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TREATMENT WITH STATINS AND INVOLVEMENT OF THE PERIPHERAL NERVOUS SYSTEM: RESULTS OF A PROSPECTIVE CLINICAL AND NEUROPHYSIOLOGICAL FOLLOW-UP

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Aims: To study the pathological changes in neurophysiological examination of lower-limb peripheral nerves in patients with long-term statin treatment.

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 20mg daily was initiated. Patients were followed for 24 months with examinations at 1, 6, 12 and 24 months after statin treatment initiation.

Results: None of the patients reported subjective symptoms typical for polyneuropathy. In laboratory findings, there was no elevation of muscle enzymes. Nevertheless, electrophysiological 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). A control group of 50 patients with combined hyperlipidemia but no statin treatment showed no changes over the same time interval. The study demonstrated that long-term

Conclusions: The study demonstrated that long-term treatment with statins might cause a clinically silent but still electrophysiologically definite damage to peripheral nerves.

INTRODUCTION

Classification of hyperlipidemia is established according to the European Atherosclerosis Society (EAS), which distinguishes three types: hypercholesterolemia, hypertriglyceridemia and mixed or combined hyperlipidemia. Statins are inhibitors of HMG-CoA reductase, cause lowering of plasma concentration of cholesterol and especially the LDL fraction by blocking intracellular synthesis of cholesterol. This results in increased expression of LDL-receptors, followed by increased LDL uptake from the plasma. Indications for 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 (simvastatin, lovastatin, atorvastatin, cerivastat), metabolized via the hepatic system of cytochrome P450 isoenzymes, especially isoenzyme CYP3A4. The second group contains hydrophilic statins (pravastatin), which are not metabolized by cytochrome P450 and s excreted by the kidney. Pravastatin metabolites do not enter liver cells and will not affect 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. Patient symptoms include sensory irritation or sensory loss, typically dysesthesias, paresthesias and impaired vibration sense. Sensory loss occurs in a typical stocking distribution in the lower extremities. Motor deficit expressed as distal lower extremity weakness and muscle atrophy is rare.

The literature describes isolated cases where the lower-limb polyneuropathy was observed during treatment with lipid-lowering agents[1–3]. Gaist et al. presented retrospective epidemiologic studies suggesting the possible increase in relative risk of lower-limb polyneuropathy during long-term use of statins[4, 5].

Our goal was to prospectively follow patients using statins for treatment of hyperlipidemia for a long period of time and focus on electrophysiologic parameters that could uncover initial changes in peripheral nerves.

MATERIAL AND METHODS

Starting in 2002, we prospectively followed patients with the aim to investigating 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 ex-

Table 1. Initial and follow-up electrophysiological results.

Time (months)	n. peroneus		
	MNCV (m/s)	F wave (ms)	CMAP (mV) m. EDB
0	49.1 (47.0 – 49.8)	46.2 (43.7 – 46.7)	4.2 (2.2 – 8.3)
12	48.5 (46.5 – 49.6)	48.1 (44.2 – 46.8)	4.3 (2.1 – 8.4)
24	48.9 (46.4 – 49.2)	48.6 (44.2 – 47.2)	4.3 (2.3 – 8.4)
	n. tibialis		
	MNCV (m/s)	F wave (ms)	CMAP (mV) m. AH
0	50.1 (47.2 – 50.6)	45.2 (43.7 – 45.7)	5.2 (2.5 – 7.5)
12	50.2 (47.0 – 50.1)	46.4 (44.9 – 46.9)	5.1 (2.2 – 7.4)
24	50.2 (47.5 – 50.5)	46.6 (45.2 – 46.8)	5.1 (2.3 – 6.9)

	n. suralis		n. peroneus superficialis	
	SNCV (m/s)	SNAP (μV)	SNCV (m/s)	SNAP (μV)
0	51.5 (47.7 – 51.7)	5.0 (4.0 – 8.3)	52.1 (48.5 – 52.5)	5.4 (4.0 – 8.9)
12	50.7 (46.5 – 50.9)	4.9 (1.9 – 8.0)	50.5 (47.8 – 51.0)	5.5 (4.1 – 7.8)
24	50.5 (46.0 – 50.8)	5.0 (3.0 – 7.8)	50.2 (47.6 – 50.9)	5.5 (4.0 – 8.5)

m. EDB = m. extensor digitorum brevis, m. AH = m. abductor hallucis, MNCV = motor nerve conduction velocity, CMAP = compound muscle action potential, SNCV = sensory nerve conduction velocity, SNAP = sensory nerve action potential. Values are presented as: mean (range)

cluded 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 disorders of peripheral nerves in the lower extremities. Electromyography was performed on the Dantec Counterpoint. The evaluation was based on normative data of the EMG laboratory of the Department of Neurology for this instrument; considering the fact that all findings were within laboratory norms, details are not provided. The diagnostic protocol consisted of 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 (SNCV) was measured bilaterally in n. peroneus superficialis and n. suralis. All examinations were performed by the same electromyographist under standard conditions.

M. tibialis anterior was examined with needle EMG. In all patients of the group, oral medication with simvastatin (Simvacard®, Zentiva) was initiated with a standard dose of 20mg administered each evening. Follow-up examinations were performed after 1, 6, 12 and 24 months of treatment, each visit included laboratory tests, complex neurological examination and EMG examination following the protocol described above. A control group comprised a total of 50 patients, 25 males (mean age 53.1 years) and 25 females (mean age 50.2 years). Control group patients underwent the same initial examinations (clinical examination, laboratory tests and EMG examination) and a diagnosis of combined hyperlipidemia was made. The control group used no lipid-lowering medication for 24 months of follow-up. Follow-up testing was done 24 months after the initial examination, using the same procedure. The acquired data were analyzed statistically with paired-sample t-test and linear regression analysis. In patients, testing was performed on the 0 vs. 12-month and 0 vs. 24-month data. In controls, the test compared 0 vs. 24 months.

