



Statin-Induced Neuropathic Pain: A Case Report

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ABSTRACT

The most reported form of statin induced pain is myalgia, conversely peripheral neuropathy is a rare side effect. We report a patient who received rosuvastatin for hypercholesterolemia and experienced episodes of pain in both hands during the night. Rosuvastatin was stopped and atorvastatin was replaced. Re-introduction with another statin resulted in a more severe form of the similar adverse effect after 4 months. This is a rare adverse effect of an extensively prescribed class of drug. Physicians should be aware of the possibility of peripheral neuropathy symptoms in patients on statin therapy.

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Introduction

As a term neuropathic pain refers to a group of neurologic disorders that are identified by chronic pain. It has been recognized that neuropathic pain with different etiologies might be expressed and described differently by the patients (1).

Statins reduce cholesterol levels in hyperlipidemic patients. These drugs are a class of 3-hydroxy-3-methylglutaryl (HMG) coenzyme A (CoA) reductase inhibitors which are extensively prescribed (2). Statins are considered as an advanced intervention for reducing the probability of cardiovascular disease (CVD) events in moderate to high risk patients. Evidence indicates that statins are safe medication. Their most frequently reported side effect is myalgia. Myalgia is dose-related (3). Peripheral neuropathy is a rare side effect related to statin therapy in comparison to myopathy (4). Several cases of peripheral neuropathy have been associated with established doses of statins (5). Typical drug induced peripheral neuropathies are with a distal “stocking-glove” pattern. Patients symptoms range from muscle weakness, paresthesia, sensory loss, to hyperesthesias (6).

Case Report

A 49-year-old woman, with hypercholesterolemia and hypertension presented with pain in both hands. Ten months prior to the onset of this episode, the patient

was prescribed 5 mg oral rosuvastatin (Ropixon® manufactured by Abidi Pharmaceutical Company, Tehran, Iran). The patient was not taking any other hypolipemic medication before the initiation of statin. Concomitant medications were included hydrochlorothiazide 25 mg twice daily, lisinopril 10 mg twice daily, and aspirin 80 mg daily as needed indicated for hypertension. She had no known drug allergies or hypersensitivity reaction in the past. She complained of episodes of pain in both hands during the night. In each episode the pain lasted for several minutes and distributed in median nerve territory. The pain was severe enough to wake her up and was resolved with shaking hands as patient described. Her chief complaint was severe pain with numbness in both hands. Rosuvastatin was stopped due to the severity of side effect. The symptoms and pain were resolved completely upon cessation of the medication which was suspected to cause the adverse effect. Three days after the symptoms were subsided, atorvastatin (manufactured by Sobhan Pharmaceutical Company, Tehran, Iran) was re-introduced. Atorvastatin usage resulted in even more severe pain in hands after four months of initiation. Patient was asked to evaluate the pain when it happened on a visual analog scale (VAS) (7) in various occasions.

She rated the pain as a 6 out of 10 on rosuvastatin and 10 out of 10 on the visual analog scale (VAS). The pain

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episodes sustained 8 months while taking rosuvastatin and 3 weeks on atorvastatin until she was referred to the neurologist. EMG study was unremarkable. Skin biopsy and autonomic testing were not performed.

A neurologist evaluated the patient for pain and paresthesia. Diclofenac 100 mg, vitamin B1 300 mg, calcium-D supplement and gabapentin 100 mg were ordered for 40 days to address the issue.

Naranjo probability scale (8) indicated a definite relationship between hands pain (neuropathic) and both of the statins in our patient. Her serum electrolytes were normal. and Blood sugar, blood urea nitrogen, complete blood count, blood potassium were also normal. ESR 1 hr. = 15 mm, TSH level was 2.5 μ IU/ml (Reference Range in adult is 0.27-5.1) and FBS was 99.

Discussion

We described a 49-year-old female who developed neurotoxicity after the administration of hypolipidemic drugs; rosuvastatin and atorvastatin. Our patient presented with neuropathic pain symptoms. Tierney et al reported an association between statin use and peripheral neuropathy (9). It has been found that users of statins are at a 1.3 to 14 fold amplified risk of developing idiopathic polyneuropathy when compared with the background incidence rate (10, 11). There are case reports and case series which have connected statin use with neuropathy (12, 13).

