The Electrophysiology Of Diabetic Neuropathy

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Citation

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Abstract

Fiber Density (FD) and Macro motor unit potential (macro-MUP) amplitude measurements have a higher sensitivity in detecting diabetic neuropathy as compared to nerve conduction studies (NCS). The the aim of this study was to evaluate asymptomatic diabetic patients and patients with normal NCS using FD and macro electromyography. 30 diabetic patients and 17 age and gender matched healthy controls were evaluated. The mean macro-MUP amplitude and the mean FD was much higher in patients compared to controls ($p < 0.05$). We found peripheral neuropathy in 5 out of 8 patients with no NCS abnormality, using MA-EMG and FD studies. Even in patients without any neurologic signs suggestive of diabetic neuropathy there may be findings of early axonal involvement that could only be detected by MA-EMG and FD. This early diagnosis is critical, because good glycemia control is very crucial to revert the ongoing process.

INTRODUCTION

Diabetes mellitus (DM) is a common cause of peripheral neuropathy worldwide[1,2,3,4]. In different studies, the incidence of neuropathy varies from 10 to 50 percent; a wide variabillity which is related to the lack of consistent criteria for the definition of peripheral neuropathy[5] Most diabetics will eventually have some evidence of neuropathy (clinical or electrophysiological), but some will stay asymptomatic[6] Although there are different types of diabetic neuropathy, the distal symmetrical sensorimotor polyneuropathy with or without autonomic involvement is the most common type[5]. The assessment of patients with diabetic neuropathy begins with a detailed neurologic and medical, history and examination and continues with electrodiagnostic studies[2] Up to this date nerve conduction studies (NCS) remain the most reliable, accurate and sensitive measure of peripheral nerve function in diabetic neuropathy; however standard electrophysiological methods do not assess the autonomic nervous system function[7].The autonomic nervous system can be evaluated with noninvasive autonomic tests such as parasympathetic tests of heart rate control to Valsalva maneuver and deep breathing; sympathetic tests of blood pressure control to standing, tilting, or sustained handgrip; sudomotor control to temperature and chemically induced sweating[2].Macro electromyography (macro-EMG) which is used to study the electrical activity of the entire motor unit and fiber density (FD) which can be obtained by single-fiber electromyography (SFEMG) assessment are useful in evaluating reinnervation. Both FD and Macro motor unit potential (macro-MUP) amplitude measurements were reported to provide a higher sensitivity in detecting diabetic neuropathy as compared to NCS, therefore they may be useful for evaluating asymptomatic diabetic patients and or patients with normal conventional NCS[8,9]

The aim of this study was to evaluate the presence of clinical or subclinical neuropathy in patients with type II diabetes mellitus performing conventional NCS, MA-EMG, FD and autonomic tests such as hyperventilation response to Valsalva Maneuver (Valsalva ratio), and deep breathing (E/I) ratio.

MATERIAL AND METHODS

The study protocol was approved by the Ethics Committee of the Medical Faculty and it was conducted according to the principles of the Declaration of Helsinki. All subjects gave their informed consent prior to the study. The study group consisted of 30 consecutive patients with the diagnosis of non-insulin dependent diabetes mellitus from the Marmara University Hospital, departments of Neurology and Endocrinology outpatient clinics. As controls, 17 age and gender matched patients with headache or vertigo complaints but without neuropathic symptoms were selected from the Neurology outpatient clinic. Patients with a family history of inherited neuropathies, occupational or environmental history of heavy metal exposure, history of lumbar or cervical radiculopathy as well as patients using

medications which could cause polyneuropathy were excluded. A neurologic examination was done by the same neurologist and all patients underwent tests for complete blood count and routine serum chemistry as well as tests for thyroid hormones, vitamin B12 and folic acid levels.

Prior to the electrophysiological testing the Neuropathy Symptom Profile (NSP) and the Neuropathy Disability Score (NDS) were applied to all patients[2,10,11].

ELECTROPHYSIOLOGICAL STUDIES

All electrophysiological studies were performed on a multiple channel EMG apparatus (Medelec Sapphire 4ME).

