

Premotor Potential Study for Diagnosis of Carpal Tunnel Syndrome

Mitsuhiko KODAMA, Michi TOCHIKURA, Naoshi SHIMODA, Chieko FUJII,
Toshiyuki FUJIWARA and Yoshihisa MASAKADO

Department of Rehabilitation Medicine, Tokai University School of Medicine

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Introduction: The second lumbrical-interossei latency difference test (2LINT) is used frequently for electrodiagnosis of carpal tunnel syndrome (CTS). A premotor potential observed with 2LINT has been identified as a median-nerve sensory nerve action potential. We evaluated the utility of the premotor potential latency analysis (i.e., premotor potential study; PPS) for CTS electrodiagnosis.

Methods: Sensitivity, specificity, and percentage “no evoked response” (%NER) values were compared prospectively among PPS, median-nerve sensory nerve-conduction studies (NCSs) for digits 1, 2, and 4, and palmar mixed NCS.

Results: Sixty-four healthy control hands and 104 hands with CTS were enrolled in this study. PPS sensitivity was superior to other sensory/mixed NCSs (75% vs. 42%–62%). All NCS specificities were acceptable (95%–97%). The %NER of PPS was lower than that of other NCSs (13% vs. 25%–44%).

Conclusion: Premotor potential could be evoked in more CTS hands and was the most sensitive among median-nerve sensory and mixed NCSs. Therefore, we could use the 2LINT with PPS as median and ulnar motor NCS as well as median sensory NCS.

Key words: premotor potential study, carpal tunnel syndrome, nerve-conduction study, second-lumbrical-interossei study, differential diagnosis

INTRODUCTION

Carpal tunnel syndrome (CTS) is the most common entrapment neuropathy in humans. A number of electrodiagnostic tests are used for its diagnosis. The second lumbrical-interossei latency difference test (2LINT) is recognized as one of the most sensitive nerve-conduction studies (NCSs) for diagnosis of mild CTS, who had normal median-nerve motor distal latency [1–7]. It is also known as sensitive test for severe CTS cases when routine median sensory and motor NCSs produce no potentials [7–10]. When this study is performed, a premotor potential preceding the second-lumbrical (2L) compound muscle action potential (CMAP) can be recorded in response to median-nerve stimulation at the wrist. Several reports on the origin of this premotor potential have suggested that it is a sensory-nerve action potential (SNAP) derived from the median nerve’s second and third digital sensory branch fibers as they pass under the recording electrode at the palm [11–13].

It has also been suggested that analysis of premotor potential parameters (i.e., a premotor potential study or PPS) may be helpful for diagnosing CTS. In our previous study, we noted strong correlations between premotor potential latency and median-nerve sensory nerve-conduction velocities (SCVs) measured from the first, second, and fourth digits [14]. Therimadasamy *et al.* reported that combined measurement of premotor potential peak latency and 2LINT was as sensitive as routine NCSs for electrodiagnosis of CTS. However, that study was conducted on a relatively small number

of CTS hands, insufficient to elucidate the characteristic features of this premotor potential parameter and how it changes with CTS severity [15].

To use PPS for routine electrodiagnosis, both diagnostic sensitivity in mild CTS hands and the utility in severe CTS cases must be compared to standard sensory NCSs. In this study, we directly compared sensitivity, specificity, and non-response rates (i.e., percentage “no evoked response” values) among these NCSs in a large sample of control and CTS hands of widely varying severity.

MATERIALS AND METHODS

The present study was approved by the clinical research review committee of the Tokai University School of Medicine and was performed in accordance with the Declaration of Helsinki. Informed consent was obtained for all electrodiagnostic testing.

Participants

We prospectively studied healthy controls and consecutive patients with symptoms and signs suggestive of CTS. Patients were referred to the electromyography laboratory after clinical diagnosis of CTS was made on the basis of the presence of at least two of the following five criteria: (1) paresthesias of the hand, (2) hypesthesias in the median-nerve distribution of the hand, (3) intermittent wrist and palm pain, (4) isolated weakness and atrophy of the abductor pollicis brevis (APB), and (5) positive Tinel’s and/or Phalen’s signs [7, 14].