This condition could occur in a time frame ranging from days to 7 years with established statin dosages (6). As mentioned earlier, the adverse effect is extremely rare. For instance in a study of over 700 participants taking a statin with a median follow-up of 5.2 years, only one patient developed peripheral neuropathy (14). However, more cases with peripheral neuropathy on these class are expected due to the fact that the indications of statins are rapidly growing.

In a case control research a trend of decreased vibration perception in the group received statin compared to the control group was observed. This result is theoretically suggestive of an association between long-term statin use and decreased peripheral sensory perception. Also, this could be linked to peripheral sensory neuropathy (15).

All the three patients who developed neuropathy on statin in a serial electrophysiological study presented with abnormal sympathetic skin responses (SSR). Upon discontinuation of the suspected drug, SSRs returned to baseline with clinical improvement. One of the three patients developed neuropathy again once the similar drug was re-started (4).

HMG-CoA reductase inhibitors may rise the risk for polyneuropathy according to the result of an European study (16).

The underlying mechanism by which statins provoke neuropathy is not fully recognized (6).

The most stated hypothesis is that statins by inhibiting HMG-CoA reductase may reduce the production of

intermediates of farnesyl pyrophosphates, predominantly ubiquinones. Cholesterol is a ubiquitous element of cell membranes. Interfering with cholesterol synthesis may lead to cell malfunction. Insufficient ubiquinone can affect neurons energy consumption (6).

Idiosyncratic reaction in liable patients has been proposed in cases of polyneuropathy related to statin therapy (11). Alternatively, it has been suggested that peripheral neuropathy related to statins or niacin might be due to hyperlipidemia and hypertriglyceridemia chylomicronemia (6).

Rosuvastatin successfully caused recovery of vasa nervorum and nerve work in diabetic neuropathy (17). In comparison to statin induced neuropathy, diabetic polyneuropathy might involve different mechanism for example vascular involvement rather than axonal disorder or demyelinating component. Also, it is unlikely that neuron demyelination be the basic mechanism. By stopping the treatment the symptoms of neuropathy are generally relieved in weeks to months (6) and rechallenges with statins are expected to text result in reappearance of neuropathic pain (11). Similar phases were experienced by our patient.

For any patient who was forced to discontinue statin due to neuropathy, it is still recommended to rechallenge with lower doses of the same statin or another statin after resolution of the undesirable symptoms (18). This is beneficial especially to verify the causality of the suspected medication if the symptoms recurred. Also, this action is of great value due to the several advantages that are achieved by using this drug class, although rechallenge could be quite risky.

When statins are not tolerated, treatments should be tailored by other hypolipidemics agents. Ezetimibe is usually a proper option (19). However, studies did not show the efficacy of ezetimibe in cardiovascular morbidity and mortality reduction unlike statins. Bile acid sequestrants (BAS) like cholestyramine are another choice which can be co-administered with ezetimibe to effect more on LDL cholesterol (20). Niacin can reduce cardiovascular morbidity and mortality even when used alone (21). Niacin may be used in combination with BAS and ezetimibe in patients with intolerance to statins (22). Reduction of dietary saturated fat intake could obviously be considered as an effective approach to reduce blood cholesterol. Also, substituting saturated fat with phytosterols could lower LDL-C (18). Natural substitutes such as viscous fibre (23), red yeast rice (24) are other options to help lowering the cholesterol.

Although, neuropathy following the use of statins has been postulated in the literature, physicians may not consider this as a drug side effect due to its rare occurrence.

Peripheral neuropathy should be suspected in patients taking statins and complain of a severe pain with abnormal sensation like stabbings pain, pins and needles, burning or cold or electric shocks sensation, numbness and itching.

