

Hyponatremia after Thyroid Hormone Withdrawal in a Patient with Papillary Thyroid Carcinoma

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Hyponatremia is an electrolyte abnormality commonly found in clinical practice. It is important to diagnose the underlying etiology of the hyponatremia and correct it appropriately because severe hyponatremia can cause serious complications and substantially increase the risk of mortality. Although hypothyroidism is known to be a cause of hyponatremia, it is rare that hyponatremia occurs in relation to hypothyroidism induced by thyroid hormone withdrawal in patients with differentiated thyroid cancer. We report a case of a 76-year-old woman with papillary thyroid carcinoma presenting with severe hyponatremia related to hypothyroidism induced by thyroid hormone withdrawal for radio-active iodine whole-body scanning, who was treated by thyroid hormone replacement and hydration. Considering that the incidence of differentiated thyroid cancer is rapidly increasing, physicians should be aware that, although uncommon, hyponatremia can occur in patients undergoing radioiodine therapy or diagnostic testing.

Keywords: Hyponatremia; Hypothyroidism; Thyroid neoplasms

INTRODUCTION

Differentiated thyroid cancer accounts for approximately 90% of all types of thyroid cancers and has relatively positive treatment outcomes. Treatment includes radioiodine therapy after total thyroidectomy, and posttherapy evaluation includes iodine whole-body scanning, thyroglobulin serum measurement, and neck ultrasonography [1,2]. When conducting radioiodine therapy and iodine whole-body scans, the regular dose of thyroid hormone is withdrawn to temporarily induce a state of hypothyroidism which improves the intake rate of radioiodine residue in the thyroid.

Hypothyroidism is a cause of hyponatremia, but severe hyponatremia associated with hypothyroidism induced by thy-

roid hormone withdrawal from a patient with thyroid cancer is only rarely observed [3-7]. Here, the authors report a case of severe hyponatremia following thyroid hormone withdrawal prior to iodine whole-body scanning in a patient with post thyroidectomy status of papillary thyroid cancer.

CASE REPORT

A 76-year-old female visited the emergency room with symptoms of communication disability, mumbling, and impatience. She was treated with total thyroidectomy and radioiodine therapy for papillary thyroid carcinoma in October 2001. In April 2011, she was treated with cervical lymphadenectomy for left cervical lymph node metastasis of papillary thyroid carcinoma,

Received: 21 November 2012, **Accepted:** 12 March 2013

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radical nephrectomy for left renal tubular carcinoma, and finally radioiodine therapy in July 2011. She was initially administered levothyroxine 0.1 mg daily and in April 2012 blood examination showed a high level of thyroglobulin at 14.67 ng/mL. The thyroid hormone was replaced by liothyronin sodium, and after 2 weeks of complete thyroid hormone withdrawal an iodine whole-body scan was conducted 5 days before admission. The level of free T4 was decreased to 0.25 ng/dL (normal range, 0.93 to 1.7) and thyrotropin (TSH) was increased to 106 μ IU/mL (normal range, 0.27 to 4.2). After examination, levothyroxine 0.1 mg daily was readministered. Because cervical node metastasis was suspected, a fine needle aspiration test was reserved before release. Dizziness and weakness were present before the iodine whole body scan, but no particular treatment was given due to its low level of severity. However, 2 days after the iodine whole body scan and 3 days before admission, she visited another hospital for pain in her heels where drugs including nonsteroidal anti-inflammatory were given twice. Her dizziness and nausea worsened after which she reported vomiting that occurred more than 10 times a day. A day before admission, the patient visited the emergency room and was examined for a suspicious gastrointestinal tract reaction induced by nonsteroidal anti-inflammatory drugs. She was administered antiemetic drugs, and sent home with a serum sodium level of 121 mEq/L. After getting home, her nausea continued despite the antiemetics and she was hospitalized in the same night from the emergency room with symptoms of communication disability, mumbling, and impatience.

The patient was diagnosed with diabetes and hypertension about 20 years ago and was on medication including oral hypoglycemic agents (pioglitazone 15 mg daily, metformin 250 mg daily) and oral antihypertensive drugs (perindopril tert-butylamine 8 mg daily, amlodipine besylate 5 mg daily). In 1999, she underwent hip bipolar hemiarthroplasty and right total knee arthroplasty (TKA) and, in 2000, left TKA.

At admission, she presented with signs of delirium and disorientation and her vital signs were as follows: blood pressure 160/80 mm Hg, pulse rate 66 times per minute, breathing rate 20 times per minute, body temperature 36.8°C, and oxygen saturation on room air was 95%. There were no reported changes in body weight.

