Nerve conduction velocities in hyperlipidemic patients

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Abstract

OBJECTIVES: Metabolic disease affect all systems in the body, including the peripheral nervous system, but there is a controversy as whether to consider hyperlipidemia is a cause of peripheral neuropathy. The aim of the present study was to evaluate whether hyperlipidemic subjects with no clinical symptom or sign of peripheral neuropathy showed nerve conduction abnormalities or subclinical peripheral neuropathy according to the universally accepted electrophysiological criteria.

METHODS: The study group consisted from 29 female and 16 male patients (mean age: 47±7) while the control group consisted from 22 female and 10 male healthy volunteer subjects with a mean age of (43±9). All participants underwent an electrographic study in the classical manner described in the literature. Median and ulnar nerves in one upper, peroneal posterior tibial and sural nerves were studied in both lower extremities.

RESULTS: Median nerve 2nd digit-wrist segment sensory nerve conduction velocity were slow and sensory nerve action potential amplitude (SNAP) were low relative to controls. Sural nerve sensory nerve conduction velocity in the lower extremities were low relative to controls.

DISCUSSION: In this study the hyperlipemic group consisted from subjects with a relatively young age and with not very high serum lipid levels. Finding abnormal nerve conduction in distal sensory nerves in both upper and lower extremities in these hyperlipidemic patients made us think that; aging or uncontrolled hyperlipidemia may make these subjects susceptible to generalized peripheral neuropathy in the future.

CONCLUSION: Hyperlipidemia may affect nerve conduction in peripheral nerves and precede peripheral neuropathy.

ORIGINAL ARTICLE

INTRODUCTION

Hyperlipidemia is a common metabolic disease characterized by abnormal lipid metabolism in which one of the plasma lipids and/or lipoproteins are elevated. Recently the incidence and the prevalence of hyperlipidemia has increased greatly which increased the risk of coronary heart disease (National Cholesterol Education Program Expert Panel on Detection and Treatment of High Blood Cholesterol in 2002).

Metabolic disease affects all systems in the body including the peripheral nervous system; but there is a controversy whether to consider hyperlipid-

emia as a cause of peripheral neuropathy or not. Many reports had suggested that hyperlipidemia can cause focal mono-neuropathy or generalized polyneuropathy (Dawoud *et al.* 2008; Hou *et al.* 2008; Drory *et al.* 1999; Kaufman 1995; McManis *et al.* 1994; Kassem *et al.* 2005). However only few cases were reported and they are often individuals involved with other illnesses that may cause neuropathy such as diabetes, hypertension, hyperuricemia and fatty liver (Dawoud 2008; Al-Rubayi 2001).

The aim of the present study was to evaluate whether hyperlipidemic subjects without any clinical symptoms nor signs of peripheral neuropathy do show nerve conduction abnormalities or subclinical peripheral neuropathy according to the universally accepted electrophysiological criteria (England *et al.* 2005).

METHODS

The study was approved by the local Ethical Committee. The study group consisted from 29 female and 16 male (mean age: 47±7) with tension type of headache who admitted to our hospital's Neurology Department Out Patient Clinic. Biochemical investigations included lipid profile, blood glucose, postprandial blood glucose (2 hours after meal), blood urea, serum creatinine, uric acid, Vit B12, thyroid and liver function tests. Patients with total cholesterol (TC) being over 200 mg/dl and/or low density lipoproteins (LDL-C) over 160 mg/dl, and/or triglycerides (TG) over 200 mg/dl were included. They had mean height of 164±0.80 cm, weight 75±11 kg, and body mass index(BMI) of 27.6±4. In each of them, hyperlipidemia were newly detected and they did not have received lipid-lowering medications.

Patients with diabetes, carcinoma, lymphoma, myeloma, gammopathy, HIV positive, hypothyroidism, Vit B12 deficiency, uremia, chronic liver disease, family history of peripheral nerve disease and those exposed to neurotoxic drugs were all excluded.

Control group consisted from 22 female and 10 male healthy volunteer subjects with a mean age of 43±9. Their mean height was 164±0.87 cm, mean body weight was 73±10 kg, and body mass index was 27.6±4.

All participants underwent a detailed neurological examination. The examination included evaluation of muscle atrophy, tendon reflexes and sensory deficit. Sensory deficit was expressed as deficit for touch, vibration-position, pain as well as aching numbness, cramps or paresthesia and definable complaints such as restless legs. Histories were reviewed for symptoms of autonomic dysfunction (orthostatic dizziness, syncope, altered gastrointestinal function, altered perspiration, hesitancy before micturation). All participants underwent an electrographic study in the classical manner described in the literature. Median and ulnar nerves in one upper, peroneal posterior tibial and sural nerves were studied in both lower extremities (England *et al.* 2005; Oh 2003). Patients with carpal tunnel syndrome were excluded from the study.

