Carpal Tunnel Syndrome in Patients With Diabetic Polyneuropathy

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OBJECTIVE — Carpal tunnel syndrome (CTS) and diabetic polyneuropathy (DPN) are common conditions in patients with diabetes and therefore frequently occur concomitantly. Diagnosis of CTS in patients with DPN is important, as therapeutic interventions directed toward relief of CTS may be effective irrespective of diffuse neuropathy. The prevalence of clinical CTS and the most efficient electrodiagnostic discriminators of CTS from diffuse neuropathy are uncertain.

RESEARCH DESIGN AND METHODS — A total of 478 subjects, including reference subjects (without diabetes and without neuropathy), nonneuropathic subjects with diabetes, and diabetic subjects with mild, moderate, and severe neuropathy, were evaluated in a cross-sectional design for clinical features of CTS. In the ascertainment of the cohort, a clinical stratification method was used to ensure a broad spectrum of neuropathy severity. All subjects underwent nerve conduction study determinations of median, ulnar, and sural nerve parameters.

RESULTS — The prevalence of clinical CTS was 2% in the reference population, 14% in diabetic subjects without DPN, and 30% in those with DPN. Multiple linear regression analysis revealed that mean electrodiagnostic parameters are not significant predictors of clinical CTS in patients with diabetes. Generally, the parameters worsened with severity of neuropathy, but none reliably distinguished diabetic patients with and without CTS.

CONCLUSIONS — Given the high prevalence of CTS in patients with DPN and that electrodiagnostic criteria cannot distinguish those with clinical CTS, it is recommended that therapeutic decisions for CTS be made independently of electrodiagnostic findings.

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Carpal tunnel syndrome (CTS) and diabetic polyneuropathy (DPN) are common conditions in patients with type 1 and type 2 diabetes (1,2). The prevalence of CTS is thought to be higher in patients with DPN (3–6) than in the general population, and the treatment less successful (2,7–10). Because the most accurate electrodiagnostic discriminator of the two conditions is unknown, the diagnosis of CTS in those with DPN is complex (7). Electrophysiological criteria designed to discriminate CTS in subjects with and without DPN are available, but their reliability is uncertain. The common practice is to apply nerve conduction study (NCS) criteria to diagnose CTS in diabetic subjects without DPN in the same manner as in the nondiabetic population.

Commonly applied criteria are a disproportionate increase of the median nerve latency compared with other upper-limb latencies; a difference in side-to-side median nerve conduction studies with more abnormality on the affected side, if clinical CTS is unilateral; and absent median nerve responses when other upper-limb responses are present (7). Another criterion is a difference in the distal sensory nerve conduction velocities such that the median nerve is <10 m/s compared with the ulnar nerve. However, these criteria for the diagnosis of CTS have generally been developed with the deliberate exclusion of subjects with both DPN and CTS, thus excluding a potential interaction effect on NCS measurements (11). In addition, therapeutic trials in DPN exclude subjects with CTS based on NCS criteria of uncertain reliability, calling into question the generalizability of results obtained from studies using these selected populations. The lack of reliable information on electrodiagnostic discriminators of CTS from DPN therefore has major implications in both clinical and research contexts.

The current study has two objectives: to estimate the point prevalence of clinical CTS in a population of subjects with diabetes and a broad spectrum of DPN severity, and to identify the most valid electrodiagnostic test for discriminating CTS from DPN in different stages of severity of DPN.

RESEARCH DESIGN AND METHODS

— The study was conducted at the Toronto General Hospital University Health Network (UHN) in the Diabetic Neuropathy Research Clinic from June 1998 to August 1999. Approval from the UHN Research Ethics Board was obtained before commencing the study.

