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Axonal Degeneration in Diabetic Neuropathy: an Assessment of Single Fiber Electromyography

Chein-Wei Chang Lee-Ming Chuang* and I-Nan Lien

Peripheral neuropathy is an important complication of diabetes mellitus. However, neuropathological changes in diabetic neuropathy with axonal degeneration or segmental demyelination are still unclear. By using a newly developing electrodiagnostic method of single fiber electromyography (SFEMG) with a computer-aided program, mean jitter value and muscle fiber density were measured in extensor digitorum communis (EDC) and anterior tibial (AT) muscles from 36 diabetic patients with neuropathy (group I) and 12 patients without neuropathy (group II) proved by nerve conduction study. The results showed an increased mean jitter value, fiber density and abnormal percentage both in EDC and AT muscles in group I and II diabetic patients comparing to the normal controls.

These findings suggest an impaired or immatured neuromuscular junctions and an evidence of reinnervation through axonal sprouting in the diabetic patients either with or without nerve conduction abnormalities. In conclusion, the changes of axonal degeneration and reinnervation are the main pathophysiological mechanism of diabetic neuropathy, and the SFEMG is more sensitive than routine nerve conduction study in the diagnosis of diabetic neuropathy.

Key words: Axonal degeneration, diabetes mellitus, neuropathy, single fiber electromyography

INTRODUCTION

Sensori-motor peripheral neuropathy is an important complication of diabetes mellitus [1,2,3], However, the neuropathological changes in this neuropathy with axonal degeneration or segmental demyelination are still controversial. Most of the clinical, pathologic and electrophysiologic features of this neuropathy suggested that it was primarily due to axonal degeneration [4,5,6,7]. On the other hand, there were some reports supported that the common type of lesion in nerve biopsies was demyelination [4,8,9].

In clinical routine neurophysiological investigation, it is somewhat difficult to differentiate the axonal from demyelinating neuropathy by needle electromyography or nerve conduction study. Single fiber electromyography (SFEMG) is a new sensitive technique for detecting signs of reinnervation [10]. These signs are the bases to differentiate axonal neuropathies from demyelinating lesions. Denervation of muscle fibers by axonal damage is followed by collateral or terminal reinnervation with rearrangement of motor unit fibers which may be detected by SFEMG study as increment of fiber density.

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The purpose of this study was to asses the SFEMG change in the diabetes with or without neuropathy and to determine the value of SFEMG in the detection of axonal degeneration in diabetic neuropathy.

SUBJECTS AND METHODS

Fourty-eight patients with clinically suspected diabetic neuropathy from diabetic clinic attended in this study. There are 18 men and 30 women, with age ranged from 36 to 77 years (mean, 58 years). All diabetic subjects were questioned regarding paresthesia, numbness, pain and motor weakness. All underwent neurologic examinations that included the sensory tests of light touch, pinprick, vibration and joint position sense, deep tendon reflexes at knee, ankle and elbows, muscle power test in upper and lower extremities including the inspection of muscular atrophy. Patients with spinal symptoms and signs of radiculopathy, or with prominent impairment of renal function were excluded.

Each patient had standard NCV studies performed on peroneal, tibial motor nerves and sural sensory nerves in both lower extremities, and median and ulnar sensory and motor nerves in one upper extremity. The results were compared with the normal values for our laboratory [11]. Slowness of sensory or motor NCV in more than two neural segments were identified to have diabetic neuropathy.

By using the electrophysiologically diagnostic criteria of NCV studies, the 48 patients were divided into two groups. Thirty-six patients with diabetic neuropathy were categorized in group I. Their age ranged from 36 to 77 years (mean, 62 years). Twelve patients without nerve conduction evidence of neuropathy were categorized in group II. Their age were between 43 and 76 years (mean, 56 years). In addition to the diabetic patients, there were 20 normal age-matched (40 to 70 years, mean 54 years) persons as controls.

