

Fenofibrate-induced rhabdomyolysis in a patient with chronic kidney disease: an unusual presenting feature of hypothyroidism

Rabdomiólise induzida por fenofibrato em paciente com doença renal crônica: uma apresentação clínica incomum do hipotireoidismo

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ABSTRACT

Clinical and most often moderate skeletal muscle involvement is a frequent problem in adults with hypothyroidism, and includes a number of different manifestations. Severe involvement with rhabdomyolysis, however, is very rare, and only a few cases have been reported to date, most of them with an additional factor of muscle injury. We described a patient with stage 3 chronic kidney disease who presented with rhabdomyolysis while taking fenofibrate, and was found to have hypothyroidism. We also highlighted the importance of excluding the diagnosis of thyroid dysfunction before treatment with lipid-lowering agents. *Arq Bras Endocrinol Metab.* 2009;53(3):383-7.

Keywords

Rhabdomyolysis; hypothyroidism; chronic kidney disease; fibrato

RESUMO

Manifestações musculoesqueléticas variadas e de moderada intensidade são comuns em adultos com hipotireoidismo. No entanto, o envolvimento muscular grave, caracterizado por rabdomiólise, é incomum. Até o momento, poucos casos foram descritos na literatura, e a maior parte deles em associação com um fator adicional de dano muscular. Descrevemos um paciente com doença renal crônica (estádio 3) que se apresentou com rabdomiólise durante o tratamento com fenofibrato e cuja investigação adicional evidenciou hipotireoidismo primário. Enfatizamos, ainda, a importância da exclusão de disfunção tireoidiana antes de iniciar terapia com agentes hipolipemiantes. *Arq Bras Endocrinol Metab.* 2009;53(3):383-7

Descritores

Rabdomiólise; hipotireoidismo; doença renal crônica; fibrato

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INTRODUCTION

Musculoskeletal symptoms in adults with hypothyroidism are frequent (1) and can be the first sign of thyroid dysfunction (2,3). Hypothyroid myopathy is usually limited to asymptomatic elevation of serum creatinine phosphokinase (CPK) concentration, myalgias, muscle stiffness, delayed relaxation of tendon reflexes, cramps and proximal muscle weakness (4,5). Prominent changes, such as acute myoedema, Hoffman's syndrome

and rhabdomyolysis, have otherwise only been rarely reported (4,6-8).

Rhabdomyolysis is a syndrome involving skeletal muscle necrosis and the consequent release of intracellular muscle proteins and electrolytes into the systemic circulation. Its severity is variable, ranging from asymptomatic elevations in serum muscle enzymes levels to life-threatening electrolyte disturbances and acute renal failure (9). The development of rhabdomyolysis is as-

sociated with a number of different conditions, such as infections, trauma, strenuous physical exertion, drugs, toxins, electrolyte abnormalities, heritable muscle enzyme deficiencies, and endocrinopathies, although in many cases the precise etiology is not readily identified (10,11). The typical clinical presentation includes muscle weakness, myalgias and dark-colored urine due to myoglobinuria, and the diagnosis is usually established by elevated serum skeletal muscle enzyme levels (12). CPK is the most sensitive indicator of muscle injury and, although there is no defined serum cut-off level for the diagnosis, many clinicians use five to ten times the upper limit of normal range (13). The mainstay of treatment is aggressive intravenous fluid administration and correction of electrolyte abnormalities, and the cause of rhabdomyolysis should always be specifically treated when identified (9,13). Additional measures include urinary alkalization and diuretic therapy when euvolemia has been achieved but, because of the lack of randomized controlled trials to investigate the effectiveness of these adjunct therapies, their use remains of unproven benefit (13). With early and vigorous hydration and other measures to preserve renal function, the overall prognosis for rhabdomyolysis is good (13).

We reported a patient with chronic kidney disease who presented with rhabdomyolysis during fenofibrate therapy for hypertriglyceridemia, and was subsequently found to have hypothyroidism.

CASE REPORT

A 54-year-old white man was admitted because of increasing myalgias and coluria.