Selection of patients

The inception cohort was ascertained from four different sources: unselected

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Abbreviations: CTS, carpal tunnel syndrome; DMMA, distal median nerve motor amplitude; DMML, distal median nerve motor latency; DMSA, distal median sensory amplitude; DMSCV, distal median sensory conduction velocity; DMSL, distal median sensory latency; DPN, diabetic polyneuropathy; DUMA, distal ulnar motor amplitude; DUML, distal ulnar motor latency; DUSA, distal ulnar sensory amplitude; DUSCV, distal ulnar sensory conduction velocity; DUSL, distal ulnar sensory latency; NCS, nerve conduction study; PMSCV, proximal median sensory conduction velocity; PMSL, proximal median sensory latency; SA, sural amplitude; SCV, sural conduction velocity; SL, sural latency; UHN, University Health Network.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Clinical stratification method*

Symptom scores	Reflex scores	Sensory test scores
Foot pain	Knee reflexes	Pinprick
Numbness	Ankle reflexes	Temperature
Tingling		Light touch
Weakness		Vibration
Ataxia		Position sense
Upper-limb symptoms		

Symptom scores graded as present = 1 or absent = 0 (numbness, tingling as perceived at toes and in feet). Reflex scores graded as absent = 2, reduced = 1, or normal = 0 for each side. Sensory test scores graded as abnormal = 1 or normal = 0. Maximum score is 19.

patients attending a diabetes clinic without known neuropathy status, patients referred to the Diabetic Neuropathy Research Clinic for suspected neuropathy, responders to advertisements in the community for patients with diabetes without known neuropathy status, and reference subjects (healthy volunteers without diabetes and without known neuropathy). Informed consent for the study was obtained from each subject.

Study protocol

All subjects underwent the following:

- A comprehensive medical and neurological evaluation in order to exclude neuropathy of other etiologies (e.g., familial, alcoholic, nutritional, and uremic) performed by the individual who obtained the informed consent.
- Carpal tunnel evaluation: specific clinical evaluation for CTS using generally accepted criteria (7,10). The presence of any four of the following six criteria established a diagnosis of CTS: history of paresthesia in hands and/or marked preponderance of sensory symptoms in the hands, nocturnal hand symptoms awakening patient, symptoms precipitated by activities such as holding a newspaper or driving a car and relieved by hand shaking, predilection for radial digits, weak thenar muscles, or upper-limb sensory loss solely within the distribution of the median nerve.
- Standardized bilateral NCS by three technologists blinded to the comprehensive medical and neurological evaluation, as well as the carpal tunnel evaluation. Counterpoint (Medtronic, Mississauga, Canada) was used for NCS in all patients. Standardized techniques for NCS with temperature control and fixed distances were applied. Measurements of latencies, distances, and amplitudes were done in a standard fashion using onset latencies and baseline-to-peak amplitudes, or for sensory curves using initial positive peak (if present) to negative peak measurements. Conduction velocities were calculated automatically by Counterpoint. The NCS included *1*) distal median nerve motor latency (DMML) and distal median nerve motor amplitude (DMMA) of the evoked motor response over the thenar muscles; *2*) distal median nerve sensory conduction studies, with distal latency (distal median sensory latency [DMSL]), distal median sensory amplitude (DMSA), and distal median sensory conduction velocity (DMSCV); *3*) proximal median nerve sensory conduction, with proximal latency (proximal median sensory latency [PMSL]), proximal amplitude (proximal median sensory amplitude [PMSA]), and proximal conduction velocity (proximal median sensory conduction velocity [PMSCV]); *4*) distal ulnar nerve motor conduction, with distal motor latency (distal ulnar motor latency [DUML]) and amplitude (distal ulnar motor amplitude [DUMA]) of the evoked motor response over the hypothenar muscles; *5*) distal ulnar nerve sensory conduction, with distal latency (distal ulnar sensory latency [DUSL]), distal ulnar sensory amplitude (DUSA), and distal ulnar sensory conduction velocity (DUSCV); and *6*) sural nerve latency (SL), sural amplitude (SA), and sural conduction velocity (SCV). All sensory nerve conduction studies were antidromic. The temperature of the limbs was controlled such that the minimum upper limb value was 32°C, and the lower limb value was 31°C. Low interobserver and intraobserver variability have been established for these measurements using the rigorous techniques described (12,13). The coefficients of variation for sensory nerve potentials are 11 and 16% in the upper and lower limb, respectively. For motor amplitudes, the values are 10 and 12% in the upper and lower limb, respectively. Motor nerve conduction velocities have a variation of 3% in upper and lower limbs, whereas sensory conduction velocities show 4–5% variation. These figures represent interobserver variability and interlaboratory variability from a 60-site study. These variances are the same for intraobserver variability within this laboratory.

