A case of recurrent hypothyroidism-induced rhabdomyolysis

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Abstract

Rhabdomyolysis due to hypothyroidism is uncommon, and there have been few case reports of repeated rhabdomyolysis in patients with hypothyroidism. We report a rare case of repeated rhabdomyolysis in a patient with hypothyroidism. The patient was a 65-year-old Japanese male who presented to an outside hospital with bilateral lower extremity weakness; he was diagnosed with hypothyroidism and successfully treated with levothyroxine. His symptoms and laboratory parameters improved with treatment such that he was safely discharged. However, the patient was non-compliant with his levothyroxine beginning at 10 weeks after his discharge and re-presented with bilateral lower extremity weakness and myalgias 18 weeks after stopping his thyroid supplementation. He was readmitted to our hospital and was again diagnosed with rhabdomyolysis secondary to Hashimoto's thyroiditis. Serological thyroid function and muscle enzymes normalized after the second dose of levothyroxine. The patient has remained symptom-free without recurrent episodes of rhabdomyolysis at two-year follow-up.

Keywords

rhabdomyolysis, hypothyroidism, Hashimoto's thyroiditis, thyroid hormone replacement

Introduction

About 79% of adult patients with untreated hypothyroidism have musculoskeletal symptoms such as myalgias, muscle cramps, and muscle stiffness (Fariduddin et al, 2022; Sindoni et al, 2016). Muscle enzymes such as creatine kinase (CK) may be elevated, but usually at levels less than ten times the upper limit of normal (Sindoni et al, 2016). Rhabdomyolysis is characterized by severe acute muscle injury resulting in myalgia, weakness, and/or swelling with release of myofiber contents into the bloodstream inducing marked elevation of serum CK (Nance et al, 2015; Zutt et al, 2014). The causes of rhabdomyolysis include vigorous exercise, drugs, electrolyte imbalance, alcohol consumption (binge drinking), seizures, trauma, infections, and endocrine disorders (Zutt et al, 2014; Vanholder et al, 2000). It can become a life-threatening disorder when severe complications such as renal failure occur. Complication rates from acute renal failure in rhabdomyolysis range from 15% to over 50% (Melli et al, 2005). The mortality rate of

rhabdomyolysis is reported at about 8%–10% (Zutt et al, 2014). Although muscle involvement is common in hypothyroidism, complications of rhabdomyolysis in patients with hypothyroidism seem to be uncommon. Moreover, there have been few case reports of recurrent rhabdomyolysis in patients with hypothyroidism; to knowledge, only one case has been reported (Boryushkina et al, 2019). Herein we report a rare case of recurrent rhabdomyolysis in a patient with hypothyroidism secondary to Hashimoto's thyroiditis (HT).

Case presentation

The patient is a 65-year-old Japanese male with a past medical history of hemorrhoidectomy and family history negative for thyroid disorders. His social history was notable for frequent alcohol consumption; he endorsed 100 g/day of ethanol consumption in the six months prior to presentation. He denied taking any medications. He had noticed cold intolerance for two years. He presented at a community hospital with a primary complaint of bilateral lower extremity weakness; he denied vigorous physical exercise or recent trauma. At the time of consultation, serological laboratory findings were as follows: AST 127 U/L, ALT 56 U/L, γ-GTP 385 (reference value <70) U/L, creatinine 1.54 mg/dL, CK 55,220 (reference value 62-287) U/L, Na 140 mEq/L, K 4.1 mEq/L, and Cl 106 mEq/L. He was admitted for non-hypokalemic rhabdomyolysis and started on intravenous fluid replacement. Serological laboratory findings after admission suggested primary hypothyroidism: free T3 (FT3) <0.2 (reference value 2.52-4.06) pg/mL, FT4 0.06 (reference value 0.75-1.45) ng/dL, and thyroid stimulating hormone (TSH) 34.6 (reference value 0.61-4.23) μIU/mL. Serological thyroid function and muscle enzymes normalized after levothyroxine administration, and he was discharged.

