

Clinical Reasoning: Rhabdomyolysis after combined treatment with simvastatin and fluconazole

O. Findling, MD
N. Meier, MD
J. Sellner, MD
K. Nedeltchev, MD
M. Arnold, MD

Address correspondence and
reprint requests to Dr. Marcel
Arnold, Department of
Neurology, University Hospital,
Inselspital, CH-3010 Bern,
Switzerland
marcel.arnold@insel.ch

SECTION 1

A 65-year-old woman with obesity, hypertension, coronary artery disease, ventricular tachycardia, and hypercholesterolemia presented with 2 weeks of progressive, proximal muscle tenderness and weakness. She was unable to walk. Neurologic examination revealed a severe proximal tetraparesis predominantly of the legs. Sensation was normal. The patellar reflex was slightly reduced on the right side. The remainder of the examination was normal. Her medical history

revealed that she had been treated 3 weeks earlier with fluconazole 800 mg daily for 3 weeks, for a *Candida albicans* infection of her internal defibrillator. Simultaneously she had been taking simvastatin 40 mg daily for 5 years.

Questions for consideration:

1. What is the differential diagnosis for symmetric proximal weakness?
2. What tests would you carry out next?

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From the Department of Neurology (O.F., N.M., K.N., M.A.), Inselspital, Bern University Hospital, and University of Bern, Switzerland; and the Department of Neurology (J.S.), Klinikum rechts der Isar, Technische Universität München, Germany.

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SECTION 2

In patients with progressive tetraparesis, myelopathy of the cervical spine must be excluded promptly. This consideration is important even in patients without additional signs of myelopathy, such as sensory loss or bladder dysfunction. In this patient, MRI scan of the cervical spine was normal.

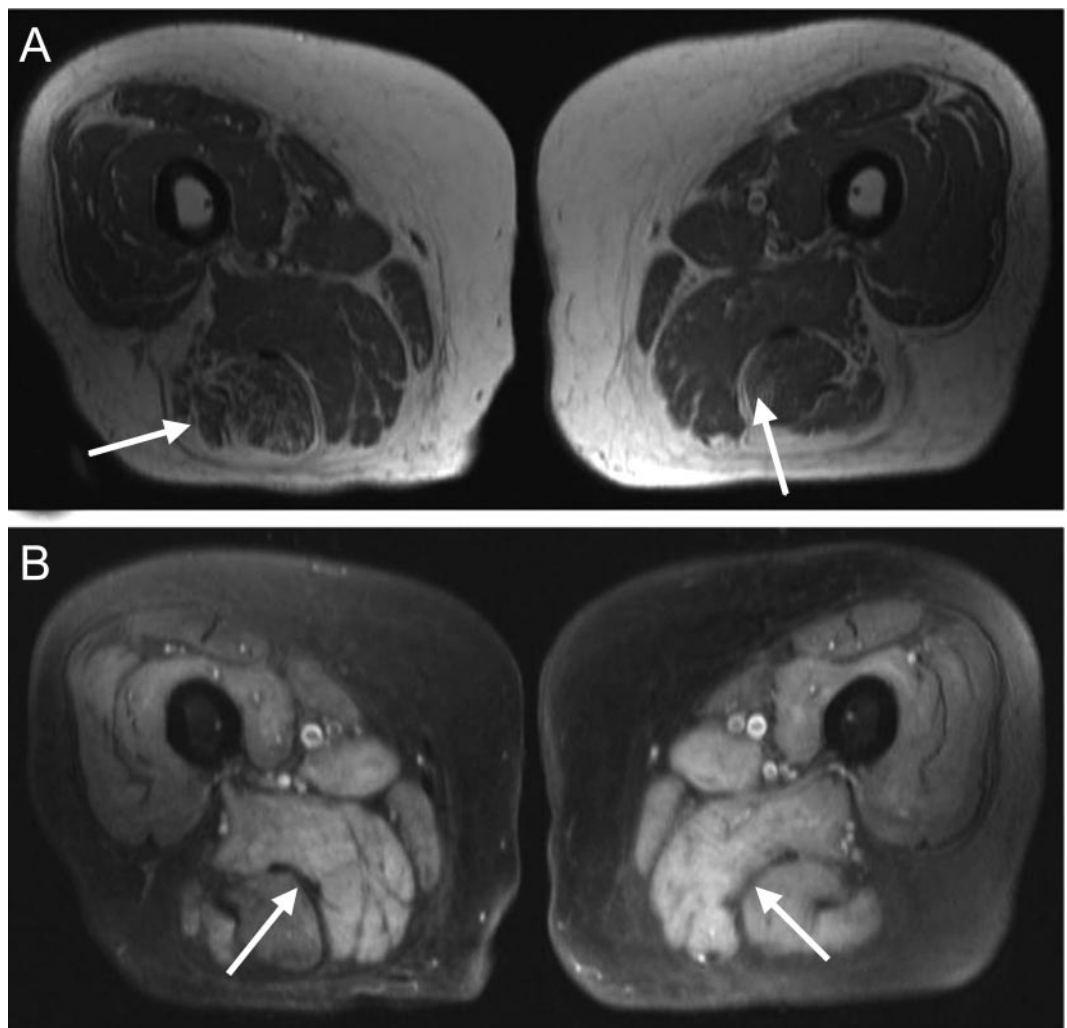
An important differential diagnosis is acute motor polyradiculoneuropathy, which is characterized by progressive motor weakness and hyporeflexia. Although neuropathic pain can occur, muscular tenderness, as in our patient, is not typical. Furthermore, our patient's tendon reflexes were normal except for a slightly reduced right patellar reflex, making radiculopathy or neuropathy less likely. Motor neuron disease, such as amyotrophic lateral sclerosis, is another differential diagnosis, but symptoms develop over months or years, and not so rapidly as in our patient. A disorder of the neuromuscular junction, such as myasthenia gravis, is possible, although there was no characteristic history of fatigue, fluctuating symp-

