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McARDLE DISEASE WITH RHABDOMYOLYSIS INDUCED BY ROSUVASTATIN

Case report

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ABSTRACT - The rosuvastatin inducing rhabdomyolysis in McArdle disease (MD) has not been reported to date. A 35-years-old man had exercise intolerance, muscular fatigue and cramps during physical activity since infancy. He presented severe rhabdomyolysis episode with seizure and coma after use of rosuvastatin. The investigation showed increased serum creatinekinase levels and the forearm ischemic exercise did not increased venous lactate. The muscle biopsy showed subsarcolemmal and central acummulation of glycogen and absence of the myophosphorylase enzyme. The statin induced myopathy is discussed and the danger of its use in MD is emphasized.

KEY WORDS: McArdle disease, toxic myopathy, rosuvastatin, rhabdomyolysis, statin myopathy.

Doença de McArdle com rabdomiólise induzida por rosuvastatina: relato de caso

RESUMO - Rosuvastatina induzindo rabdomiólise na doença de McArdle (MD) não foi relatada até o momento. Descrevemos o caso de um homem de 35 anos que desde a infância apresentava sintomas de intolerância aos exercícios, fadiga muscular e cãibras durante o esforço físico, porém após o uso de rosuvastatina apresentou episódio de rabdomiólise com crises convulsivas e coma. A investigação mostrou creatinoquinase sérica elevada e teste do esforço isquêmico sem aumento no lactato venoso. A biópsia muscular revelou acúmulo central e subsarcolemal de glicogênio nas fibras e ausência da enzima miofosforilase. Discutimos as estatinas induzindo miopatia, enfatizando o risco do seu uso na MD.

PALAVRAS-CHAVE: doença de McArdle, miopatia tóxica, rosuvastatina, rabdomiólise, miopatia por estatina.

McArdle disease (MD) or glycogenosis type V, is the most common disorder of muscle carbohydrate metabolism, caused by deficiency of myophosphorylase enzyme[1,2]. Only striated muscles are involved, leading to exercise intolerance, muscle cramps and myoglobinuria secondary to rhabdomyolysis[1]. This predisposition to rhabdomyolysis may exclude the use of certain drugs in MD patients[2]. Although statins, an inhibitor of enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, are generally well tolerated, muscle related side effects ranging from mild muscle pain to severe rhabdomyolysis with myoglobinuria have been reported, and these can occur in the presence of normal or elevated serum creatinekinase (CK) levels[2-4].

Rosuvastatin (RS) is a lipid-lowering drug (LLD) very well tolerated, but adverse muscular effects have been described. Rhabdomyolysis induced by use of RS in MD patients has not reported to date[5-7] as in the case we report.

CASE

A 35-year-old man had exercise intolerance, muscular fatigue, muscle spasms, myalgia and cramps in exercising muscles in the beginning of the physical activity and episodes of seizures after prolonged physical activity (as playing soccer) since infancy. At 34-years of age the gait become more difficult and the stiffness more pronounced in the lower limb muscles during forced physical activity. At age 35, it was discovered hyperlipidemia, wich was treated with RS (10 mg/day) due to the estimated cardiovascular risk.

He was admitted in an intensive care unit of other hospital following eighth day use of RS after episode of syncope, seizures and important reduction of muscle strength in upper and lower limbs associated with myoglobinuria.

