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STATIN AND FIBRATE ASSOCIATED MYOPATHY

Study of eight patients

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ABSTRACT - Lipid-lowering drugs have been occasionally associated with neuromuscular symptoms and muscle biopsy changes. We reported the clinical course and the muscle biopsy in eight patients with hyperlipoproteinemia, treated with lipid -lowering drugs (statins/fibrates). Five patients had myalgias while; in two cases there was proximal muscle weakness. All patients became asymptomatic after the withdrawal of the drug, although creatine kinase remained elevated. We performed muscle biopsy in six cases from three months to two years after suspension of the drug. We found variation in fibers diameters in all cases, with necrosis of fibers in five cases, inflammatory infiltration in one case, the presence of vacuolated fiber in one patient and ragged-red fibers in three subjects. We concluded that although the muscle biopsy findings were not specific, the prolonged use of statins and or fibrates might induce a chronic myopathy even in the absence of symptoms.

KEY WORDS: statins, fibrates, myopathy, muscle biopsy, creatine kinase.

Miopatia associada a estatina e fibrato: estudo de oito pacientes

RESUMO - As drogas redutoras de colesterol são ocasionalmente associadas a sintomas neuromusculares e alterações morfológicas observadas na biopsia muscular. Relatamos o curso clínico e achado da biopsia muscular em oito pacientes com hiperlipoproteinemia tratados com drogas redutoras de colesterol (estatinas/fibratos). Cinco pacientes tiveram mialgia e em dois havia fraqueza muscular proximal. Todos os pacientes ficaram assintomáticos após retirada da medicação embora a creatinoquinase permanecesse elevada. Analisamos a biopsia muscular em seis casos realizados entre três meses e dois anos após a suspensão da droga. Encontramos variação no calibre das fibras em todos os casos com necrose de fibras em cinco, infiltrado inflamatório em um caso, presença de vacúolos em um e "ragged red fiber" em três deles. Concluímos que, embora os achados da biopsia muscular não fossem específicos, o uso prolongado de estatinas e/ou fibratos pode induzir a uma miopatia crônica até mesmo na ausência de sintomas.

PALAVRAS-CHAVE: estatinas, fibratos, miopatia, biopsia muscular, creatinoquinase.

Lipid-lowering drugs are considered as the first choice drugs in the control of dyslipidemies and they are well tolerated by most patients. They have occasionally been associated with myopathy. The most common adverse drug reactions are constipation, flatulence, dyspepsia, nausea and elevated transaminase levels[1]. Adverse reactions affecting the skeletal muscle have been reported, such as myalgia, muscle cramps, rhabdomyolysis, aching, proximal weakness and elevation of creatine kinase (CK). The most severe risk of these drugs is myositis with rhabdomyolysis. Rapid remission of symptoms after discontinuation of therapy has frequently been reported[1-9].

We describe the clinical findings in eight patients, along with muscle biopsy in six of these. They all had chronic hyperlipoproteinemia and were treated with lipid-lowering drugs (statins/fibrates).

CASES

We studied eight patients from October , 2001 to August, 2002 (Table 1).

One patient did not present muscular symptomatology. Five reported muscular pains, and there was proximal muscular weakness in two. Electroneuromyography was carried out in five subjects, revealing standard myopathic findings in three. One patient was

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Table 1. Analysis of patients.

Case	Gender	Race	Age (years)	Drug	Time Of Using	CM
1	M	W	61	SIMV 20mg /day	3y	NONE
2	M	W	48	FLUV 20mg /day	15d	HT
3	M	W	42	CER0.4 mg/d GEMF 600 mg/day	15d	NONE
4	F	W	69	SIMV 20 mg/day	3m	DM
5	M	W	38	ETOFI 500 mg/day	28d	NONE
6	M	W	44	SIMV 20 mg/day	6y	NONE
7	M	W	56	ATORV 10 mg/day	4y	NONE
8	F	W	60	FLUV 20 mg/day	15d	HT

M, male; F, female; W, white; CM, comorbidity; HT, hipothyroidism; DM, diabetes mellitus; SIMV, Sinvastatin; FLUV, fluvastatin; CER, cerivastatin; GEMF, genfibrosyl; ETOFI, etofibrate; ATORV, atorvastatin; y, years; m, months; d, days.

diabetic whereas two had hypothyroidism controlled with specific medication. CK was elevated in all patients (Tables 1 and 2).

