

Electrophysiological Changes in Patients with Impaired Glucose Tolerance

Serdar Güler*
Hilmi Uysal***

Dilek Berker**
Yalçın Aral*

Hüseyin Tuğrul Atasoy***

Bekir Çakır**

Ankara Education and Research Hospital, Departments, Ankara, Turkey

* Endocrinology and Metabolism

** Internal Medicine

*** Neurology

The effect of impaired glucose tolerance on neuropathy is not well characterized. This study is performed to clarify the status of peripheral neuropathy in patients with impaired glucose tolerance with no symptoms of neuropathy. Twenty-two patients with impaired glucose tolerance with no signs of neuropathy, and 11 healthy controls are examined with electromyoneurography. We have found electrophysiological changes in 13 of 22 patients with IGT, and in only one case of the 11 subjects in the control group. Mean H reflex latencies of the right and left medial vastus muscles were significantly longer in the patient group than the control group (17.0 ± 1.7 vs. 15.6 ± 2.5 msec, $p < 0.02$; and 17.1 ± 1.8 vs. 15.7 ± 2.4 msec; $p < 0.01$, respectively). Our results indicate that electrophysiological changes of the peripheral nerves are very common in patients with impaired glucose tolerance. Early diagnosis and management of impaired glucose tolerance may be particularly important in order to prevent the development of chronic complications.

Key words: Impaired glucose tolerance, polyneuropathy, electromyoneurography, electrophysiological studies, electrophysiological abnormalities

Introduction

Diabetes Mellitus (DM) is one of the most frequent causes of peripheral neuropathy (1). Thus, diabetic neuropathy is a commonly encountered problem by clinicians. Although diabetic neuropathy is rarely observed before the fifth year of diabetes, it occurs in at least 50 % of diabetic patients in time (2). Diabetic neuropathy is an important cause of foot ulceration, Charcot joints and amputation leading to increased morbidity and mortality.

Correspondence address:

Serdar Güler
Ulucanlar Caddesi 68/5 Cebeci
06590 ANKARA / TURKEY
Tel: +90-532-427 59 58
Fax: +90-312-323 49 23
sgulers@yahoo.com

Activation of polyol pathway, nonenzymatic glycosylation, epineural vascular atherosclerosis, endoneurial microvascular disease, dysfunction of endothelial cells, thickening of the basal membrane and autoimmunity are responsible factors in the pathogenesis of diabetic neuropathy (3). It is also supposed that there may be defect in nerve growth factor (NGF) secretion from target tissues and blunted response to this factor in patients with diabetic neuropathy (3). Also it has been shown that increase in concentrations of several other growth factors due to increased oxidative stress in DM may cause proliferation of vascular smooth muscle cells, which has important role in the development of micro- and macro-vascular complications of DM.

Although neuropathy is an extensively studied issue in patients with diabetes mellitus, the effect

of impaired glucose tolerance (IGT) on neuropathy is not well characterized. This study is performed to clarify the status of peripheral neuropathy in patients with impaired glucose tolerance with no symptoms of neuropathy.

Methods

Twenty-two patients (16 female and 6 male) with IGT are involved in our study. Eleven (10 female and 1 male) age and sex matched volunteers with normal response to oral glucose tolerance test (OGTT) formed the control group. Patients over 60 years of age, body mass index over 27 kg/m² and who revealed clinical and laboratory signs of any disease that may effect the results of OGTT such as liver disease, renal insufficiency, heart failure, hyperthyroidism, Cushing syndrome, acromegaly, past or present pancreatic disease, and pheochromocytoma are excluded. Patients who currently use any drugs that may interfere with the results of OGTT (i.e. glucocorticoids, beta blockers, diuretics, antidepressants, aspirin, oral contraceptives, laxatives, barbiturates, etc.) are also not included.

All of the cases are examined clinically and blood sample is withdrawn after 12 hours of fasting at 08-09 AM for complete blood count and biochemical parameters. Plasma glucose, serum cholesterol, triglyceride, HDL cholesterol, creatinine, AST, ALT, sodium, potassium, phosphorus, magnesium and blood urea nitrogen are measured with known methods (Abbott Spectrum Autoanalyzer, USA).

