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Median neuropathy at the wrist as an early manifestation of diabetic neuropathy

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ABSTRACT

Aims/Introduction: To elucidate the clinical significance of median neuropathy at the wrist (MN) in patients with diabetes.

Materials and Methods: In total, 340 patients with diabetes who were hospitalized for glycemic control were enrolled in the present study. The diagnoses of MN and diabetic polyneuropathy (DPN) were based on electrophysiological criteria. A total of 187 patients were divided into four subgroups: patients without MN or DPN; patients with MN without DPN; patients with MN and DPN; and patients with DPN without MN. Intergroup comparisons of clinical characteristics and results of nerve conduction studies were carried out.

Results: A total of 71 patients had neither MN nor DPN; 25 had MN, but no DPN; 55 had MN and DPN; and 36 had DPN, but no MN. In comparison with the MN and DPN group, the MN without DPN group included more patients in the early phase of diabetes (diagnosed within the past 5 years) and fewer patients with diabetic microangiopathy. Comparative median nerve conduction studies showed significantly lower motor and sensory nerve conduction velocities, longer F-wave latencies, and smaller sensory nerve action potentials in patients with MN and DPN than in those without DPN.

Conclusions: MN in patients with diabetes could be attributed to an impairment in axonal function at common entrapment sites, and could be used to identify an early manifestation of diabetic neuropathy.

INTRODUCTION

Entrapment disorders are highly prevalent in patients with diabetes[1], the most common neuropathy being carpal tunnel syndrome (CTS)[2], which is classified as a focal limb disease[3]. Generally, CTS is more common in females than in males, in obese individuals than in non-obese individuals and in the dominant hand versus the non-dominant hand[4]. The high prevalence of CTS among patients with diabetes might be as a result of repeated undetected trauma, metabolic changes, accumulation of fluid or edema within the confined space of the carpal tunnel and/or diabetic cheiroarthropathy[2]. CTS in patients with diabetes is frequently asymptomatic, and is identified through electrophysiological tests. Additionally, there is no demonstrable correlation between the appearance of CTS and the stage of diabetic polyneuropathy (DPN)[5,6]. The clinical diagnosis of CTS depends on a combination of appropriate clinical symptoms; therefore, most clinicians require electrophysiological confirmation of median neuropathy at the wrist (MN) before establishing a diagnosis of CTS[6].

Nerve conduction studies (NCS), the most sensitive diagnostic method for detecting MN and DPN, provide the only available technique to diagnose subclinical cases. NCS are also useful in differentiating entrapment from distal symmetric polyneuropathies[2]. In order to elucidate the clinical significance of MN in patients with diabetes, we compared clinical and electrophysiological data between patients with MN without DPN, and those with MN and DPN.

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MATERIALS AND METHODS

Patients

The current study was carried out at the Kagoshima City Hospital, Kagoshima, Japan, between February 2007 and September

2012. We recruited 340 patients (156 women and 184 men) with diabetes mellitus who were hospitalized for hyperglycemia management during the study period. The mean age of the patients was 56.8 ± 11.7 years, with a mean duration of diabetes of 9.3 ± 7.8 years; 309 patients had type 2 diabetes, whereas 31 patients had type 1 diabetes. Glycated hemoglobin (HbA1c) levels were 9.8 ± 2.2%. Routine biochemical and hematological tests, NCS and screening for diabetic complications were carried out for all patients. All patients with a medical history of serious trauma to the limbs, excessive alcohol consumption, use of neurotoxic medication and/or evidence of neuromuscular disease were excluded from the study in order to omit neuropathy as a result of other etiologies. Patients aged over 75 years were excluded because sensory nerve action potentials (SNAPs) of the nerves are largely dependent on age. Informed consent was obtained from all patients before their inclusion in the study.