His past medical history was remarkable for stage 3 chronic kidney disease secondary to polycystic kidney disease, which was diagnosed seven years before and managed expectantly, and also for arterial hypertension and hypertriglyceridemia. He was being treated with nifedipine OROS 30 mg bid and propranolol 40 mg bid. Micronized fenofibrate (200 mg q.d.) was added in the last two months, because of persistent hypertriglyceridemia despite nonpharmacologic measures. The patient had been relatively stable until three months before admission, when he insidiously developed fatigue, dry and pale skin, coarseness of his voice, maleolar edema and loss of body hair (predominantly in the legs). Five days before admission, he began to haveodynophagia, dry cough, headache and malaise, and was evaluated in the emergency department. Acute

sinusitis was diagnosed, azithromycin and nimesulide were started, but all symptoms persisted. Three days before admission, the patient developed myalgias, which were most severe in the proximal muscles of his upper extremities, and also noticed coluria. He reported exercising regularly (30-minute brisk walk, three times a week), but denied any form of moderate to strenuous physical activity. He reported family history of hypothyroidism due to Hashimoto's thyroiditis and type 1 *diabetes mellitus*.

On physical examination, the patient appeared pale, had periorbital puffiness, dryness and coarseness of the skin, loss of the lateral aspects of his eyebrows, hair loss in the distal part of his lower extremities, and a multinodular goiter. Heart rate was normal (72 beats/min.), muscle strength was 3/5, and relaxation of deep tendon reflexes was delayed. No other abnormalities were detected on physical examination.

Initial laboratory tests revealed normocytic-normochromic anemia (hematocrit: 32,7%, reference range: 37,8-48,6), glucose 78 mg/dL (reference range: 70-99), Na 137 mEq/L (reference range: 135-150), K 6,3 mEq/L (reference range: 3,5-5,0), albumin 3,7 g/dL (reference range: 3,4-4,8) and increased creatinine levels (4,9 mg/dL, reference range: 0,7-1,2). Serum muscle enzyme levels were markedly elevated: CPK 52.749 IU/L (reference range: 39-308), lactic dehydrogenase 1.444 IU/L (reference range: 100-190) and aspartate aminotransferase 200 IU/L (reference range: < 37). His baseline creatinine level (measured four months before admission) was 2,54 mg/dL, and a lipid profile obtained two months earlier showed total cholesterol 204 mg/dL (reference range: < 200), LDL-cholesterol 107 (reference range: < 100), HDL-cholesterol 36 (reference range: > 40) and triglyceride 304 (reference range: < 150). Other laboratory values are shown in table 1.

Urinary analysis disclosed 3+ proteinuria and 2+ hematuria with dipstick, 16 red cells per high-power field and no pigmented casts. Thyroid-stimulating hormone (TSH) serum concentration was 86,5 mcUI/mL (reference range: 0,4-4,0), free thyroxin levels were < 0,2 pmol/L (reference range: 0,75-1,85) and triiodothyronine levels were < 40 ng/dL (reference range: 60-200). Thyroid peroxidase antibody titer was strongly positive (2.135 IU/L), and thyroid ultrasonography revealed a diffusely heterogeneous gland with three hyperechogenic and two cystic nodules at the right lobe (3 to 7 mm), and a hyperechogenic nodule with cystic areas at the left lobe (22 mm).

Table 1. Blood chemical values during hospital stay

Variable	Hospital day						Reference range
	1 st	3 rd	5 th	7 th	9 th	11 th	
CPK (IU/L)	52.749	31.000	14.400	3.591	1.890	755	39 - 308
Lactic dehydrogenase (IU/L)	1.444	1.760	2.020	1.514	1.362		100 - 190
Aspartate aminotransferase (IU/L)	200	1,750	1.230	512	268	162	< 37
Urea (mg/dL)	121	103	103	89	84	79	10 - 50
Creatinine (mg/dL)	4,9	4,7	5,0	3,9	3,8	3,4	0,7 - 1,2

Note: on the first hospital day, after the results of initial laboratory tests were obtained, fenofibrate and propranolol were discontinued, and the patient was carefully treated with intravenous fluids, urinary alkalization and levothyroxine.