Controls were healthy volunteers with normal phys-

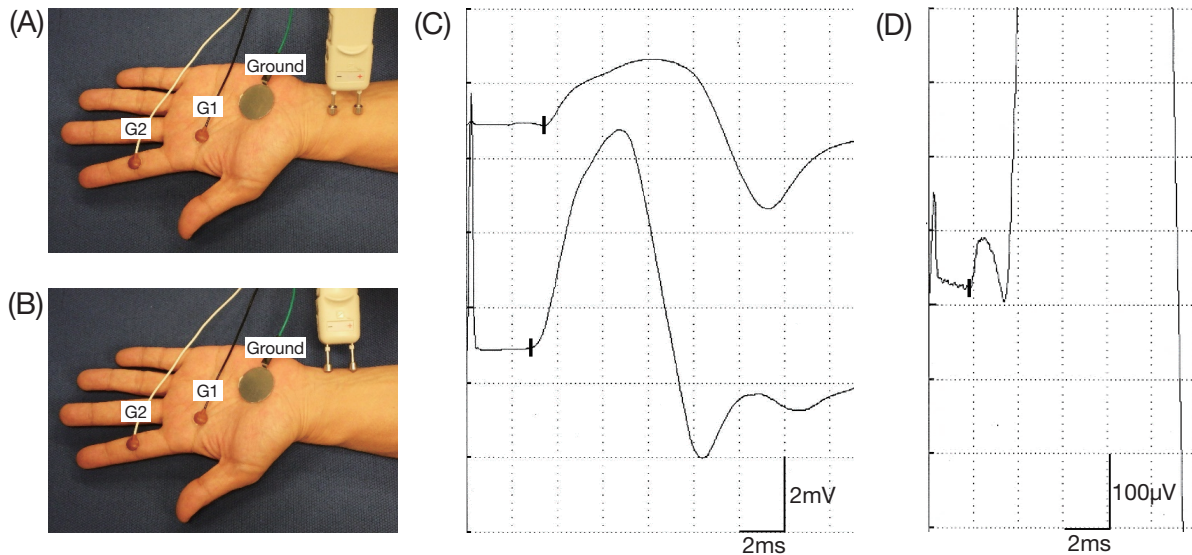


Fig. 1 The premotor potential study combined with the second lumbrical-interossei latency difference test. (A) Median nerve stimulation site, G1: active electrode, G2: reference electrode. (B) Ulnar nerve stimulation site (C) Representative waveforms of the second lumbrical-interossei latency difference test in a control hand. Top trace: second-lumbrical CMAP. Bottom trace: Interossei CMAP. (D) A representative waveform of premotor potential preceding second lumbrical CMAP.

ical examination findings and without neurological symptoms or signs suggestive of neuromuscular disorders.

Nerve conduction studies

The Neuropack MEB 2200 (Nihon-Koden, Tokyo, Japan) was used with a bandpass filter of 10–5000 Hz for acquisition of motor NCSs and 20–2000 Hz for acquisition of sensory and palmar mixed NCSs. Each action potential was evoked using 10-mm Ag/AgCl surface electrodes (NE-132B; Nihon-Koden, Tokyo, Japan) or ring electrodes (NM-450S; Nihon-Koden, Tokyo, Japan). Measurement sensitivity was between 2 and 5 mV/div for the motor NCSs and between 10 and 50 µV/div for the sensory and mixed NCSs as appropriate for the size of the response. Sweep time was 2 ms/div. The median, ulnar, and radial nerves were stimulated with 0.2-ms pulses delivered from a bipolar electrical stimulator. Latencies were measured from stimulus onset to the negative onset of each action potential waveform. Distances between stimulating and recording electrodes were measured using a flexible tape measure. Multiple responses were averaged (maximum of 20) if individual SNAPs or mixed-nerve action potentials were too small to be clearly resolved. An infrared heater was used to maintain hand and forearm skin temperatures at $\geq 32^{\circ}\text{C}$.

