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## Agreement between Clinical Screening Procedures for Neuropathy in the Feet

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### Abstract

**Introduction**—The correlation between monofilament testing, symptom surveys and electrodiagnostic studies for the diagnosis of axonal polyneuropathy has not been well studied. This study was to assess the agreement between these procedures in a non-random sample of volunteers.

**Methods**—The evaluated procedures included electrodiagnostic tests of the sural nerve, monofilament testing of the great toe, a symptom survey and a body diagram. Kappa coefficients, sensitivity and specificity, using nerve conduction as a ‘gold standard’, were used to determine the agreement between various combinations of procedures.

**Results**—Poor agreement (Kappa values:  $-0.12 \sim 0.44$ ) and sensitivity (sensitivity < 30%) were found for all combinations of symptoms and monofilament results in comparison with sural peak latency and amplitude.

**Discussion**—Overall, the results demonstrated a low discriminatory power for the screening procedures for identifying persons with impaired sural nerve function. The results highlight the need for further development and evaluation of screening methods for distal neuropathy in population-based studies.

### Keywords

Nerve Conduction; Sural Nerve; Monofilament; Symptom; Agreement

## 1. Introduction

Peripheral neuropathy in the lower extremity is clinically important in the general population. Polyneuropathy can have a variety of causes, including exposure to toxins, metabolic disorders, or infection. The detection of mild peripheral neuropathy may require careful clinical examination and/or the use of electrodiagnostic testing. The American Academy of Neurology and others have offered consensus definitions of polyneuropathy<sup>1</sup>.

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Quick and accurate screening and clinical diagnosis rely on high sensitivity and specificity of the methods employed. The sensitivity and specificity of the techniques employed significantly affect the outcomes of clinical screening and are also important for epidemiological research of peripheral neuropathy in the lower extremity.

Several tools and procedures such as electrodiagnostic testing, quantitative sensory tests, physical examination procedures, body diagrams and symptom questionnaires have been employed for screening and epidemiological research of peripheral neuropathy. Each of these tools and procedures has strengths and weaknesses. Both electrodiagnostic testing and quantitative vibratory quantitative sensory tests are highly reproducible and complementary to each other<sup>2-4</sup>. However, the role of quantitative vibratory tests in diagnosis of distal neuropathy needs to be studied further<sup>1</sup>. The advantage of electrodiagnostic testing is that it provides an objective measure of peripheral nerve function, which clinical psychophysical examinations do not offer. Therefore, to detect peripheral neuropathy in the lower extremities, sural nerve conduction testing is considered to be an appropriate tool<sup>5</sup>. However, electrodiagnostic testing requires specific equipment and training for examiners.

The objective of this study was to assess the agreement between electrodiagnostic testing, monofilament testing, a lower extremity symptom survey and a body diagram in identification of possible peripheral neuropathy in the feet. The analysis for the assessment was carried out in a population of dental professionals.

## 2. Materials and Methods

Subjects were recruited during the Michigan Dental Association (MDA) annual conventions held in 2009 (n=232) and 2010 (n=283). They represented a convenience sample of dental professionals who attended the conventions and were recruited for a gene-environment study that investigated the relationship of nerve conduction tests with urinary and hair mercury biomarkers in dental professionals. Each participant signed a written informed consent approved by the University of Michigan Institutional Review Board (HUM00027621).

### 2.1 Electrodiagnostic Testing

Nerve conduction tests performed included amplitude, onset latency and peak latency of the sural nerve in the right ankle. We chose to only present results based on amplitude and peak latency, and not onset latency. The latter is highly correlated with peak latency, and measurement of peak latency tends to have better reliability than onset latency<sup>4</sup>. A TECA Synergy (Oxford Instrument, Hawthorne, NY) was used to record the amplitude and peak latency after stimulation was applied on the posterior aspect of the right calf, 14cm proximal to the standard recording electrode placed behind the lateral malleolus in the lower extremity. The temperature of the right midfoot was recorded at the time of measurement. Feet were warmed with electric heating pads if the limb temperature was initially below 32 °C. The peak latency (milliseconds-ms) was defined as the time required for an electrical stimulus to reach peak deflection from baseline of an action potential waveform. The amplitude (microvolts- $\mu$ V) was defined as the baseline-to-peak voltage difference of the waveform. We took the best supramaximal stimulation of several trials for our amplitude measurements. All parameters were recorded in accordance with the guidelines outlined by the American Association of Electrodiagnostic Medicine<sup>6</sup>.

