BMJ Case Reports

Unexpected outcome (positive or negative) including adverse drug reactions

# My legs are getting old: sinvastatin-induced polyneuropathy

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## Summary

Axonal degeneration is the most common type of neuropathy induced by medication. The literature describes isolated cases in which polyneuropathy of the lower limb was observed during treatment with statins.

The authors present a case of polyneuropathy associated with the use of a statin. An 82-year-old female patient presented with a complaint of weakness and discomfort in her lower limbs after 7 years of therapy with simvastatin. The results of an electromyographic study were compatible with polyneuropathy (sensorimotor axonal neuropathy – moderate to severe). One month after the therapy with simvastatin was discontinued, the symptoms were reduced.

## BACKGROUND

Weakness, discomfort or fatigue, and frequent pain in the lower limbs are common complaints encountered in the practice of geriatric medicine. These complaints are often disregarded as a psychosomatic illness or a result of the normal ageing process. This case report examines an elderly patient suffering from polyneuropathy associated with atypical symptoms, which was attributed to the use of sinvastatin.

Statins are used to reduce cholesterol by inhibiting HMG-CoA reductase. Their use is associated with a reduction in the morbidity and mortality associated with chronic hyperlipidaemia. The side effects observed are generally mild and transient and include gastrointestinal problems, insomnia, headache, allergic conditions, rash and myalgia.[1] Evidence from case reports and case series suggests that statins can also cause sensory axonal polyneuropathy or multiple mononeuropathy.[2–5]

Adverse outcomes in users of statins, such as neuropathy, are expected to become more common as the use of the drugs becomes more widespread.

## CASE PRESENTATION

An 82-year-old widowed Brazilian woman was evaluated at the Brasilia University Hospital in response to a complaint of weakness and discomfort in the legs. Her medical history was remarkable for hypertension, osteoporosis, asthma, hypoacusis, knee osteoarthritis, nodular goitre (euthyroid) and hyperlipidaemia. Her medications included amlodipine 5 mg/day, alendronate sodium 70 mg/weekly, calcium carbonate 500 mg/day, inhaled formoterol 6 mcg/day and simvastatin 20 mg daily. She had taken simvastatin for 7 years. She had no history of diabetes, smoking, alcohol consumption or family history of neuropathy. She presented to a geriatric center having weakness and discomfort in her lower limbs, but without numbness or burning. The patient said, jokingly, "I feel that my legs are getting old".

The patient did not report muscle tenderness or paralysis and had no difficulty in walking. The findings of the physical and neurological evaluations were unremarkable, with the exception of hyporeflexia in the lower limbs. The laboratory studies showed that the hepatic panel, lipid panel and complete blood count were normal. Serum Monoclonal immunoglobulin was within normal range. Absence of urinary light chains or proteinuria. The levels of glucose, vitamin B12 and serum folate were normal. The level of serum creatinine phosphokinase (CPK) was 362 IU/l (reference range 30–190). An electromyographic (EMG) study was compatible with polyneuropathy (sensorimotor axonal neuropathy – moderate to severe).

## OUTCOME AND FOLLOW-UP

One month after the therapy with simvastatin was discontinued, the symptoms were reduced and the level of CPK normalised. A follow-up EMG study was not performed because the patient refused consent.

## DISCUSSION

These symptoms were probably related to statin therapy, since it disappeared after discontinuation of the treatment with simvastatin. This patient is the oldest among reported cases of statin-induced neuropathy.[2–5] Interestingly, she did not complain of muscle pain, despite high levels of CPK. Muscle pain is a well-recognised side effect of these drugs.

The most common causes of neuropathy can be identified from the history, examination and laboratory investigations.[6] The patient did not present a previous history of diabetes, alcohol consumption or family history of neuropathy.

If the cause of the neuropathy is not clear, neurophysiological testing should be considered. Sometimes, the differentiation between axonal and demyelinating neuropathies is not simple. Slowing of conduction velocity, frequent in demyelinating neuropathies, may also accompany severe axonal loss.[7] The differential diagnosis of peripheral neuropathy include: inflammatory, HIV infection, renal failure, hereditary neuropathy, amyloidosis, porphyria, lymphoma, Sjögren's syndrome, non-systemic vasculitic,

Crohn's disease, chronic gluten enteropathy, paraproteinaemia, B12, B1 and E vitamins deficiency, B6 excess, malnutrition, hypothyroidism, as well as exposure to heavy metals and solvents.[8] Additional causes may include other drug intoxication (disulfiram, isoniazid, ethionamide, metronidazole, nitrofurantoin, vincristine, chloramphenicol, phenytoin, dapsone, lithium, alfa interferon).[9] Alcoholism and diabetes can both cause small fiber neuropathy, similar to that induced by statins, with the difference that the condition does not resolve completely after treatment. The attentive diagnosis of peripheral neuropathy is important with respect to the therapeutic possibilities and limitations. Prompt treatment may prevent further irreversible nerve damage. Clinicians should be alert for treatable neuropathies, as mentioned above.