PPS could be recorded at the same time as the 2LINT, which was conducted according to the original method of Preston and Logigian [1, 2]. The median and the ulnar nerves were stimulated at the wrist 10 cm from the active electrode over the belly of the second lumbrical and interossei (slightly lateral to the midpoint of the third metacarpal) with the reference placed over the proximal interphalangeal joint of digit 2 (Fig. 1A and B). Sensitivity was initially set at 2 mV/div (Fig. 1C). When CMAP was detected in response to median-nerve stimulation, the sensitivity was changed by 100 µV/div to confirm the presence or absence of

the premotor potential (Fig. 1D). If it was present, the latency was measured as the delay between the stimulus and the onset of the potential [14]. The second-lumbrical CMAP latency (2LL) was determined carefully as the onset of the negative deflection from baseline following the premotor potential waveform. The onset latency difference between the second-lumbrical-interossei CMAP was calculated as an index of delay in median-nerve conduction due to CTS.

Median-nerve antidromic SNAP onset latency was obtained from digits 1 (M1L), 2 (M2L), and 4 (M4L) in response to median-nerve stimulation at the wrist 10, 14, and 14 cm proximal to each active recording electrode, respectively. For the palmar mixed NCS, the mixed-nerve action potential was recorded at the wrist using surface electrodes over the median nerve in response to stimulation of the palm 8 cm distal to the active electrode.

The following comparative and segmental NCS parameters were measured in all subjects to detect Minimal CTS (described as follows) according to procedures described in detail elsewhere [7]: median-nerve latency versus radial-nerve latency difference to digit 1, median-nerve latency versus ulnar-nerve latency difference to digit 4, and palmar mixed-nerve latency difference. The median-nerve segmental (wrist to palm) sensory latency was calculated by subtracting the antidromic SNAP latency obtained by palmar stimulation from M2L [16]. To detect the most severe cases of CTS, median-nerve motor distal latency (MDL) was also measured at 7 cm between the wrist and the active electrodes on the belly of APB. The reference electrode was placed on the tendon.

Neurophysiological classification

On the basis of neurophysiological classification [17], CTS hands were divided into six severity classes: Extreme, Severe, Moderate, Mild, Minimal, and Negative. Extreme CTS was defined by absence of

Table 1 Demographic and clinical characteristics of controls and patients with carpal tunnel syndrome

	Control	Patients			
		Mild	Moderate	Severe	Overall
No. of hands	64	31	44	29	104
Age (yr)	52 ± 15	49 ± 14	55 ± 14	61 ± 15*	55 ± 15
Male/Female	30/34	6/25	15/29	7/22	76
Right/Left	37/27	17/14	30/14	14/15	61/43

Age presented as mean ± standard deviation. *: $P < 0.05$ compared to controls and both Mild-CTS and Moderate-CTS subgroups.

Table 2 Nerve-conduction study (NCS) values in controls and patients with carpal tunnel syndrome

NCS	Controls	Normal limit	Patients			
			Mild	Moderate	Severe	Overall
Sensory and mixed NCSs						
PPS	1.8 ± 0.2	2.1	2.3 ± 0.4	3.2 ± 0.6	4.4 ± 0.9	3.1 ± 1.0
M1L	2.1 ± 0.2	2.5	2.6 ± 0.5	3.4 ± 0.7	3.8 ± 1.1	3.1 ± 0.8
M2L	2.6 ± 0.2	3.1	3.1 ± 0.5	4.0 ± 0.7	absent	3.7 ± 0.7
M4L	2.6 ± 0.2	3.1	3.4 ± 0.8	4.4 ± 0.8	6.3 ± 1.2	3.9 ± 1.1
MNL	1.5 ± 0.2	1.9	2.1 ± 0.5	2.8 ± 0.8	3.5 ± 1.0	2.5 ± 0.8
Motor NCSs						
2LL	3.2 ± 0.2	3.7	3.9 ± 0.7	5.2 ± 1.0	7.2 ± 1.6	5.4 ± 1.7
MDL	3.5 ± 0.4	4.3	3.8 ± 0.4	5.5 ± 1.0	7.5 ± 1.5	5.4 ± 1.7