### 2.2 Self-administrated Symptom Questionnaire and Body Diagram

Each subject completed a self-administered questionnaire to collect information on demographics and current symptoms of the lower extremities along with pre-existing diseases. If subjects reported any symptoms in their feet in the week prior to the survey, they were asked to report the duration of time they felt numbness and/or tingling in their feet in

the following format: < 6 weeks, 6–12 weeks, or > 12 weeks (Sx). Due to small numbers, the duration of symptoms was excluded from subsequent analyses.

Subjects also completed a self-administrated full-body symptom diagram. They were asked to shade areas where numbness, tingling, burning or pain had occurred more than three times, or had lasted more than one week in the previous six months. In this analysis, only areas at or below the right ankle were reviewed and scored independently by two raters for symptoms consistent with neuropathy in the feet. Any discrepancies were reconciled between the two raters through consensus. The results of body diagram symptoms (BDS) were classified into three categories with respect to symptom distribution consistent with neuropathy in the feet, including probable, possible, and unlikely (See Appendix for specific definitions). Symptoms consistent with neuropathy in the feet were defined in different ways using combinations of the body diagram and symptom questionnaire.

### 2.3 Monofilament Testing

The plantar surface of the great toe on the right foot was tested for peripheral sensation using a 5.07-gauge Semmes-Weinstein nylon monofilament (Wound Central, Aurora, IL) <sup>7</sup>. We chose one monofilament instead of all 20 monofilaments in order to simplify the data collection by minimizing the time spent on each subject and maximizing the sample size of the study. The 5.07-gauge monofilament has been shown to be the best predictor among all 20 monofilaments to determine the loss of protective sensation in the feet among diabetic subjects <sup>8</sup>. The use of a single monofilament resulted in a single outcome (“positive” or “negative”). Prior to the test, patients were asked to feel the monofilament on their fingertip. The monofilament was then applied up to three times to the right great toe with sufficient force to bend the filament. Patients were asked to indicate when a touch occurred. The test result was recorded as abnormal if a subject did not indicate a monofilament touch on two consecutive tries.

### 3. Statistical Analyses

Abnormal sural nerve function was defined by two separate criteria used by the University of Michigan Electroneuromyography Laboratory: 1) age-adjusted peak latency >4.1ms (20–60 years old) or >5ms (>60 years old); 2) age-adjusted amplitude  $\geq 6\mu\text{V}$  (20–60 years old) or  $\geq 5\mu\text{V}$  (>60 years old). In addition to age adjustment, the corrected peak latency was defined by adjusting to a standard temperature of 32 °C based on the following formula:  $\text{latency}_{\text{corrected}} = \text{latency}_{\text{initial}} - 0.3\text{msec} \cdot (32^\circ\text{C} - \text{temperature in } ^\circ\text{C})$  <sup>9</sup>. No temperature adjustment was applied to amplitudes, because in our data temperature was not a predictor of the sural amplitude in multivariate linear regression analysis (not shown). Due to missing values (n=56) for foot temperature, the sample size for peak latency was smaller than that for amplitude.

Since nerve conduction and monofilament tests were conducted only on the right foot, all analyses describe results only in the right foot. All analyses were performed using SAS 9.2 (SAS Institute, Inc. Cary, NC). Agreement of electrodiagnostic findings with symptoms consistent with neuropathy in the feet and monofilament results, respectively was assessed by kappa coefficients. Separate kappa coefficients were calculated for all subjects, diabetic subjects, and non-diabetic subjects. Kappa results were interpreted as excellent (>0.75), fair to good (0.40~0.75) and poor (<0.40) <sup>10</sup>. Pearson chi-square tests or Fisher exact tests were performed to assess the association of electrodiagnostic findings with symptoms consistent with neuropathy in the feet and monofilament results. Using sural nerve function (peak latency and/or amplitude) as the gold standard, sensitivity and specificity of various combinations of the other tests (body diagram, symptom questionnaire, and monofilament) were calculated. To reflect the clinical relevance of the nerve function as continuous

measurements, we also calculated the mean nerve function stratified by various combinations of the clinical tests discussed above. Normality tests showed the distributions were not normal for temperature- and age-adjusted peak latency (Shapiro-Wilk = 0.98;  $p < 0.0001$ ) and amplitude (Shapiro-Wilk = 0.94;  $p < 0.0001$ ). The mean amplitude and corrected peak latency were compared between test strata using non-parametric Mann-Whitney tests.