Nerve Conduction Study

All patients underwent conventional sensory and motor NCS. The median, ulnar, tibial, and sural nerves were tested in the upper and lower limbs. All studies were carried out using a standard electromyography machine with stimulating and recording electrodes (Viking Select; Nicolet Biomedical Japan, Tokyo, Japan). SNAPs of the nerves in the upper limb were recorded orthodromically. Median motor distal latencies were recorded using an interelectrode distance of 8 cm (stimulating the wrist and recording the thenar), while median sensory peak latencies were measured using a stimulation-to-recording electrode distance of 14 cm (digit 2 to wrist). Stimulations in the palm were carried out with an electrode distance of 7 cm (palm to wrist), and skin temperature was maintained above 32°C on the forearm and 31°C on the mid-leg. Electrophysiological criterion for the diagnosis of MN was determined as a prolongation in either median motor latency or sensory palm latency (>4.5 and 1.8 ms, respectively). Importantly, the criterion required that the difference in sensory onset latency between the palm to wrist and digit 2 to palm was higher than 0.4 ms[7]. DPN was defined as a distal symmetric sensorimotor polyneuropathy by using recommendations of the American Academy of Electrodiagnostic Medicine[8], and was diagnosed if there was a reduction of SNAPs in the median nerve (<7 μV), ulnar nerve (<6.9 μV) and sural nerve (<5 μV). The cut-off value of SNAPs was determined to be the lower limit of the normal range commonly used in our laboratory. Although diabetes can involve multiple common entrapment sites, median-ulnar or median-radial comparative studies were not carried out. Therefore, patients were excluded from the study if they showed absent motor or sensory potentials in the median and ulnar nerves, presented with mononeuropathy other than MN and/or if the MN group had pathological electrophysiological findings in the ulnar nerve. On the basis of the results of the NCS, patients were divided into four subgroups: patients without MN or DPN (MN–/DPN–); patients with MN without DPN (MN+/DPN–); patients with MN and DPN (MN+/DPN+); and patients with DPN without MN (MN–/DPN+). The clinical characteristics of patients and results of the NCS were compared between groups.

Statistical Analyses

Data are expressed as means and standard deviations. Statistical analyses were carried out using Excel 2011 (Microsoft, Redmond, WA, USA) with the add-in software Statcel 3 (OMS, Tokyo, Japan). Data were analyzed by one-way analysis of variance (ANOVA), and then statistical significance of differences among the four groups was calculated using Tukey–Kramer or Steel–Dwass post-hoc tests or χ^2 statistics followed by the Bonferroni adjustment. *P*-values <0.05 were considered statistically significant.

RESULTS

Of the 340 patients examined, just 187 were included in the current study. Incidentally, 153 patients were excluded from the study; 43 patients with absent motor or sensory potentials in the median and ulnar nerves, 51 patients with mononeuropathy other than MN, 40 patients with pathological electrophysiological findings in the ulnar nerve in the MN group, and 19 patients with pathological electrophysiological findings in the ulnar and sural nerve.

The demographic data for the 187 participants are provided in Table 1. A total of 71 patients had neither MN nor DPN; 25 had MN, but no DPN; 55 had MN and DPN; and 36 had DPN, but no MN. There was no significant difference in sex, body mass index or HbA1c levels between the four subgroups. Compared with the MN+ or –/DPN+ group, the MN+/DPN– group had diabetes for a significantly shorter period, and showed preserved urinary C-peptide immunoreactivity. Additionally, the prevalence of diabetic retinopathy and diabetic nephropathy was significantly lower in the MN+/DPN– group than in the MN+ or –/DPN+ group. Within the MN–/DPN– group and MN+/DPN– group, there was no significant difference in age, duration of diabetes, urinary C-peptide immunoreactivity or the prevalence of diabetic retinopathy and diabetic nephropathy. Among the patients with DPN, none of the clinical characteristics differed significantly between the MN+/DPN+ group and the MN–/DPN+ group. The percentage of patients having a diabetes duration of 5 years or less was significantly higher among MN–/DPN– group and MN+/DPN– group than among the MN+/DPN+ group and MN–/DPN+ group (Figure 1). In particular, there was a significant difference between the MN+/DPN– group and MN+/DPN+ group. The results of the median NCS for the 187 participants are provided in Table 2. When comparing the MN+/DPN– group with the MN+/DPN+ group, the latter group was found to have significantly lower motor and sensory nerve conduction velocities, as well as prolonged F-wave latencies than the former group. The amplitude of compound muscle action potentials (CMAP) was not different between the two groups, whereas the SNAPs were significantly smaller in the MN+/DPN+ group than in the MN+/DPN– group. Among the

