CASE REPORT

Protocols cure diseases, not patients: flaccid paresis in post-NSTEMI statin treatment

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SUMMARY

An 82-year-old white woman presented at our Internal Medicine ward with flaccid tetraparesis. Two months earlier, she had suffered a non-ST elevation myocardial infarction treated with percutaneous coronary intervention (PCI) and stenting, and she had been prescribed the classical post-PCI therapy (β -blockers, statins and antiplatelet agents). At admission, she was haemodynamically stable and the physical examination revealed reduced reflexes in the four limbs. Urgent laboratory findings revealed mild hypokalaemia. Considering the high statin doses she was taking, we also performed an urgent creatine phosphokinase test, which indicated rhabdomyolysis. Statin therapy was immediately stopped and aggressive fluid treatment begun, supplemented with potassium for increased urinary potassium losses. The patient progressively regained muscle strength.

BACKGROUND

For lipid-lowering therapy, the current (2012) European Society of Cardiology (ESC) guidelines for myocardial infarction state that “statins should be used in all patients after acute myocardial infarction, irrespective of cholesterol levels. However, in patients at increased risk of side-effects from statins (eg, the elderly, patients with hepatic or renal impairment or with the potential for interaction with essential concomitant therapy), lower-intensity statin therapy should be considered.¹ In Italy, the annual incidence of myocardial infarction has been estimated to be about 150 cases/100 000 inhabitants, who will probably be prescribed a therapeutic protocol based on ESC guidelines. In this case report, we will describe the deleterious consequences of the strict application of a protocol applied to a frail patient.

CASE PRESENTATION

An 82-year-old Caucasian woman returned to her general practitioner 60 days after having had a percutaneous coronary intervention (PCI) with placement of a drug-eluting stent in the anterior intraventricular coronary artery for a non-ST elevation myocardial infarction (NSTEMI), because she had experienced a mild febrile episode with cough, and was prescribed a combined therapy with clarithromycin and amoxicillin/clavulanic acid. Two days after the start of the antibiotic treatment, the patient reported of progressive asthenia, first at the lower limbs and then at the upper limbs, bilaterally. The asthenia worsened, and the patient could not stand up and walk, so she was brought to the

emergency room of the nearest hospital, where laboratory findings revealed severe hypokalaemia (K^+ 2.2 mEq/L). The patient was treated with an intravenous infusion of 80 mEq of KCL and, once potassium levels had been restored, she was dismissed with oral potassium supplementation at home. Three days later, she was brought to the emergency room of our hospital again, due to the persistence and worsening of symptoms (the patient was now unable to walk). Her home therapy was: KCL Retard 600 mg orally (8 mEq), Omeprazole 20 mg, levothyroxin 75 μ g, metoprolol 100 mg $\frac{1}{2}$ cp $\times$ 2, acid acetylsalicylic 100 mg, clopidogrel 75 mg and atorvastatin 80 mg. On arrival at our emergency room, her vital signs were normal and the clinical examination revealed flaccid tetraparesis with decreased reflexes. She could only slightly flex and extend the forearms, wrists, thighs and limbs bilaterally. The Babinski sign was absent. The rest of the physical examination was normal, apart from the presence of oral mycosis.

INVESTIGATIONS

Initial laboratory findings indicated mild normocytic anaemia (haemoglobin 10.6 g/dL, volume globulaire moyen 84.6 fL), mild renal failure (creatinine 0.8 mg/dL), neutrophilic leucocytosis (white cell count 16.250/ μ L, N 76%), elevated transaminases (aminotransferase 150 U/L, alanine transaminase 70 U/L) and mild hypokalaemia (3.29 mEq/L). An arterial blood gas analysis was normal. An urgent creatine phosphokinase (CPK) test was performed later that evening, which confirmed the diagnosis of rhabdomyolysis (CPK 11.410 mg/dL).

A 24 h urine potassium collection revealed high urinary potassium secretion (60 mEq/24 h), in spite of the presence of the mild hypokalaemia. Since normal kidneys can suppress urinary potassium excretion in case of low-serum potassium levels, this could be attributed to an initial postrhabdomyolysis tubular injury.² Myoglobin and CPK levels were monitored on a daily basis and showed a slow but progressive decrease (table 1). For diagnostic purposes, we also performed an urgent neurological examination with electronystagmography and electromyography, which highlighted the mixed—myopathic and neurogenic—nature of the lesions (presumably at the neuromuscular junction level). Furthermore, a liquor examination showed a normal albumin quotient (anti-GM1 antibodies were also negative), which excluded Guillain-Barré syndrome.