The patient was non-compliant with his levothyroxine and discontinued it ten weeks after discharge. He experienced recurrent symptoms (myalgia and bilateral lower extremity weakness) 18 weeks after discontinuing the medication. He presented to our hospital, and he denied alcohol ingestion in the preceding nine months. At the time of consultation his height was 163.4 cm and body weight was 75.2 kg. His blood pressure was 110/70 mmHg, pulse rate 72 beats/min, and temperature 35.1℃. The patient was alert and conscious. His conjunctiva was normal. A thyroid goiter was not appreciated. The cardiopulmonary and abdominal examinations were normal. The extremities were not edematous, and a skin exam was negative for wounds or lesions. Manual muscle testing of bilateral upper extremities was 5/5 (good), whereas that of bilateral lower extremities was 3/5 (fair). Laboratory findings were as follows: white blood cells 5,010/μL, hemoglobin 10.0 g/dL, total protein 6.9 g/dL, total bilirubin 0.9 mg/dL, AST 67 U/L, ALT 12 U/L, lactate dehydrogenase 1130 U/L, γ-GTP 45 U/L, BUN 17.9 mg/dL, creatine 1.40 mg/dL, CK 10,770 U/L, myoglobin 631.7 (reference value <154.9) ng/mL, aldolase 14.0 (reference value 2.1-6.1) U/L, Na 138 mEq/L, K 3.9 mEq/L, Cl 104 mEq/L, P 2.9 (reference value 2.5-4.5) mg/dL, C-reactive protein 0.3 mg/dL, FT3 <0.2 pg/mL, FT4 0.20 ng/dL, TSH 79.6 μIU/mL, anti-thyroglobulin antibody 745.2 (reference value <19.3) IU/L, thyroid peroxidase antibody 227.3 (reference value <3.3) IU/L. Urinalysis was negative for protein, but positive for occult blood. Chest radiograph revealed mild cardiomegaly (cardiothoracic ratio was 55%), and echocardiogram revealed a small pericardial effusion. Thyroid ultrasound showed slight thyromegaly bilaterally. The patient was diagnosed with rhabdomyolysis secondary to hypothyroidism due to HT. His serum creatinine normalized with intravenous fluid replacement. He was started on 25 μg/day of levothyroxine with symptomatic improvement thereafter. Serum levels of FT3, FT4, and muscle enzymes normalized within 8 weeks. Serum level of TSH normalized within 12 weeks (Table 1). Pericardial effusion resolved within four weeks and his body weight decreased by 3.8 kg after six weeks of levothyroxine replacement. He was discharged safely and has been followed as an

outpatient. Serological thyroid function and CK levels have been monitored, and they remain within normal limits two years after his second hospitalization.

Discussion

In our case, hypothyroidism was secondary to HT, which is an autoimmune disease (Weetman, 2021; Caturegli et al, 2014). HT is the most common cause of primary hypothyroidism in iodine-sufficient areas, including Japan (Chaker et al, 2017). The diagnosis of HT relies on the demonstration of circulating antibodies to thyroid antigens (mainly thyroperoxidase and thyroglobulin), and concordant sonographic features (Caturegli et al, 2014). In our case, thyroid-specific autoantibodies, such as anti-thyroglobulin antibody and thyroid peroxidase antibody, were positive and ultrasound demonstrated symmetric thyromegaly. The clinical picture was consistent with HT.

The common symptoms in adults with hypothyroidism are fatigue, lethargy, cold intolerance, weight gain, constipation, changes in voice, and dry skin; however, hypothyroidism can impact all major organs (Chaker et al, 2017). About 79% of adult patients with hypothyroidism have various forms of musculoskeletal involvement (Fariduddin et al, 2022; Sindoni et al, 2016). Symptoms range from muscle weakness and myalgias, to rhabdomyolysis and Hoffman's syndrome (pseudohypertrophy of the muscle) (Sindoni et al, 2016; Ahmed et al, 2014). Muscular complaints also can be possible clues for the diagnosis of hypothyroidism. Although serum elevation of CK can be observed in 57% to 90% of patients with hypothyroidism, the degree of CK elevation does not necessarily correlate with the severity of musculoskeletal involvement, and complications from rhabdomyolysis in patients with hypothyroidism seem to be uncommon (Sindoni et al, 2016; Kuo et al, 2010). Although the precise mechanisms leading to musculoskeletal involvement in hypothyroidism remain uncertain, it is hypothesized that hypothyroidism induces biological changes in muscle fibers from fast-twitching type II to slow-twitching type I fibers, deposits glycosaminoglycans, and attenuates the contractility of actin-myosin units, which results in low myosin ATPase activity and low ATP turnover in the skeletal muscles (Fariduddin et al, 2022; Wiles et al, 1979). Therefore, an inhibition of mitochondrial activity in muscle cells, as well as dysregulation of many metabolic pathways, such as fatty acid catabolism and glycolytic energy production, have been involved as possible explanations for hypothyroidism-induced rhabdomyolysis (Varalakshmi et al, 2020; Katipoglu et al, 2016; Kisakol et al, 2003; Barahona et al, 2002; Djouadi et al, 1997). Moreover, hypothyroidism-induced rhabdomyolysis appears to be more common in males, despite that hypothyroidism is more common in women (Salehi et al, 2017). Similarly, patients with HT and hypothyroid myopathy have no differences in gender distribution, although HT occurs more often in females (Weetman, 2021; Sindoni et al, 2016).