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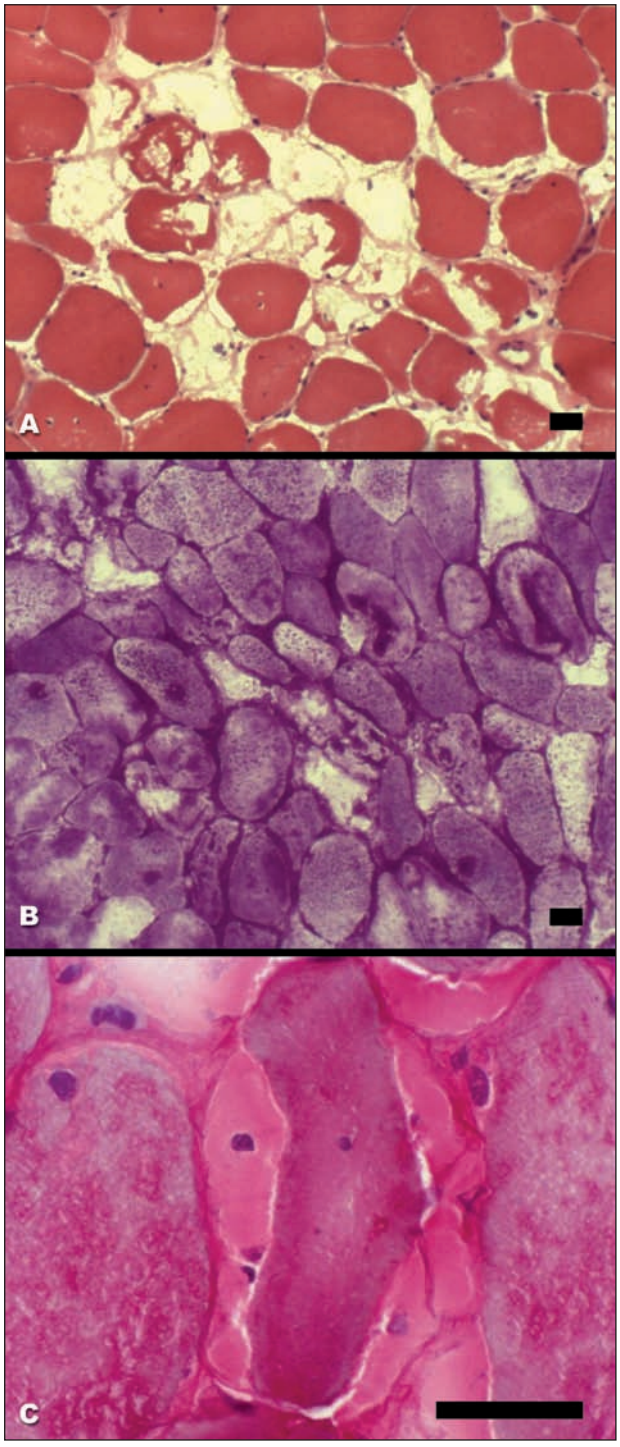

Fig 1. The muscle biopsy specimens revealed numerous subsarcolemmal and central vacuoles in hematoxylin-eosin stained (A) with periodic acid-Schiff (B) and Siryus red (C) vacuoles positives. Bar: 50 μm.

Routine hematological and biochemical screening showed normal blood counts, creatinine was 1.7 mg/dL (normal <1.3), urea nitrogen 57 mg/dL (normal <25), serum potassium 6.3 mEq/L (normal <5.5), serum aspartate aminotransferase 3970 U/L (normal <38), serum alanine aminotransferase 996 U/L (normal <41), serum lactate dehydrogenase