NERVE CONDUCTION STUDIES

The electrodiagnosis protocol recommended by the American Diabetes Association was used for the NCS[12]. Median, ulnar and peroneal motor fibers, median and ulnar sensory fibers and sural nerves were studied. The compound muscle action potentials (CMAP) were recorded with surface recording bar electrodes, which were placed over the main bulk of abductor pollicis brevis, abductor digiti minimi and extensor digitorum brevis for the median, ulnar and peroneal nerves respectively. A bipolar percutaneous stimulator was located at the wrist 7 cm proximal to the active recording electrode for median and ulnar motor NCS. Proximally the median nerve was stimulated just medial to the biceps tendon at the elbow crease and the ulnar nerve was stimulated below and above the elbow with a distance of at least 14 cm. The stimulation was delivered between the tendons of tibialis anterior and extansor hallicus longus muscles 9 cm proximal to the active recording electrode and from the fibular head for the peroneal motor NCS. A supramaximal stimulation of 0.1 ms duration was delivered for all the motor NCS. The sensory nerve action potentials (SNAP) were recorded by antidromic tecniques. The recording electrode was placed on the 3rd and the 5th digit for median and ulnar nerves respectively with stimulating 13 cm proximally from the wrist just medial to the flexor carpi radialis tendon for the median nerve and 11 cm proximally just posterior to the flexor carpi ulnaris tendon for the ulnar nerve. The recording electrode for sural nerve studies was placed behind the lateral malleolus and it was stimulated in the midcalf 14 cm proximal to the active recording electrode. All SNAP's were recorded using 0.1 ms stimulus duration. Filter settings were 2Hz and 10 kHz for motor studies and 20 Hz and 2 kHz for the sensory studies.

Conventional methods for the measurement of nerve conduction were employed. The latencies were measured from the onset of the action potential. The amplitudes were measured from the baseline to the negative peak of the CMAPs and peak to peak of the SNAPs. The distance between the distal and proximal stimulations was recorded for motor nerve conduction velocity (NCV) determination. Sensory nerve conduction velocities were calculated from the onset latencies. The ground electrode was placed between the the stimulation and recording electrodes for all studies. The room temperature was kept between 22-24 C, and before the testing it was made sure that the limbs were warm enough; at least 32 C.

The patients were divided into three groups according to their NDS an NCS findings. First group (GR-1) included 13 patients with both NDS and NCS abnormalities, the second group included 8 patients who had abnormal NDS but normal NCS (GR-2), and the third group included 9 patients with normal NDS (a NDS score lower than 2) and NCS (GR-3).

MACRO EMG (MA-EMG)

The biceps brachii muscle was evaluated with the standart MA-EMG method[13]. The recording electrode was a 40 mm long modified single fiber EMG (SFEMG) electrode with the cannula teflon insulated except for the distal 15 mm. An SFEMG recording surface was exposed 7.5 mm from the tip. Recording was made on two channels. Channel one consisted of the MA-EMG needle electrode's port referenced to the remote surface electrode. The SFEMG was displayed (using the cannula as reference) on this channel and used to identify the motor unit and to trigger an averaging procedure. Filter for this channel was 500 Hz- 10 kHz. Channel two comprised electrode's cannula referenced to the same remote surface electrode. On this channel the activity from cannula (using a remote surface electrode as reference) was averaged until a smooth baseline and a constant macro-MUP (MA-MUP) was obtained. Filter settings were 5 Hz-10KHz for this channel. MA-MUP amplitude was measured from the potentials initial major positive to the subsequent potentials major negative peak.