#### 4. Results

The prevalence of self-reported diabetes was approximately 4% (Table 1). Diabetic subjects were significantly older and had higher BMI than non-diabetic subjects. The proportions of positive findings for the various symptom criteria (Table 2) are shown in Table 3. Except for peak latency, the proportions of positive findings in the diabetic subjects were higher than those in the non-diabetic subjects. In general, the proportion of abnormal nerve function findings was usually higher than that of abnormal monofilament results.

The main results were summarized in Table 4. Overall, kappa values ( $-0.12$ – $0.44$ ) were mostly poor, sensitivity was low, and specificity was high. Monofilament testing appeared to perform slightly better than symptom surveys among non-diabetic subjects. Not surprisingly, results among diabetic subjects were somewhat better than among non-diabetic subjects. However, the number of diabetic subjects was small, so the confidence intervals tend to be broad, and none of the results achieved statistical significance. Chi-square test statistics and  $p$ -values showed that significant associations in all subjects occurred only in those combinations whose kappa values were among the highest. In Supplemental Tables 1–3, we also showed kappa values, sensitivity and specificity for the combinations of monofilament findings and symptom results in comparison with abnormal amplitude or peak latency, abnormal peak latency alone, or abnormal amplitude alone, respectively. We observed similar patterns in the low kappa coefficients, high sensitivity and low specificity.

Comparisons of means of nerve function between screening test strata were performed using Mann-Whitney tests (See Supplemental Tables 4–5). Given the small numbers, none of the means differed significantly for either sural amplitude or peak latency among diabetic subjects. Results for all subjects and for non-diabetic subjects were similar. The means of peak latency did not differ significantly for any screening outcome defined purely on the basis of the body diagram with or without symptoms. In contrast, the comparison of mean amplitudes differed significantly in the expected direction for the body diagram and for most combinations of the body diagram with symptoms. The mean peak latency among all subjects with a positive monofilament test (mean = 4.13 ms) was significantly greater than among those with a negative monofilament test (mean = 3.51 ms;  $p = 0.05$ ). Consistent with the latency results, the mean amplitude among all subjects with a positive monofilament test (mean = 6.71  $\mu$ V) was significantly lower than among those with a negative monofilament test (mean = 13.12  $\mu$ V;  $p < 0.0001$ ). Despite these differences, the overlap of the distributions of nerve test results when stratified by screening test outcome was considerable (See Supplemental Figures 1a–2b).

#### 5. Discussion

We assessed the agreement between electrodiagnostic testing results (sural nerve peak latency and amplitude), monofilament findings and symptoms consistent with neuropathy in the right foot of a non-random convenience sample of dental professionals. Overall, the low kappa coefficients showed poor agreement between electrodiagnostic tests and the other procedures. Kappa coefficients in diabetic subjects were somewhat higher than in non-diabetic subjects.

Using nerve conduction as the gold standard, the sensitivity and specificity of various combinations of the screening tests were mostly low and high, respectively. The results of mean differences in nerve function (See Supplemental Tables 4–5) revealed some significant differences, but the clinical utility of these differences may be limited by the observed considerable overlap of the distributions of ‘normal’ and ‘abnormal’ screening results. These results highlighted the potential influence of nerve function cutoff values and the potential importance of using nerve function as a continuous versus dichotomous outcome in comparing test procedures. Unlike some other clinical procedures that produce binary outcomes, nerve conduction is measured on a continuum. Peripheral neuropathy, defined by measured nerve function, is therefore a continuum. This might have had an impact on the results of poor agreement between the screening procedures, although the direction of such an impact was not clear. However, as was shown in Supplemental Figure 1, there was considerable overlap of the distributions of nerve conduction parameters among those with normal and abnormal screening test results based on monofilaments, body diagrams, or symptoms.