oms, or ocular symptoms. Furthermore, a disorder of the neuromuscular junction would not explain the proximal pain.

Myopathy (polymyositis or rhabdomyolysis) is one of the most likely diagnoses in our patient. Laboratory evaluation showed a creatine kinase (CK) up to 32,000 U/L (normal <167 U/L). Sedimentation rate was 51 mm/hour (normal <20) and C-reactive protein was 22 mg/L (normal <5). Blood chemistry showed increased transaminases (aspartate transaminase 1,461 U/L [normal 10–37], alanine transaminase 671 U/L [normal 5–41]) and lactate dehydrogenase 3,139 U/L (normal <480). Serum electrophoresis was normal; urine electrophoresis showed myoglobinuria.

Electromyography of the right vastus medialis and iliopsoas, erector spinae, and left deltoid and tibialis anterior muscles showed no signs of denervation, but a myopathic interference pattern analysis. An MRI scan of the proximal leg muscles revealed edematous swelling and contrast agent enhancement, especially in the adductors (figure).

Figure MRI of thigh showing muscular atrophy on native T1 imaging with fat suppression (A) and diffuse contrast agent enhancement (B) especially in the adductor muscles



Different types of myopathies such as toxic, metabolic, infectious, autoimmune-mediated, and hereditary myopathies are to be considered. Blood examination showed no evidence of parasitic, bacterial, or viral infection as a reason for infectious disease. Furthermore, there were no signs of autoimmune-mediated myopathy (negative antinuclear antibody and antineutrophil cytoplasmic antibody, negative antibodies to double stranded-DNA, histones, nucleosome, cardiolipin-, and ribonucleoprotein). In addition,

biopsy of the left vastus medialis muscle revealed no signs of metabolic or hereditary myopathy. The onset of hereditary myopathies is often in childhood and symptoms develop over months to years.

Question for consideration:

1. What is the diagnosis and what treatment would you recommend?

GO TO SECTION 3

SECTION 3

The history of exposure to both simvastatin and fluconazole, in combination with the electrodiagnostic, laboratory, and MRI findings, led to a diagnosis of statin-induced rhabdomyolysis.