In the presence of CTS, the expectation is that the DMML and DMSL are prolonged and the DMMA, DMSA, and DMSCV are reduced. The PMSL is prolonged, and the PMSCV and motor conduction velocity may be reduced. Other NCS parameters are normal. The ratios of median-to-ulnar or median-to-sural NCS parameters would change in the direction of the median nerve changes noted above. The degree of change in the NCS parameters depends on the severity of the CTS and the specific nerve fibers involved, as some patients primarily have motor impairments, whereas others mainly have sensory changes. Many patients have changes in both motor and sensory fibers.

Clinical stratification method

Subjects were graded as to neuropathy severity using six symptom scores, i.e., foot pain, numbness, tingling, weakness, imbalance, and upper limb symptoms, all as present or absent; eight reflex scores, i.e., bilateral knee and ankle reflexes, each graded as absent, reduced, or normal; and five physical examination scores, i.e., pinprick, temperature, light touch, vibration, and position sense, as present or absent, for a total of 19 possible points (Table 1). Assessment of numbness and tingling in this scoring system was referable to the toes and feet. The clinical sensory examination was done at the first toe bilaterally. Grading was stratified such that 0–5 indicated no neuropathy, 6–8 indicated mild neuropathy, 9–11 indicated moderate neuropathy, and ≥12 indicated severe neuropathy. The demographic data for the 478 participants are shown in Table 2. The presence of complications was determined by the history provided by the patient without further testing.

Table 2—*Demographic data for 478 subjects*

Variable	Reference	Diabetes			
Neuropathy status	None	None	Mild	Moderate	Severe
n (%)	52 (11)	81 (17)	94 (20)	109 (23)	134 (30)
Sex (% male)	46	68	65	75	65
Age (years)	37.6 ± 10.4	51.0 ± 10.8	56.8 ± 8.5	57.7 ± 10.1	57.0 ± 9.5
Type 1 diabetes (%)	N/A	19	13	13	20
Diabetes duration (years)	0	9.4 ± 9.9	11.2 ± 11.0	13.3 ± 10.7	15.8 ± 11.7
HbA_{1c} (%)	5.5 ± 0.04	8.3 ± 1.4	8.1 ± 1.9	8.0 ± 1.7	8.7 ± 1.6
Neuropathy duration (years)	N/A	N/A	2.9 ± 4.1	4.2 ± 4.3	5.1 ± 5.0
Clinical CTS (%)	2	14	31	23	34
Foot ulcer history (%)	0	0	9	27	64
Retinopathy (%)	0	11	10	20	36
Nephropathy (%)	0	18	14	25	43
Erectile dysfunction (% male)	1.9	27	43	56	49
Orthostatic hypotension (%)	0	9	16	27	28

Data are means ± SD unless otherwise indicated. NA, not applicable.

Statistical analyses

Ratios of electrophysiological parameters were calculated as follows: DMML-to-DUML, DMSL-to-DUSL, DMMA-to-DUMA, DMSA-to-DUSA, DMSCV-to-DUSCV, PMSCV-to-DMSCV, DMSL-to-SL, DMSA-to-SA, DMSCV-to-SCV, DMML-to-SL, and DMMA-to-SA. Statistical analyses were performed using Statview version 5.0 (SAS Institute, Cary, NC) for MacIntosh. The point estimates of clinical CTS were obtained by the proportion of patients with clinical CTS in a particular category. ANOVA was used to calculate the mean values of NCS parameters and ratios in different clinical groups. The multiple linear regression method, or method of generalized least squares, was used to determine whether CTS or DPN was the major determinant of the electrodiagnostic values in patients with clinical CTS. The analysis was repeated for different patient clusters: CTS + DPN, CTS − DPN, and no CTS regardless of DPN status.

RESULTS — Significant differences were observed among the defined clinical neuropathy strata in patient age (reference group as younger, $P < 0.0001$), in duration of diabetes (longer for more severe neuropathy, $P < 0.0001$), and in duration of neuropathy (longer for more severe neuropathy, $P < 0.0001$). Contingency table analyses revealed a significantly increasing prevalence of history of foot ulcer, retinopathy, nephropathy, and erectile dysfunction with stage of neuropathy, as previously described (14).