Standard OGTT with 75 g glucose is performed in the morning after 12 hours of fast after consuming normal diet (sufficient calories and at least 250 grams carbohydrate per day) for three days. All the cases were in resting position and did not smoke during OGTT. All cases took 75 grams of glucose (dissolved in 300 millilitres of water) within 5 minutes and venous blood samples are obtained in 0, 30, 60, 90, and 120 minutes for determination of plasma glucose. Diagnosis of IGT is done according to the criteria of WHO. A portion of the 0 minute blood is separated for serum insulin determination centrifuged immediately and stored in -20 °C until analysed. Serum insulin is analysed by radioimmunoassay using a commercial kit (DPC, California, USA).

In all cases QT interval on ECG is measured and corrected QT interval is calculated according to the Bazett formula. A neurologist who was unaware about the group the case belonged to has performed the electromyoneurography. For the determination of polyneuropathy median, ulnar, and sural nerve sensory conduction velocities and median, ulnar, fibular and posterior tibial motor nerve conduction velocities are examined. H response latency and amplitudes of medial vastus (left and right) and of gastrocnemius muscle are also measured. Gastrocnemius H reflex response is the most frequently examined response in neurophysiological H reflex measurements, and thus involved in the study. But, because this response is also effected in diseases other than polyneuropathy such as S1 radiculopathy and narrow spinal channel, medial vastus muscle, which is not effected in other disorders, is also involved in the study protocol. We accepted the following as abnormal electrophysiological measures:

1. Sensory action potential <15 microvolt in the upper extremity (antidromics: wrist-thumb, wrist-5th finger segment)
2. Sensory conduction velocity <40 m / second
3. Motor conduction velocity <50 m/second in the upper extremity and/or <40 m/second in the lower extremity
4. Absence of sural sensory action potential in the lower extremity.
5. H response of medial vastus muscle >18.6 milliseconds
6. H response of gastrocnemius muscle >30.0 milliseconds

A case is considered to have sensory neuropathy if the sensory nerve action potential (SNAP) of the studied nerve of the upper extremity was absent or below the normal lower limit, or if the sural nerve response was not obtained together with slowing in sensory nerve conduction velocity (NCV) in the lower extremity. In addition to these findings, if the motor response [combined muscle action potential (CMAP) amplitude] was absent or below the normal lower limit together with slowing in motor NCV, the case is accepted to have mixed type polyneuropathy.

We used statistical package for the social sciences (SPSS version 9.0) for the statistical analysis of the obtained data. Fisher exact chi-square, Mann-Whitney U, Wilcoxon matched pairs signed ranks and Student Newman Keuls test are used for the analyses. A p value <0.05 is considered as statistically significant. Written informed consent has been given to all cases involved in this study, and the study is approved by the local ethics committee.

Results

Twenty-two patients (16 females and 6 males; mean age of 51.8 ± 8.9) with impaired glucose tolerance and 11 volunteers (10 female and 1 male; mean age of 42.0 ± 14.5 years) are involved in the study. The two groups were similar with regard to age ($p = 0.1$) and sex ($p = 0.31$).

Electromyoneurographic Findings

We have found abnormality in electrophysiological measures in 13 of 22 patients with IGT, and in only one case of the 11 subjects in the control group. Of the 13 IGT patients with neuropathy 6 had sensory and 3 had mixed type neuropathy, while we detected carpal tunnel syndrome in 2 and prolonged H-reflex latency in another 2 [H reflex values (msec) of the first case: right medial vastus (MV): 19.8; left MV: 19.4; right gastrocnemius

(G): 30.4; left G: 30.8; H reflex values (msec) of the second case: right MV: 20.2; left MV: 19.8; right gastrocnemius (G): 31.2; left G: 30.4]. Hence, 9 IGT patients (40.9 %) had polyneuropathy (6 sensory and 3 mixed type). The single neuropathy case in the control group was sensory in type.