SFEMG were performed in the extensor digitorum communis (EDC) muscle and anterior tibial (AT) muscle in each diabetic patient and normal control using the standard methods designed by Stalberg and Trontelj [10]. The jitter was measured with an automatic analyzer (Jittermaster; Medelec, England) and a computer EMG (Swedish Electro-physiologic Software, Sweden) interfaced to an MS 92a EMG machine (Medelec, England) and and Apple IIe computer (Apple, US). For the determination of abnormality of the jitter, we used the following guidelines: 1) When more than 10 potential pairs are obtained, any one of the following 3 criteria is used in judging abnormality of jitter [12]; (a) mean "mean consecutive interpotential difference (MCD)" value exceeds the normal limit (36.7 μ s in EDC muscle, 42.1 μ s in AT muscle), (b) more than 10% of potential pairs have jitter greater than the upper limit of an individual MCD (55.4 μ s in EDC muscle, 61.2 μ s in AT muscle), or (c) blocking is frequently seen in the tested muscle, so that it is impossible to calculate the MCD. 2) When fewer than 10 potential pairs are obtained, the jitter is considered abnormal when one of the following 2 criteria is met; (a) at least 2 potential pairs have jitter greater than the upper limit of an individual MCD (55.4 μ s in EDC muscle, 61.2 μ s in AT muscle), (b) blocking is frequently seen in the majority of fiber pairs in a muscle, so that it is impossible to calculate the MCD.

The fiber density was measured from 10 to 20 different sites using the conventional methods and was considered abnormal when it was higher than the mean plus 2.5 standard deviations from the normal control group.

RESULTS

The clinical findings and NCV findings in 48 diabetic patients are listed in Table 1.

Table 1. Clinical and nerve conduction velocity (NCV) findings in 48 diabetic patients.

Clinical findings:	Number	Percentage
Altered sensory perception	32	66.7%
Decreased or absent tendon reflexes on knee or ankle	27	56.3%
Decreased tendon reflex on elbow	15	31.3%
Muscle weakness	8	16.7%
Muscle atrophy	4	8.3%
NCV findings:		
Slow sensory NCV	31	64.6%
Slow motor NCV	16	33.3%
Slow motor and sensory NCV	13	27.1%

Thirty-two patients (66.7%) had sensory alternation and 16.7% of patients had motor weakness. DTR decreased in 56.3% of patients in lower extremities and 31.3% in upper extremities. Slow sensory NCV was found in 64.6% of patients.

The results of MCD, fiber density and abnormal percentage obtained in EDC and AT muscles from patient groups and normal controls were shown in Tables 2 and 3. In diabetic groups I and II, the mean for MCD, fiber density and abnormal percentage were all increased in comparing to control group (t test, $p<0.01$, respectively). MCDs obtained in EDC muscles are higher in diabetic group I than in diabetic group II ($p<0.05$), but there were no MCD difference between the two groups in AT muscle ($p>0.1$). Fiber densities obtained from two diabetic patient groups were not different in EDC and AT muscles ($p>0.1$, respectively).

Linear relationship was found between fiber density and MCD in EDC muscles ($r=0.471$, $p<0.01$) and in AT muscles ($r=0.386$, $p<0.02$) in the group I diabetic patients (Fig.1, A and B). In MCD findings, 75% of the diabetic group I patients and 33.3% in group II patients were abnormal in EDC muscles. Eighty-three percent of diabetic group I and 75% of group II patients had abnormal MCD values in AT muscles.

In the fiber density examination, 27.8% of diabetic group I patients and 25% of group II patients showed abnormal in EDC muscles. Fifty-eight point three percents of diabetic group I patients and 41.7% of group II patients showed abnormal fiber densities in AT muscles.

DISCUSSION

SFEMG is a neurophysiologic technique which is able to assess axonal degeneration with compensatory reinnervation. Fiber density is an index of the number of muscle fibers in a motor unit that lie within 300 μ m of the active recording surface of the SFEMG electrode [10]. Fiber density is usually normal in the neuromuscular transmission disorders, mildly increased in myopathies, and moderately increased in denervation disorders [10,12]. In denervation process, the fiber density is increased due to collateral sprouting of surviving axons during reinnervation. Thus, an increased fiber density reflects a state of axonal degeneration. Jitter, a measurement of the

Table 2. Mean consecutive difference (MCD) (mean ± 1SD) measured in extensor digitorum communis (EDC) and anterior tibial (AT) muscles.

	Number of subjects	EDC muscle MCD(μs)	EDC muscle Abnormal number(%)	AT muscle MCD(μs)	AT muscle Abnormal number(%)
Diabetes					
Group I	36	45.8±13.3	27(75%)	57.9±22.0	30(83.3%)
Group II	12	35.5±15.3	4(33.3%)	57.2±23.1	9(75%)
Normal control	20	28.2± 3.4	0(0%)	36.6± 4.2	0(0%)
Normal value*		≦36.7		≦42.1	

* Normal MCD value was obtained from mean plus 2.5 standard deviations from normal control group.