Studies were performed in a warm room, with the extremity skin temperature 32 °C or above at the side where nerve conduction velocity (NCV) measurement was done. There were no statistical significant difference in the limb temperatures between hyperlipidemic and control subjects. Nerve conduction studies were performed by a single physician to ensure uniformity of technique and interpretation; using Nihon Kohden/Neuropack MEB-5504K electromyography (EMG) machine, with a filter setting of 20 Hz–10 kHz and a sweep speed of 5 ms/cm for motor and a bandpass filter of 20 Hz to 2 kHz with a sweep speed of 1ms/cm for sensory nerve conduction. For recordings Dantec 13K60 surface recording electrodes were used.

The median and ulnar nerves were stimulated at the wrist and elbow with recording from abductor pollicis brevis and abductor digiti quinti; respectively the peroneal nerves were stimulated at the ankle and fibular head with recording from the extensor digitorum brevis muscle. The posterior tibial nerves were stimulated behind the medial malleous and at the popliteal fossa with recording from the abductor hallucis muscle. The sural nerves were stimulated between the heads of gastrocnemii with recording from the lateral malleous. Median and ulnar sensory conduction velocity was performed orthodromically; while sural sensory conduction was studied antidromically. The distal latencies (DL), nerve conduction velocities, motor and sensory amplitudes were collected for each of the above nerves. (Oh 2003)

Abnormality was defined as minimum case definition criterion for electrodiagnostic confirmation of distal symmetrical polyneuropathy is an abnormality (≥99th or≤1st percentile) of any attribute of nerve conduction in two separate nerves, one of which must be the sural nevre (England *et al.* 2005). When there were only electrophysiologic findings without a clinical counterpart, the definition of subclinical neuropathy was used (Oh 2003). Results were compared to normal's values and considered abnormal if they fall above or below(±) 2 standard deviations (SD) of reported normal distal latencies, conduction velocities and amplitudes.

Statistical Analysis

Statistical analysis were performed using the SPSS 15.0 software package (SPSS Inc). 'Shapiro-Wilk' test was used to assess whether the data of demographic and physical characteristics of hyperlipidemic and control subjects had been normally distributed. Significance of differences between means of two groups showing normal distribution was evaluated with 'Student's t test', while those showing non-normal distribution was evaluated with 'Mann-Whitney-U'. There were not any significant difference between hyperlipidemic and control subjects ($p<0.05$).

'Spearman's rank order correlation coefficient' was used for assessing associations. Values of $p<0.05$ were accepted as statistically significant.

RESULTS

These were patients with newly discovered hyperlipidemia and none of them was on any lipid lowering medication before the electrophysiological examination. Diabetes was excluded according to American Diabetes Association (2012) which defines fasting blood glucose level higher than 126 mg/dl and postprandial blood glucose level higher than 200 mg/ml as a reliable indicator of diabetes (American Diabetes Association 2012). Biochemical values of hyperlipidemic patients and control subjects are shown in Table 1. As seen in Table 1; TG, TC, LDL-C, VLDL-C (very low density lipoprotein cholesterol) levels are significantly higher relative to controls.

Electrophysiological values of control and hyperlipidemic group are shown on Table 2.

Median nerve 2nd digit-wrist segment sensory nerve conduction velocity (p=0.003) was slow and sensory nerve action potential amplitude (SNAP) were low relative to controls (p=0.024).

Sural nerve sensory conduction velocity was lower than the controls(p=0.005); while no motor conduction abnormality was seen in the posterior tibial and peroneal nerves.

Next, we analyzed the data of each patient individually. Considering mean ± 2 SD as the cut-off, abnormal sural nerve conduction was present in seven(15.5%) hyperlipidemic patients. In three (6.6%) of those seven, conduction abnormalities in more than two nerves, one being the sural nerve, were present. In these three patients mean triglycerides values were much higher than the rest of the patients and control group. (Normals: 93±40 mg/dl, Hyperlipidemic patients: 184±76 mg/dl, the three patients: 325±72 mg/dl)

No correlation was present in between nerve conduction parameters with TC, TG, LDL-C, VLDL-C, HDL-C (high density lipoprotein cholesterol) values.