Patients with hypothyroidism may be more susceptible to rhabdomyolysis in the presence of other precipitating factors such as vigorous exercise, seizures, and drugs (Fariduddin et al, 2022; Gurala et al, 2019; Rabhi et al, 2006; Barahona et al, 2002; Sekine et al, 1993). However, there have been more than ten case reports of hypothyroidism-induced rhabdomyolysis without obvious precipitating factors (Varalakshmi et al, 2020; Gurala et al, 2019; Katipoglu et al, 2016; Altay et al, 2010; Kuo et al, 2010; Nikolaidou et al, 2010; Chowta et al, 2008; Rabhi et al, 2006; Kisakol et al, 2003; Barahona et al, 2002; Jain et al, 1999). Hypothyroidism-induced rhabdomyolysis usually responds very well to thyroid hormone replacement; most patients experience symptomatic recovery and normalization of thyroid function (Fariduddin et al, 2022; Kuo et al, 2010).

Several studies indicate that acute alcohol intoxication or chronic alcoholism can cause rhabdomyolysis (Nance et al, 2015; Hewitt et al, 1995). Alcohol-related rhabdomyolysis has been attributed to a direct toxic effect on muscle and secondary metabolic changes associated with

alcohol abuse (Efstratiadis et al, 2007; Hewitt et al, 1995). Muscle dysfunction in the setting of alcoholic dysfunction is multifactorial, and is attributable to a combination of immobilization, acid-base and electrocyte imbalances (i.e., hypokalemia, hypomagnesemia, and hypophosphatemia), agitation, and/or direct myotoxity (Manappallil et al, 2021; Mahendran et al, 2019; Vanholder et al, 2000; Haller, 1985). Moreover, alcohol abuse also induces the hepatic cytochrome P450 incorporating toxic metabolites (Efstratiadis et al, 2007). There were also several experimental studies demonstrating alcoholic myotoxicity in animal models. One study demonstrated that alcohol-fed animals developed biochemical features of rhabdomyolysis, with glycogen depletion being the underlying pathophysiology in affected muscle fibers (Haller, 1985). A second study indicated that chronic administration of alcohol may result in focal myofibrillar necrosis and disintegration of the basal lamina of muscle, and also may be capable of causing direct injury to the sarcolemma (Ferguson et al, 1984). A third study indicated that acute ethanol intoxication exacerbates the effects of rhabdomyolysis on muscular and rhabdomyolysis-induced organ damage (Tsai et al, 2017). In our case, the patient denied ingestion of alcohol in the nine months preceding the second episode of rhabdomyolysis. Serum γ-GTP was 385 U/L in the first episode (reference value <70), but normal (45 U/L) in the second episode. Therefore, ingestion of alcohol (about 100g/day of ethanol) in the setting of hypothyroidism may have precipitated the first episode. The second episode may have been induced by self-cessation of levothyroxine.

To our knowledge, there has only been one case report of recurrent hypothyroidism-induced rhabdomyolysis; The case reported on a middle-aged male with hypothyroidism who developed recurrent rhabdomyolysis precipitated by deep muscle injury, seizure, and non-compliance with medications (Boryushkina et al, 2019). Given the scarcity of similar reports, it appears that our case is quite rare.

Conclusion

We report a rare case of recurrent rhabdomyolysis in a patient with hypothyroidism. Hypothyroidism-induced rhabdomyolysis may be associated with elevation of CK, and it may occur without any obvious precipitating factors. The diagnosis of hypothyroidism should be considered when a patient presents with rhabdomyolysis in the absence of other causes.

Table 1 Changes in serological thyroid function and muscle enzymes before and after thyroid hormone replacement

Variable	Reference range	before	1 week	2 weeks	4 weeks	8 weeks	12 weeks
CK	62-287 (U/L)	11053	4425	1735	431	117	74
Myoglobin	<154.9 (ng/mL)	668	322	181	86		
Free T4	0.75-1.45 (ng/dL)	0.2			1.03	1.38	1.33
TSH	0.61-4.23 (μIU/mL)	79.6			20.1	9.3	4.1

CK: creatine kinase; TSH: thyroid stimulating hormone

Conflict of interests

There was no funding support and there is no conflict of interests to declare.

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