Values are presented as mean (ms) ± standard deviation. Latencies were significantly prolonged in every CTS severity subgroup (Mild, Moderate, Severe) compared to controls ($P < 0.001$). Abbreviations: NCS, nerve-conduction study; PPS, premotor potential study; M1L, median-nerve digit-1 sensory action latency; M2L, Median-nerve digit-2 sensory latency; M4L, Median-nerve digit-4 sensory latency; MNL, median-nerve mixed-nerve latency; 2LL, second-lumbrical compound muscle action potential latency; MDL, median-nerve motor distal latency.

APB-motor and median-nerve digit-2 SNAPs, Severe by the absence of median-nerve digit-2 SNAPs and delayed MDL, Moderate by delayed MDL and M2L, Mild by delayed M2L and normal MDL, Minimal by normal M2L and MDL with abnormal comparative NCS parameters, and Negative as normal for all NCSs. Results from patients with Negative, Minimal, and Mild CTS were combined into the subgroup “Mild-CTS,” whereas results from those with Severe and Extreme CTS were combined into the subgroup “Severe-CTS.” The Moderate CTS patients constituted a separate subgroup.

Statistical analysis

For the NCS parameters of controls, normal limits were determined by the mean ± 2 standard deviations (SDs) if assumptions of normality and homogeneity were satisfied. Normality was checked using the Komolgorov-Smirnov 1-sample test and by histogram inspection. Sensitivity and specificity was calculated for each NCS. In the sensitivity calculation, if a NCS yielded no median-nerve response, we excluded it because the lesion was not specifically localized [6]. Consequently, the sensitivity of each NCS was calculated as (number of CTS hands with an abnormal study result without an absent response/total number of CTS hands) × 100. Specificity was calculated as (number of control hands with a normal test result/number of

control hands) × 100. The percentage of hands with no evoked response (%NER) was also calculated for each median-nerve NCS. The differences in NCS parameters between CTS patients and controls were assessed using the two-sample *t*-test or the equivalent nonparametric Mann-Whitney *U*-test. McNemar’s chi-square test was used to assess differences between paired categorical data. All statistical analyses were performed using IBM SPSS statistics Version 23 (IBM Corp., New York, USA) with statistical significance set at $P < 0.05$.

RESULTS

Demographic and clinical characteristics of participants are summarized in Table 1. Sixty-four hands from 38 healthy subjects were evaluated by NCSs. All NCS parameters, including PPS, were measurable and the distributions normal ($P > 0.05$). Mean values (± SD) and the normal limits of all NCSs are summarized in the left-most columns of Table 2. On the basis of these limits, 101 of 104 CTS hands (97%) exhibited NCS abnormalities. On the basis of neurophysiological criteria [17], three patients were classified as Negative and 13 with Minimal, 15 with Mild, 44 with Moderate, 22 with Severe, and seven with Extreme CTS. Two hands with abnormal MDL and normal M2L were classified as Moderate CTS because both hands had borderline abnormal M2L. Therefore, 31 hands with Negative to Mild CTS and 29 hands with Severe/