There are a few studies reporting the prevalence of polineuropathies in the elderly. Kararizou *et al*,[10] in a retrospective study, evaluated 74 patients over 65 years of age with clinical, laboratory, electrophysiological and sural nerve biopsy findings of different types of polyneuropathy. Vasculitic polyneuropathy was the commonest cause of neuropathy in the group (28.3%), followed by paraneoplasia (19.8%) and diabetes (16.2%). There was no statin-induced polyneuropathy. In other studies, diabetes was found to be the most common recognisable aetiology.[11] After exhaustive investigation, no clear cause is found in about 25% of patients.[6] Such chronic idiopathic axonal neuropathy usually occurs in elderly people and is often indolent, predominantly sensory, and length dependent. Notably in elderly patients, the coexistence of a series of underlying diseases as well as the side effects of medications can further mimic or mask the symptoms.

In statin-induced neuropathy, the condition will resolve completely after medication has stopped. However, mild distal involvement may remain without clinical consequences.[12] Although a prospective study demonstrated that long-term treatment with simvastatin at 20 mg may cause clinically silent but electrophysiologically detectable damage to peripheral nerves,[13] there is no reason to request an electrophysiological study in all patients that use statins.

The exact cause of the neuropathy associated with statins is unknown, but the involvement of key components of cellular function has been proposed. These agents include ubiquinone-coenzyme Q10, which has antioxidant activity, and mevalonate, which might reduce the formation of specific selenoproteins that are required for the structural integrity of a nerve.[12]

There is no clear relationship between the duration of statin use and the onset of clinical symptoms of neuropathy; the side effects can occur days or years after use.[2]

Although reports about neuropathies are more frequent among the lipophilic statins (ie, simvastatin, atorvastatin and lovastatin), there have been reports of neuropathy with pravastatin (a hydrophilic statin), which suggests a class effect that involves all statins and not only those with physico-chemical similarity (if hydrophilic or lipophilic).

Statins might interact with other drugs as a result of co-metabolism by cytochrome P450. In addition, elderly patients have a reduced functional reserve in various organs and also tend to take more drugs that might interact with the P450 system. All these factors contribute to a higher risk of neuropathy in older people. Our patient did not use other medications that require significant metabolism by cytochrome P450. The use of both statins and fibrates (due metabolisation by P450 isoenzymes) is associated with an increased risk of peripheral neuropathy.[3]

Gaist *et al*[4] reported an OR for idiopathic polyneuropathy with the use of statins of 3.7 (95% CI 1.8 to 7.6) for all cases (ever used) and for patients treated for 2 years the OR was 26 (95% CI 7.8 to 45.4). However, the conclusions of this study have been rebutted and opposed by others investigators, and, given the substantial cardiovascular protective effect of statins in higher risk populations, concerns about polyneuropathy should not limit their use.[14 15]

The increased prevalence of chronic systemic disorders causing neuropathy, as well as the use of neurotoxic drugs in older patients, contributes to the onset of neuropathy.[16] Distal symmetric neuropathies are an age-associated condition, but the frequency of diabetic distal symmetric neuropathies declines with age, coincident with an increase in non-diabetic cases.[17]

Although weak evidence, a greater risk of myopathic events has been attributed to Caribbean and Black African[18] and Chinese and Japanese descent,[19] but not to neuropathies.

Given the results of the EMG, the absence of other causes of polyneuropathy, and the substantial clinical improvement after withdrawal of medication, we conclude that our patient suffered from sinvastatin-induced polyneuropathy.

Despite the considerable benefits to be gained from the treatment of dyslipidaemia with statins, effects of the drugs on the peripheral nerves should be suspected in the follow-up of patients who complain of weakness, discomfort, fatigue or pain in the lower limbs.

## Learning points

- Despite the fact that muscle pain is a well-recognised side effect of statins, long-term use of simvastatin can be associated with polyneuropathy.
- A neuropathy should be considered in patients taking statins who report weakness, discomfort, fatigue, or pain in the lower limbs.
- Ageing causes changes in drug pharmacokinetics and pharmacodynamics, so adverse effects should be monitored more frequently in the elderly.

**Competing interests** None.

**Patient consent** Obtained.

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