FIBER DENSITY

This study was performed on the extensor digitorum communis muscle with a SFEMG needle electrode with a surface of 25 micromm designed to record only one muscle fiber potential. Filter settings were 200 Hz-10kHz. More than 20 different sites were investigated and action potentials with amplitudes higher than 200 μV and a rise time lower

than 300 μs were selected for calculating the fiber density (FD). The single fiber potential components were divided by 20 and the result was considered as the mean FD; values above 1.4 were considered abnormal[14]

PARASYMPATHETIC AUTONOMIC SYSTEM ASSESSMENT

Autonomic tests were applied under standardized conditions between 09.00 and 12.00 am, at least 2 hours after following a light breakfast. Patients and controls were requested to stop taking any medications with anticholinergic affects 48 hours prior to the testing. The patients were not allowed to drink coffee or tea or smoke on the day of the testing. A 12-lead electrocardiogram (ECG) was obtained at a paper velocity of 25 mm/sec. Ectopic heart beats were excluded. The patients and controls were evaluated with two tests of cardiovascular autonomic function; the heart rate response variability to three consecutive valsalva maneuvers and to hyperventilation[15,16,17]

VALSALVA MANEUVER

In a sitting position, patients were asked to blow into a manometer tube against a force enough to sustain a pressure of 40 mmHg for 15 seconds, followed by normal breathing. The valsalva ratio was calculated as the quotient between the R-R interval during the post-strain phase and the shortest R-R interval during the strain phase. Valsalva ratio greater than 1.21 was accepted as normal[18]

HEART RATE RESPONSE DURING DEEP BREATHING

This maneuver was performed in a supine position. Resting heart rate was calculated after a period of 20 minutes of supine rest. Patients were asked to inspirate deeply for 5 seconds and than expirate deeply for 5 seconds for 6 consecutive respiratory cycles. Expiration/inspiration (E/I) R-R ratio was calculated as the average of the quotient between the longest R-R intervals during expiration and shortest R-R intervals during inspiration (E/I) ratio). Values equal to or higher than 1.1 were accepted as normal [19].The normative values for the electrophysiological and autonomic tests were derived from 17 controls (mean ±. 2SD).

STATISTICS

Summary data were expressed as means SD. Differences between group means were calculated with Student's t test or Mann Whitney's U test. Correlations between electrophysiological findings and varibles such as age, disease duration and gender were studied with Pearson's Correlation test. p values < 0.05 were considered significant.

RESULTS

Nineteen female and 11 male patients were evaluated with a mean age of 57 8 (range 40-70). The mean disease duration was 6 3 years (range 1-10 years) and the mean HbA1c value was 6.8% (range 5.9-7.7%). There was no correlation between peripheral and autonomic neuropathy frequency and age, HbA1c level or disease duration (p > 0,05). Overall 27 (90%) patients had motor, 27 patients (90%) had sensory and 21 patients (70%) had autonomic symptoms. GR-1 patients significantly had more neuropathic signs compared to the GR-2 and GR-3 (p <0,001). In GR-3 patients, with no neuropathic signs and normal NCS, 6 (66%) patients reported motor, 8 patients (88%) reported sensory and 3 patients (33%) reported autonomic symptoms on NSP.

The results of HgbA1c, NSP and NDS are detailed in Table 1.

Figure 1

Table 1: The mean values of HgbA1c, NSP and NDS, Macro MUP, FD and autonomic tests in 3 different groups

	number of patients	HgbA 1c	NSP-M	NSP-S	NSP-A	NDS	E/I	V	Macro MUP	FD
GR-1	13	7,1	2,23	6,15	1,84	4,92	1,13	1,22	457	1,5
GR-2	8	6,9	1,87	4,62	1,12	2,87	1,22	1,44	330	1,4
GR-3	9	6,93	1,11	3,88	0,44	0,33	1,32	1,5	243	1,26
p value	p<0,05*	p>0,05	p<0,05*	p>0,05	p<0,05*	p<0,001*	p<0,05*	p>0,05	p>0,05	p<0,05*

NSP-M: Neuropathy Symptom Profile Motor, NSP-S: Neuropathy Symptom Profile Sensory, NSP A: Neuropathy Symptom Profile Autonomic, NDS: Neuropathy Disability Score, E/I Expiration/inspiration ratio, V:valsalva ratio, FD:fiber density

The sensory and motor NCV's were significantly slower and the CMAP-SNAP amplitudes were significantly lower in the GR-1 patients compared to the other groups (p < 0.05) and controls (p < 0.001) (Table 2).