Muscle biopsy was performed in 6 of these patients at between 3 months and 2 years after withdrawal of the drug (Table 2). Tissue samples from muscle biopsy (biceps brachial) were fresh frozen in liquid nitrogen and were fixed for pathologic analysis according to standardt techniques[10]. The following alterations were observed: 1) disproportion of fibers diameters in all cases and necrosis of fibers in five cases (Fig 1A), 2) vacuolated fibers PAS negative in one case (Fig 1B), 3) inflammatory infiltrates in one patient (Fig 1C), 4) ragged-red fibers - COX positive in two cases and no ragged red fibers - COX negative in one case (Fig 2 and 3).

Those patients with some muscular symptoms become symptom-free on discontinuing the use of the drugs. The CK remained elevated even after the withdrawal of the medications. The patients whose muscle biopsies showed mitochondrial dysfunction were receiving statins only. Three patients had rhabdomyolysis (cases 2, 3, 8) but only the case 3 were using associated therapy (statin and fibrate). Lactate dosage was normal in our cohort. The three patients presenting mitochondrial dysfunction were asymptomatic and presented no signs of compromise to other systems.

DISCUSSION

The adverse side effects resulting from the prolonged use of cholesterol-reducing drugs are well known, particularly nauseas, dyspepsia, flatulence and intestinal constipation[1-3]. Recently, both muscular and peripheral nervous system disturbances have been cited. An incidence of 2% - 7% has been

Table 2. Analysis of patients.

Cases	Symptoms	CK(U/L)	ΔT	Biopsy	ENMG
1	none	303	8m	RRF; VDF	MYOP
2	myalgia	17000	8m	RRF; VDF	NL
3	myalgia hematuria	6060	-	NOT DONE	not done
4	proximal weakness	515	3m	IM; VDF	not done
5	arthralgia	2484	3m	VM; VDF	MYOP
6	myalgia arthralgia	279	2y	RRF; VDF	not done
7	myalgia	286	3m	I ; VDF	not done
8	myalgia proximal weakness	16890	-	NOT DONE	MYOP

CK, creatine kinase; ΔT, interval of time between withdrawal of drug and biopsy; m, months; y, years; ENMG, Electroneuromyography; RRF, ragged red fiber; IM, inflammatory myopathy; VM, vacuolar myopathy; I, inspecific pathologic findings; VDF, variation of diameter fibers; NL, normal.

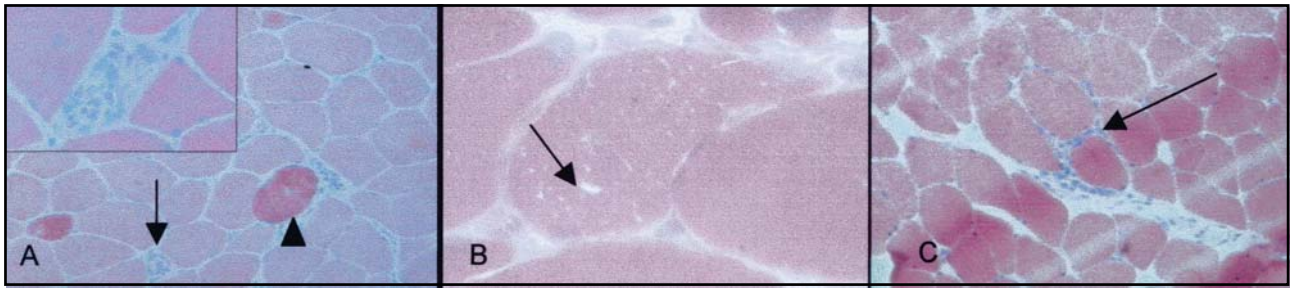

Fig 1. A- hematoxylin-eosin stain : fiber diameter disproportion; necrotic fiber (arrrow); hypercontracted fiber (arrowhead); B- vacuolated fiber; C- Iinfomononuclear infiltrate.

