Hypothyroidism-induced Acute Kidney Injury and Hyponatremia

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ABSTRACT
Thyroid hormones affect every organ system in the body including renal development and physiology, and electrolyte and water homeostasis. These effects happen as a consequence of the combination of direct effects of thyroid hormones on renal tubules and hemodynamic effects of thyroid hormones. As a consequence, both hypothyroidism and hyperthyroidism significantly affect renal function. This case describes a patient with hypothyroidism-related acute kidney injury without rhabdomyolysis, and no additional precipitating factor. While there are many case reports describing hypothyroidism-related rhabdomyolysis leading to acute kidney injury, there are only a handful of case reports on hypothyroidism-related acute kidney injury without rhabdomyolysis.

KEYWORDS: hypothyroidism, acute kidney injury, rhabdomyolysis, hyponatremia

INTRODUCTION
Hypothyroidism affects every organ system in the body, including the central nervous system, cardiovascular system, gastrointestinal system, musculoskeletal system, and the metabolic rate. Hypothyroidism is associated with an underappreciated but clinically significant alteration of renal physiology. While there are many case reports describing hypothyroidism-related rhabdomyolysis leading to acute kidney injury [AKI], there are only a handful of case reports on hypothyroidism-related AKI without rhabdomyolysis. This case describes a patient with hypothyroidism and AKI without rhabdomyolysis, and no additional precipitating factor.

CASE PRESENTATION
An 82-year-old male with past medical history of colorectal cancer (in remission for 15 years), hypertension, hypothyroidism and hyperlipidemia, presented from home with a change in mental status. According to family, the patient lived alone but his daughter visited frequently. At his baseline, he was fully oriented and able to take care of himself. Two days prior to presentation, his daughter noted that the patient complained of lethargy and lower back pain, with poor appetite and decreased oral intake. His mental status continued to worsen, and so his daughter brought him to the emergency department. Upon presentation, the patient was unable to recall life events and did not know why he was in the hospital. He denied fever, chills, chest pain, shortness of breath, cough, nausea, vomiting, abdominal pain, diarrhea, constipation, dysuria, urgency, peripheral edema or any focal neurological complaint.

Daily medications included levothyroxine, aspirin, fenofibrate, lisinopril, omепразоле, and vitamin D supplements. The patient had a two-pack-year smoking history but quit smoking decades prior to presentation. The family reported he ingested 5–7 standard alcoholic drinks per week. He was retired and spent most days at home.

Initial vital signs were the following: temperature 97.2°F, heart rate 48 regular beats per minute, respiratory rate 20/min, blood pressure 152/63 mmHg and oxygen saturation was 97% on room air. The patient was alert but oriented only to self. Cardiac exam revealed bradycardic S1S2. On neurological exam he was able to follow commands and had no focal deficits. The rest of his physical examination was within normal limits.

Laboratory results are included in Table 1. Urinalysis was unremarkable. EKG showed decreased voltage in precordial leads. TSH was 132.994 uIU/mL (normal range 0.35–5.5 uIU/ml), with free T4 low at 0.16 ng/dl (normal range 0.8–1.8 ng/dl) and T3 low at <20.0 pg/dL (normal range 230–420 pg/dl). CT of the brain without IV contrast, renal ultrasound, chest x-ray and CT of the abdomen and pelvis without IV contrast were unremarkable. Due to the hyponatremia, acute kidney injury, and profound hypothyroidism, the patient was admitted to the medical service.

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Both nephrology and endocrine were consulted for acute kidney injury, hyponatremia, and hypothyroidism. The patient received 500mL of intravenous 0.9% normal saline and was then fluid restricted to 1L/day. He was not given any maintenance intravenous fluids. He was also started on intravenous levothyroxine. His serum creatinine and serum sodium level normalized to 1.1 mg/dl and 138 meq/L, respectively, over the next 4–6 days. His mental status also improved by the time of discharge and remained stable at a 3 month follow-up visit. As a result of his rapid improvement with thyroxine and fluid restriction alone, his AKI and hyponatremia were thought to be directly related to myxedema.
The principal mode of AKI in myxedema is thought to be due to the reduced renal blood flow (RBF) and glomerular filtration rate (GFR), but the exact pathogenesis remains unclear and is thought to be multifactorial. Studies have described both genomic and nongenomic signaling by thyroid hormones.