Figure 2

Table 2: The results of the Nerve conduction studies from the patients and controls, together with the normal values of our laboratory

Conduction velocities m/sec	Controles	GR-1	GR-2	GR-3	Normal values
median motor	59,3 ± 3,2	43,8 ± 2,4	52,3 ± 2,4	56±2,0	≥ 49
median sensory	61,4±3,0	43,4 ± 2,8	54,9 ± 2,3	56,3 ± 3,0	≥ 50
ulnar motor	59,7 ± 3,7	45,1 ± 2,1	53,7 ± 2,4	55,7 ± 2,1	≥ 49
ulnar sensory	58,5 ± 3,7	42,6 ± 2,8	55,3 ± 2,2	55,4 ± 1,3	≥ 50
peroneal motor	57,4 ± 3,6	39,8 ± 2,3	46,9 ± 1,5	53,6 ± 1,5	≥ 44
sural sensory	55,6 ± 2,2	34,1± 4,3	46,0± 3,4	53,6± 1,5	≥ 40
Motor amplitudes (mV)					
Median	8,3 ± 1,4	3,2 ± 0,5	5,00 ± 0,7	7,1 ± 1,0	≥ 4
Ulnar	12,3 ± 2,0	4,2 ± 0,9	10,7 ± 1,2	10,7 ± 1,2	≥ 5
Peroneal	7,6 ± 1,6	1,4 ± 0,3	5,4 ± 1,2	6,4 ±1,2	≥ 5
Sensory amplitudes (µV)					
Median	36,6 ± 6,6	7,0± 1,3	27,2 ± 2,9	29,4 ± 4,9	≥ 20
Ulnar	29,7 ± 4,0	6,3 ± 1,3	19,7 ± 1,9	23,8 ± 9,6	≥ 17
Sural	14,0 ± 1,5	3,4 ± 1,0	6,2 ± 2,1	9,6 ± 1,8	≥ 6

The mean E/I ratio was significantly different between the three groups of patients (table 1). Overall cardiac autonomic system was affected in 12 patients (40%). Four patients (13%) had both valsalva and E/I ratio tests positive and 8 patients only had one autonomic test abnormal; five (16%) with an abnormal E/I ratio and three (10%) with an abnormal Valsalva ratio. The mean valsalva ratio and E/I were significantly different in patients and controls (p<0,001) (table 3).

Figure 3

Table 3: Comparison of the mean values ± SD in the patient group and controls

	Macro-MUP (µV)	**FD**	**E/I**	**V**
Patients	359,4± 145,4	1,41 ± 0,16	1,2 ± 0,15	1,39±0,2
Controls	132,0± 27,6	1,22 ± 0,1	1,4 ± 0,12	1,67±0,23
p value	p<0,001	p<0,05	p<0,001	p<0,001

Although there was no significant difference between patient groups for the MA-MUP amplitude (p>0,05) (table 2) the mean MA-MUP amplitude was much higher in the patients compared to the controls (p< 0.001) (table 3). Similarly the mean FD was significantly higher in patients in GR-1 compared to controls (p<0,005). (Table 2).

The details of macro-EMG, fiber density study and autonomic tests are given in table 4. All patients in GR-1 had increased MA-MUP and FD (100%), 4 patients had increased valsalva ratio (30%) and 5 patients had increased E/I ratio (38.7 %). In GR-2 5 patients had increased MA-MUP and FD (63 %), 2 patients had increased valsalva ratio (25%) and 1 patient had increased E/I ratio (13 %). In GR-3 three patients had increased MA-MUP (33%), 1 patient had increased FD (11 %), no patients had increased valsalva ratio (0%) and 2 patients had increased E/I ratio (22 %) (figure 1). MA-MUP and FD were both increased in 13 patients in the first group, 5 patients in the second (63%) and one patient in the third group (11%) (table 4).

