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A SELF-TEST ON A CLINICAL CASE

An 85-year-old with muscle pain

An 85-year-old man with hypertension, hyperlipidemia, and coronary artery disease presented to our clinic with diffuse muscle pain. The pain had been present for about 3 months, but it had become noticeably worse over the past few weeks.

He was not aware of any trauma. He described the muscle pain as dull and particularly severe in his lower extremities (his thighs and calves). The pain did not limit his daily activities, nor did physical exertion or the time of day have any effect on the level of the pain.

His medications at that time included metoprolol, aspirin, hydrochlorothiazide, simvastatin, and a daily multivitamin.

He was not in acute distress. On neurologic and musculoskeletal examinations, all deep-tendon reflexes were intact, with no tenderness to palpation of the upper and lower extremities. No abnormalities were noted on the joint examination. He had full range of motion, with 5/5 muscle strength in the upper and lower extremities bilaterally and normal muscle tone. He was able to walk with ease. Results of initial laboratory testing, including creatine kinase and erythrocyte sedimentation rate, were normal.

1 What should be the next best step in the evaluation of this patient's muscle pain?

- ☐ Order tests for cyclic citrullinated peptide (CCP) antibody and rheumatoid factor
- ☐ Advise him to refrain from physical activity until his symptoms resolve
- ☐ Take a more detailed history, including a review of medications and supplements
- ☐ Recommend a trial of a nonsteroidal anti-inflammatory drug (NSAID)
- ☐ Send him for radiographic imaging

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Since his muscle pain has persisted for several months without improvement, a more detailed history should be taken, including a review of current medications and supplements.

Testing CCP antibody and rheumatoid factor would be useful if rheumatoid arthritis were suspected, but in the absence of demonstrable arthritis on examination, these tests would have low specificity even if the results were positive.

An NSAID may temporarily alleviate his pain, but it will not help establish a diagnosis. And in elderly patients, NSAIDs are not without complications and so should be prescribed only in appropriate situations.

Imaging would be appropriate at this point only if there was clinical suspicion of a specific disease. However, our patient has no focal deficits, and the suspicion of fracture or malignancy is low.

The medical history should include asking about current drug regimens, recent medication changes, and the use of herbal supplements, since polypharmacy is common in elderly patients with multiple comorbidities.

On further questioning, our patient said that his dose of simvastatin had been increased from 40 mg daily to 80 mg daily about 1 month before his symptoms appeared. He was taking a daily multivitamin but was not using herbal supplements or other over-the-counter products. He did not recall any constitutional symptoms before the onset of his current symptoms, and he had never had similar muscle pain in the past.

His simvastatin had been increased from 40 mg daily to 80 mg daily 1 month before his symptoms appeared

2 Based on the additional information from the history, what is the most likely cause of his muscle pain?

- ☐ Limited myositis secondary to recent viral infection
- ☐ Rhabdomyolysis

- ☐ Hypothyroidism
- ☐ Drug-drug interaction
- ☐ Statin-induced myalgia

Our patient's history provided nothing to suggest viral myositis. Hypothyroidism should always be considered in patients with myalgia, but this is not likely in our patient, as he does not display other characteristics, such as diminished reflexes, hypotonia, cold intolerance, and mood instability. Even though calcium channel blockers have been known to cause myalgia in patients on statins, a drug-drug reaction is not likely, as he had not started taking a calcium channel blocker before his symptoms began. This patient did not show signs or symptoms of rhabdomyolysis, a type of myopathy in which necrosis of the muscle tissue occurs, generally causing profound weakness and pain.[1]

Therefore, statin-induced myopathy is the most likely cause of his diffuse muscle pain, particularly since his simvastatin had been increased 1 month before the onset of symptoms.

3 What should be the next step in his management?

- ☐ Decrease the dose of simvastatin to the last known dose he was able to tolerate
- ☐ Continue simvastatin at the same dose and then monitor
- ☐ Switch to another statin
- ☐ Add coenzyme Q10
- ☐ Stop simvastatin

Restarting the same statin, even at a lower dose, will likely cause his symptoms to recur

Decreasing the statin dosage to the last well-tolerated dose would not be appropriate in a patient with myopathy, as the symptoms would probably not improve.[2–4] Also, one should not switch to a different statin while a patient is experiencing symptoms. Rather, the statin should be stopped for at least 6 weeks or until the symptoms have fully resolved.[1]

Adding coenzyme Q10 is another option, especially in a patient with previously diagnosed coronary artery disease,[5] when continued statin therapy is thought necessary to reduce the likelihood of repeat coronary events.

We discontinued his simvastatin. Follow-up 3 weeks later in the outpatient clinic showed that his symptoms were slowly improving. The symptoms had resolved completely 4 months later.

4 How should we manage our patient's hyperlipidemia once his symptoms have resolved?

- ☐ Restart simvastatin at the 80-mg dose
- ☐ Restart simvastatin at the 40-mg dose
- ☐ Start a hydrophilic statin at full dose
- ☐ Use a drug from another class of lipid-lowering drugs
- ☐ Wait another 3 months before prescribing any lipid-lowering drug

His treatment for hyperlipidemia should be continued, considering his comorbidities. However, restarting the same statin, even at a lower dose, will likely cause his symptoms to recur. Thus, a different statin should be tried once his muscle pain has resolved.