Mean H reflex latency of the right medial vastus muscle was significantly higher in the patient group than the control group (17.0 ± 1.7 vs. 15.6 ± 2.5 msec, respectively; $p < 0.02$). Mean H reflex latency of the left medial vastus muscle was also significantly longer in the patient group than the control group (17.1 ± 1.8 vs. 15.7 ± 2.4 msec; $p < 0.01$) (Table 1).

Mean H reflex latency of the right gastrocnemius muscle was similar between the patient and the control groups (28.6 ± 2.4 vs. 27.6 ± 2.6 msec, respectively; $p > 0.05$). Mean H reflex latency of the left gastrocnemius muscle of the patient and the control groups were also similar (28.3 ± 2.5 vs. 27.8 ± 2.3 msec, respectively; $p > 0.05$) (Table 1).

Table 1. Mean H reflex latency of the medial vastus and gastrocnemius muscles in the patient and control groups.

Muscle Examined	Patient Group	Control Group	P
Right medial vastus	17.0 ± 1.7	15.6 ± 2.5	<0.02
Left medial vastus	17.1 ± 1.8	15.7 ± 2.4	<0.01
Right gastrocnemius	28.6 ± 2.4	27.6 ± 2.6	NS*
Left gastrocnemius	28.3 ± 2.5	27.8 ± 2.3	NS

*NS: Not statistically significant

Table 2. Sensory nerve action potential (SNAP), nerve conduction velocity (NCV), combined muscle action potential (CMAP), and motor distal latency in patients with abnormal electrophysiological findings.

CASES	Median Nerve					Ulnar Nerve					Sural Nerve		Posterior Tibial Nerve		Fibular Nerve	
	Sensory		Motor			Sensory		Motor			SNAP (μV)	NCV (m/sec)	CMAP (mV)	NCV (m/sec)	CMAP (mV)	NCV (m/sec)
	SNAP (μV)	NCV (m/sec)	CMAP (mV)	NCV (m/sec)	MDL (m/sec)	SNAP (μV)	NCV (m/sec)	CMAP (mV)	NCV (m/sec)	MDL (m/sec)						
1	12	46	6	54	3.2	14	44	7	58	2.8	NR	NR	2.6	44	4	51
2	10	48	10	54	2.8	15	46	11	54	2	NR	NR	3	44	3	48
3	10	44	7	56	3.2	13	41	10	51	2.4	2	39	4.5	47	4	45
4	4	38	5	52	3.2	10	42	8	54	2.8	NR	NR	3	46	3.5	44
5	NR*	NR	5	53	3.2	6	37	7	52	2.4	NR	NR	4	48	4	49
6	3	36	6	54	2.8	8	41	8	53	2	NR	NR	5	43	2.5	44
7	7	39	3	51	3.2	12	40	5	52	2.4	NR	NR	1.5	41	0.75	39
8	NR	NR	2	44	3.2	6	39	2	44	2.8	NR	NR	1	36	0.6	33
9	10	41	2.8	48	3.6	13	44	4	52	2.8	3	41	0.6	38	1.5	41
10	NR	NR	3	52	4.8	21	49	6	56	2.8	16	44	4	46	7	48
11	4	38	4	54	4.4	26	48	8	58	2.4	15	43	5	49	6	51
12 ^a	10	44	6	56	2.8	12	50	8	60	2.4	NR	NR	6	48	5	56

The first 11 cases belong to IGT group. Cases from 1 to 6 had sensory, and 7 to 9 had mixed neuropathy, while case no. 10 and 11 had carpal tunnel syndrome. aCase no. 12 is the control case with sensory neuropathy.

*NR: No response.

Sensory nerve action potential (SNAP), nerve conduction velocity (NCV), combined muscle action potential (CMAP), and motor distal latency values of the patients with abnormal electrophysiological findings are presented in Table 2.

Biochemistry

The biochemical analysis of the patient and control group is summarized in Table 3.

Table 3. Biochemical characteristics of the patient and the control groups.