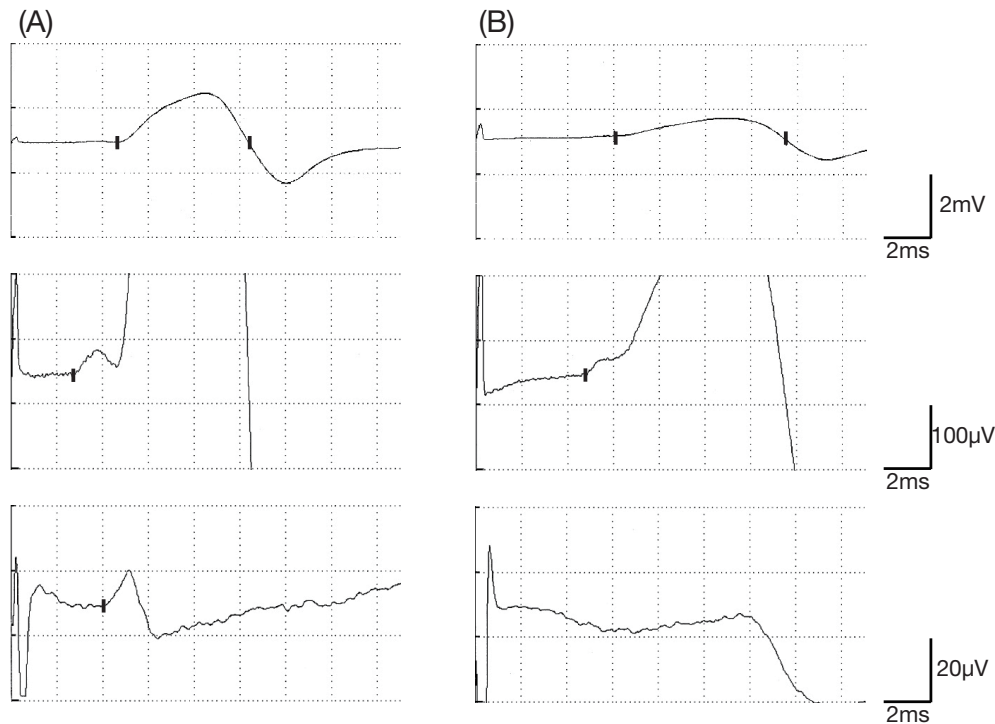


Fig. 2 Second-lumbrical CMAPs, premotor potentials and sensory nerve action potentials in CTS hands. (A) Mild CTS; (B) Severe CTS. Top traces: second-lumbrical CMAP, median nerve stimulation, recording from the second-lumbrical. Middle traces: premotor potential preceding second-lumbrical CMAP. Bottom traces: SNAP, median nerve stimulation, recording from digit 2.

Extreme CTS were combined separately into Mild-CTS and Severe-CTS subgroups. The large Moderate CTS cohort formed the Moderate-CTS subgroup. Sex ratio and handedness did not differ significantly among the control and CTS subgroups, whereas patients in the Severe-CTS subgroup were significantly older than in the control group ($P < 0.01$).

Representative waveforms of second-lumbrical CMAP, premotor potential and digit-2 SNAP recorded in patients with Mild and Severe CTS are shown in Fig. 2A and B, respectively. The onset latency of the premotor potential was prolonged and was progressively associated with CTS severity. In the Severe-CTS hand, no digit-2 SNAP was evoked. However, the premotor potential could be evoked from the same hand. The mean (\pm SD) NCS parameters of the three CTS subgroups and the total CTS group (Overall-CTS group) are summarized in the right-most columns of Table 2. Latencies were prolonged significantly in the total CTS group and all three subgroups compared to the control group ($P < 0.001$).

Table 3 presents the sensitivities and specificities of all NCSs. All had high specificity for distinguishing CTS patients from controls, ranging from 95% to 97%. In the Mild-CTS subgroup, the sensitivity of PPS was 58%, higher than that of M1L, M2L, and M4L, but lower than that of MNL. However, these differences did not reach statistical significance. In the Moderate-CTS subgroup, the sensitivity of PPS was significantly higher than that of M4L ($P < 0.001$). Sensitivity values were significantly higher for PPS than all-sensory and mixed NCSs in the Severe-CTS subgroup ($P < 0.05$) and the Overall-CTS group ($P < 0.05$). The %NER

values of all NCSs are shown in Table 4. The %NER for the premotor potential was significantly lower than that for the digit-4 SNAP in the Moderate-CTS subgroup ($P < 0.001$). The %NER values of the premotor potential in the Severe-CTS subgroup and Overall-CTS group were 45% and 14%, respectively, significantly lower than all sensory and mixed NCS %NER values ($P < 0.05$).