Other classes of lipid-lowering drugs are usually less efficacious than statins, particularly when trying to control low-density lipoprotein (LDL) cholesterol, so a drug from another class should not be used until other statin options have been attempted.[2,6,7]

Simvastatin is lipophilic. Trying a statin with hydrophilic properties (eg, pravastatin, rosuvastatin, fluvastatin) has been shown to convey similar cardioprotective effects with a lower propensity for myalgia, as lipophilic statins have a higher propensity to penetrate muscle tissue than do hydrophilic statins.[3,4,8]

Once his symptoms resolved, our patient was started on a hydrophilic statin, fluvastatin 20 mg daily. Unfortunately, his pain recurred 3 weeks later. The statin was stopped, and his symptoms again resolved.

5 Since our patient was unable to tolerate a second statin, what should be the next step in his management?

- ☐ Restart simvastatin
- ☐ Use a drug from another class to control the hyperlipidemia
- ☐ Wait at least 6 months after symptoms resolve before trying any lipid-lowering drug
- ☐ Initiate therapy with coenzyme Q10 and fish oil
- ☐ Wait for symptoms to resolve, then restart a hydrophilic statin at a lower dose and lower frequency

Restarting simvastatin will likely cause a recurrence of the myalgia. Other lipid-lowering drugs such as nicotinic acid, bile acid resins, and fibrates are not as efficacious as statins. Coenzyme Q10 and fish oil can reduce lipid levels, but they are not as efficacious as statins.

In view of our patient's lipid profile—LDL cholesterol elevated at 167 mg/dL, high-density lipoprotein cholesterol 31 mg/dL, triglycerides 47 mg/dL—it is important to treat his hyperlipidemia. Therefore, another attempt at statin therapy should be made once his symptoms have resolved.

Studies have shown that restarting a statin at a low dose and low frequency is effective in patients who have experienced intolerance to a statin.[3,4] Our patient was treated with low-dose pravastatin (20 mg), resulting in a moderate improvement in his LDL cholesterol to 123 mg/dL.

STATIN-INDUCED MYOPATHY: ADDRESSING THE DILEMMA

Treating hyperlipidemia is important to prevent vascular events in patients with or without coronary artery disease. Statins are the most effective agents available for controlling hypercholesterolemia, specifically LDL levels, as well as for preventing myocardial infarction.

Unfortunately, significant side effects have been reported, and myopathy is the most prevalent. Statin-induced myopathy includes a combination of muscle tenderness, myalgia, and weakness.[2–11] In randomized controlled trials, the risk of myopathy was estimated to be between 1.5% and 5%.[6] In unselected clinic patients on high-dose statins, the rate of muscle complaints may be as high as 20%.[12]

The cause of statin-induced myopathy is not known, although studies have linked it to genetic defects.[7] Risk factors have been identified and include personal and family history of myalgia, Asian ethnicity, hypothyroidism, and type 1 diabetes. The incidence of statin-induced myalgia is two to three times higher in patients on corticosteroid therapy. Other risk factors include female sex, liver disease, and renal dysfunction.[7,8]

A less common etiology is anti-HMG coenzyme A reductase antibodies. Studies have shown that these antibody levels correlate well with the amount of myositis as measured by creatine kinase levels. However, there is no consensus yet on screening for these antibodies.[13]

Statin therapy poses a dilemma, as there is a thin line between the benefits and the risks of side effects, especially statin-induced myopathy.[3,4] Current recommendations include discontinuing the statin until symptoms fully resolve. Creatine kinase levels may be useful in assessing for potential muscle breakdown, especially in patients with reduced renal function, as this predisposes them to statin-induced myopathy, yet normal values do not preclude the diagnosis of statin-induced myopathy.[3,4,7,8]

Once symptoms resolve and laboratory test results normalize, a trial of a different statin is recommended. If patients become symptomatic, a trial of a low-dose hydrophilic statin at a once- or twice-weekly interval has been recommended. Several studies have assessed the efficacy of a low-dose statin with decreased frequency of administration and have consistently shown significant improvement in lipid levels.[3,4] For instance, once-weekly rosuvastatin at a dose between 5 mg and 20 mg resulted in a 29% reduction in LDL cholesterol levels, and 80% of patients did not experience a recurrence of myalgia.[3] Furthermore, a study of patients treated with 5 mg to 10 mg of rosuvastatin twice a week resulted in a 26% decrease in LDL cholesterol levels.[4] This study also showed that when an additional non-statin lipid-lowering drug was prescribed (eg, ezetimibe, bile acid resin, nicotinic acid), more than half of the patients reached their goal lipid level.[4]

The addition of coenzyme Q10 and fish oil has also been suggested. Although, the evidence to support this is inconclusive, the potential benefit outweighs the risk, since the side effects are minimal.[1] However, no study yet has evaluated the risks vs the benefits in patients with elevated creatine kinase.

Statin-induced myopathy is a commonly encountered adverse effect. Currently, there are no guidelines on restarting statin therapy after statin-induced myopathy; however, data suggest that statin therapy should be restarted once symptoms resolve, and that variations in dose and frequency may be necessary.[1–8,14]

Data suggest that statin therapy should be restarted once symptoms resolve, and that variations in dose and frequency may be necessary

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