Treatment with statins and peripheral neuropathy: results of 36-months a prospective clinical and neurophysiological follow-up

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Abstract
OBJECTIVES: To confirm the changes in the results of EMG assessment of lower-limb peripheral nerves in patients treated with statins in the longer follow-up period of 3 years.
BACKGROUND: Long-term treatment with statins may have adverse effects: affection of muscles or peripheral nervous system. The frequency of affection of the peripheral nervous system has not been thoroughly investigated; our previous study showed the signs of peripheral nerve damage in the results of EMG assessment.
DESIGN/METHODS: Forty-two patients (23 males, 19 females, mean age 51.9 and 52.3 years) with a definitive diagnosis of combined hyperlipidemia were studied. Other metabolic disorders or chronic ethanol abuse were excluded. Initial examinations included laboratory and neurophysiological measures (peroneal and tibial nerves: MNCV, CMAP, F-wave mean latency; superficial peroneal and sural nerve: SNCV, SNAP). Subsequently, treatment with simvastatin 20 mg daily was initiated. Patients were followed for 36 months with repeated neurophysiological examinations on 24 and 36 months after statin treatment initiation.
RESULTS: None of the patients reported subjective symptoms typical for peripheral neuropathy. Neurophysiological examination of lower-limb peripheral nerves demonstrated statistically significant prolongation of F-wave mean latency on peroneal and tibial nerves (p<0.0001, paired t-test).
CONCLUSIONS: The study confirmed that long-term treatment with statins caused a clinically silent but still definite damage to peripheral nerves when the treatment lasts longer than 2 years.

INTRODUCTION
Classification of hyperlipidemias is established according to the European Atherosclerosis Society (EAS), which distinguishes three types: hypercholesterolemia, hypertriglycerideremia and mixed or combined hyperlipidemia. Lipid-lowering drugs fall into four categories, namely statins, fibrates, nicotinic acid and resins. Treatment choice is made according to the type of metabolic disturbance – statins have effect mostly on LDL cholesterol and total cholesterol, fibrates increase HDL cholesterol a lower triglycerides. Statins are inhibitors of HMG-CoA reductase, cause lowering of plasma concentration of cholesterol and especially the LDL fraction by blocking intracel-
lular synthesis of cholesterol. This results in increased expression of LDL-receptors, followed by increased LDL update from the plasma. Indications to treatment with statins are pure hypercholesterolemia or combined hyperlipidemia with dominant elevation of LDL-cholesterol. Statins are classified according to their physical-chemical properties into two major groups: The first group is lipophilic metabolized via a hepatic system of cytochrome P450 isoenzymes, especially isoenzyme CYP3A4. The second group contains hydrophilic statins, which is practically not metabolized by cytochrome P450 and is excreted by the kidney. Metabolites do not enter liver cells and will not affect the intracellular enzyme (HMG-CoA reductase).

Most common neurological manifestations of lipid-lowering drug treatment are muscular complications. These range from minimum muscle weakness to the most serious forms associated with rhabdomyolysis, myoglobinuria and renal failure. The second neurological complication is the appearance of peripheral neuropathy. Literature describes isolated cases where appearance of lower-limb polyneuropathy was observed during treatment with lipid-lowering agents (Silveberg 2003; Ahmad 1995; Jacobs 1994). Gaist et al. (2001, 2002) presented retrospective epidemiologic studies suggesting the possible increase in the relative risk of lower-limb polyneuropathy during long-term use of statins. Our goal was to prospectively follow patients using statins for a long period of time and focus on electrophysiologic parameters that could uncover initial changes in the peripheral nerves.

### MATERIAL AND METHODS:

Starting in 2002, we have prospectively followed patients with the aim to find the incidence of peripheral neuropathy in long-term treatment with statins. The group consisted of patients followed up in a special metabolism clinic for hyperlipidemia. The prospective study included 42 patients, 19 males (mean age 52.3 years (SD=9.8)) and 23 females (mean age 51.9 years (SD=11.2). All patients had combined hyperlipidemia confirmed by laboratory tests. Laboratory tests also excluded the following diseases: diabetes mellitus, renal failure, hepatopathy, thyreopathy, hypovitaminosis B12, paraproteinemia, and chronic alcohol abuse. Serologic testing excluded Lyme disease.

Patients underwent complex clinical neurological examination and a standardized electromyographic examination to exclude pre-existing affection of peripheral nerves of the lower extremities. Electromyography was performed on the Dantec Counterpoint. The diagnostic protocol consisted of the measurement of motor nerve conduction velocity (MNCV), in the peroneal and tibial nerves bilaterally, with measurement of compound muscle action potential (CMAP) amplitude and F-wave latency in both nerves. Furthermore, sensory nerve conduction velocity (SNVC) was measured bilaterally in n. peroneus superficialis and n. suralis. The temperature of the examined limbs and the room temperature were monitored, and they were constant during all examination sessions. The mean temperature measured at the limbs was 31°C, the room temperature was kept to 27°C. In all patients of the group, oral medication with simvastatin (Simvacard®, Zentiva, Prague, Czech Republic) was initiated with a standard dose of 20 mg administered each evening. Follow-up examinations were performed after 24 and 36 months of treatment, each visit included laboratory tests, complex neurological examination and EMG examination following the protocol described above.