The second-lumbrical CMAP could be evoked in all CTS hands. The sensitivity of its latency was 87%, the highest of all-single NCSs (i.e., without comparative tests). The sensitivity of the 2LINT was 92% for the Overall-CTS group. However, two hands with prolonged premotor potential latency were still within the normal limits of 2LINT. Conversely, six hands with prolonged 2LINT had normal PPS latency. Thus, 98 of 104 hands (94%) were confirmed as CTS by the 2LINT with PPS, a slight increase compared to 2LINT alone.

DISCUSSION

This is the first study to assess the potential electrodiagnostic utility of the premotor potential preceding the second-lumbrical CMAP for CTS. In our entire cohort of CTS patients, the sensitivity of PPS latency was highest among all sensory and mixed NCSs tested, and PPS sensitivity was as high as all others in Mild-CTS subgroup. In addition, the premotor potential was the most frequently preserved of all median-nerve-evoked sensory and mixed action potentials. Further, our study protocol meets all six criteria recommended by the American Association of Electrodiagnostic Medicine Quality Assurance Committee [18]. Thus, these find-

Table 3 Sensitivity and specificity for all-nerve conduction study parameters

NCS	Sensitivity				Specificity
	Mild (n = 31)	Moderate (n = 44)	Severe (n = 29)	Overall (n = 104)	
Sensory and mixed NCSs					
PPS	58	100*	55**	75 [†]	97
MIL	52	89	24	60	97
M2L	48	95	0	55	96
M4L	55	57	7	42	95
MNL	65	84	24	62	97
Motor NCSs					
2LL	58	98	100	87	97
MDL	0	100	76	63	97

*: The sensitivity of PPS was significantly higher than that of M4L in the Moderate-CTS subgroup ($P < 0.001$).

**[†]: There were significant differences in sensitivity between PPS and MIL, M2L, M4L, and MNL in the Severe-CTS subgroup ($P < 0.05$) and the Overall-CTS group ($P < 0.05$). All abbreviations as in Table 2.

Table 4 Percentage “no evoked response” values for all-nerve conduction study parameters

NCS	%NER			
	Mild (n = 31)	Moderate (n = 44)	Severe (n = 29)	Overall (n = 104)
Sensory and mixed NCSs				
PPS	0	4*	45**	13 [†]
MIL	0	11	72	25
M2L	0	0	100	28
M4L	3	41	93	44
MNL	0	16	76	28
Motor NCSs				
2LL	0	0	0	0
MDL	0	0	24	7

*: The %NER of PPS was significantly higher than that of M4L in the Moderate-CTS subgroup ($P < 0.001$).

**[†]: There were significant differences in the %NER between PPS and MIL, M2L, M4L, and MNL in the Severe-CTS subgroup ($P < 0.05$) and the Overall-CTS group ($P < 0.05$). All abbreviations as in Table 2.

ings suggest that this premotor potential latency may be useful for clinical diagnosis of CTS.

Therimadasamy *et al.* also examined the diagnostic utility of the premotor potential and other 2LINT-associated parameters [15], but found that premotor potential peak latency was less sensitive than the median-nerve sensory-conduction velocity (SCV) for identifying CTS. In contrast, we observed a PPS sensitivity of 75% in the total CTS group, higher than that of M2L. A difference in premotor potential latency assessment method may account for this discrepancy. Our recent study revealed that the premotor potential measured over the palm is composed of SNAP arising from palmar sensory branches (i.e., a near-field potential) and a far-field potential generated by the median-nerve digital sensory branch fibers as they pass from the palm into digit 2 [13]. The far-field potential at the palm was

a negative deflection superimposed over the near-field potential. Thus, the peak latency may reflect not only the near-field conduction but also far-field potential component. We therefore suggest that onset latency of the premotor potential may be a clearer indication of median-nerve sensory branch fiber conduction.

