CASE REPORT

Hypothyroidism and acute kidney injury: an unusual association

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SUMMARY

Association between severe hypothyroidism and acute kidney injury (AKI) is rare. A 40-year-old woman presented with 15 days history of generalised muscle pain, weakness, weight gain and oedema. Medical history: hypertension and hypothyroidism. Physical examination: dry skin, peripheral/periorbital oedema, slow thought and speaking, thyroid increased. Laboratory examinations: high levels of creatine kinase, creatinine, uric acid and lactate dehydrogenase. Free T4 was very low (<0.3 ng/dL) and thyroid-stimulating hormone was high ($21.7 \mu\text{IU/mL}$). Urinalysis showed haem pigment without haematuria. We performed the diagnosis of AKI secondary to hypothyroidism-induced rhabdomyolysis. Intravenous fluids were started, urinary alkalisation and increased l-thyroxine dose replacement. On the day after admission, forced diuresis with furosemide was introduced leading to a progressive improvement of symptoms. Although hypothyroidism and AKI is unusual, it should be suspected in patients presenting decrease of renal function and high creatine kinase in the absence of other causes of rhabdomyolysis.

BACKGROUND

In hypothyroidism muscle involvement is common. However, severe rhabdomyolysis and acute kidney injury (AKI) are rare and only a few cases have been reported.^{1–4} We report a case of severe hypothyroidism leading to rhabdomyolysis and AKI, without any additional precipitating factor.

CASE PRESENTATION

A 40-year-old woman was admitted to the hospital with 15 days history of generalised muscle pain, weakness, weight gain (5 kg in 10 days), progressive oedema and oliguria. She reported tiredness which had caused a reduction in her daily activities. She denied vigorous physical exercise. Her medical history included hypertension and hypothyroidism after radioactive iodine therapy. Her medication consisted of nifedipine, captopril, hydrochlorothiazide and l-thyroxine (with no use in past 2 months).

Physical examination revealed dry and pale skin, moderate peripheral and periorbital oedema, slow thought and speaking. Her pulse rate and blood pressure were normal (90 bpm and 100×80 mm Hg, respectively). Thyroid size had increased twice, without nodules. No signs suggesting an associated infectious or systemic inflammatory disease were found. No changes on physical examination of heart, lung and abdominal were observed.

INVESTIGATIONS

On admission, laboratory measurements revealed elevated CK 6629 U/L (30–135 U/L), serum creatinine (Cr) 1.7 mg/dL, blood urea nitrogen 51 mg/dL, potassium 3.7 mmol/L (3.6–5.0 mmol/L), sodium (Na) 133 mmol/L (137–145 mmol/L), calcium 11.6 mg/dL (8.4–10.2 mg/dL), phosphorus 5.3 mg/dL (2.5–4.5 mg/dL), aspartate aminotransferase (AST) 343 IU/L (9–52 IU/L), alanine aminotransferase (ALT) 178 IU/L (11–41 IU/L), lactate dehydrogenase (LDH) 461 IU/L (50–245 IU/L), uric acid (UA) 541 mmol/L (90–420 mmol/L), total bilirubin 4.1 mg/dL (0.2–1.3 mg/dL), unconjugated bilirubin 3.3 mg/dL (0.0–1.1 mg/dL), conjugated bilirubin 0.8 mg/dL (0.0–0.3 mg/dL), albumin 4.3 g/dL (3.5–5.0 g/dL) and glucose 106.0 mg/dL (<100 mg/dL), triglycerides 166.0 mg/dL (<150 mg/dL), total cholesterol 168.0 (<200 mg/dL), C-reactive protein 1.4 mg/dL (<1.0).

Haematological tests showed haemoglobin 9.4 g% (12–16 g%), white cell count $9000/\text{mm}^3$, thrombocytopenia, macrocytosis and absence of schistocytes. Thyroid function tests confirmed the diagnosis of severe hypothyroidism (free T4 <0.3 ng/dL (1.71–2.8 ng/dL) and thyroid stimulant hormone $21.7 \mu\text{IU/mL}$ (0.35–5.5 $\mu\text{IU/mL}$)). Urinalysis showed pH 5.0, density 1035, haem pigment without pyuria or haematuria and proteinuria was negative. Fraction excretion of Na and urinary Na were high (1.9% and 44 mEq/L, respectively). Renal tract ultrasonography was normal. We performed the diagnosis of AKI secondary to hypothyroidism-induced rhabdomyolysis.

DIFFERENTIAL DIAGNOSIS

Hepatitis, cytomegalovirus and leptospirosis serologies were negative.

TREATMENT

Intravenous fluids were started immediately, as urinary alkalisation with sodium bicarbonate and increased l-thyroxine dose replacement (250 $\mu\text{g/day}$). On the day after admission, forced diuresis with furosemide (60 mg/day), as well as folic acid (5 mg/day) and B vitamin (5000 $\mu\text{g/month}$) were introduced leading to a progressive improvement of symptoms in a few days.