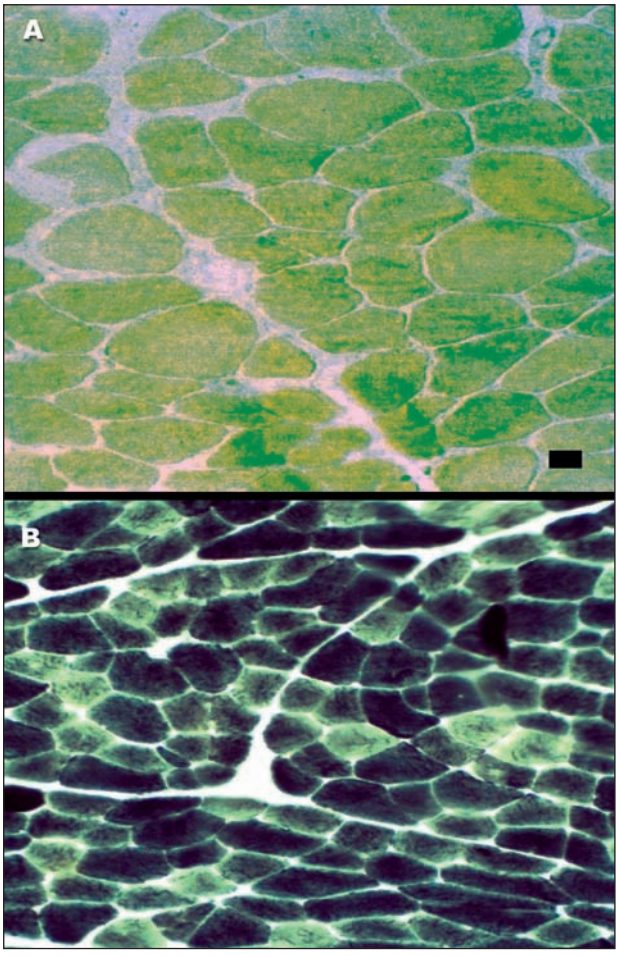

Fig 2. The histochemical reaction analysis of the myophosphorylase enzyme of muscle biopsy of the patient (A) compared with a normal control subject (B). Bar: 50 μm.

38020 U/L (normal <480), serum creatinekinase (CK) 236160 U/L (normal <190), proteinuria and macroscopic hematuria in urinary analysis. A brain magnetic resonance image (MRI) and electroencephalogram were normal. The diagnosis of rhabdomyolysis induced by used of RS was made and the drug was withdrawal with improvement after ten days. Also, the drug oxcarbazepine (600 mg/day) was introduced for the control of seizures.

During the follow-up (4 months) the neurological examination was normal, but the serum CK level persisted elevated (always greater than 4 times the normal upper limit) and the patient was referred to our hospital. Due to persistent CK increase the exercise forearm test and muscle biopsy were made. The ischemic exercise forearm test did not increase the venous lactate levels post-exercise (10.7 mg/dL immediately after ischemic exercise and 13.7, 14.1, 13.9, 15.9 and 16.4, after 1, 2, 4, 6 and 10 minutes, respectively), when compared with a normal control subject. A muscle biopsy processed by frozen sections and histochemical analysis, according to our standard procedures was done[8]. The muscle biopsy showed myopathic changes with subsarcolemmal and central vacuolar glycogen accumulation (Fig 1) and the myophosphorylase enzyme was absent (Fig 2), supporting the diagnosis of McArdle disease.

DISCUSSION

Myotoxicity is well known side effect of LLD, as the statins, cause myopathic abnormalities in up to 7% of treated patients, with severe rhabdomyolysis occurring in 0.5% of cases[2,3,9]. Underlying metabolic muscle diseases, as MD, have not been evaluated extensively in patients using LLD. The incidence of underlying metabolic muscle disorders is approximately 25% in patients evaluated for symptoms after LLD-induced rhabdomyolysis[2]. The LLD may act as unmasking agents in asymptomatic patients with a latent metabolic myopathy[10]. Vladuti et al. showed that 10% of patients with LLD-induced myopathies, who were referred for genetic testing, had mutations causing one of the three metabolic myopathies evaluated: MD, myoadenylate deaminase and carnitine palmitoyltransferase II deficiencies[2]. Also, the carrier frequency for McArdle disease in LLD-induced myopathies was increased 20 times over that expected in the general population and 12 times over the general population control group in the study[2]. This finding demonstrates that inherited metabolic myopathy are not rare among patients with LLD-induced myopathies and muscle biopsy and genetic testing to carrier status alone for MD be adequate to confer increased risk for myopathic outcomes.

The exact mechanisms that determine the myotoxic potential of LLD are unknown, but the ability to penetrate into muscle tissues may be a possible factor[3,11,12]. The lipophilic statins can enter peripheral tissues by passive diffusion, they may be more likely to penetrate muscle and cause myotoxic effects[3]. Therefore, abnormalities that can influence circulating levels of a statin, reduction of the metabolism or excretion, and the presence of an active uptake mechanism could lead to increase the concentration of statin in muscle tissue and may enhance the potential for myotoxic effects[3]. Although theses findings indicate that relatively hydrophilic drugs may have a reduced potential for myotoxic events compared with lipophilic agents, there is little clinical evidence to support this and the controversy persists[3,4].

