16:259–65.
10. Paragliola RM, Lovicu RM, Locantore P, Senes P, Concolino P, Capoluongo E, Pontecorvi A, Corsello SM. Differentiated thyroid cancer in two patients with resistance to thyroid hormone. Thyroid. 2011;21(7):793–7.
11. Kim HK, Kim D, Yoo EH, Lee JI, Jang HW, Tan AH, Hur KY, Kim JH, Kim KW, Chung JH, Kim SW. A case of resistance to thyroid hormone with thyroid cancer. J Korean Med Sci. 2010; 25:1368–71.
12. Canadas KT, Rivkees SA, Udelsman R, Breuer CK. Resistance to thyroid hormone associated with a novel mutation of the thyroid β receptor gene in a four-year-old female. Int J Pediatr Endocrinol. 2011;2011(1):3.
13. Yen PM. Molecular basis of resistance to thyroid hormone. Trends Endocrinol Metab. 2003;14:327–33.
14. Usala SJ, Bale AE, Gesundheit N, Weinberger C, Lash RW, Wondisford FE, McBride OW, Weintraub BD. Tight linkage between the syndrome of generalized thyroid hormone resistance and the human c-erbA beta gene. Mol Endocrinol. 1988;2:1217–20.
15. Sakurai A, Takeda K, Ain K, Ceccarelli P, Nakai A, Seino S, Bell GI, Refetoff S, DeGroot LJ. Generalized resistance to thyroid hormone associated with a mutation in the ligand-binding domain of the human thyroid hormone receptor beta. Proc Natl Acad Sci USA. 1989;86:8977–81.
16. Rosen MD, Privalsky ML. Thyroid hormone receptor mutations in cancer and resistance to thyroid hormone: perspective and prognosis. J Thyroid Res. 2011;2011:361304.
17. Suzuki H, Willingham MC, Cheng SY. Mice with a mutation in the thyroid hormone receptor beta gene spontaneously develop thyroid carcinoma: a mouse model of thyroid carcinogenesis. Thyroid. 2002;12:963–9.