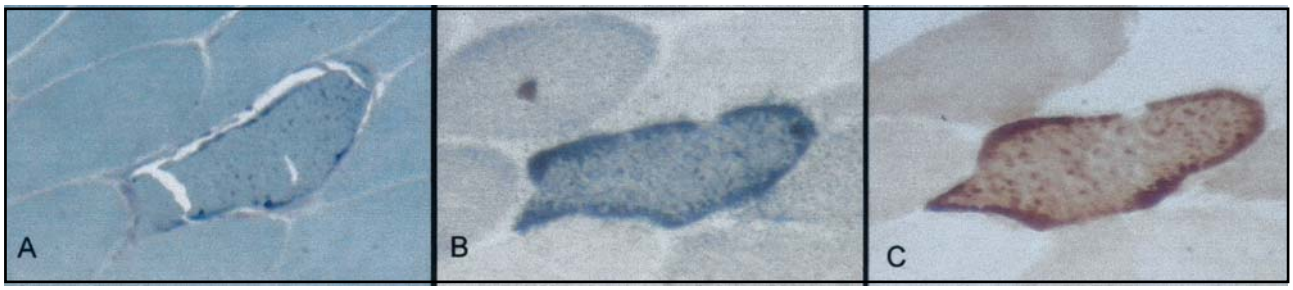

Fig 2. A- Gomori trichrome stain demonstrating ragged red fiber; B- Succinate dehydrogenase stain demonstrates intense activity in one fiber ; C- Cytocrome oxidase stain is positive.

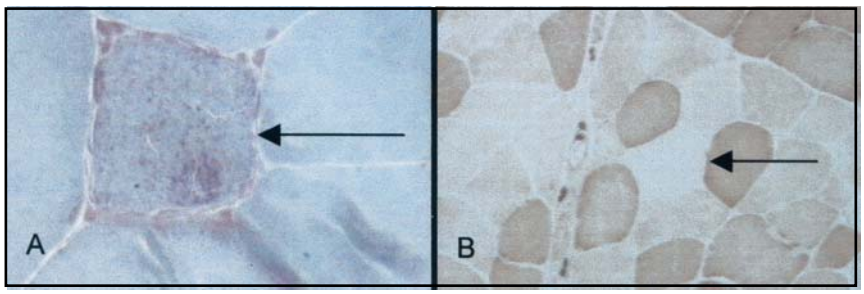

Fig 3. A- Gomori trichrome stain demonstrating ragged red fiber; B- Cytocrome oxidase stain negative fiber / no ragged red fiber.

reported for muscular aches and 0.1% - 0.2% for myopathies. The latter can be acute with grossly elevated CK, myoglobinuria and renal dysfunction characterizing rhabdomyolysis or generalized muscular aching and/or weakness, mainly in proximal muscles. The incidence of these manifestations rises when fibrates and statins are associated[3,11]. Moreover, microscopic muscular alterations have been reported, such as variations in the diameter of muscle fibers, necrosis, lymphomononuclear infiltration, vacuoles and ragged red fibers[11,12].

The cases we report show clinical manifestations in some subjects such as myalgia (cases 2, 3, 6, 7, 8), hematuria (case 3), proximal muscular weakness (cases 4, 8) and arthralgia (cases 5, 6). In addition, we found unspecific myopathic changes in all muscle biopsies performed (6) which, in conjunction with clinical disturbances and persistently elevated CK levels, imply to muscular compromise resulting from the prolonged use of statins, be this alone or associated with fibrates.

The monitoring of CK levels is considered a useful parameter in tracing myotoxicity in patients using anti-lipemics[3,8], including those who are assymptomatic[5,6], although there are reports of confirmed toxic myopathy cases with normal muscle biopsy and normal CK[12]. A rise in CK during therapy with statins is well documented, ranging between 0.1% and 10%[6], usually not exceeding 10 times over the upper limit of normal[3,5]. When the level surpass this value may occur myoglobinuria and renal dysfunction associated with muscular damage[5,8,11]. The levels of CK in our cases ranged from 2 to 100 times above normal. Cases 2, 3 and 8 presented a clinical and laboratorial picture compatible with rhabdomyolysis.

Fibrates may have a direct toxic action on muscle cells in

patients with an unrecognized predisposition to myopathy[1]. One of the mechanisms by which they cause muscle damage is by increase in lipoprotein lipase activity. They also led to a defect in the cholesterol-like molecules of muscle membrane, resulting in increased ionic permeability especially to calcium and, as a result, the cascade of myofibre necrosis initiates[11].

The 3-hidroxi-3-methilglutaryl coenzyme A reductase (HMG-CoA-reductase) catalyzes the formation of mevalonate from HMG-CoA, an important precursor of cholesterol, ubiquinone and isoprenylated proteins involved in cellular replication[5, 8]. Statins inhibit the HMG-CoA-reductase resulting in lower intracellular cholesterol levels. This later is an important component of cell membranes modulating their fluidity [1-5]. Myotoxicity associated to the use of statin is complex, involving mechanisms on the structure and function of the cellular membrane, mitochondrial dysfunction, and changes in the duplication of the myocyte[1-8,13-15]. A reduction in plasmatic and intracellular cholesterol can result in reduced levels of the membrane cholesterol leading to physical changes in this and a decrease in cell proliferation. Such changes can result in a compromising of the Na/K pump function with irreversible damage to the cell[8].