	Patient	Control	p
OGTT (mmol/l)			
0	6.5±0.6	5.2±0.6	<0.001
30	9.8±2.0	7.4±1.5	<0.001
60	11.1±2.0	5.9±1.5	<0.001
90	13.1±2.6	5.6±0.9	<0.001
120	9.2±0.8	5.1±0.9	<0.001
Na (mmol/l)	142.1±3.5	142.4±2.9	NS
K (mmol/l)	4.4±0.4	4.4±0.4	NS
Ca (mmol/l)	2.3±0.2	2.2±0.1	NS
P (mmol/l)	1.11±0.2	1.1±0.2	NS
Mg (mmol/l)	0.93±0.1	0.9±0.1	NS
Cholesterol (mmol/l)	5.6±1.2	4.3±1.4	0.003
Triglyceride (mmol/l)	1.9±0.8	1.4±0.5	0.05
HDL-cholesterol (mmol/l)	1.3±0.4	1.2±0.3	NS
LDL-cholesterol (mmol/l)	3.6±1.2	2.3±1.0	0.005
Insulin (mIU/ml)	21.2±12.9	11.9±4.9	NS

*NS: Not statistically significant

Mean plasma glucose at 30, 60, 90 and 120. minute of OGTT was significantly higher in the patient group than the control group.

Patient group had significantly higher serum cholesterol level than the control group (5.6±1.2 vs. 4.3±1.4 mmol/l, respectively; $p<0.01$). Mean triglyceride level was similar in the patient and control groups (1.9±0.8 vs. 1.4±0.5 mmol/l, respectively; $p=0.05$). Mean HDL cholesterol level was also not different between the patient and the control groups (1.3±0.4 vs. 1.2±0.3 mmol/l, respectively; $p>0.05$). Patient group showed significantly higher LDL-cholesterol levels than the control group (3.6±1.2 vs. 2.3±1.0 mmol/l, respectively; $p<0.05$).

Although mean serum insulin level in the patient group was higher than in the control group, this difference was not significant (21.2 ± 12.9 vs. 11.9±4.8 mIU/ml, respectively; $p>0.05$).

Serum electrolyte levels were similar between the patients and the controls, and between the IGT patients with neuropathy and IGT patients without neuropathy.

Electrocardiography

Corrected QT interval (QTc) was similar in the patient and control groups (0.43 vs. 0.42 second).

Correlation Analyses

None of the parameters had significant correlation with either each other or with any of the study parameters measured in electromyoneurography.

Discussion

Excluding traumatic neuropathy, diabetic neuropathy is the most frequent cause of peripheral neuropathy, and early diagnosis is very important in its management. Diabetic complications are also encountered in subjects with impaired glucose tolerance, which may be considered a transitory state to diabetes mellitus (4).

Neuropathy is the most difficult among the major diabetic complications for appropriate epidemiological investigations (5). Several reports of diabetic neuropathy are criticized for equivocal and insufficient terminology, diagnostic criteria and selection of the patients (6). Frequently clinical neuropathy cannot be discriminated from subclinical neuropathy.

The prevalence of neuropathy in diabetic population has been reported between 0 % and 93 % (5). The prevalence has been found very low in investigations using only clinical findings and very high in investigations that used electrophysiological methods (7). Typical neurophysiologic defect in DM is a decrease in motor and sensory nerve conduction velocity. Nerve conduction velocity decreases progressively in both type I DM and type II DM depending significantly on the duration of disease. Segmental demyelination observed in nerve biopsy specimens is responsible for this decrease in nerve conduction velocity. It is widely accepted today that peripheral neuropathy first begins in axons, and then segmental demyelination due to damage to Schwann cells follows (8). But, transient Schwann cell injury may also be responsible inde-

pendent of the axonal degeneration. Young et al reported that decrease in nerve conduction velocity is not solely caused by Schwann cell disorder, but also related to axonal dysfunction (9). The decrease in nerve conduction velocity may also result from direct axonal degeneration due to the metabolic disorder, besides increased permeability in capillaries supplying nerves and microangiopathy (10). Some data from animal studies showed that decrease in nerve conduction velocity is secondary to metabolic disorder rather than structural disorder (11). This decrease in conduction velocity is strongly related to poor control of diabetes and severity of the disease (8), and normoglycemia achieved by strict control results in significant improvements in nerve conduction and sense of vibration (12). Axonal degeneration causes a decrease in sensory motor amplitude and demyelination results in decreased nerve conduction velocity.