Simvastatin was stopped, therapy with methylprednisolone 1,000 mg IV daily was begun (for 3 days, until normal muscle biopsy results returned), and bicarbonate infusions were performed.

Muscle strength slowly increased after 1 week, and muscle pain remitted after 2 weeks. All laboratory values normalized within 4 weeks. After 9 weeks of an inpatient rehabilitation program, she was able to walk 500 meters without assistance.

DISCUSSION Rhabdomyolysis is characterized by widespread muscle pain, tenderness, weakness, and dark urine. Laboratory findings include elevated transaminases, myoglobinuria, elevated CK, rapidly rising serum creatinine, and metabolic acidosis. MRI shows muscle edema and contrast enhancement. Electromyographic findings often show nonspecific signs of myopathy. Biopsy findings such as multiple necrotic fibers invaded by macrophages can support the diagnosis. However, there is limited sensitivity, and a negative biopsy cannot exclude the diagnosis.^{1,2}

Risk factors for statin-induced rhabdomyolysis include older age, female sex, obesity, renal or liver dysfunction, diabetes, infections, major surgery or trauma, alcoholism, drug interactions, excessive exercise, and exorbitant consumption of grapefruit or cranberry juice.³

Simvastatin, which our patient had taken for 5 years, is metabolized by the cytochrome P 450 system, especially by the CYP 3A4 isoenzyme. Inhibitors of P450 include fluconazole, as well as erythromycin, troleandomycin, nefazodone, ritonavir, and grapefruit juice.^{4,5} For lovastatin, simvastatin, and atorvastatin, which are metabolized by CYP 3A4, an incidence of 0.73 cases/million prescriptions has been reported. For pravastatin (excreted to a significant extent unchanged in the urine, CYP3A4 plays only a minor role) and fluvastatin (oxidized by

CYP 2A9), which are not oxidized by the cytochrome P 450 system, the rate is 0.15/million prescriptions.⁴

The pathogenesis of statin-induced myopathies is not completely understood. Possibly, a disturbance of the plasma membrane of muscle cells and influx of calcium ions leads to overcontraction and breakdown of the contractile apparatus. Ensuing disturbance of protein synthesis and mitochondrial metabolism may cause cell death.^{3,6,7}

Management consists of discontinuing the triggering agent. Additional measures are bicarbonate infusion to prevent dissociation of nephrotoxic myoglobin, fluid replacement, and promotion of diuresis.⁸ The prognosis after stopping the trigger is good, but in severe cases muscle paresis can persist.

Drugs that are well-tolerated when used separately may induce serious side effects when used in combination. If simvastatin had been temporarily discontinued during the treatment with fluconazole this side effect may have been avoided.

REFERENCES

1. Melli G, Chaudhry V, Cornblath DR. Rhabdomyolysis: an evaluation of 475 hospitalized patients. *Medicine* 2005; 84:377–385.
2. Moratalla MB, Braun P, Fornas GM. Importance of MRI in the diagnosis and treatment of rhabdomyolysis. *Eur J Radiol* 2008;65:311–315.
3. Mukhtar RY, Reckless JP. Statin-induced myositis: a commonly encountered or rare side effect? *Curr Opin Lipidol* 2005;16:640–647.
4. Law M, Rudnicka AR. Statin safety: a systematic review. *Am J Cardiol* 2006;97:S52–60.
5. Spina E, Scordo MG, D'Arrigo C. Metabolic drug interactions with new psychotropic agents. *Fund Clin Pharmacol* 2003;17:517–538.
6. Hodel C. Myopathy and rhabdomyolysis with lipid-lowering drugs. *Toxicol Lett* 2002;128:159–168.
7. Owczarek J, Jasinska M, Orszulak-Michalak D. Drug-induced myopathies. An overview of the possible mechanisms. *Pharmacol Rep* 2005;57:23–34.
8. Jain K. *Drug-Induced Neurological Disorders*. 2nd ed. Göttingen-Seattle-Bern: Hogrefe & Huber; 2001:243–273.

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