OUTCOME AND FOLLOW-UP

Table 1 shows laboratory results during follow-up.

DISCUSSION

The present case describes a patient with hypothyroidism and AKI due to rhabdomyolysis, with no

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additional precipitating factor. Prakash *et al*⁵ observed there is an inverse relation in the serum levels of thyroid hormones and CK in hypothyroid patients and concluded that the estimation of serum CK levels can be extremely valuable in screening for hypothyroid patients. Although the main features of rhabdomyolysis are muscular symptoms and increased CK concentrations, it can become a life-threatening disorder when complicated by AKI (10–50%).⁶

In most of previously reported cases of rhabdomyolysis associated with hypothyroidism, an aggravating factor has been identified.^{1–4} Although hypothyroidism is frequently accompanied by asymptomatic mild to moderate CK elevations, usually less than 10 times the upper normal limit, to our knowledge, few previous cases of AKI due to rhabdomyolysis have been associated with hypothyroidism alone.⁷

In our patient, CK was elevated and the presence of urinary myoglobin confirmed rhabdomyolysis.

The exact cause of rhabdomyolysis in hypothyroidism remains unclear, but both impaired glycogenolysis and impaired mitochondrial oxidative metabolism have been involved, and an autoimmune mechanism could be possible.⁸

It has been suggested that haem proteins can induce renal dysfunction by a variety of mechanisms in presence of hypovolaemia and aciduria, which are crucial factors in the development of myoglobinuric AKI. Three mechanisms influence haem proteins toxicity: renal vasoconstriction resultant ischaemia and ATP depletion, intraluminal cast formation and direct haem protein-induced cytotoxicity, leading to activation of cytokine cascade and endothelin receptors consequent upon free radical formation manifested mainly as lipid peroxidation.^{9–10}

AKI can be caused by a tubular obstruction causing increased intraluminal pressure and thus opposing glomerular filtration and by oxidative damage to the renal tubule induced by haem-produced free radical.

Although the patient history and physical examination can provide clues, the diagnosis of rhabdomyolysis is confirmed by laboratory studies. As it is a condition in which damaged skeletal muscle tissue breaks down rapidly, products of damaged muscle cells are released into the bloodstream and some of these are protein myoglobin, UA, LDH, AST and ALT.¹¹ CK levels are the most sensitive indicators of myocyte injury in rhabdomyolysis. CK rises within 12 h of the onset of muscle injury, peaks in 1–3 days and declines 3–5 days after the cessation of muscle

injury. CK levels of 5000 U/L or greater is in relation to AKI.² In this case, the patient's CK levels started declining from 5 days after the thyroid hormone replacement was initiated, and her Cr levels normalised after 9 days of the cessation of the muscle injury.

The management of patients with rhabdomyolysis includes advanced life support followed by measures to preserve renal function. Retrospective analysis demonstrated that early aggressive fluid replacement with saline is beneficial in minimising the occurrence of AKI.^{9–10,12–15} The use of alkalinising agents (bicarbonate) and forced diuresis (mannitol or furosemide) following the initial resuscitation with saline and started within 6 h of admission have been reported to minimise the risk of AKI. Their objectives are to minimise intratubular haem pigment deposition and to act as a free-radical scavenger, thereby minimising cell injury.^{9–12–15} This patient received vigorous hydration and bicarbonate within 6 h of admission and forced diuresis was initiated on the day after admission. Thyroid hormone replacement therapy was added early and this adequate treatment brought complete recovery of rhabdomyolysis and renal function.

Learning points

- ▶ Hypothyroidism is a rare cause of acute kidney injury.
- ▶ It should be suspected in patients presenting muscles aches, high creatine kinase and creatinine in the absence of other more common causes of rhabdomyolysis.
- ▶ As soon the diagnosis is made, measures to recover renal function and thyroid hormone replacement should be started.

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Table 1 Main laboratory results on admission and during follow-up

Laboratory examinations	Time since diagnosis				
	0 day	3 days	5 days	14 days	30 days
CK (U/L)	6629.0	6961.0	3266.0	318.0	39.0
Output urine 24 h (mL)	400	1700	4000	2050	–
Creatinine (mg/dL)	1.7	2.2	1.2	0.9	0.8
UA (mmol/L)	541	471	409	117	–
LDH (U/L)	461	411	309	66	–
AST (U/L)	343	–	187	48	–
P (mg/dL)	5.3	5.1	4.8	3.8	–
FT4 (ng/dL)	<0.3			2.22	2.50
TSH (μIU/mL)	21.7			10.8	3.24
Thyroxine dose (μg)	250	250	250	250	200

CK, creatine kinase (30–135 U/L); AST, aspartate aminotransferase (9–52 U/L); LDH, lactate dehydrogenase (50–245 U/L); UA, uric acid (90–420 mmol/L); P, phosphorus (2.5–4.5 mg/dL); FT4, free thyroxine 4; TSH, thyroid-stimulating hormone.

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