The study examined the agreement between different screening tools and procedures for neuropathy in the lower extremity in a non-random convenience sample of volunteers. A similar study that investigated such agreement in the upper extremity also reported relatively poor agreement between physical examinations, electrodiagnostic findings and symptoms consistent with carpal tunnel syndrome <sup>11</sup>. The results of the present study point to a need for further development and evaluation of the methods used to screen for neuropathy in the feet. The low prevalence of positive findings highlighted the challenge of developing a screening tool for peripheral neuropathy for use in non-clinical populations, because positive predictive value and negative predictive value are a function of prevalence, and not just sensitivity and specificity. Overall, the results demonstrated a low discriminatory power between the screening procedures for identifying persons with impaired sural nerve function in a non-random convenience sample of volunteers.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

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## Abbreviations

<b>BDS</b>	Body Diagram Symptom
<b>MDA</b>	Michigan Dental Association
<b>MF</b>	Monofilament
<b>Sx</b>	Symptom

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## Appendix

The criteria for defining neuropathy in the feet:

- 
- |   |          |  |
|---|----------|--|
| 2 | Probable | <ul style="list-style-type: none"> <li>• If both feet are entirely shaded</li> <li>• If a large portion of both feet, including all toes, is shaded</li> <li>• If all toes are shaded in both feet</li> </ul>  |
| 1 | Possible | <ul style="list-style-type: none"> <li>• If shaded areas include one or more but not all of the toes</li> <li>• If shaded areas include anywhere in the foot but not toes</li> <li>• If shaded areas include anywhere in the foot including toes</li> <li>• If one foot is fully shaded but the other foot has only partial shading</li> </ul> |
| 0 | Unlikely | <ul style="list-style-type: none"> <li>• If no shading anywhere on feet below ankle</li> </ul>   |

- If other non-lateral parts of foot are shaded; toes are not shaded
  - No shading anywhere on toes regardless of shading elsewhere
  - Shading present on only one foot
-

Table 1

## Demographic Characteristics of Subjects

	N	Overall	Diabetic (n=23)	Non-diabetic (n=492)	Men (n=197)
Age(years)	512	52.00	56.77 *	51.79 *	59.28
BMI(kg/m <sup>2</sup> )		26.41	29.15 †	26.29 †	26.91

\*  $P < 0.05$ ;†  $p < 0.0005$



**Table 2**

## Neuropathy Definitions from Results of Body Diagram Scores and Symptom Questionnaire

<b>Symptom Consistent with Neuropathy</b>	<b>Abbreviation</b>	<b>Definition</b>
Definition a: Body diagram score	BDS	Probable or possible body diagram score for neuropathy
Definition b: Body diagram score & numbness and/or tingling in feet	BDS & Sx	Probable or possible body diagram score for neuropathy and numbness and/or tingling in feet
Definition c: Body diagram score or numbness and/or tingling in feet	BDS or Sx	Probable or possible body diagram score for neuropathy or numbness and/or tingling in feet

**Table 3**  
Prevalence of Subjects with Positive Findings among All Subjects, Diabetic and Non-diabetic Subjects

	Total Subjects		Total Subjects with findings		Diabetic Subjects w/findings		Non-diabetic Subjects w/findings	
	Total Subjects	Diabetic subjects	Total Subjects with findings	%	Diabetic Subjects w/findings	%	Non-diabetic Subjects w/findings	%
<b>Temperature and Age-adjusted Nerve Conduction Test</b>								
Peak latency > 4.1 ms (or 5ms)	453	19	85	18.76	3	15.79	82	18.89
Amplitude <= 6μV (or 5μV)	491	20	50	10.18	4	20.00	46	9.77
Peak latency > 4.1ms (or 5ms) and amplitude <= 6μV (or 5μV)	453	19	16	3.53	2	10.53	14	3.23
Peak latency > 4.1ms (or 5ms) or amplitude <= 6μV (or 5μV)	491	20	119	24.24	5	25.00	114	24.20
<b>Symptom Consistent with Neuropathy in Feet</b>								
BDS	515	23	35	6.80	4	17.39	31	6.30
BDS & Sx	515	23	27	5.24	3	13.04	24	4.88
BDS or Sx	515	23	75	14.56	10	43.48	65	13.21
<b>Monofilament test</b>								
Monofilament test	501	21	17	3.39	3	14.29	14	2.92