Table 1 | Clinical characteristics of patients

	(MN–/DPN–)	(MN+/DPN–)	(MN+/DPN+)	(MN–/DPN+)
n	71	25	55	36
Sex (% male)	57.7	32.0	61.8	55.6
Age (years)	52.4 ± 13.4**†	58.4 ± 8.9	61.5 ± 10.5**	59.8 ± 12.3†
Body mass index (kg/m^2)	23.8 ± 4.3	24.2 ± 6.4	23.5 ± 4.4	22.9 ± 5.1
Type 1/type 2	16/55*	3/22	2/53*	2/34
Duration (years)	5.4 ± 6.4**††	5.7 ± 5.6‡§§	13.4 ± 8.4**‡	13.3 ± 8.5††§§
HbA1c (%)	10.1 ± 2.1	9.2 ± 2.2	9.7 ± 2.4	10.0 ± 2.3
Urinary CPR (μg/day)	57.2 ± 37.9	76.0 ± 81.3‡§	40.3 ± 39.8‡	44.5 ± 39.3§
Diet/oral/insulin/none	3/31/6/31*	1/14/1/9	0/21/19/15*	1/21/7/7
Retinopathy (%)	19.7**††	36.0‡§	81.8**‡	75.0††§
PPDR or PDR (%)	1.4**††	12.0‡§§	70.9**‡	61.1††§§
Nephropathy (%)	19.7**††	40.0‡§	80.0**‡	75.0††§

CPR, C-peptide immunoreactivity; PDR, proliferative diabetic retinopathy; PPDR, preproliferative diabetic retinopathy. Data are expressed as mean ± standard deviation. *Patients without median neuropathy at the wrist (MN) or diabetic polyneuropathy (DPN; MN–/DPN–) and patients with MN and DPN (MN+/DPN+), $P < 0.05$; **(MN–/DPN–) and (MN+/DPN+), $P < 0.01$; †(MN–/DPN–) and patients with DPN without MN (MN–/DPN+), $P < 0.05$; ††(MN–/DPN–) and (MN–/DPN+), $P < 0.01$; ‡patients with MN without DPN (MN+/DPN–) and (MN+/DPN+), $P < 0.01$; §(MN+/DPN–) and (MN–/DPN+), $P < 0.05$; §§(MN+/DPN–) and (MN–/DPN+), $P < 0.01$.

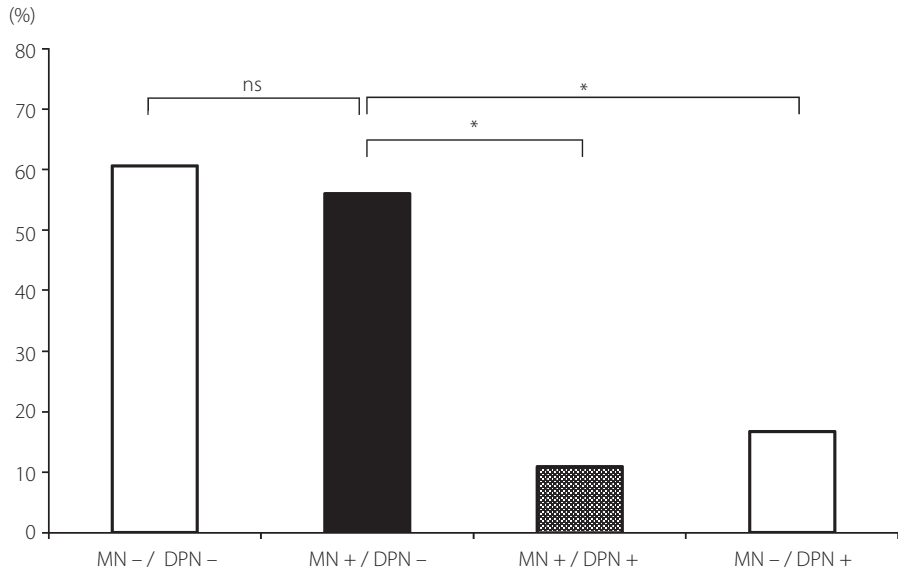

Figure 1 | Percentage of diabetes duration of 5 years or less in the four groups. Data were analyzed by χ^2-test (all significant differences remained after Bonferroni adjustment). *$P < 0.01$. DPN, diabetic polyneuropathy; MN, median neuropathy at the wrist; NS, not significant.

patients with DPN, the MN+/DPN+ group was found to have significantly lower sensory nerve conduction velocities, as well as prolonged median motor latency, sensory palm latency and F-wave latencies than the MN–/DPN+ group. Motor nerve conduction velocities, amplitude of CMAP and SNAPs were not different between the two groups.