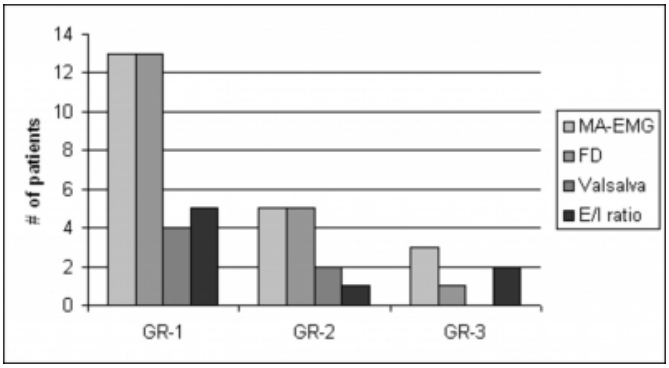
Figure 4

Table 4: The macro-EMG, fiber density and autonomic test results in 30 patients

Group 1	**Macro MUP amplitude (µV)**	Fiber Density	E/I ratio	Valsalva ratio
1	367,9	1,45	1,04	1,23
2	617,5	1,4	1,18	1,7
3	578,3	1,7	1,16	1,42
4	413,5	1,45	1,09	1,25
5	436	1,4	1,15	1,17
6	326	1,5	1,07	1,17
7	**490,3**	1,6	1,09	1,16
8	425,5	1,45	1,08	1,35
9	435	1,5	1,16	1,31
10	526	1,45	1,12	1,21
11	**521**	1,75	1,26	1,73
12	411	1,4	1,21	1,41
13	398	1,6	1,1	1,12
Group 2				
1	338,9	1,45	1,28	1,38
2	**536,5**	1,5	1,13	1,56
3	**466,8**	1,4	1,16	1,07
4	196	1,35	1,3	1,53
5	426	1,6	1,08	1,16
6	189,4	1,25	1,37	1,67
7	175,5	1,2	1,24	1,76
8	**318**	1,45	1,26	1,46
Group 3				
1	190,5	1,1	1,35	1,73
2	175,3	1,15	1,32	1,41
3	**180**	1,25	1,73	1,88
4	**197,2**	1,25	1,12	1,28
5	219	1,3	1,33	1,29
6	589,5	1,5	1,09	1,37
7	171,8	1,15	1,42	1,57
8	275,3	1,35	1,07	1,28
9	**191,1**	1,35	1,45	1,69

Figure 5

Figure 1: Comparison of abnormal findings



DISCUSSION

Peripheral neuropathy is a major complication of diabetes mellitus and marked differences can be observed in the types of nerve fibers involved[5,20]. In the present study 90% of the diabetic patients had sensory and motor symptoms, while

autonomic symptoms were positive only in 70%. The majority of patients reported mild or moderate symptoms on NSP. Although the highest NSP scores were found with GR-1 patients, followed by GR-2 patients. as expected, up to 88% of the patients from GR-3 (no clinical sign and normal NCS) also reported neuropathic symptoms on NSP. Similarly in the Rochester Diabetic Neuropathy study, NSP was found not to be highly reproducible[21]. Contrary to the subjectivity of NSP, NDS reveals affection of peripheral nerves quantitatively not qualitatively.

Autonomic dysfunction is an important complication of diabetes and may be associated with an increased risk of mortality[22,23]. Non-invasive autonomic testing is a sensitive method for identifying autonomic dysfunction in diabetic subjects. The RR interval variation is a parasympathetic reflex that originates in the vagus nucleus and generates a tonic cardioinhibitor outflow transmitted to the heart by thinly myelinated vagal fibers[24] The most widely used and most reliable test of cardiovagal function is the heart rate response to valsalva maneuver and to standing[25] The sensitivity of E/I ratio and the valsalva ratio are similar[26]. Ewing reported the percentage of heart rate test abnormality as 40%, while Low demonstrated that 67% of 73 patients with diabetic neuropathy had R-R interval abnormalities[27,28]. Similarly in the present study according to the results of heart rate variation 12 patients (40%) had cardiac autonomic neuropathy. Parasympathetic system abnormalities were positive in 38% of patients in GR-2 and 22 % of patients in GR-3. A finding that suggests these tests might be useful in patients without NCS abnormalities in order to reveal the beginning of the neuropathic process. Four patients (13%) had both valsalva and E/I ratio tests positive and 8 patients only had one autonomic test abnormal; five (16%) with an abnormal E/I ratio and three (10%) with an abnormal Valsalva ratio. In this study we only tested parasymptathetic system, using valsalva and E/I ratio. Therefore we do not know if there were any sympthetic system involvement, and to what extent.