The frequency of clinical CTS was 2% in the reference stratum, 14% in nonneuropathic diabetic subjects, and 30% in those with DPN. The presence of CTS was related to the duration of diabetes such that those with CTS had diabetes for a mean of 14.0 ± 12.5 years compared with those without CTS who had diabetes for 10.8 ± 10.7 years. Metabolic control was not different in the two groups; both had a mean glycosylated hemoglobin value of 8.1% with an SD of 1.7 and 1.9%.

Table 3 shows a sampling of the electrodiagnostic results for the different clinical categories of subjects studied. Mean values in each category for those with and without CTS were not different other than the DMSA-to-DUSA for reference subjects. In this stratum, the subjects with clinical CTS had an abnormal ratio of DMSA-to-DUSA of ~1/2 that of those without CTS. All other parameters are the same in both groups. The reference population is limited in that only one subject had clinical CTS. Mean values for electrodiagnostic parameters tended to worsen with worsening neuropathy status, as shown by the changes in mean values of the different parameters in Table 3. Among patients with DPN, having CTS is not a major determinant of the outcome variables other than for DMML-to-SA. The significance of this finding is lost when the association is adjusted for clinical neuropathy stratum.

CONCLUSIONS — These results demonstrate that electrodiagnostic parameters in subjects with diabetes are not different in those with and without CTS, placing a limit on the value of NCS in the diagnosis of clinical CTS in these subjects. The assumption that the electrodiagnostic criteria for CTS are the same in diabetic subjects without DPN as in the general nondiabetic, reference population (7) is therefore misleading and can result in the inaccurate diagnosis of CTS in subjects with diabetes. The electrodiagnostic features for CTS in the reference population cannot be ascertained from this study, given that only 1 of 50 reference subjects had clinical CTS in this subgroup. An older reference population without diabetes might have more frequent CTS than observed in the younger reference population in this study. Cohorts of nondiabetic subjects with clinical CTS have been extensively studied in the past in order to evaluate the different electrodiagnostic parameters associated with clinical CTS (15,16).

The cross-sectional prevalence of clinical CTS in a mixed population of subjects with diabetes and varying degrees of DPN is remarkably high. Our finding of a point prevalence of 30% CTS in subjects with DPN is higher than in previous reports, although many studies report the prevalence of CTS in those with diabetes without considering the presence of DPN (7). Some of the difficulty in comparing series is that the diagnostic approaches for CTS are not uniform (7). More recently, Dyck et al. (2) reported the prevalence of symptomatic CTS in those with diabetes as 11 and 6% in type 1 and type 2 diabetic patients, respectively, but these are not subjects with DPN. The prevalence of

Table 3—*Electrodiagnostic results in different subject categories with and without CTS: sampling of electrodiagnostic variables assessed*