DISCUSSION

Peripheral nerve conduction abnormalities can be identified in patients with mild hyperlipidemia in the absence of symptoms (Hou *et al.* 2008; Drory *et al.* 1999; McManis *et al.* 1994). Fesel (1971) in 1971 described a syndrome of lipid disorder with increased serum lipids and peripheral neuropathy in 6 patients while Sandbank *et al.* (1973) during the same year observed severe electron microscopic alterations of myelin sheets in sural nerve obtained by biopsy in a patient with hyperlipidemia and peripheral neuropathy (Fesel 1971; Sandbank 1973).

The data from the studies performed previously clearly demonstrated that sensory neuropathy may occur in patients with hyperlipidemia but usually of subclinical type which can be presented more frequently in patients with very high mean serum of TG, TC, and LDL-C (Dawoud 2008).

In our study sural and median nerve sensory conduction velocities were slowed, while no major abnormality was seen in motor conduction velocities. Hyperlipidemia effected conduction velocities, especially in lower extremity peripheral nerves, and effects were seen distally and primarily in sensory nerves. These changes were present despite the fact that the patients were newly diagnosed with hyperlipidemia and asymptomatic neurologically. This type of neuropathy may occur more frequently in patients with very high triglycerides levels as shown by previous studies (Hou *et al.* 2008; Drory *et al.* 1999; Kaufman *et al.* 1995; McManis *et al.* 1994) because 3 of our patients with very high triglyceride levels had fulfilled the electrophysiological criteria of subclinical peripheral neuropathy. Electrophysiological parameters and lipid levels did not correlated probably because other metabolic and constitutional conditions may be interfered with the results.

In an experimental study performed on rats fed with hyperlipidemic diet for a period of ranging from 3 weeks to 3 months had showed changes in myelin sheets and axons. The myelin sheets showed hypermyelination and dysmyelination manifested by disorganization of the lamella. Axons were displaced with condensed neurofilaments and was assumed that the lesions are result of hyperlipidemia induced by experimental diet.(Sandbank & Bubis 1973)

Tab.1. Biochemical values of hyperlipidemic patients and control subjects.

	Control Subjects (Mean±SD)	Hyperlipidemic Subjects (Mean± SD)	*p*-value
Age	43.87±9.83	47.31±7.16	0.098
Fasting blood glucose (mg/dl)	89.31±7.63	92.55±9.89	0.124
Postprandial blood glucose (mg/dl)	101.37±11.10	100.60±19.41	0.840
Total chol (mg/dl)	165.25±21.63	228.31±42.07	**0.00**
Triglyceride (mg/dl)	93.46±40.98	184.44±76.67	**0.00**
LDL-C (mg/dl)	99.64±21.44	146.40±38.11	**0.00**
VLDL-C (mg/dl)	18.71±8.15	36.92±15.31	**0.00**
HDL-C (mg/dl)	46.68±10.43	45.33±12.95	0.626
BUN (mg/dl)	12.37±4.08	12.78±3.07	0.244
Creatinine (mg/dl)	0.87±0.14	0.87±0.13	0.405
AST (U/L)	17.18±5.07	18.88±5.94	0.125
ALT (U/L)	15.25±6.47	22.00±8.17	0.122
ST4 (ng/dl)	1.05±0.14	1.03±0.38	0.065
TSH (ulU/ml)	1.55±1.07	1.82±1.19	0.334
Vitamin B12 (pg/ml)	262.28±106.61	281.84±145.20	0.672
Folat (ng/ml)	7.82±3.98	8.66±4.16	0.385

Tab. 2. Electrophysiological values of hyperlipidemic and control subjects.