### RESULTS

Within evaluation of subjective symptoms, 2 patients stated muscle pain and 1 patient felt muscle weakness after 1 month of treatment. No changes on the clinical neurological examination were documented in any of the patients. Table 1 summarizes the initial and follow-up results from electrophysiology. Paired t-test demonstrated a significant ($p<0.0001$) slowing of motor conduction velocity in the peroneal nerves.

F-wave latency in the peroneal and tibial nerves was significantly prolonged ($p<0.0001$). Regression analysis demonstrated that F-wave latency in the peroneal and tibial nerves increases significantly over time.

### Tab. 1. Initial and follow-up electrophysiological results.

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>MNCV (m/s) n. peroneus prof.</th>
<th>MNCV (m/s) n. tibialis</th>
<th>F wave (ms) n. peroneus prof.</th>
<th>F wave (ms) n. tibialis</th>
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<tr>
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<td>Minimum</td>
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MNCV—motor nerve conduction velocity

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DISCUSSION

Epidemiological studies investigated the possible association of treatment with statins and increased risk of polyneuropathy (Gaist et al. 2001, 2002). In 2001, a cohort study based on data from British general practitioners. The observations uncovered increased relative risk of idiopathic polyneuropathy in patients treated with statins but the interpreted data suffered from low power. The other retrospective study from the same authors ran in the case-control format using a database of examinations in patients from non-psychiatric departments. The authors verified a diagnosis of idiopathic polyneuropathy in 166 cases. The odds ratio linking idiopathic polyneuropathy with statin use was 3.7 (95% CI 1.8 to 7.6). The corresponding odds ratio in current users was 4.6 (2.1 to 10.0). For patients treated with statins for 2 or more years the odds ratio was 26.4 (7.8 to 45.4). The authors reported that long-term exposure statins might increase the risk of polyneuropathy.

The risk of nervous system affection increases with longer treatment duration and with higher cumulative dose. The most recent epidemiological study from Italy ran in the case-control format, and confirmed the higher risk of the appearance of polyneuropathy linked to treatment with statins and fibrates (Corrao et al. 2004).

The suggested mechanism of polyneuropathy development includes possible alteration in the function of nerve membranes, since cholesterol forms a part of cell membrane structures. Lipophilic statins penetrate into cells and can inhibit not only the synthesis of cholesterol but also of other essential compounds, for example, mevalonic acid. This gives rise to ubiquinone (coenzyme Q10), necessary for the activity of the oxidative metabolic system of the mitochondria. Ubiquinone is synthesized in the liver and supplied to cells that need it. It is also synthesized in other tissues, e.g., the myocardium. It is thus possible that as statins suppress its synthesis, they also lower the capacity of mitochondria in myocardial cells to deliver energy to the heart muscle and thus impair the capacity for myocardium concentration. In this manner, lipophilic statins may impair signal transfer in cells, such as myocytes, which may explain the pathogenesis of rhabdomyolysis. Statins interfere with endogenous cholesterol synthesis by inhibiting its key enzyme HMG-CoA-reductase, simultaneously blocking the synthesis of dolichylphosphate. This is a very important cofactor at enzymatic glycosylation of cellular, especially secreted proteins, growth factors, but also proteins of cell membranes and the inner mitochondrial membrane. According to some studies, it was demonstrated that mesenchyme cells suffer a disturbance in DNA replication, cells cannot enter the S-phase of the cell cycle and cannot upon its surface express receptors for growth factors (e.g., IGF-1). These processes likely lead to induction of muscle cell apoptosis.

Newly postulated are hypotheses that the statins interfere with the enzymatic isopenetylisation of selenocysteine-tRNA and prevent its maturation to a functional tRNA molecule. The result is selenium deficiency and the development of muscle or nerve complications (Moosmann & Behl 2004). Another hypothesis is that statins damage the myelin sheath by the induction of its severe vacuolization; however, this has been described only in the animal experiment (Daglioglu et al. 2010).

There is no prediction regarding who is at risk, no laboratory diagnostic test. When administering statins, one needs to exercise caution in combination with other medications regarding undesirable interactions. The possibility of damage to muscle tissue is potentiated by simultaneous administration of drugs that are metabolized through cytochrome P450.

In a group of prospectively followed patients, we have acquired statistically significant data demonstrating damage to peripheral nerves, linearly dependent on time (Otruba et al. 2007). Current long-term prospective continuation of our previous study demonstrated affections that were clinically silent but apparent in the results of repeated electrophysiological examinations of peripheral nerves of lower limbs. The study does not intend to limit indications to medical treatment of hyperlipidemia, rather, to emphasize that treatment should be initiated after careful consideration, including possible drug interactions that could accelerate impairment of the peripheral nerves. In general, we would recommend electromyographic examination of lower limb peripheral nerves before initiation of treatment with lipid-lowering agents and a regular follow-up examination in the period of 1 year.

REFERENCES