Table 4

Agreement of Nerve Conduction with Symptoms and Monofilament Test Results

Symptom Consistent with Neuropathy in Feet	Overall							Diabetic subjects							Non-diabetic subjects						
	Simple Kappa coefficient (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	Pearson $\chi^2$	$\chi^2 p$ value	Simple Kappa coefficient (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	Fisher exact (one-tail) p	Fisher exact (two-tail) p	Simple Kappa coefficient (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	Fisher exact (one-tail) p	Fisher exact (two-tail) p	Simple Kappa coefficient (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	Fisher exact (one-tail) p	Fisher exact (two-tail) p	
BDS	0.10 (-0.05, 0.24)	18.75% (0, 0.38)	94.28% (0.92, 0.96)	4.52	<b>0.03</b>	0.44 (-0.21, 1)	50.00% (0, 1)	94.12% (0.83, 1)	0.20	0.20	0.06 (-0.07, 0.19)	14.29% (0, 0.33)	94.29% (0.92, 0.96)	0.16	0.20	0.06 (-0.07, 0.19)	14.29% (0, 0.33)	94.29% (0.92, 0.96)	0.16	0.20	
BDS & Sx	0.12 (-0.04, 0.27)	18.75% (0, 0.38)	95.42% (0.93, 0.97)	-	<b>0.04</b> <sup>1</sup>	0.44 (-0.21, 1)	50.00% (0, 1)	94.12% (0.83, 1)	0.20	0.20	0.08 (-0.07, 0.23)	14.29% (0, 0.33)	95.48% (0.94, 0.97)	0.12	0.14	0.08 (-0.07, 0.23)	14.29% (0, 0.33)	95.48% (0.94, 0.97)	0.12	0.14	
BDS or Sx	0.04 (-0.04, 0.13)	25.00% (0.04, 0.46)	85.81% (0.82, 0.89)	-	0.27 <sup>1</sup>	0.07 (-0.28, 0.42)	50.00% (0, 1)	64.71% (0.42, 0.87)	0.49	1	0.03 (-0.05, 0.12)	21.43% (0, 0.43)	86.67% (0.84, 0.90)	0.19	0.41	0.03 (-0.05, 0.12)	21.43% (0, 0.43)	86.67% (0.84, 0.90)	0.19	0.41	
Monofilament test (MF)	0.16 (-0.03, 0.34)	18.75% (0, 0.38)	97.02% (0.95, 0.99)	-	<b>0.02</b> <sup>1</sup>	-0.12 (-0.23, -0.003)	NA	88.24% (0.73, 1)	0.79	1	0.19 (-0.02, 0.30)	21.43% (0, 0.43)	97.37% (0.96, 0.99)	<b>0.007</b>	<b>0.008</b>	0.19 (-0.02, 0.30)	21.43% (0, 0.43)	97.37% (0.96, 0.99)	<b>0.007</b>	<b>0.008</b>	
BDS & MF	0.09 (-0.09, 0.27)	6.25% (0, 0.18)	99.31% (0.98, 1)	-	0.13 <sup>1</sup>	-	NA	NA	-	-	0.10 (-0.10, 0.30)	7.14% (0, 0.21)	99.29% (0.98, 1)	0.12	0.12	0.10 (-0.10, 0.30)	7.14% (0, 0.21)	99.29% (0.98, 1)	0.12	0.12	
BDS & Sx & MF	0.10 (-0.09, 0.28)	6.25% (0, 0.18)	99.54% (0.99, 1)	-	0.10 <sup>1</sup>	-	NA	NA	-	-	0.11 (-0.10, 0.32)	5.56% (0, 0.16)	99.52% (0.99, 1)	0.09	0.09	0.11 (-0.10, 0.32)	5.56% (0, 0.16)	99.52% (0.99, 1)	0.09	0.09	
BDS or Sx & MF	0.16 (-0.05, 0.37)	12.50% (0, 0.29)	98.86% (0.98, 1)	-	<b>0.02</b> <sup>1</sup>	-0.08 (-0.18, 0.03)	NA	94.12% (0.83, 1)	0.89	1	0.18 (-0.05, 0.42)	14.29% (0, 0.33)	99.05% (0.98, 1)	0.01	<b>0.01</b>	0.18 (-0.05, 0.42)	14.29% (0, 0.33)	99.05% (0.98, 1)	0.01	<b>0.01</b>	

<sup>1</sup> Fisher' exact p value is reported instead because the expected number of subjects in at least one of Chi-square 2x2 table cells is smaller than 5.

<sup>2</sup> Pearson Chi-square is reported instead because the expected number of subjects in all Chi-square 2x2 table cells is greater than 5.

<sup>3</sup> '-.' denotes the expected number of subjects in at least one of Chi-square 2x2 table cells is zero.

<sup>4</sup> 'NA' denotes that the expected number of subjects needed to calculate sensitivity or specificity is zero.

CI = Confidence Interval