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## Statin neuropathy?

No one connected this patient's neuropathy to the statin he once took. The connection became clear, though, when he resumed statin therapy and his symptoms worsened.

It took 13 years before an 82-year-old patient learned what had caused the pain and tingling in his feet that he'd been living with all those years.

**In 1996 he had a coronary stent insertion**, and after the procedure, began taking a beta-blocker and atorvastatin. He subsequently noticed a sensory change in his toes bilaterally. This slowly progressed to paresthesia in the anterior segments of both feet on the plantar and dorsal surfaces.

**A nerve conduction study (TABLE)** confirmed the presence of a sensorimotor polyneuropathy, despite the fact that he did not have diabetes, or any other condition known to predispose him to polyneuropathy. The patient's left sural peak latency and amplitude, a measure of sensory nerve action potential (SNAP), was absent. The right sural SNAP demonstrated a mild decrease of the amplitude with a normal distal latency. The left peroneal F wave response (a measure of nerve conduction velocity) was within the upper limits of normal. The left tibial F wave response was normal. The left peroneal and left tibial CMAPs (compound muscle action potentials) were normal.

A nerve biopsy was not considered for this patient because its main use is in the identification of specific lesions that are generally lacking in acquired, distal, symmetrical sensory neuropathy. (Plus, biopsy gives no more information than electrophysiological tests.)<sup>1</sup>

### Connecting the dots years later

Neither the patient's cardiologist, nor his general physician, was aware of any connection between statins and neuropathy, but the patient stopped taking the drug in 2003. And while the neuropathy never went away, it did subside slightly to a fairly constant level.

In August 2009, because of suboptimal levels of low-density lipoprotein (LDL), high-density lipoprotein (HDL), and C-reactive protein, his cardiologist prescribed simvastatin 5 mg daily.

On the third day, the patient experienced a marked increase of the neuropathy, which extended above his ankles. Cutaneous sensory loss became more extensive and pronounced. He stopped the statin that day, but the paresthesia did not lessen. In addition, he developed intermittent pins and needles in both hands and some instability in his gait. To date, there has been no improvement in his symptoms. Nerve conduction studies were not repeated.

### Discussion: The various causes of neuropathy

In 2003, this journal published a question, "Do statins cause myopathy?"<sup>2</sup> The item concluded that if they did, the risk was very low, although isolated case reports suggested a myopathy risk for all statins, ranging from benign myalgia to fatal rhabdomyolysis.

It is now widely acknowledged that statins can cause myopathy in as many as 10% of patients taking these drugs.<sup>3</sup>

TABLE

## A look at the patient's nerve conduction results

Nerve and site	Peak latency (ms)	Amplitude (mV)	Segment	Latency difference (ms)	Distance (mm)	Conduction velocity (m/s)
<b>Sensory nerve conduction</b>						
Sural nerve (left) Lower leg	0.0	0.0		N/A	N/A	N/A
Sural nerve (right) Lower leg	4.0	2		N/A	N/A	N/A
<b>Motor nerve conduction</b>						
Peroneal nerve (left) Ankle	4.3	1.9		N/A	N/A	N/A
Fibular head	13.2	1.6	Ankle-fibular head	8.9	358	40
Knee	16.2	1.5	Fibular head-knee	3.0	115	38
Tibial nerve (left) Ankle	4.2	2.9		N/A	N/A	N/A
Popliteal fossa	15.4	2.6	Ankle-popliteal fossa	11.2	450	40

ms, millisecond; m/s, meters/second; mV, millivolt; N/A, not applicable.

The involvement of peripheral nerves bilaterally, usually affecting distal axons of the feet and legs, is the most common form of polyneuropathy and its presentation generally excludes consideration of other forms of neuropathy, such as the mononeuropathies and neuritis. Affected nerves may be sensory, motor, or autonomic.

Symptoms include all varieties of paresthesia, sensory loss, muscle weakness, and pain. The most common cause is diabetes mellitus, which must be the first condition to be excluded. Other conditions, such as vitamin deficiencies, have also been linked with this complication.

■ **Laboratory work-up**, aside from blood glucose testing for diabetes, should include routine complete blood count and SMA-12, as well as thyroid profile and vitamin deficiency status (particularly vitamins B12 and B1).

### Is a medication—perhaps a statin—to blame?

Numerous drugs are known to be associated with neuropathy.<sup>4</sup> These include chemotherapy agents (cisplatin, taxoids), certain antibiotics, nucleoside analogs, dap-

sone, metronidazole, and certain cardiovascular drugs (amiodarone, hydralazine, statins).<sup>4</sup> Recent work has indicated that simvastatin inhibits central nervous system remyelination by blocking progenitor cell differentiation.<sup>5</sup> By extension, it probably inhibits progenitor cells in the peripheral nervous system.

The possibility of an association between statins and peripheral neuropathy has expanded from several case reports to a population-based study involving 465,000 subjects.<sup>6</sup> More recently, a review of the literature<sup>7</sup> concluded that exposure to statins may increase the risk of polyneuropathy and that statins should be considered the cause when other etiologies have been excluded. The authors suggested that the incidence of peripheral neuropathy due to statins is approximately 1 person/14,000 person-years of treatment.

### An exposure, a “break,” and another exposure

The reappearance or aggravation of symptoms after cessation of statin therapy and subsequent second exposure has been described in the literature.<sup>8</sup> In the case described here, the time between re-exposure and symptoms

➤ The patient's sudden exacerbation of persisting symptoms after a long withdrawal from statin therapy strongly suggested a delayed hypersensitivity reaction.

was suggestive of a T-cell-mediated hypersensitivity reaction. It has been proposed that tumor necrosis factor (TNF)-alpha released by T cells may contribute to the pathogenesis of demyelinating neuropathy.<sup>9</sup>

### Managing this patient's lipid levels going forward

The patient described in this report is now receiving ezetimibe 10 mg daily, which reduces the absorption of cholesterol from the diet, and niacin 2 g daily, which he can tolerate. His most recent fasting lipid panel showed the following results: cholesterol, 171 mg/dL; LDL cholesterol, calculated, 113 mg/dL;

HDL cholesterol, 37 mg/dL; triglycerides, 106 mg/dL; and non-HDL cholesterol, 134 mg/dL.

Controlling the patient's pain was another matter. Drugs commonly used for par-esthesia and pain (including opiates) did not provide relief. Pregabalin (Lyrica) also had little effect. Transcutaneous electrical nerve stimulation did not perceptibly lessen his symptoms, and was also discontinued.

At the present time, this patient is not on any specific treatment for his neuropathy. **JFP**

#### CORRESPONDENCE

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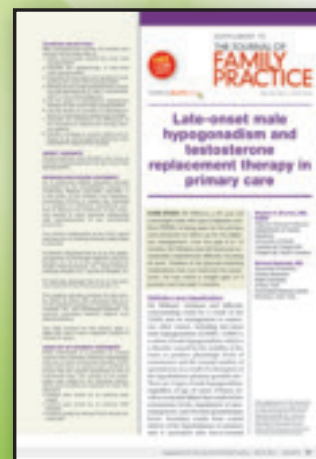
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