References

- Backonja MM, Stacey B. Neuropathic pain symptoms relative to overall pain rating. *J Pain* 2004;5(9):491-7.
- Zhang L, Zhang ZG, Liu XS, Hozeska-Solgot A, Chopp M. The PI3K/Akt pathway mediates the neuroprotective effect of atorvastatin in extending thrombolytic therapy after embolic stroke in the rat. *Arterioscler Thromb Vasc Biol* 2007;27(11):2470-5.
- Auer J, Sinzinger H, Franklin B, Berent R. Muscle-and skeletal-related side-effects of statins: tip of the iceberg? *Eur J Prev Cardiol* 2016;23(1):88-110.
- Lo Y, Leoh T, Loh L, Tan C. Statin therapy and small fibre neuropathy: a serial electrophysiological study. *J Neurol Sci* 2003;208(1):105-8.
- Weimer LH, Sachdev N. Update on medication-induced peripheral neuropathy. *Curr Neurol Neurosci Rep* 2009;9(1):69.
- Chong PH, Boskovich A, Stevkovic N, Bartt RE. Statin-associated peripheral neuropathy: review of the literature. *Pharmacotherapy* 2004;24(9):1194-203.
- Hawker GA, Mian S, Kendzerska T, French M. Measures of adult pain: Visual analog scale for pain (vas pain), numeric rating scale for pain (nrs pain), mcgill pain questionnaire (mpq), short-form mcgill pain questionnaire (sf-mpq), chronic pain grade scale (cpgs), short form-36 bodily pain scale (sf-36 bps), and measure of intermittent and constant osteoarthritis pain (icoap). *Arthritis Care Res (Hoboken)* 2011;63(S11):S240-S52.
- Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981;30(2):239-45.
- Tierney EF, Thurman DJ, Beckles GL, Cadwell BL. Association of statin use with peripheral neuropathy in the US population 40 years of age or older. *J Diabetes* 2013;5(2):207-15.
- Corrao G, Zambon A, Bertù L, Botteri E, Leoni O, Contiero P. Lipid lowering drugs prescription and the risk of peripheral neuropathy: an exploratory case-control study using automated databases. *J Epidemiol Community Health* 2004;58(12):1047-51.
- Beltowski J, Wojcicka G, Jamroz-Wisniewska A. Adverse effects of statins-mechanisms and consequences. *Curr Drug Saf* 2009;4(3):209-28.
- Ziajka PE, Wehmeier T. Peripheral neuropathy and lipid-lowering therapy. *South Med J* 1998;91(7):667-8.
- Jeppesen U, Gaist D, Smith T, Sindrup S. Statins and peripheral neuropathy. *Eur J Clin Pharmacol* 1999;54(11):835-8.
- Lovastatin 5-year safety and efficacy study. Lovastatin Study Groups I through IV. *Arch Intern Med* 1993;153(9):1079-87.
- West B, Williams CM, Jilbert E, James AM, Haines TP. Statin use and peripheral sensory perception: a pilot study. *Somatosens Mot Res* 2014;31(2):57-61.
- Anderson JL, Muhlestein JB, Bair TL, et al. Do statins increase the risk of idiopathic polyneuropathy? *Am J Cardiol* 2005;95(9):1097-9.
- Ii M, Nishimura H, Kusano KF, et al. Neuronal nitric oxide synthase mediates statin-induced restoration of vasa nervorum and reversal of diabetic neuropathy. *Circulation* 2005;112(1):93-102.
- Mancini GJ, Baker S, Bergeron J, et al. Diagnosis, prevention, and management of statin adverse effects and intolerance: proceedings of a Canadian Working Group Consensus Conference. *Can J Cardiol* 2011;27(5):635-62.
- Stein EA, Ballantyne CM, Windler E, et al. Efficacy and tolerability of fluvastatin XL 80 mg alone, ezetimibe alone, and the combination of fluvastatin XL 80 mg with ezetimibe in patients with a history of muscle-related side effects with other statins. *Am J Cardiol* 2008;101(4):490-6.
- Zema MJ. Colesevelam HCl and ezetimibe combination therapy provides effective lipid-lowering in difficult-to-treat patients with hypercholesterolemia. *Am J Ther* 2005;12(4):306-10.
- Berge K, Canner P, Group CDPR. Coronary drug project: experience with niacin. *Eur J Clin Pharmacol* 1991;40(1):S49-S51.
- Insull Jr W. Clinical utility of bile acid sequestrants in the treatment of dyslipidemia: a scientific review. *South Med J* 2006;99(3):257-74.
- Jenkins DJ, Leeds AR, Gassull MA, Cochet B, Alberti GM. Decrease in postprandial insulin and glucose concentrations by guar and pectin. *Ann Intern Med* 1977;86(1):20-3.
- Halbert SC, French B, Gordon RY, et al. Tolerability of red yeast rice (2,400 mg twice daily) versus pravastatin (20 mg twice daily) in patients with previous statin intolerance. *Am J Cardiol* 2010;105(2):198-204.