Table 3. Fiber density (FD) (mean ± 1SD) obtained in extensor digitorum communis (EDC) and anterior tibial (AT) muscles.

	Number of subjects	EDC muscle FD	EDC muscle Abnormal number(%)	AT muscle FD	AT muscle Abnormal number(%)
Diabetes					
Group I	36	2.07±0.31	10(27.8%)	2.45±0.47	21(58.3%)
Group II	12	1.99±0.50	3(25.0%)	2.15±0.71	9(41.7%)
Normal control	20	1.61±0.14	0(0%)	1.70±0.16	0(0%)
Normal value*		≦1.96		≦2.10	

* Normal value was obtained from mean plus 2.5 standard deviations from normal control group.

variability of interdischarge intervals between two muscle fibers in the same motor unit, represents the integrity of neuromuscular transmission. The jitter is increased minimally in myopathies, moderately in denervation disorders, and most prominently in the neuromuscular transmission disorders [10,12]. In denervation processes, an increased jitter is due to disturbed conduction of an impulse in degenerating or reinnervating nerve twigs and to synaptic delay in immature, newly formed endplates and thus reflects the degree of impared neuromuscular transmission in these immature nerve terminals [10,12]. Increased fiber density and/or with increasing jitter are encountered in many neurogenic disorders

[13,14,15,16] and indicative of axonal degeneration with reinnervation.

Our findings of increased fiber density and jitter in the diabetic patient groups imply that diabetic polyneuropathy is primarily an axonal degeneration. The linear relationship between the jitter and fiber density suggests that axonal degeneration with reinnervation is the primary mechanism of the increased jitter.

In 1975, Thiele and Stalberg [13] observed normal fiber density, jitter and blocking in SFEMG of the muscles in 19 patients with diabetic neuropathy. They proposed as the most plausible explanation for the relatively normal SFEMG in this neuropathy that no axonal damage has taken place because this is primary demyelinating neuropathy. In 1987, Shields [15] found increased fiber density and jitter in the AT muscle in 93% of 30 patients with diabetic neuropathy and concluded that axonal degeneration is a primary pathologic mechanism in diabetic neuropathy. Bril and Web [17] also found increased fiber density in the AT muscle in all of 12 patients with diabetic neuropathy and abnormal jitter in 67%. The discrepancy between Thiele and Stalberg's observation and these two studies is partly due to different muscles they studied. Their contradictory conclusions reflect the different views concerning the pathogenetic mechanism of diabetic neuropathy prevalent in the 1970s and 1980s [1,3].

Our SFEMG study included both the assessments in EDC and AT muscles. The findings showed that there were increasing fiber densities and jitters both in EDC and in AT muscles. The increased fiber density and jitter are larger in AT muscles than in EDC muscles. These findings suggested that axonal neuropathy with reinnervation might occur disseminately in upper and lower extremities. The grade of axonal neuropathy with reinnervation is higher in lower extremities than in upper which is well correlated with the classical elec-