RESULTS

For evaluation of subjective symptoms, 2 patients experienced 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 in the patient group (data from 1 and 6 months not shown). All data were within the normal range. Needle EMG of m. tibialis anterior did not show any occurrence of spontaneous pathological activity, reduction in voluntary contraction activity or significant changes in the turns/amplitude analysis. Similarly, no abnormal values of muscle enzymes were

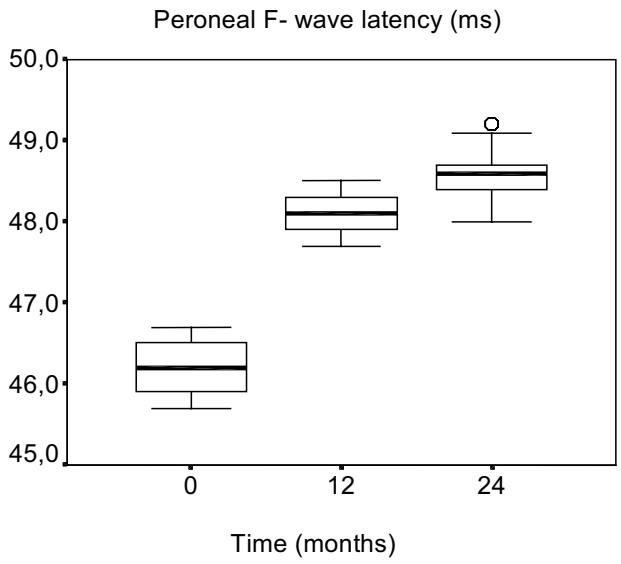

Fig. 1. Linear regression analysis demonstrates statistically significant prolongation of F-wave in n. peroneus over time in the patient group

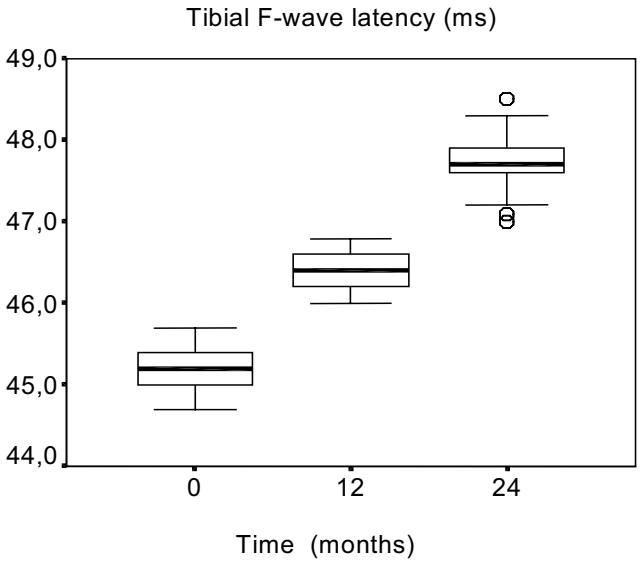

Fig. 2. Linear regression analysis demonstrates statistically significant prolongation of F-wave in n.tibialis over time in the patient group.

found in any of the patients. 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 increased significantly over time (Fig.1, 2). Data from the control group with combined hyperlipidemia but no statin treatment yielded no statistically significant changes in the electrophysiological parameters over the investigated period (data not shown).

DISCUSSION

Epidemiological studies have investigated the possible association of treatment with statins and increased risk of polyneuropathy[4, 5]. In 2001, a cohort study based on data from British general practitioners, uncovered increased relative risk of idiopathic polyneuropathy in patients treated with statins. The other retrospective study from the same authors run in a 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 peripheral nervous system involvement increases with longer treatment duration and with higher cumulative dose. In our study, where all patients were treated with the same statin dose, not changing over time, we cannot separate the two factors. The most recent epidemiological study from Italy, run in the case-control format, confirmed the higher risk of the appearance of polyneuropathy linked to treatment with statins and fibrates[6].

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 reduces the production of 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 dolychylphosphate. This is a very important cofactor for enzymatic glycosylation of cellular, especially secreted proteins, growth factors and also proteins of the cell membranes and the inner mitochondrial membrane. According to some studies, it has been demonstrated that mesenchyme cells suffer a disturbance in DNA replication, cells cannot enter the S-phase of the cell cycle and cannot express receptors for growth factors upon its surface (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

isopentenylation 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[7]. 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. These include: cyclosporine A, macrolide antibiotics (erythromycin, clarithromycin), the lipid-lowering drug gemfibrozil or nicotinic acid, antimycotics (itraconazole, ketoconazole, fluconazole), Ca antagonists (diltiazem, verapamil), digoxin, protease inhibitors (indinavir, nelfinavir, nitonavir, saquinavir) used to treat AIDS, anticonvulsants (phenytoin, valproate), alcohol abuse.

In a group of prospectively followed patients, we have acquired statistically significant data demonstrating changes of peripheral nerves, linearly dependent on time. This prospective study during long-term administration of statins demonstrated disturbances that are clinically silent but clearly demonstrated by electrophysiological examination of lower-limb peripheral nerves. Significant changes were only registered in examination of late responses. All acquired data are within the limits of normative values of the laboratory. Observed changes are not sufficient to support the hypothesis of affection in the proximal nerve sections. The study does not intend to limit indications for medical treatment of hyperlipidemia, rather, to emphasize that treatment should be initiated after careful consideration, including possible drug interactions that could increase the risk of peripheral nerve damage. In general, we would recommend electromyographic examination of lower-limb peripheral nerves before initiation of treatment with lipid-lowering agents and a follow-up examination 1 year later.

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