DISCUSSION

CTS is reported to occur in 2.6–20% of all patients with diabetes[9]. In the Rochester Diabetic Neuropathy cohort, clinical evidence for MN was found in 9% of patients with type 1 diabetes mellitus and in 4% of patients with type 2 diabetes mellitus. Electrophysiological evidence of asymptomatic MN was found in 22% of patients with type 1 diabetes and 29% of patients with type 2 diabetes[10]. In the current study of patients with poorly managed diabetes, asymptomatic MN was found in 22% of patients with type 1 diabetes and 46% of patients with type 2 diabetes. The prevalence of asymptomatic MN without DPN was 13%, whereas the prevalence of asymptomatic MN with DPN was 29%. This finding is in agreement with previously published data on the prevalence of CTS for this population (14% for CTS without DPN, and 30% for CTS with DPN)[5].

Table 2 | Comparison of median nerve conduction studies of patients

	(MN–/DPN–)	(MN+/DPN–)	(MN+/DPN+)	(MN–/DPN+)
Distal latency (ms)	3.9 ± 0.4**†‡	5.1 ± 0.6**‖	5.4 ± 0.6†¶	4.3 ± 0.4‡‖¶
CMAP (mV)	6.6 ± 1.6**†‡	5.2 ± 1.5**	4.3 ± 1.4†	4.9 ± 1.7‡
MCV (m/s)	53.7 ± 2.7*†‡	51.8 ± 3.0*§§‖	47.1 ± 3.1†§§	48.7 ± 3.4‡‖
F-latency (ms)	26.0 ± 2.0*†‡	27.5 ± 1.8*§§	30.7 ± 3.0†§§¶	29.1 ± 2.8‡¶
SNAP (μV)	18.3 ± 5.5**†‡	10.4 ± 3.9**§§‖	4.1 ± 3.4†§§	5.8 ± 2.6‡‖
SCV (m/s)	54.7 ± 4.4**†‡	42.2 ± 2.9**§‖	39.3 ± 4.8†§¶	49.3 ± 4.7‡‖¶
Palm-latency (ms)	1.5 ± 0.1**†‡	2.1 ± 0.2**‖	2.3 ± 0.3†¶	1.7 ± 0.2‡‖¶

CMAP, compound muscle action potential; MCV, motor nerve conduction velocity; SCV, sensory nerve conduction velocity; SNAP, sensory nerve action potential. Data are expressed as mean ± standard deviation. *Patients without median neuropathy at the wrist (MN) or diabetic polyneuropathy (DPN; MN–/DPN–) and patients with MN without DPN (MN+/DPN–), $P < 0.05$; **(MN–/DPN–) and (MN+/DPN–), $P < 0.01$; †(MN–/DPN–) and patients with MN and DPN (MN+/DPN+), $P < 0.01$; ‡(MN–/DPN–) and patients with DPN without MN (MN–/DPN+), $P < 0.01$; §(MN+/DPN–) and (MN+/DPN+), $P < 0.05$; §§(MN+/DPN–) and (MN+/DPN+), $P < 0.01$; ‖(MN+/DPN–) and (MN–/DPN+), $P < 0.01$; ¶(MN+/DPN+) and (MN–/DPN+), $P < 0.01$.

Interestingly, the frequency of CTS increases after the diagnosis of diabetes in comparison with the rate of CTS before clinical diagnosis. This is because before diagnosis, exposure to hyperglycemia is generally shorter and less severe[11]. On the basis of these reports, we postulate that asymptomatic MN in patients who do not have DPN might be an early manifestation of diabetes. In the current study, compared with the MN and DPN group, the MN without DPN group comprised more patients in the early phase of diabetes (diagnosed within the past 5 years), and fewer patients with diabetic microangiopathy. The present results suggest that MN is found in the early phase of diabetes when DPN has not developed yet.