NCS measure the ability of peripheral nerves to conduct electrical signals and are abnormal when pathological changes are present in the myelin, nodes of Ranvier or axons. The dynamics of the reinnervation process can be studied with SFEMG and MA-EMG[29] In most situations of reinnervation, the local FD as indicated by SFEMG, and the total motor unit size as indicated by the MA-EMG amplitudes, are increased, this increase is due to reinnervation after denervation, leading to increased number of muscle fibers per motor unit and loss of small motor units[30]. SFEMG parameters are more frequently abnormal than that of NCS, because onset of axonal degeneration with reinnervation could be much earlier than it becomes detectable with classic electrophysiological tests[31,32].

Following MA-EMG and FD studies in three different groups, we found that MA-EMG amplitudes increased in 21 out of 30 (69%), FD values increased in 19 (63%). All patients in the first group and 5 patients in the second group (63%) had both MA-MUP and FD increase, while in the third group only one patient (11%) had both MA-MUP and FD increased. This finding suggests that between patients with NCS abnormality and clinical signs in the first group and patients with neither NCS abnormalities nor clinical findings on neurological examination in the third group, there was considerable difference regarding axonal involvement[33]. None of the patients had increased FD while MA-EMG was normal and this finding is in agreement with literature[29]. Increase in MA-EMG amplitude not accompanied by an increase in FD, which may indicate a dropout of small motor units, is a unique finding observed in diabetic and uremic neuropathies in previous studies[34]. Similarly in the present study in GR-3 two patients (22%) with normal FD had increased MA-MUP amplitudes, and this is in agreement with the literature.

The increase in FD, in our study was lower than previous studies a result which may be related to the muscle selection, we studied a forearm muscle, extensor digitorum communis[8,30,35]. Since the lower limbs are more severely affected in diabeic neuropathy, for future studies we propose that tibialis anterior should be the muscle of choice when examining asymptomatic or mildly affected patients.

Diabetic neuropathy affects sensory, motor and autonomic nerve fibers diffusely leading to progressive degeneration and nerve fiber loss[36] In our study in GR-1 group with NCS abnormality, three patients had abnormal MA-MUP amplitude, FD, E/I and valsalva indexes, and in these patients both peripheral and cardiac autonomic involvement were present. In GR-2, one patient had all the tests abnormal. On the other hand, in GR-1, 2 patients had increased MA-MUP amplitude, FD and E/I ratio, 2 patients had increased MA-MUP amplitude, FD and valsalva ratio. In GR-2 MA-MUP and FD were increased together with valsalva ratio in one patient, and in GR-3, one patient with increased MA-MUP amplitude and FD had also abnormal E/I ratio, and one patient with increased MA-MUP had

increased E/I ratio. This implied that, in GR-3 although no neurological signs or NCS abnormality, one patient had involvement of peripheral nervous system and parasympathic system.

In this study, we were able to find peripheral neuropathy in 5 out of 8 patients with neuropathic signs but no NCS abnormality (GR-2), using MA-EMG and FD studies. More interestingly, in GR-3 patients with no neurological signs or NCS abnormality one patient had both MA-EMG and FD abnormality and two patients had abnormal MA-EMG studies.

In conclusion; diabetic neuropathy is a constellation of motor, sensory and autonomic involvements[20]. With NCS, MA-EMG and FD studies it is possible to record MUPs, evaluate axonal involvement and as a result get different but complementary results about changes in fiber distribution. Even in patients without any neurologic signs suggestive of diabetic neuropathy there may be findings of early axonal involvement that could only be detected by MA-EMG and FD. This early diagnosis is critical, because in the early stages of denervation process, good glycemia control is very crucial to revert the ongoing process. Since it has become clear that the 5 year mortality of patients with autonomic involvement is three times higher when compared to patients without autonomic involvement it is recommended to supplement tests of perpheral nervous system with tests of autonomic system in order to get further information about the coexistence of peripheral and autonomic neuropathy, and to reveal those with beginning autonomic disturbances.

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