On the 13th day of hospitalisation and after the normalisation of serum potassium levels, the

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Table 1 Myoglobin and CPK levels

Day	1	2	3	4	7	9	17
Myoglobin (ng/mL)	–	30.000	30.000	21.851	10.393	7.480	82
CPK (U/L)	11.410	19.962	21.694	12.854	5.497	3.816	79

CPK, creatine phosphokinase.

patient was still presenting proximal muscle weakness, so we performed a muscle biopsy, which indicated a non-specific inflammatory myopathy, as in the case of post-rhabdomyolysis myopathic injury (figure 1).

DIFFERENTIAL DIAGNOSIS

The initial differential diagnosis included acute polyneuropathy, paroxysmal hypokalaemic paralysis and rhabdomyolysis. While the paroxysmal hypokalaemic paralysis could be excluded because the symptoms persisted even after restoring potassium levels, the common Guillain-Barré acute polyneuropathy could also be excluded since the liquor examination showed a normal albumin quotient.

TREATMENT

Atorvastatin was immediately stopped and aggressive fluid administration started (>2 L/die), with supplementation for the renal potassium loss, initially only with intravenous KCL, and later with intravenous KCL and antialdosterone agents (potassium canrenoate) IV, since maintaining normal serum potassium values was particularly challenging due to the initial tubular damage. Small doses of oral bicarbonate were also administered daily in order to prevent tubular damage, at least to some extent. We also started prophylaxis for deep venous thrombosis with LMWE and an antifungal treatment for the oral mycosis.

Figure 1 Biopsy specimen of the left quadriceps in 20× extension, showing non-specific inflammatory myopathy.

OUTCOME AND FOLLOW-UP

The patient was discharged after 17 days of hospitalisation. At the time of discharge, she could walk and reported only of mild proximal muscle asthenia, with normal CPK and myoglobin levels (79 U/L and 82 ng/mL, respectively). Despite the tubular damage, renal function remained normal thanks to aggressive hydration. The patient was discharged with the following therapy: omeprazole 40 mg, acetylsalicylic acid 100 mg, clopidogrel 75 mg, levothyroxin 75 µg, metoprolol 100 ½×2, KCL 600 mg and potassium canrenoate 100 mg.

At 1-month follow-up, her CPK, myoglobin and serum potassium levels were normal, while she was still presenting mild asthenia of the four limbs. Potassium supplementation was gradually stopped and, at 2-month follow-up, the patient had a complete remission of the asthenia and normal CPK and serum potassium levels.

DISCUSSION

In this era of evidence-based medicine, most practitioners treat their patients on the basis of the currently applicable guidelines. While this is not a wrong approach, medical doctors must always first consider the specific patient they are seeing when deciding about the intensity of treatment (eg, a 50-year-old man with NSTEMI vs an 82-year-old woman with NSTEMI). Second, when statin therapy is administered, patients should be closely monitored, particularly when multi-drug schemes are used or new treatments prescribed.^{3–5} In this case report, we have shown the deleterious effects of a treatment administered exclusively on the basis of guideline recommendations rather than by taking into consideration the specific needs of the individual patient. Even though 80 mg of atorvastatin is the dose recommended by the current ESC guidelines for post-AMI lipid-lowering treatment, in this case our patient experienced some of the risk factors, including increased-statin induced myopathy, which should instead have required a lower-intensity statin therapy^{6–8} (box 1). The use of 80 mg of atorvastatin brought the patient to a potentially lethal syndrome, rhabdomyolysis, which, although not complicated by acute renal failure, led to flaccid paresis and to initial tubular damage with potassium leakage persisting for almost 2 months.

Box 1 Risk factors of statin-induced myopathy

- ▶ Advanced age
- ▶ Female sex
- ▶ Low Body Mass Index
- ▶ Diminished liver function
- ▶ Untreated hypothyroidism
- ▶ Vigorous exercise
- ▶ Severe trauma or major surgery
- ▶ Diet (excessive grapefruit or cranberry juice)
- ▶ Drug interactions, especially with drugs that are inhibitors or substrates of the cytochrome P450 pathway (eg, fibrates, nicotinic acid, calcium channel blockers, ciclosporin, amiodarone, thiazolidinediones, macrolide antibiotics, azole antifungals, protease inhibitors, warfarin)
- ▶ Multisystem diseases (eg, diabetes mellitus)
- ▶ Genetic factors (eg, polymorphisms of cytochrome P450 isoenzymes)

Learning points

- ▶ Pay attention to drug interactions when prescribing drugs to patients on statin treatment (box 1).
- ▶ The presence of severe hypokalaemia in patients who are not taking hypokalaemic drugs (eg, diuretics) should always be further investigated.
- ▶ An inflexible application of treatment protocols may be hazardous for patients, especially in the elderly; treatment should always be personalised according to the needs and specific frailty of each patient.

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