Effect of hypothyroidism on hemodynamics

The effects of hypothyroidism on the cardiovascular system have been extensively studied and well documented. Thyroid hormones affect the cardiovascular system by both genomic and non-genomic pathways which widely overlap. Thyroid hormones regulate positive and negative expression of genes for structural and regulating proteins of cardiomyocytes, thus affecting both contraction and electro-chemical signaling pathways. Thyroid hormone fine-tunes the expression of genes for myosin heavy chain, which is the main structural part of the sarcomere. Thyroid hormone regulates the expression of sarcoplasmic reticulum Ca2+-ATPase (which plays a role in relaxation time during diastole), b1-adrenergic receptors (increase receptor function and density), guanine nucleotide regulatory proteins, Na+-K+-ATPase, voltage gated potassium channels and Na+/Ca2+ exchanger.

Effect of hypothyroidism on GFR

Subclinical and clinical hypothyroidism is a common problem in CKD patients. Elevated creatinine can be seen within two weeks of severe hypothyroidism. Creatinine often improves very quickly after appropriate treatment of hypothyroidism but sometimes patients can have slower improvement.
response or incomplete renal recovery with prolonged and severe hypothyroidism. Hypothyroidism may also cause increased glomerular capillary permeability which leads to proteinuria. Proteinuria often precedes the reduction in GFR in hypothyroidism.

Because creatinine-based equations are used to estimate GFR, it is unclear how much of an elevated creatinine level reflects the true drop in GFR. Creatinine levels can be altered by myopathy, decreased tubular secretion or creatinine metabolism. Cystatin C blood level cannot be used as a marker of GFR in this patient population as the levels are generally low in hypothyroid patients and elevated in hyperthyroid patients. The exact mechanism is unknown but it is thought to be related to direct effects of thyroid hormone on cystatin C production. In one study, Villabona and colleagues noted increased renal plasma flow [from 542.8 ml/min to 717 ml/min] and GFR [from 99.6 to 125.7 ml/min measured with Cr-EDTA clearance] after thyroid hormone replacement in overt hypothyroidism patients.

**Effect of hypothyroidism on Tubular function**
Thyroid hormones affect renal tubular function by both genomic and nongenomic pathways. Hypothyroidism affects renal tubular secretory and reabsorptive processes by upsetting the expression and activity of various ion channels/transporters. Thyroid hormones also influence the renal tubular physiology by alternating the responses to different hormones (Increased ADH sensitivity).

Hypothyroidism causes renal tubular down regulation of Na+-K+ ATPase, H+-ATPase, Na+-HCO3 exchanger, Na+-H+ exchanger, Na+/Pi IIa exchanger, Na+-sulfate exchanger, Na+-K+-2 Cl- cotransporter, Na+-Ca2+ exchanger, Cl- channel and up regulation of aquaporin (AQP) 1 and 2. As one can imagine, hypothyroidism will lead to impaired urinary concentrating ability, increased urinary sodium excretion, increased fractional excretion of sodium and decreased free water clearance. Hypothyroidism results in low cardiac output which triggers the carotid baroreceptors and consequently increases the non-osmotic ADH secretion. All of these effects of hypothyroidism on sodium and water homeostasis will lead to hypothyroidism-induced hyponatremia.

**Effect of hypothyroidism on Skeletal muscle**
Hypothyroidism causes rhabdomyolysis by inducing structural abnormalities in the setting of metabolic impairment. Structural abnormalities include decline in fast-twitch type II muscle fiber mass, increase in slow-twitch type I muscle fiber mass, decrease in muscle carnitine and glycosaminoglycan deposition. Metabolic abnormalities include inhibition of mitochondrial activity, decreased protein turnover,
impaired carbohydrate metabolism, low myosin ATPase activity and low ATP turnover. In turn, rhabdomyolysis causes AKI through intraluminal obstruction by myoglobin, uric acid casts, direct myoglobin toxicity and production of free radicals.

CONCLUSION

This case illustrates how severe symptomatic hypothyroidism can lead to severe renal dysfunction without rhabdomyolysis. Clinicians should be aware of this rare association and patients with unexplained AKI should be worked up for hypothyroidism.

References