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Invited Editorial / *Davetli Editöryal Yorum*

Peripheral polyneuropathy in patients receiving long-term statin therapy

Uzun dönem statin kullanan hastalarda periferik polinöropati gelişimi

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Although drug-induced neuropathies (DIN) are not very common, they are one of the main reasons of peripheral neuropathies.[1] DIN cause to sensory, motor, and autonomic dysfunctions depending on the type of the peripheral nerve involvement. As significant recovery could be observed after discontinuation of the causal agent drug, early diagnosis is important. However, symptoms of DIN are usually seen after months or years of exposure.[2] Therefore, defining the causal relationship between the drugs and long term side effects like drug-induced peripheral neuropathies is not easy always, and commonly missed. Electrodiagnostic tests are the most important methods to confirm tthe peripheral neuropathy.[3] We classify the type of neuropathy, the location and severity of the nerve injury by electroneuromyography (ENMG).

Statins are one of the most important drugs to lower cholesterol and reduce cardiovascular morbidity and mortality. However, discontinuation and nonadherence to statin therapy remains a very important problem. The major reason for discontinuation of statin therapy is statin-associated muscle symptoms (SAMs). The role of statins in peripheral neuropathy has not yet been clearly shown, and there are few studies that included case reports, case series, and small epidemiological studies.[4,5] The probable mechanism was thought to be the change in the integrity of the neuronal cell membranes, in which cholesterol plays an important role. Statins also inhibit Coenzyme Q10, an enzyme which could alter the neurons' energy utilization.[6] On the contrary; some animal studies have reported that statins provided a neuroprotective effect against peripheral nerve injury.[7] In a recent Danish case-control study, use of statins in 370 cases, was not associated with an elevated risk of polyneuropathy. Similarly, no association was observed between polyneuropathy risk and long-term high-intensity statin.[8]

Abbreviation:

DIN	*Drug-induced neuropathies*
ENMG	*Electroneuromyography*
SAMs	*Statin-associated muscle symptoms*

In this issue of the Archives of Turkish Society of Cardiology, Ozdemir et al. reported increased peripheral polyneuropathy rates (66%) in patients after one year of statin therapy.[9] In this study, the comparison of polyneuropathy between the statin group (either on atorvastatin or rosuvastatin) with the control group revealed a significant difference by neurological examination and ENMG ($p<0.01$).

The study is of importance for supporting the relationship of long –term statin therapy and peripheral polyneuropathy. The comparison of different statins with different doses with the control group by both neurological examination and ENMG is also a valuable study design. However, there are some issues about the study that should be discussed. First of all, the prospective nature of the study is questionable and the number of patients on atorvastatin and rosuvas-

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tatin is not enough to compare these statins with each other and also with the control group. The direct linkage of polyneuropathy to statin therapy is not clear in the study, because many etiological or confounding factors were not evaluated in detail like concomitant drug interactions. On the other hand, the control group consisted of relatively younger patients. The prevalence of peripheral neuropathy is approximately 2.4%, but increases up to 8% over the age of 55[10] and although it is not significant, this age difference could affect the results of this study.

Furthermore, dose-dependent effects of statins on polyneuropathy were not observed in the study. There was no significant difference between the incidence of polyneuropathy detected by ENMG and by neurological exam among groups on different doses of atorvastatin and rosuvastatin. The effect of the duration of statin therapy was also not significant between groups. Neuropathies due to statin therapy usually occur years after the beginning of medication and the risk was reported to increase after long-term exposure.[11,12] Therefore, the results of this study contradict with the previous data.

Ozdemir et al., stated that neurological examination is superior to ENMG to identify the statin induced polyneuropathy and they concluded this as the effect of the involvement of thin myelinated fibers. However, the accuracy of this statement is controversial. In order to evaluate the functions of small fibers, the diagnosis should be confirmed by pain- heat examinations or skin biopsy. The routine use of neurologic examination in patients on long term statin therapy to identify peripheral neuropathy could overestimate the pathology and many statins could be discontinued. It would be appropriate to distinguish patients as symptomatic or asymptomatic, as we usually prefer to discontinue statins in patients with SAMs; which is more important than the laboratory findings.

This study is important for physicians to be aware of the risk of peripheral neuropathy in patients on statin therapy. Neurological symptoms such as numbness, pain, tingling, and tremor in the hands and feet should be questioned in such patients on follow-up visits, as authors stated.[9] Neurological examination is performed in patients with suspected polyneuropathy and ENMG could be performed if necessary. However, when statin-induced peripheral neuropathy is suspected, switching to another statin after recovery to prevent further nerve damages is also questionable. Prospective studies are needed for more rational data.

In conclusion; statin therapy could lead changes in the peripheral nerves with mainly axonal involvement; however, in many cases, these changes do not cause evident clinical symptoms, especially when the treatment period is not that long. It should also be kept in mind that an important amount of polyneuropathies are still idiopathic. Therefore, the main issue is to evaluate patients in detail before discontinuation of the statin therapy, which is one of the main treatment strategies in patients with cardiovascular diseases.

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