Skin tension was not decreased, there was no conjunctival pallor or sclera jaundice, and the papillary reflex was normal. Cervical lymphadenopathy was not diagnosed, and both cardiac and breathing sounds were normal on chest examination.

On abdominal examination, bowel sound was normal, and there were no masses or pain. There was no limb edema on examination of the peripheral extremities.

Peripheral blood examination showed a white blood cell count, hemoglobin concentration, and platelet count as 7,700/mm³, 9.7 g/dL, and 144,000/mm³, respectively. Electrolyte tests showed a sodium of 110 mEq/L, a potassium of 3.9 mEq/L, and a chloride of 82 mEq/L which suggested hyponatremia. Serum osmolality was 233 mOsm/kg and a urine osmolality was 418 mOsm/kg, indicating a severe hypotonic hyponatremia. Biochemical blood tests showed a blood glucose of 133 mg/dL, a blood urea nitrogen of 11 mg/dL, a creatinine of 1.2 mg/dL, a total protein of 6.7 g/dL, albumin of 4.0 g/dL, total bilirubin of 0.71 mg/dL, aspartate aminotransferase 61 IU/L, alanine aminotransferase 25 IU/L, alkaline phosphatase 175 IU/L, r-guanosine triphosphate 11 IU/L, creatine kinase 1,380 IU/L, lactic dehydrogenase 779 IU/L, and total cholesterol was 206 mg/dL. Serum C-reactive protein, PT, and aPTT was 0.1 mg/dL, 11.5 seconds (INR 1.06), 28.1 seconds, respectively.

Hepatitis testing was hepatitis B surface antigen negative, antihepatitis B surface antibody negative, and antihepatitis C virus negative. Chemical urinalysis showed sodium, potassium, chloride, and creatinine to be 50, 41.6, 58.1 mEq/L, and 63.65 mg/dL respectively. Electrocardiogram showed normal sinus rhythm (66 times per minute).

A hormone test was conducted to identify the cause of hyposmolar hyponatremia, and the result showed that the TSH was 90.78 μ IU/mL with a free T4 of 0.61 ng/dL, an ACTH of 33.3 pg/mL, and a cortisol of 341.84 ng/mL (Table 1).

Brain magnetic resonance imaging and computed tomographic features showed no signs of acute lesions, and chest and abdominal X-ray, and echocardiography results gave no significant diagnosis.

The patient showed signs of severe hyponatremia with continuous nausea and disorientation and had a serum sodium level of 110 mEq/L, so 3% normal saline was injected. On the second day after admission, levothyroxine 0.2 mg was admin-

Table 1. Sequential Thyroid Function in Response to Levothyroxine

	1 Week prior to admission	Admitted day 1	Admitted day 6	Admitted day 22
TSH, μ IU/mL	106.30	90.78	18.96	0.28
Free T4, ng/dL	0.23	0.61	1.31	1.95

TSH, thyrotropin.

Table 2. Comparison of Characteristics in the Literature Review Patients

Sex	Age, yr	Types of thyroid cancer	Na+, mEq/L	THW vs. rhTSH	Low iodine diet	Thiazide intake	References
F	87	Follicular	118	THW	Yes	No	Shakir et al. [6]
F	66	PTC	114	THW	Yes	No	Shakir et al. [6]
F	72	PTC	121	THW	Yes	No	Shakir et al. [6]
M	68	PTC	115	THW	Yes	No	Shakir et al. [6]
F	71	Follicular	110	THW	Yes	No	Shakir et al. [6]
M	70	PTC	115	THW	Yes	No	Krishnamurthy et al. [4]
F	81	PTC	116	rhTSH	Yes	Yes	Krishnamurthy et al. [4]
F	66	PTC	107	rhTSH	Yes	Yes	Al Nozha et al. [3]
F	77	PTC	98	THW	Yes	No	Nozu et al. [5]
F	76	PTC	110	THW	Simplified LID ^a	No	Present case

THW, thyroid hormone withdrawal; rhTSH, recombinant human thyrotropin; F, female; PTC, papillary thyroid carcinoma; M, male; LID, low iodine diet.

