MYOTONIC POTENTIALS IN STATIN-INDUCED RHABDOMYOLYSIS

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Lipid lowering drugs are used worldwide to control dyslipidemias. The muscle disorder associated with them are coined cholesterol-lowering agents myopathy (CLAM)[1]. The annual incidence of rhabdomyolysis in patients taking statins is 3.4 per 100000 persons[2]. Between 1987 and 2001 there were 42 deaths +related to statin-induced rhabdomyolysis, resulting in a mortality rate of 0.15 per million of prescriptions[3]. Although myotonic potentials have been described in some drug-related myopathies, they are rarely reported in CLAM. Though there are a few experimental myotonic myopathy associated with statin in rabbits[4-6], there was only one single report describing 5 patients with this finding in humans[7].

We report a patient with statin-related rhabdomyolysis and profuse myotonic potentials in the needle EMG with clinical and electrophysiological recovery shortly after the statin interruption.

CASE

A 68 year-old Asian Brazilian woman was admitted with progressive painless weakness for one week, started on the proximal muscles of the four limbs and neck flexors with rapid progression to inability to walk and elevate the limbs. Urine was red-brown in color. Thirty days before the admission she was put on simvastatin due to hypercholesterolemia. Other medication she was taking was enalapril for mild hypertension. There was no personal or family history of myopathy. On neurological examination, abnormal findings were grade 2 (MRC) strength in the proximal lower limb muscles and grade 3 in the proximal upper limb muscles, grade 4 in the distal muscles and hypoactive deep tendon reflexes. No clinical myotonia was detected.

A complete blood count, electrolytes, creatinine, glucose, TSH, and free T4 were all normals. Myoglobin was detected in the urine. CPK was 22.260 U/l on the admission day and 55.000 U/l on the third day. AST and ALT were 790 and 750 U/l, respectively. The nerve conduction studies perfomed in both arms and legs showed normal results in the median, ulnar, superficial radial, tibial, peroneal, superficial peroneal and sural nerves bilaterally. The F wave latencies were normal in the median, ulnar, fibular and tibial nerves bilaterally. The needle EMG perfomed with disposable monopolar needle in cervical paraspinal, supraspinatus, deltoid, triceps, abdutor pollicis brevis and first dorsal interosseus in the upper right limb and tibialis anterior, gastrocnemius, vastus lateralis and iliopsoas in the right lower limb showed rare positive sharp waves and fibrillations in the right supraspinatus muscle, as well as a few small amplitude and short duration (SASD) motor unit potentials (MUP) in the right iliopsoas muscle. On the other hand, the needle study showed profuse amount of myotonic potentials in deltoid, supraspinatus, iliopsoas and cervical paraspinal muscles on the right side (Fig 1).

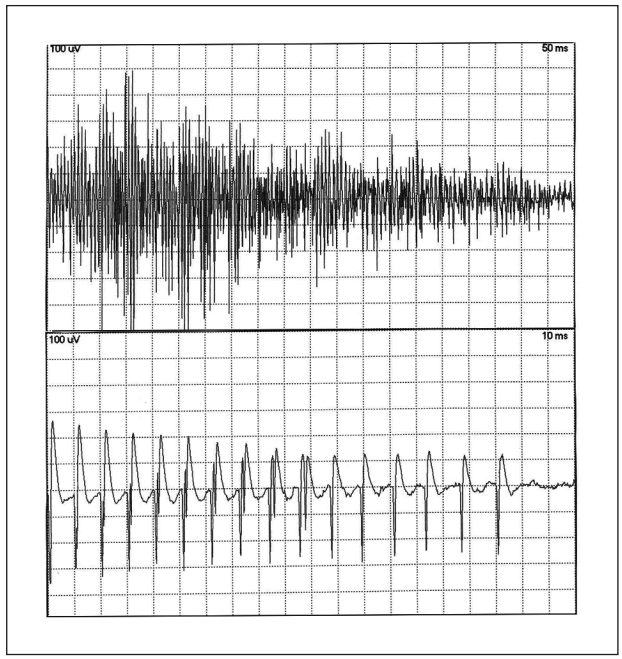

Figure. Myotonic potentials in the right deltoid muscle.

Simvastatin was stopped and vigorous hydration was started to prevent acute renal failure. She was discharged two weeks later with normal strength, renal function and CPK levels. A second needle EMG performed 30 days after the hospital discharge

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Table. Reported cases with myotonic potentials in statin-induced myopathy.