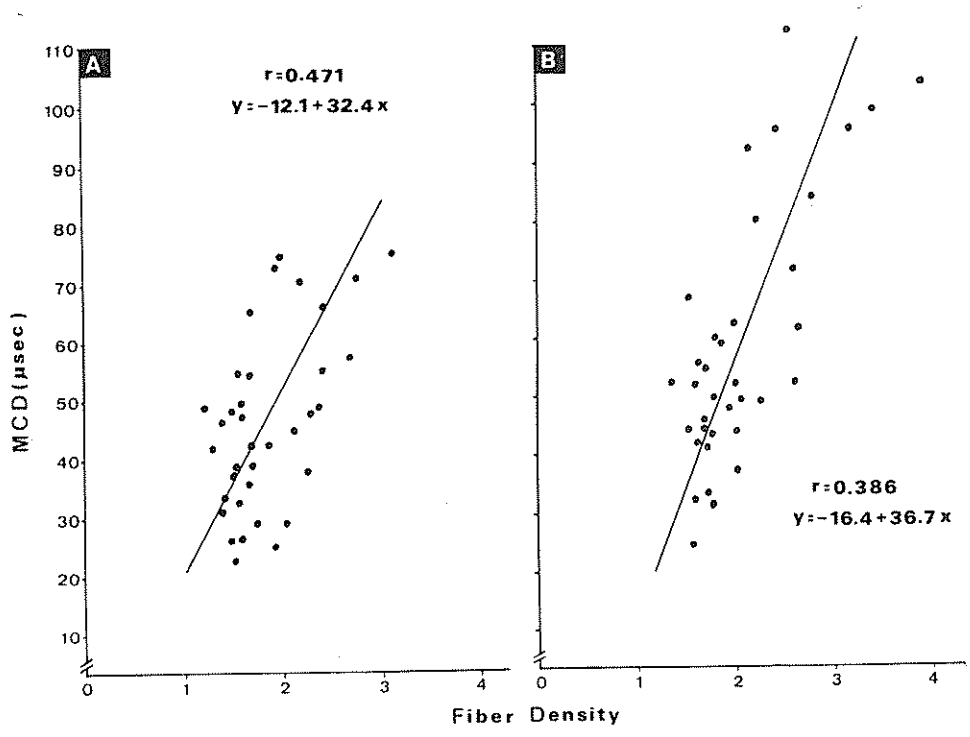

Figure 1. Linear regression of mean consecutive difference (MCD) and fiber density in EDC muscles (A, y=-12.1+32.4x, r=0.471, p<0.01) and in AT muscles (B, y=-16.4+36.7x, r=0.386, p<0.02) in group I diabetic patients, where y=MCD in μ s and x=fiber density.

trophysiological findings in diabetic neuropathy [18].

With routine neurophysiological investigation, nerve conduction studies were normal in 12 diabetic patients. SFEMG studies in these patients showed an increased MCD in EDC muscles in 4 patients (33.3%) and an increased MCD in AT muscles in 9 patients (75%). Fiber density increased in 3 patients (25%) in EDC muscles and 5 patients (41.7%) in AT muscles. These findings also suggested that SFEMG might detect abnormalities in muscles on clinically routine normal NCV examinations.

In conclusion, the present SFEMG study indicates that the changes of axonal degeneration and reinnervation are the main pathophysiological mechanism in diabetic neuropathy. Also, the SFEMG used in the diagnosis of diabetic neuropathy is more sensitive than a routine motor NCV study.

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糖尿病神經病變中的神經軸退化現象：單纖維肌電圖檢查

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末稍神經病變是糖尿病的重要併發症之一，但造成糖尿病神經病變的病變機轉是神經軸退化或去髓鞘現象目前仍未明瞭，因單纖維肌電圖可測神經之再分佈情形及神經肌肉交接處的穩定度，故可間接了解神經軸的退化及再生現象。本文以48位糖尿病患作研究，先以神經傳導速度檢查區分，第一組36倍糖尿病患合併神經病變及第二組12位無神經病變的病患，並以20位正常人作對照組，取每一位受試者的伸指總肌及脛前肌作單纖維肌電圖檢查測其連續波間值差異（mean consecutive difference）及肌纖維密度（fiber density）。

結果顯示兩組糖尿病病患的連續間值差異，肌纖維密度及不正常比率比對照組顯著增加（t試驗，依序 $p<0.01$），在第一組糖尿病患中，伸指總肌的連續波間值差異比第二組高（$p<0.05$），而連續波間值差異與纖維密度之間也成線性相關的增加（伸指總肌，$r=0.471$，$p<0.01$；脛前肌，$r=0.386$，$p<0.02$），在伸指總肌測得的連續波間值差異上，第一組糖尿病患有75％不正常，第二組有33.3％不正常，而在脛前肌的連續波間值差異上，第一組糖尿病患有83.3％不正常，第二組有75％不正常，在肌纖維密度的測定中，第一組糖尿病患的伸指總肌有27.8％不正常，脛前肌有58.3％不正常，第二組病患的伸指總肌有25％不正常，脛前肌有41.7％不正常，此結果表示糖尿病神經病變造成的神經肌肉交接處不穩定及有神經軸再生的重分佈現象，因此也證實糖尿病神經病變的主要病理機轉爲神經軸的退化所致，而在診斷上，單纖維肌電圖檢查的敏感度也比運動神經傳導速度檢查爲高。

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