Ubiquinone (Coenzyme Q_{10}) is used by mitochondria in transporting electrons and in the consequent formation of ATP in the respiratory chain. Hence, HMG-CoA inhibitors would cause a reduction in ubiquinone synthesis with consequent mitochondrial dysfunction demonstrated by ragged red fibers, deficient activity for cytochrome c oxidase (COX) and insufficient rise in lactate/pyruvate[4,5,8,14]. The mitochondrial proliferation that results in ragged red fiber pathology is presumably an attempt by the cell to compensate for the respiratory chain defect, however, the signals that stimulate mitochondrial biogenesis in this circumstance are unknown[16]. England et al.[14] believe that the statins can produce a mitochondrial myopathy with ragged red fibers and parcial COX deficiency. We have the findings in one patient - the presence of ragged red fiber / COX - positive and no ragged red fibers / COX - negative (Fig.3). Furthermore, a reduction in mevalonate metabolites (farnesol and geranylgeraniol) by HMG-CoA reductase inhibitors would have an affect on the activation of certain regulatory proteins (Ras, Rac and Ro) responsible for the maintenance, growth and mediation of apoptosis[5]. The pathogenesis of the presence of inflammatory infiltration remains unknown. It must be similar to that described in idiopathic polymyositis with fiber necrosis and invasion of non-necrotic fibers by lymphocytes. The drug-induced inflammatory reaction can be interstitial only (perivascular), as seen in some collagen diseases[11,15,17,18].

Myopathy caused by hypolipidemic can also provoke vacuolar lesion, characterized by the presence of vacuoles with increased lysosomal activity and without the glycogen or fat accumulation (as was seen in case 5) although those vacuolated fiber seen in our patient could represent a early stage of necrosis fiber (Fig 1B). It is known that in the various manifestations of toxic myopathies, the vacuolar and mitochondrial changes are usually painless, and with raised CK[13] as seen in cases 1,2,5, and 6, or even normal CK[12]. In cases with rapid onset, muscular pain tends to predominate[13], however weakness in proximal musculature predominated in two of our cases (cases 2 and 8).

Regarding morbidity is known the higher predisposition of muscular symptoms in those patients with thyroideopathies, metabolic disorders, and who are post-surgery or with renal insufficiency, epilepsy, hypoxia, infections and base neuromuscular diseases. Concomitant administration of HMG-CoA reductase inhibitors with P450 system inhibitors, results in increased plasmatic concentrations of the HMG-CoA reductase inhibitors[1-3,5-9]. There appears to be a link between the dose of the drug and myotoxicity[3,8], although we did not observe this association in our cases (Tables 1 and 2). Although two of our cases did present hypothyroidism the changes observed in muscular biopsy were not compatible with those observed in hypothyroid myopathy usually represented by mild type 2 atrophy. Therefore signs and symptoms usually improve on correction of the hypothyroid state.

Studies suggest that the mechanism of myotoxicity through statin and fibrate are not precise, since complex and multifactorial mechanisms play a role, such as genetic predisposition, physico-chemical properties, pharmacokinetics, dose and drug interaction[5-8]. There is a report that does not exclude the possibility that these drugs simply aggravate, and thereby make manifest a latent pre-existing mitochondrial myopathy. It is also possible that they can accelerate the normal decrease in human muscle mitochondrial respiratory chain activity associated with aging, or accelerate the rate of mitochondrial DNA deletions in skeletal muscle[14].

In conclusion, in spite of the adverse side effects of the statins on the skeletal muscle, they remain the first choice drugs in the treatment of the dyslipidemias. When side effects, which are rare, are presented, a favorable evolution has been seen. Rhabdomyolysis is a significant side effect of statins even when used without fibrate association. Our results indicate that statins, like fibrates, may induce a chronic myopathy even in the absence of symptoms.

In view of our findings, we recommend performing a muscular biopsy on those patients using anti-lipemics and presenting neuromuscular symptoms, and/or elevated CK levels, with the aim of defining the degree of muscular compromise and thereby establishing the best approach for each patient.

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