It has been reported that the digit-2 sensory NCS is less sensitive than the digit-1 [19, 20] or digit-4 sensory NCS [21, 22]. This may be explained by considering the anatomy of the median-nerve within the carpal tunnel. Nerve fascicle innervating digit 1 and 4 lie, respectively, in the anterolateral and the anteromedial portions of the nerve beneath the transverse carpal ligament, where compression or ischemia occur frequently in the early stage of CTS. Alternatively, the fascicles to digit 2 lie at the posteromedial portion of the nerve, where it is preserved. In the present study,

M2L was the least sensitive among the sensory latencies in Mild-CTS subgroup. Although the premotor potential latency relates strongly to conduction of digit-2 sensory branch fibers [14], these measurements do not always have the same sensitivity. PPS was actually more sensitive than M1L and M4L, but these differences were not significant. PPS is more strongly dependent on changes at the carpal tunnel than M2L because of the shorter distance between stimulation and recording sites (10 cm from wrist to palm vs. 14 cm from wrist to digit). This could ameliorate the detection of conduction delays localized to the affected part of the median nerve (without changing the normal conduction of the unaffected part of the nerve between palm and digit 2).

We also investigated the sensitivity of median-nerve mixed-nerve latency (MNL) as a single-nerve conduction parameter [23]. MNL is advantageous for the diagnosis of CTS compared to PPS for two reasons. First, it is measured at a very short distance (8 cm). As mentioned above, this factor may be beneficial for the detection of localized nerve lesions (i.e., CTS) Second, mixed nerve action potential consists of both motor and sensory nerve fibers. The sensory nerve fibers carry the cutaneous sensory and muscle sensory fibers, including Ia afferents, which are the largest fibers and susceptible to demyelination in the earlier phase of CTS. Lew *et al.* also suggested that the coefficient of variance of MNL is smaller than that of other digital sensory NCSs in healthy controls [23]. Although MNL was slightly more sensitive than PPS in the current study, the difference was not statistically significant; thus, we suggest that MNL measurement has no substantial advantage over PPS.

The %NER of PPS was only 13% in the entire CTS cohort, lowest among NCSs without motor-nerve conduction studies, again advantageous for broad clinical use. Several factors may contribute to this high rate of preservation. Takahashi *et al.* reported that the premotor potential may arise from activity in median nerve's sensory fibers in digits 2, 3, and (sometimes) 4 [11]. The amplitude of SNAP, which is the sum of all-sensory fiber potentials, is large compared to each individual digit sensory response. Thus, the premotor potential waveform could remain even if sensory fiber responses are decreased because of conduction block and (or) axonal loss. In addition, the distance between the stimulation and the recording site is shorter than for other sensory NCSs. Even if conduction slowing occurs with CTS, the shorter distance would result in relatively less neurophysiological phase cancelation.

This study has a few limitations. We did not investigate a median-nerve digit-3 sensory NCS in patients with CTS. Existing evidence suggests that sensory fibers from digits 2 and 3 equally contribute to the premotor potential. Elucidating the precise source of this potential will help determine why it is so well preserved in CTS compared to other NCS parameters. Moreover, a study including a greater number of hands in Mild CTS subgroup may help define an order of priority for other NCSs after 2LINT + PPS.

We conclude that PPS may be beneficial for detecting abnormalities of median-nerve sensory nerve conduction in CTS hands. Therefore, the 2LINT with PPS could be used for median-nerve motor NCS, ul-

nar motor NCS, and comparative median-nerve versus ulnar motor NCS as well as median-nerve sensory NCS.

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