^aLess restrictive diet that avoids high-iodine-containing food.

istered for 3 days at 6 hours intervals, then reduced to 0.1 mg every 12 hours for 8 days, and finally maintained at 0.1 mg every 24 hours. On the third day of admission, consciousness and nausea had improved. The electrolyte levels gradually improved, and normalized by the 12th day. On the fifth day of admission, external tube feeding began. On the sixth day, full consciousness returned enabling oral feeding. On the 13th day, after the volume of food had increased and the serum sodium level normalized, fluid infusion was stopped, and the serum sodium level was maintained without fluid infusion.

DISCUSSION

Thyroid cancer is the most common endocrine cancer, and the prevalence of thyroid cancer is increasing all over the world [8]. In Korea, the prevalence of thyroid cancer has increased, becoming the most frequent cancer in 2009, and for women the annual increase in the rate of thyroid cancer has been shown to be an average of 25.4% [9,10]. Papillary and follicular thyroid cancer accounts for 90% of thyroid cancers, and has relatively positive treatment outcomes. A maximum of 30% of these can recur, but 2/3 of locally recurrent patients and 1/3 of remote metastatic patients can be cured completely with the proper treatment. Follow-up examination for recurrence and remote metastasis is essential [1]. Treatment for differentiated thyroid cancer includes surgery and thyroid hormone supplementation after radioiodine remnant ablation with radioiodine. The follow-up examinations consist of iodine whole body scanning,

serum thyroglobulin measurement, and neck ultrasound examination [1,2].

When conducting radioiodine remnant ablation and iodine whole-body scanning, it is necessary to apply thyroid hormone withdrawal 4 weeks before radioiodine infusion to increase the rate of radioiodine intake to residual thyroid tissue, and to change the thyroid medication for 2 weeks to tetronine (lithyronin sodium) which has a shorter half-life. It is also necessary to have a low-iodine diet. Inducing distinctive hypothyroidism with thyroid hormone withdrawal and a low-iodine diet is an essential condition for accurate examination. However, there is a possibility that related complications can occur [3-6,11].

Hyponatremia is the most common electrolyte abnormality in clinical practice and generally has no symptoms and positive treatment outcomes. However, in severe cases, there can be neurological symptoms and even death. Therefore the diagnosis must be recognized and treatment must be undertaken.

Hypothyroidism is well known as a cause of hyponatremia. However, there is no clearly known mechanism behind this. It is hypothesized that hypothyroidism causes decreased urine output and renal insufficiency which delays water excretion leading to hyponatremia. This first hypothesis relates to a malfunction of the controlling mechanism of antidiuretic hormone secretion induced by plasma osmolality and the increase of antidiuretic hormone induced by decreased metabolic clearance of antidiuretic hormone. A second hypothesis is that the abnormal water excretion is due to a decreased glomerular filtration rate and renal plasma flow that might occur with hypothyroid-

ism. The third hypothesis is that decreased synthesis and secretion of atrial natriuretic peptide which leads to decreased serum atrial natriuretic peptide concentration and subsequently to a decreased glomerular filtration rate and renal plasma flow contributes to decreased water excretion. Consequently, water retention caused by oversecretion of antidiuretic hormone and renal insufficiency from hypothyroidism can induce hyponatremia [12].

Through these mechanisms, it is possible that hyponatremia can be caused by hypothyroidism. However, it is rare to find severe hyponatremia related to hypothyroidism caused by thyroid hormone withdrawal in a patient with thyroid cancer [3-7]. Baajafer et al. [7] reported that there were no complications by hypothyroid status induced by thyroid hormone withdrawal among 128 patients who underwent surgery with differentiated thyroid cancer, only five of them were presenting hyponatremia with a serum sodium level of 135 mEq/L and no cases were witnessed with a serum sodium level lower than 130 mEq/L.

There are case reports of severe symptomatic hyponatremia being induced by a low-iodine diet as pretreatment before radioiodine remnant ablation and iodine whole-body scanning [3-6]. In two out of nine cases, recombinant human thyrotropin (rhTSH) was alternatively infused instead of thyroid hormone withdrawal, and in seven cases thyroid hormone administration was ceased. In the two cases of rhTSH injection, hydrochlorothiazide was taken. There are also cases in which patients, perceiving low-iodine diet to be the same as low-sodium diet, stopped taking sodium. These suggest that diuretic administration and a low-sodium diet can also cause hyponatremia (Table 2).