Category	*n*	Parameter						
		DMML	DMSL	DMSA-to-DUSA	DMSCV-to-DUSCV	DMSA-to-DSA	DMSCV-to-SCV	DMSCV-to-PMSCV
Reference patients								
No CTS	49	3.45 ± 0.56 (3.3, 0.5)	2.37 ± 0.32 (2.3, 0.3)	1.15 ± 0.38 (1.1, 0.3)	1.05 ± 0.13 (1.1, 0.1)	2.53 ± 1.05 (2.6, 1.3)	1.07 ± 0.14 (1.1, 0.2)	0.88 ± 0.10 (0.9, 0.1)
CTS	1	3.30 (3.3, N/A)	2.10 (2.1, N/A)	0.52 (0.5, N/A)	1.03 (1.0, N/A)	0.89 (0.9, N/A)	1.10 (1.1, N/A)	1.01 (1.0, N/A)
Diabetic patients without DPN								
No CTS	70	4.09 ± 1.09 (3.9, 0.9)	2.74 ± 0.64 (2.7, 0.5)	1.36 ± 0.69 (1.3, 0.7)	0.94 ± 0.22 (1.0, 0.2)	3.32 ± 2.33 (2.8, 2.6)	1.07 ± 0.20 (1.1, 0.2)	0.83 ± 0.15 (0.8, 0.2)
CTS	11	4.02 ± 1.26 (3.7, 0.9)	2.79 ± 0.71 (2.7, 0.7)	1.17 ± 0.47 (1.3, 0.8)	1.11 ± 0.25 (1.1, 0.2)	3.18 ± 1.86 (2.3, 3.0)	1.06 ± 0.18 (1.1, 0.1)	0.84 ± 0.12 (0.9, 0.1)
Mild DPN patients								
No CTS	65	4.45 ± 1.10 (4.1, 0.9)	3.13 ± 0.92 (3.0, 0.9)	1.46 ± 1.14 (1.1, 1.0)	0.93 ± 0.24 (1.0, 0.3)	3.18 ± 2.11 (2.3, 2.7)	1.06 ± 0.23 (1.1, 0.3)	0.80 ± 0.16 (0.8, 0.2)
CTS	28	4.25 ± 0.97 (4.0, 0.5)	2.85 ± 0.44 (2.9, 0.5)	1.32 ± 0.87 (1.1, 0.8)	0.98 ± 0.19 (1.0, 0.2)	4.19 ± 3.68 (2.7, 2.9)	1.08 ± 0.24 (1.1, 0.2)	.081 ± 0.14 (0.8, 0.2)
Moderate DPN patients								
No CTS	84	4.46 ± 0.90 (4.3, 0.9)	3.08 ± 0.75 (3.0, 0.8)	1.37 ± 0.90 (1.2, 0.8)	0.94 ± 0.19 (0.9, 0.2)	3.91 ± 2.96 (2.4, 3.2)	1.07 ± 0.21 (1.1, 0.3)	0.79 ± 0.15 (0.8, 0.2)
CTS	25	4.61 ± 0.84 (4.5, 0.9)	3.25 ± 0.60 (3.2, 0.8)	1.01 ± 0.60 (0.8, 0.9)	0.94 ± 0.22 (0.9, 0.4)	3.23 ± 2.54 (2.4, 2.8)	1.53 ± 0.25 (1.1, 0.4)	0.77 ± 0.11 (0.8, 0.2)
Severe DPN patients								
No CTS	92	4.45 ± 0.76 (4.7, 1.5)	3.10 ± 0.79 (3.1, 0.6)	1.67 ± 1.09 (1.5, 1.2)	1.00 ± 0.23 (1.0, 0.2)	4.07 ± 2.83 (1.3, 3.3)	1.14 ± 0.22 (1.1, 0.2)	0.86 ± 0.19 (0.9, 0.2)
CTS	48	4.96 ± 1.47 (4.3, 0.9)	3.17 ±1.18 (3.3, 0.8)	1.47 ± 1.22 (1.2, 1.2)	0.98 ± 0.35 (1.0, 0.3)	2.75 ± 1.95 (0.0, 2.2)	1.00 ± 0.24 (1.0, 0.4)	0.78 ± 0.16 (0.8, 0.2)

Data are means ± SD (median, interquartile difference) unless not applicable (NA) (one patient).

asymptomatic CTS in both type 1 and type 2 diabetes was considerably higher. The frequency of electrophysiological and clinical CTS in diabetic subjects with and without DPN demands an etiological explanation. It is hypothesized that the median nerve is made more susceptible to the pressure effects existing in the carpal tunnel when underlying DPN, a length-dependent axonopathy, is present. The anatomy of the carpal tunnel may produce local vascular compromise, which is superimposed on the metabolically disordered nerve or a nerve with established endoneurial ishemia, leading to frequent dysfunction in this short nerve segment. This combination of insults may result in impaired axonal transport (17), producing local pathology and retrograde nerve dysfunction.

A further implication of these results relates to the selection of subjects with DPN for research studies. Patients with clinical or electrophysiological criteria for CTS have commonly been excluded from clinical trials. The results of this study indicate that the presence of clinical CTS does not modify the electrophysiological measure of DPN. We therefore recommend that CTS criteria not be used as exclusion criteria in clinical trials using NCS as an outcome measure for DPN.

NCS has a clear role in determining the presence and severity of DPN (18,19) but does not reliably distinguish the presence or the absence of CTS in subjects with diabetes. Given the high prevalence of clinical CTS in subjects with DPN, it is recommended that therapeutic decisions in patients with clinical criteria for CTS should be made independently from NCS findings. Specifically, a trial of therapy should be strongly considered in patients with both diabetes and clinical CTS without undue reliance on electrodiagnostic results.

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