Patient	1 (±)	2 (±)	3 (±)	4 (±)	5 (±)	6 (*)
Age	76 y	58 y	37 y	74 y	62 y	68 y
Duration of treatment	3 weeks	2 weeks	3 weeks	2 weeks	6 weeks	4 weeks
Statin	• simvastatin	• simvastatin	• atorvastatin • simvastatin	• simvastatin	• pravastatin	• simvastatin
Concurrent drugs	• glipizide • estrogen	• cyclosporine • prednisone • thyroid hormone	• thyroid hormone • insulin • losartan • famotidine	• cyclosporine • prednisone • thyroid hormone • lansoprazole	• cyclosporine • prednisone • cholestyramine • prilosec	• enalapril
Other disorders	• diabetes	• liver transplant • hypothyroidism	• bone marrow transplant • hypothyroidism • Hodgkin's disease • acute myeloid 0leukemia	• corneal transplant • hypothyroidism	• liver transplant	• hypertension
Clinical manifestations	• myalgias • proximal weakness	• myalgias • proximal weakness • neck flexors weakness • dyspnea	• myalgias • proximal weakness • neck flexors weakness • dyspnea	• myalgias • proximal weakness • neck flexors weakness • dyspnea	• myalgias • proximal weakness • neck flexors weakness • dyspnea	• proximal weakness • distal weakness • neck weakness
Peak CK (U/L)	14.621	14.004	1.029	78.472	24.243	55.000
Urine myoglobin	present	not done	not done	present	present	present
NCS	axonal polyneuropathy	normal	normal	normal	normal	normal
Needle EMG	• myotonia • PSW/fibrilations • SASD MUP's • early recruitment	• myotonia • SASD MUP's • early recruitment	• myotonia • PSW/fibrilations • SASD MUP's • early recruitment	• myotonia • SASD MUP's • early recruitment	• myotonia • SASD MUP's • early recruitment	• myotonia • PSW/fibrilations • SASD MUP's • early recruitment
Muscle biopsy	type II fiber atrophy mild inflammation	type II fiber atrophy	type II fiber atrophy	not done	type II fiber atrophy	not done

NCS, nerve conduction studies; PSW, positive sharp waves; SASD, small amplitude and short duration; MUP's, motor unit potentials; ±Meriggioli et al.[7]; *Almeida et al. (present case)

showed no myotonic potentials. More than three years after the recovery she remains asymptomatic.

The patient has authorized the publication of her clinical data for scientific purposes.

DISCUSSION

Severe muscle damage is an important concern during statins treatment. Advanced age, renal and hepatic failure, thyroid dysfunction, hypertriglyceridemia, exercise, Asian race and perioperative period are accepted risk factors[8]. Despite the fact of CLAM has been described as a necrotizing myopathy[9], some authors have noted relative absence of muscle fiber degeneration, even in patients with marked weakness and elevated CPK[7]. They suggest that statins can modify the excitation-contraction coupling due to increased intracytoplasmatic calcium concentration as a result of dysfunction of the sarcoplasmic reticulum.

Nerve conduction studies are usually normal and needle EMG is useful to detect myopathic changes in some, but not in all patients. The relative absence of abnormal spontaneous activity and myopathic MUP's in patients with severe weakness and extremely high CK levels was previously noted in rhabdomyolysis and constitute a dissociation between clinical and electrophysiological findings[10]. The pathophysiological explanations for such dissociation are unknown. This electromyographic findings are in agreement with muscle membrane leakage and absence of severe muscle necrosis in the pathologic studies[9]. These electrophysiological findings are helpful to differentiate rhabdomyolysis from fulminant inflammatory myopathies, avoiding muscle biopsy in the former[10].

Myotonic potentials have been described in experimental statin-induced myopathy, but only one isolated report of five patients has shown such potentials in humans[7]. The Table summarizes the data of those patients, as well as our patient data. A decreased chloride channels conductance was the thought mechanism in rabitts. This conductance is regulated by the calcium-phospho-

lipid-dependent protein kinase, a known lipid-regulated protein[11]. The dysfuntion of the sarcoplasmatic reticulum membrane may activate the protein kinase and decrease of chloride conductance, resulting in myotonia[12]. In animal models, myotonic potentials are the cardical feature. However, the rarity of myotonic potentials in humans when compared with animal models suggests a different pathophysiologic mechanism.

Tavee and Panettiere[13] reported a family with myotonia unmasked by simvastatin prescribed for familial hyperlipidemia. Electrophysiological and genetic testing were consistent with autossomal dominant myotonia congenita. The clinical and electrophysiological myotonia persisted even after the discontinuation of the statin. The authors believe that the medication may have been a triggering factor of the chloride channel dysfunction in a genetically susceptible patient for clinical and electrical myotonia.

We did not perform a muscle biopsy or genetic tests in our patient to rule out an underlying myopathy. However, the complete recovery of both clinical and electrophysiological abnormalities after the statin discontinuation suggests a direct effect of the drug in the pathophysiology of the muscle disorder in our patient. Although inflammatory myopathy can be acompanied by myotonic potentials in the needle EMG, the absence of profuse abnormal insertional activity as well as the rarity of myopathic motor unit potentials, and the spontaneous improvement of the clinical, laboratory and electrophysiological abnormalities after discontinuation of the statin make this diagnosis unlikely.

In conclusion, transient myotonic potentials can be seen in patients with CLAM, particularly in statin-induced rhabdomyolysis. CLAM should be included in the differential diagnosis of incidentally found myotonic potentials during needle EMG. Further studies to better define the relationship between myotonic potentials and CLAM are necessary.

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