In this paper's study case, the patient had difficulty adhering properly to a low-iodine diet due to her low socioeconomic status and age; only laver, seaweed, and tangleweed were restricted on her diet, and the level of sodium and the volume of water intake was not changed. Therefore, in the absence of an adequately low-iodine and low-sodium diet, the cause for her hyponatremia occurring from hypothyroidism has to be associated with thyroid hormone withdrawal. Since residual thyroid tissue is thyroid stimulating hormone dependent, the blood concentration of thyroid stimulating hormone has to be increased to improve the efficiency of radioiodine intake. Conventionally, this has been done through thyroid hormone withdrawal. However, recent studies suggest that hypothyroidism induced by thyroid hormone withdrawal degrades the quality of the patient's life, and an alternative way to increase the blood concentration of thyroid stimulating hormone was intro-

duced by way of rhTSH injection [11]. rhTSH injection is preferred as an alternative treatment since it has a similar residual thyroid tissue stimulation rate to that of thyroid hormone withdrawal, but has a lower radiation exposure level for tissues other than the thyroid [13].

Several factors, including thyroid stimulating hormone and iodine content in the body, affect radioiodine remnant ablation and iodine whole-body scanning, and a low-iodine diet with 50 µg/day iodine level is required to enhance radioiodine intake of the focus at least 2 weeks prior to examination [14]. This low-iodine diet can cause symptomatic hyponatremia, and some studies suggest that diets excluding only food with a high iodine level can have similar treatment effects to a strict low-iodine diet. Therefore, a simple diet excluding foods with high levels of iodine can be considered for elder patients instead of a low-iodine diet [15].

However, as witnessed in the case report, injecting recombinant human thyroid hormone can also cause hyponatremia in a patient with normal thyroid function and on a diet avoiding lava, seaweed, and tangleweed rather than a thorough low-iodine diet. This shows that the incidence of hyponatremia can be affected by various factors other than hypothyroidism and a low-iodine diet. Therefore, clinical doctors must anticipate the possibility of various complications during the pretreatment stage of a thyroid cancer patient. In particular, elder patients taking diuretics or on a low-iodine diet can acquire hyponatremia for which they must be carefully monitored [3].

In this case, the serum creatinine concentration of the patient was 1.2 mg/dL which has no significant diagnostic significance compared to the 1.34 mg/dL recorded in April 2011 when the patient underwent radical nephrectomy for left renal tubular carcinoma. However, the patient was treated with drugs for diabetes and hypertension for about 20 years, and only has the right kidney function remaining. The patient also showed chronic renal insufficiency with 31.6 mL/min of creatinine clearance (Cockcroft-Gault equation) on admission. Therefore, it was assumed that the hyponatremia of this patient could easily be caused by hypothyroidism associated with thyroid hormone withdrawal compared to other thyroid cancer patients without any comorbidities [7,16].

Hyponatremia is accompanied by other symptoms in the elderly, and it can be difficult to diagnose the cause [17,18]. In this case, when the patient was admitted to the emergency room with nausea and vomiting, it was considered to be a gastrointestinal reaction to nonsteroidal anti-inflammatory drugs and she was treated for this presumed adverse reaction. How-

ever, the patient's hyponatremia symptoms became worse and the patient was readmitted for altered mental status. Therefore, care must be taken to distinguish causes of nausea, vomiting, headache, and the altered mental status of elderly patients with hyponatremia.

Treatment for the hyponatremia of acute hypothyroidism in thyroid cancer patients depends on timely thyroid hormone injection and water restriction [19].

In this case, administering thyroid hormone with hypertonic solution was more effective in correcting the hyponatremia than using hypertonic solution alone, and administering both hypertonic solution and thyroid hormone lead to full recovery without any complications.

The volume and frequency of thyroid hormone dosage and ideal administration route has not been established, but care must be taken since a high volume of thyroid hormone can induce reactions such as arrhythmia [20].