Electrophysiological abnormalities have been found in one fourth of asymptomatic diabetic patients (13). In our study, we found abnormality in neural electrophysiological measures in 11 of 22 patients with IGT. Six had sensory, and 3 had mixed type neuropathy. About 7.5 to 11.5 % of the patients with carpal tunnel syndrome have diabetes mellitus, and the risk of carpal tunnel syndrome is increased 2.2 fold in female, and 2.5 fold in male patients with diabetes mellitus (13). Carpal tunnel syndrome was present in two patients without any finding compatible with polyneuropathy or lengthening in H-latency. Because there was no other electrophysiological abnormality in these two cases with carpal tunnel syndrome, we think that this syndrome did not develop on a polyneuropathy basis and is discovered incidentally. We have detected an increase in H reflex latency in another two patients without any other electrophysiological abnormalities in our IGT group. Only one case from the control group showed sensory type neuropathy. Our data revealed significantly higher incidence of neuropathy than the other studies. This higher incidence may be due to the technique we have used to detect polyneuropathy.

Absence or prolongation of H reflex response latency, or a decrease in the amplitude of H reflex have been reported in alcoholic, uremic and diabetic neuropathies even when classical neurophysio-

logical measurements yielded normal results, in some studies in the last decade (12, 15). This reflex is most frequently examined in the gastrocnemius muscle, using the posterior tibial nerve. But, the facts that this nerve has a long route, the most frequently encountered clinical entities are L5 and S1 radiculopathies, and bilateral clinical presentation of S1 radiculopathy limit the usefulness of gastrocnemius H reflex latency for diagnostic purposes in neuropathies. H reflex response can also be easily obtained from medial vastus muscle by stimulating femoral nerve above the inguinal ligament (16). H response is either prolonged or absent in both axonal and demyelinating nerve lesions. Frequently, abnormalities in H response are the first and only sign of distal symmetric diabetic polyneuropathy (15). After distal symmetric neuropathy, femoral nerve and L2-L4 roots are the most frequently involved peripheral nerves and roots among diabetic neuropathies. Thus, L2-L4 roots and femoral nerve absolutely must be examined in diabetic patients considered to have neuropathy. In our study, although H reflex latency of the gastrocnemius muscle was not different, H reflex latency of the medial vastus muscle was significantly higher in the patient group compared to the control group. Differences of medial vastus and gastrocnemius H reflex latencies between control group and patients with IGT but without neuropathy had borderline significance ($p=0.05$). Medial vastus H reflex latency examines more proximal segments. Different medial vastus H reflex latency but relatively similar gastrocnemius H reflex latency may be due to frequent involvement of L2-L4 roots, and 60 % co-existence of distal symmetric neuropathy with L2-L4 radiculopathy. New large scale studies are needed to clarify the role of medial vastus H reflex latency in the early diagnosis of diabetic neuropathy.

Lachman et al have studied H response in neuropathies due to several causes and have shown abnormal H response in 18 % of patients found normal on classical electromyoneurography (14, 15). Results of several studies indicate that a significantly high number of patients found normal on classical electrophysiological studies have higher than normal H reflex latency when sensory and motor conduction velocity and sensory action potential

amplitudes are normal. Thus, increase in H-reflex latency may be the initial sign of neuropathy (14).

In conclusion we have found neural electrophysiological abnormalities in a significant percentage of patients with IGT without any symptoms of neuropathy. Our results clearly show that patients with IGT must be examined in detail as at least as those with diabetes mellitus for the presence of peripheral neuropathy. Because achievement of normoglycemia may restore electrophysiological abnormalities, early diagnosis and management of IGT seems to be particularly important in order to prevent the development of chronic complications at the very beginning.

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