A metabolic abnormality, attributed to deficiencies of synthetic products of the HMG-CoA reductase pathway, may be another cause of statin-induced myopathy[3,4,11,12]. The most common explanations invoke the deficiency of one of three main end products: cholesterol deficiency with secondary abnormal membrane behaviors, coenzyme Q_{10} deficiency causing abnormal mitochondrial respiratory function, or prenylated protein abnormalities causing imbalances in intracellular protein signaling[3,4,11]. Statins inhibit the formation of mevalonate, a precursor of cholesterol produced by HMG-CoA reductase[3,11]. However, mevalonate is also a precursor of ubiquinone (coenzyme Q_{10}), a powerful antioxidant and membrane stabilizer that is utilized by mitochondria for electron transport[3,11]. Hence, by inhibiting the production of ubiquinone, statins may alter membrane properties and inhibit the production of mitochondrial adenosine triphosphate (ATP), thereby impairing energy metabolism in myocytes[3,11]. This effect could predispose patients with MD to worsening muscular symptoms, due to block ATP formation from glycogen in skeletal muscle by defects of the myophosforylase (genetics factor) and by mevalonate deficiency (acquired factor), inducing increase of the myocytes lesions.

Alsheikh-Ali et al. observed that when compared with the three most widely used statins in the United States, RS was several-fold more likely to be associated with the composite end point of rhabdomyolysis and increased rate of muscle toxicity without rhabdomyolysis[6]. Therefore, the controversy persists because some postmarketing studies showed that the absolute incidence rates of rhabdomyolysis and myopathy were reassuringly low among all statin initiators but remain too small for firm conclusions to be drawn on any difference between the statins[5,7]. However, very few patients had serum CK levels elevations over 10-fold the upper limit of normal (0.2-0.4% of patients) or treatment-related myopathy (≤0.1%), such as, muscle pain or weakness plus with elevated serum CK levels, at dosages of 5-40 mg/day of RS[5]. Also, the event of LLD-induced rhabdomyolysis associated with acquired or inherited muscle disorders can occur. Several lines of evidence suggest that patients who have LLD-induced rhabdomyolysis may have an underlying metabolic predisposition to this reaction[2,4,10]. Consequently, we refer patients with persistent muscular symptoms or elevated CK after statin withdrawal for muscle biopsy, according to standard procedures, when is needed to have alternate or associated diagnoses excluded, as in this case[2,8]. Mutation screening for MD can be also recommended for these patients[2].

The LLD therapy after episode of statin-induced rhabdomyolysis recommendation for MD patients is to discontinue statins[2,4]. The patient should be carefully monitored for recurrence, persistence, or worsening of muscular symptoms while on therapy and after its withdraw[2]. Other alternatives LLD have been considered when the statin myotoxicity is a concern, but when ezetimibe was used on patient with MD this drug also precipitated rhabdomyolysis[9]. Glycogen

phosphorylase is the enzyme that catalyzes the rate-limiting step in glycogenolysis, exists as three isoforms named according to the tissues they predominate in liver, skeletal muscle (myophosphorylase) and brain[13-15]. The isoforms differ in their responses to activation by phosphorylation and allosteric control, and can thus meet the energy requirements of different tissues or cells[13]. The exact functional significance of glycogen phosphorylase in the brain has not been clearly elucidated and participation in brain glycogenolysis appears to be its primary role[14].

As in the brain, all cell types with glycogen phosphorylase could express two or even three isozymes simultaneously, but in the brain the brain isoform is predominant and the lack of central nervous system symptoms is attributed to its abundant activity[13,15]. The suggestion that these cell types are the predominant sites of glycogen breakdown in the brain, in cases of metabolic stress[14]. In our patient, this raised the possibility that seizures may be symptomatic of abnormal glycogen metabolism or accumulation.

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