Although it is not conclusive that diabetes mellitus is a predisposing factor to CTS, the fact known as the "double crush" hypothesis[12], that the median nerve might become more susceptible to pressure effects in the carpal tunnel when underlying diabetic neuropathy is present[9], suggests it. However, CTS without DPN is found in 14% of patients with diabetes worldwide. Additionally, the severity of DPN does not associate with the prevalence of CTS among patients with diabetes[5,6]. Therefore, the double crush hypothesis might not completely account for the mechanisms underlying CTS in patients with diabetes.

Metabolic factors should also be considered when investigating entrapment syndromes in patients with diabetes[2]. Interestingly, glycemic control[13] and aldose reductase inhibitor (ARI) treatment[14] result in the improvement of nerve conduction velocities across the carpal tunnel. This suggests that the mechanisms of CTS in patients with diabetes result from the metabolic factors related to hyperglycemia. The major metabolic factors involved in diabetic neuropathy include activation of the polyol pathway and a decrease in Na^+-K^+ adenosine triphosphate (ATP)ase activity[15]. Both impaired Na^+-K^+ pump function by inactivation of Na^+-K^+ ATPase activity, and increased intra-axonal sorbitol concentration would cause intra-axonal Na^+ accumulation, leading to axonal edema[16]. Accumulation of intra-axonal Na^+ would decrease the Na^+ gradient across the axolemma, resulting in reduced Na^+ currents when generating an action potential[17]. ARI treatment increases nodal Na^+ currents and improves the slowing of nerve conduction across the carpal tunnel[18]. ARI treatment could then decrease the pressure of the carpal tunnel; this would be consistent with a lessening of axonal edema[18]. Thus, axonal edema could have a significant impact at common sites of entrapment in patients with diabetes.

DPN results from a complex interaction between functional nerve impairment mediated by metabolic factors directly related to hyperglycemia and structural changes, such as axonal degeneration and demyelination, caused by microangiopathy[15,19,20]. In NCS, diabetic neuropathy is characterized by the coexistence of nerve conduction abnormalities at common sites of entrapment and dying-back degeneration[21]. In the present study, median SNAP was relatively normal, and the degree of axonal dysfunction was milder in patients with MN without DPN than in those with MN and DPN. A slowing of nerve conduction across the carpal tunnel in patients with diabetes without DPN could principally be as a result of an impairment in axonal function. When comparing patients with MN without DPN with those with MN and DPN, the latter are considered dying-back axonal polyneuropathy, whereas the former might partly constitute the pathophysiology of diabetic neuropathy at common sites of entrapment. We speculate that metabolic factors related to hyperglycemia lead to axonal edema, and could contribute to median nerve compression at common sites of entrapment in the early phase of diabetic neuropathy.

Assessment of nerve conduction abnormalities across the carpal tunnel is difficult in patients with DPN, because MN and DPN might affect median nerve conduction in a similar manner. Electrodiagnostic criteria for the diagnosis of MN in patients with an underlying DPN have not been established. Several electrodiagnostic techniques have been proposed to determine MN in patients with DPN[7]. Comparative median-radial sensory nerve studies appear to be the most sensitive electrodiagnostic tests in the detection of MN in diabetic patients[21]. As routine nerve conduction tests were carried out

in the current study, prolongation of the difference in sensory onset latency between the palm to wrist and digit 2 to palm was used in the evaluation of MN. Therefore, many patients were excluded from the analysis to avoid complications caused by the inclusion of other neuropathies. Furthermore, we assessed polyneuropathy as a reduction of SNAPs in the median, ulnar and sural nerves. Patients with more severe symptoms were considered to have polyneuropathy.

At the point of diagnosis, DPN is generally identified by structural changes that are irreversible. Therefore, early detection of neuropathy is important to prevent the progression of DPN. Further investigations using a large sample size and sensitive electrodiagnostic tests will be required to elucidate the mechanisms of functional nerve impairment in patients with diabetes.

In conclusion, abnormalities in nerve conduction across the carpal tunnel are found in the early phase of diabetes at a time when DPN has not developed yet. Asymptomatic MN in patients with diabetes without DPN might be caused by an impairment in axonal function mediated by metabolic factors at common entrapment sites. These findings could be used as guidelines to assist in the identification of early manifestations of diabetic neuropathy.

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