Nerve Conduction	Control Subjects	Upper/Lower Values Mean±2SD	Hyperlipidemic subjects	*p*-value
Median Nerve (motor)				
Distal Latency (ms)	2.70±0.39	<3.48	2.78±0.50	0.351
Wrist-elbow NCV (m/s)	57.95±4.30	>49.35	57.94±4.37	0.990
Amplitude (mv)	11.61±4.04	>3.52	12.75±4.71	0.270
F-wave latency (ms)	27.38±2.77	<32.92	26.78±3.50	0.710
Median Nerve (sensory)				
2nd digit-wrist NCV (m/s)	47.52±5.31	>36.9	44.77±4.50	**0.003****
2nd digit-wrist amplitude (μv)	22.25±6.07	>10.11	18.99±7.88	**0.024****
Palm-wrist NCV (m/s)	44.19±4.6	>34.99	41.35±5.83	0.256
Palm-wrist amplitude (μv)	51.80±17.36	>17.08	47.77±19.73	0.275
Wrist-elbow NCV (m/s)	55.01±3.18	>48.65	54.38±3.66	0.346
Wrist-elbow amplitude (μv)	28.39±12.00	>4.39	28.38±14.12	0.698
Ulnar nerve (motor)				
Distal Latency (ms)	2.01±0.28	<2.57	2.12±0.34	0.169
Wrist-Elbow NCV (m/s)	63.00±5.52	>51.96	62.83±3.97	0.872
Amplitude (mv)	14.09±3.49	>7.10	12.79±2.65	0.068
Ulnar nerve (sensory)				
5th digit-wrist NCV (m/s)	44.91±3.32	>38.25	43.52±3.39	0.078
5th digit-wrist amplitude (μv)	14.13±4.95	>4.33	15.32±5.94	0.423
Deep Peroneal Nerve				
Distal Latency (ms)	3.63±0.76	<5.03	3.57±0.64	0.918
Ankle-knee NCV (m/s)	50.36±3.56	>43.24	49.51±3.94	0.979
Amplitude (mv)	7.59±2.93	>1.72	7.57±3.22	0.338
F-wave latency (ms)	46.07±4.12	<54.31	46.04±3.66	0.970
Posterior Tibial Nerve				
Distal Latency (ms)	3.31±0.61	<4.52	3.30±0.60	0.807
Ankle-knee NCV (m/s)	48.08±4.04	>40	47.67±3.89	0.338
Amplitude (mv)	12.78±4.48	>3.80	13.17±3.70	0.970
F-wave latency (ms)	47.60±3.36	<54.32	47.43±2.71	0.382
Sural Nerve				
NCV (m/s)	42.38±3.10	>36.18	40.19±3.59	**0.005****
Amplitude (μv)	14.16±5.9	>2.36	12.88±6.39	0.171

Many theories have been postulated to explain the possible relationship between lipid disorders and peripheral neuropathy. The turn over of lipids in the outer layer of the myelin sheath is considered to be rapid than the inner layers. There is a great possibility that serum lipid abnormality have an effect on cell membrane and might influence the structure of outher layers of myelin sheath (Dawoud *et al.* 2008). Also serum lipid abnormality might mediate nerve infarction via fat embolism or lipid–induced platelet aggregation. Lipids have an important influence on the coagulation mechanism. In general, platelet adhesiveness and aggregation are enhanced by lipoproteins and electrophoretic mobility of platelets is altered by plasma factors which include low density lipoproteins, lecithin and lysolecithin (Fessel 1971).

In Dawoud's (Dawoud 2008) study; the amplitude of sensory nerve action potential was affected more than distal sensory latency and conduction velocity. He stated that the underlying mechanism of the condition may be a mixed axonal degeneration and segmental demyelination. However segmental demyelination is

thought to be secondary to axonal degeneration. The electrophysiological abnormalities in their study were found to affect both sides of the body equally which they thought to indicated; that the peripheral neuropathy associated with hyperlipidemia is of symmetrical type. Median nerve was effected more frequently than ulnar nerve while the common peroneal and posterior tibial nerves are affected to a certain degree equally. The affection of nerves of lower extremities was more than that of the upper which indicated that the effect of hyperlipidemia on the long nerves is more than that of the short nerves (Dawoud *et al.* 2008).

We believe the disorder seems usually mild and subclinical although occasionally more severe cases as those reported by McManis (McManis *et al.* 1994) and Kaufman (Kaufman 1995) may be encountered.

We conclude from this study that hyperlipidemia effects conduction parameters in peripheral nerves and the effect is more commonly seen distally and primarily in the sensory nerves. This is consistent with early peripheral neuropathy (Kassem *et al.* 2005). As stated in the previous studies; our results are consistent with the view that the effect was found to be distal while the proximal segment is usually spared as its function was assessed by measurement of F-wave latency and conduction velocity which were normal (Dawoud 2008).

In this study; the hyperlipidemic group consisted from subjects with a relatively young age and with not very high serum lipid levels. Finding abnormal nerve conduction in distal sensory nerves in both upper and lower extremities in these hyperlipidemic subjects made us think that; aging or uncontrolled hyperlipidemia may make these subjects susceptible to generalized peripheral neuropathy in the future.

CONCLUSION

Hyperlipidemia may affect nerve conduction in peripheral nerves and precede peripheral neuropathy. It will be useful to determine lipid levels in patients with a clinical or electrophysiological picture of peripheral neuropathy especially if no other etiology is present. Early recognition and aggressive management of hyperlipidemia may prevent the complications of severe peripheral neuropathy (Hou *et al.* 2008).

Observational data suggests that chronic statin use may increase the risk of peripheral neuropathy (Backes & Howard 2003). So we believe consecutive studies with more patient participation are needed also to determine the effects of lipid lowering treatment on nerve conduction velocities.

Conflict of interest: *The authors declare that they have no financial or other conflicts of interest in relation to this research and its publication.*

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