Fenofibrate and propranolol were discontinued on admission, and the patient was carefully treated with intravenous fluids, urinary alkalization and levothyroxine. He had progressive improvement of symptoms and muscle strength, and the serum concentration CPK gradually decreased. Renal function improved but did not return to baseline levels (Table 1).

DISCUSSION

The present report described a patient with chronic kidney disease and undiagnosed primary hypothyroidism, who presented with rhabdomyolysis while taking fenofibrate for the treatment of hypertriglyceridemia.

Hypothyroid myopathy includes a wide clinical spectrum, and is frequently correlated to the duration and biochemical severity of hypothyroidism (6,7). Overt rhabdomyolysis, even in the most severe cases of thyroid dysfunction, is rarely precipitated by hypothyroidism alone (14-16). Most cases described to date have been associated with an additional factor of muscle injury, such as strenuous physical activity (17), infection, trauma (18), lipid-lowering agents (19), alcohol or other toxic agents, or with previous unrecognized congenital deficiency of muscle enzymes (4) or chronic kidney disease (4,8,20,21).

The precise pathophysiology of rhabdomyolysis in hypothyroidism is currently not clear (22). Skeletal muscle cell metabolic abnormalities are currently believed to be the basis of hypothyroid myopathy, in particular mitochondrial dysfunction. Thyroid hormone has been shown to regulate the expression of genes encoding structural and regulatory proteins involved in mitochondrial respiratory function (23), and their expression has been found to be reduced in skeletal muscle of hypothyroid patients (24). Because the deficiency of these proteins has been implicated in some primary mi-

tochondrial disorders with musculoskeletal involvement (25), it could also be a possible mechanism underlying hypothyroid myopathy. Muscle involvement in hypothyroidism is characterized by decreased concentration of fast twitching type II fibers and increased concentration of slow twitching type I fibers, low myosin ATPase activity, and low ATP turn-over in skeletal muscle (8). Hypothyroidism is also associated with impairment of mitochondrial oxidative metabolism and many other metabolic pathways, such as Krebs cycle, fatty acid catabolism and glycolytic energy production (5,7,26). These metabolic abnormalities might sensitize muscle cells to other factors related to muscle injury and increase the risk of rhabdomyolysis (6,7,27).

It has been also suggested that an autoimmune mechanism could play a role (27). However, the histological findings of fiber necrosis in the absence of an inflammatory infiltrate suggest that an autoimmune basis is unlikely (20).

The diagnosis of rhabdomyolysis in this patient was established on the basis of myalgia, muscle weakness, prominent elevation of serum levels of CPK, lactate dehydrogenase, aspartate aminotransferase and also creatinine. Nevertheless, the cause of rhabdomyolysis cannot be precisely defined. Since fenofibrate monotherapy-induced rhabdomyolysis is extremely rare and most of the cases described so far have been associated with an additional factor of muscle injury (28), it seems reasonable to speculate that both therapy with fenofibrate and undiagnosed hypothyroidism were involved, and also that chronic kidney disease might have had a contributory role.

Hypothyroidism represents a rare but definite cause of rhabdomyolysis, and should always be suspected in patients presenting with muscle aches and high serum concentrations of muscle enzymes – even in the presence of other determinants of muscle injury (20,27,29,30). As pre-

sented in this report and by others (7,31), the association of lipid-lowering agents and hypothyroidism as a cause of rhabdomyolysis suggests the need for evaluation of thyroid function when therapy with fibric acid derivatives or statins is considered, especially in patients with chronic kidney disease (32,33). Assessment of thyroid status is also recommended when patients on lipid-lowering agents develop myopathic symptoms or resistance to therapy (26). Not only hypothyroidism is an established secondary cause of dyslipidemia, but it might also potentiate the risk of myopathy induced by lipid-lowering agents (34-37).

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