Statins and peripheral neuropathy: causation or coincidence?

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Case report
A 50-year-old man presented with clinical features of peripheral neuropathy with numbness in both feet. He had been prescribed statin therapy for a mixed hyperlipidaemia following a myocardial infarction at 40 years of age. After four years of continuous statin therapy the development of neuropathic symptoms prompted the patient to request further evaluation. Clinical examination at this time revealed bilateral sensory loss in all modalities tested but was otherwise unremarkable. Nerve conduction studies were performed and indicated an axonal sensory neuropathy. He consumed between 20 and 30 units of ethanol per week which he reduced. Extensive investigation revealed no secondary cause, including normal fasting glucose, renal and thyroid function, serum B12 level, autoantibody screen, syphilis serology and lumbosacral MRI. At the time it was suggested that statins could be responsible for his symptoms, but as these were not progressive and his cardiovascular risk high, statin therapy was continued. He had previously used simvastatin and atorvastatin but was switched to rosuvastatin 10 mg o.d. with the view that this might ameliorate his neuropathic symptoms. No improvement was noted with this change; however, the patient noticed a significant reduction in symptoms approximately two weeks after deliberately discontinuing his statin at a later date, which then returned within one week of restarting.

Comment
The temporal association of statin withdrawal and re-challenge with clinical features of peripheral neuropathy suggests a causal link. The clinical importance for the case described needs to be placed in context that his symptoms were relatively mild, and that statin therapy effectively improved his lipid profile.

Peripheral neuropathy is reported as a defined side-effect of statin therapy. Evidence for this has been derived in the most part from observational case reports. No randomised trial of statin use has had peripheral neuropathy as a major adverse drug reaction. One of the first case reports had an association inferred from improvement and aggravation of neuropathic symptoms following cessation and reintroduction of the statin; although a larger series (n=7) found symptoms persisted after the statin was stopped. Another study used retrospective case-control methodology, in which cases (n=166) of idiopathic peripheral neuropathy were identified from patient registries and matched to healthy controls in a ratio of 1:25, and then assessed for statin exposure from prescription records. This suggested that the risk of peripheral neuropathy was significantly increased (OR 3.7, 95% CI 1.8–7.6), especially in those treated with statins for more than 2 years (OR 6.6, 95% CI 2.6–16.5). The authors of the study downplay the possibility of ascertainment bias because at the time peripheral neuropathy was not well recognised as a possible statin adverse effect. A prospective study found significant electrophysiological changes in peripheral nerves in patients (n=42) treated with simvastatin for 2 years compared with placebo, although there were no linked symptoms. Histological changes consistent with peripheral nerve damage have been observed in rats treated with simvastatin.

Proposed mechanisms for a statin–neuropathy link include neuronal membrane effects due to reductions in cholesterol (an essential membrane component) and mitochondrial toxicity leading to altered intracellular energy production. Evidence at the cellular level exists for a role for these mechanisms in statin muscle effects but this has not been established in peripheral nerves.

The above findings should be taken in the context of the accumulating evidence in major randomised controlled trials of statin monotherapy, in which the increased risk of peripheral neuropathy has not been observed. While these trials were not designed to look for this effect, there would have been a signal of hazard from the several meta-analyses and post-marketing studies of statin usage. It is of interest that there is one prospective cohort study in patients with type 2 diabetes mellitus treated with statins which showed a protective effect on the development of peripheral neuropathy.

Statin therapy is now considered routine practice for those with vascular disease or for those at high cardiovascular risk. Peripheral neuropathy is also common, with a reported
population prevalence of approximately 5%, increasing with age, of which approximately 25% are apparently idiopathic. Consequently, coincidental association is inevitable.

In summary, there is at present insufficient evidence to conclusively implicate statin therapy as a common cause of peripheral neuropathy; however, it is plausible that its occurrence associated with statin therapy is rare and idiosyncratic.

References