In summary, hyponatremia is a clinically common electrolyte abnormality, but it is rare that severe hyponatremia is caused by hypothyroidism associated with thyroid hormone withdrawal in a thyroid cancer patient. There are rare patient cases with severe symptomatic hyponatremia after pretreatment with a low-iodine diet during thyroid hormone withdrawal. Globally, the incidence of thyroid cancer has increased and considering the low mortality of thyroid cancer, the number of patients who underwent radio iodine treatment and scanning for recurrence and remote metastasis will be increased. The authors have reported a case of a thyroidectomy patient with papillary thyroid carcinoma who presented with severe hyponatremia upon thyroid hormone withdrawal for iodine whole-body scanning, and who showed improvement after thyroid hormone and hypertonic solution injection.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. Pacini F, Castagna MG, Brilli L, Pentheroudakis G; ESMO Guidelines Working Group. Differentiated thyroid cancer: ESMO clinical recommendations for diagnosis, treatment and follow-up. *Ann Oncol* 2009;20 Suppl 4:143-6.
2. National Comprehensive Cancer Network. NCCN guidelines for thyroid carcinoma version 3. NCCN guidelines for treatment of cancer by site [Internet]. Fort Washington: National Comprehensive Cancer Network; c2014 [cited 2012 Jul 3]. Available from: http://www.nccn.org/professionals/physician_gls/pdf/thyroid.pdf.
3. Al Nozha OM, Vautour L, How J. Life-threatening hyponatremia following a low-iodine diet: a case report and review of all reported cases. *Endocr Pract* 2011;17:e113-7.
4. Krishnamurthy VR, McDougall IR. Severe hyponatremia: a danger of low-iodine diet. *Thyroid* 2007;17:889-92.
5. Nozu T, Yoshida Y, Ohira M, Okumura T. Severe hyponatremia in association with I(131) therapy in a patient with metastatic thyroid cancer. *Intern Med* 2011;50:2169-74.
6. Shakir MK, Krook LS, Schraml FV, Hays JH, Clyde PW. Symptomatic hyponatremia in association with a low-iodine diet and levothyroxine withdrawal prior to I131 in patients with metastatic thyroid carcinoma. *Thyroid* 2008;18:787-92.
7. Baajafer FS, Hammami MM, Mohamed GE. Prevalence and severity of hyponatremia and hypercreatininemia in short-term uncomplicated hypothyroidism. *J Endocrinol Invest* 1999;22:35-9.
8. Kilfoy BA, Zheng T, Holford TR, Han X, Ward MH, Sjoedin A, Zhang Y, Bai Y, Zhu C, Guo GL, Rothman N, Zhang Y. International patterns and trends in thyroid cancer incidence, 1973-2002. *Cancer Causes Control* 2009;20:525-31.
9. National Cancer Center. Annual report of cancer statistics in Korea in 2009 [Internet]. Goyang: National Cancer Center; 2009 [cited 2012 Mar 31]. Available from: http://www.ncc.re.kr/manage/manage03_033_view.jsp?bbsnum=229&hSe1Search=&hTxtKeyword=¤t_page=1&cd=null.
10. National Cancer Center. Cancer facts & figures 2012 in the Republic of Korea [Internet]. Goyang: National Cancer Center; 2012 [cited 2012 Jul 3]. Available from: http://www.cancer.go.kr/mbs/cancer/jsp/album/gallery.jsp?addCancerTitle=&spage=2&boardId=31817&boardSeq=84813&mcategoryId=&id=cancer_050207000000#.
11. Duntas LH, Biondi B. Short-term hypothyroidism after Levothyroxine-withdrawal in patients with differentiated thyroid cancer: clinical and quality of life consequences. *Eur J Endocrinol* 2007;156:13-9.
12. Kimura T. Potential mechanisms of hypothyroidism-induced hyponatremia. *Intern Med* 2000;39:1002-3.
13. Pacini F, Castagna MG. Diagnostic and therapeutic use of recombinant human TSH (rhTSH) in differentiated thyroid cancer. *Best Pract Res Clin Endocrinol Metab* 2008;22:1009-21.

14. Mazzaferri EL, Massoll N. Management of papillary and follicular (differentiated) thyroid cancer: new paradigms using recombinant human thyrotropin. *Endocr Relat Cancer* 2002;9:227-47.
15. Morris LF, Wilder MS, Waxman AD, Braunstein GD. Re-evaluation of the impact of a stringent low-iodine diet on ablation rates in radioiodine treatment of thyroid carcinoma. *Thyroid* 2001;11:749-55.
16. Montenegro J, Gonzalez O, Saracho R, Aguirre R, Gonzalez O, Martinez I. Changes in renal function in primary hypothyroidism. *Am J Kidney Dis* 1996;27:195-8.
17. Upadhyay A, Jaber BL, Madias NE. Incidence and prevalence of hyponatremia. *Am J Med* 2006;119(7 Suppl 1):S30-5.
18. Lien YH, Shapiro JI. Hyponatremia: clinical diagnosis and management. *Am J Med* 2007;120:653-8.
19. Verbalis JG, Goldsmith SR, Greenberg A, Schrier RW, Sterns RH. Hyponatremia treatment guidelines 2007: expert panel recommendations. *Am J Med* 2007;120(11 Suppl 1):S1-21.
20. Klubo-Gwiedzinska J, Wartofsky L. Thyroid emergencies. *Med Clin North Am* 2012;96:385-403.