AGREEMENT BETWEEN CLINICAL SCREENING PROCEDURES FOR NEUROPATHY IN THE FEET

YI WANG, PhD,[1] JACLYN M. GOODRICH, PhD,[1] ROBERT WERNER, MD,[3] BRENDA GILLESPIE, PhD,[2] NILADRI BASU, PhD,[1] and ALFRED FRANZBLAU, MD[1]

[1] Department of Environmental Health Sciences, School of Public Health, University of Michigan, M1835 SPH I, 1415 Washington Heights, Ann Arbor, Michigan 48109-2029, USA
[2] Department of Biostatistics, School of Public Health, University of Michigan, Ann Arbor, Michigan, USA
[3] Department of Physical Medicine and Rehabilitation, University of Michigan, Ann Arbor, Michigan, USA

Accepted 5 November 2011

ABSTRACT: *Introduction:* The correlation between monofilament testing, symptom surveys, and electrodiagnostic studies for the diagnosis of axonal polyneuropathy has not been well studied. This investigation was done to assess the agreement between these procedures in a non-random sample of volunteers. *Methods:* The procedures evaluated included electrodiagnostic tests of the sural nerve, monofilament testing of the great toe, a symptom survey, and a body diagram. Kappa coefficients and 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 −0.12–0.44) and sensitivity (sensitivity <30%) were found for all combinations of symptoms and monofilament results in comparison with sural peak latency and amplitude. *Conclusions:* 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.

Muscle Nerve **45:** 653–658, 2012

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.[1] Quick and accurate screening and clinical diagnoses rely on high sensitivity and specificity for 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 sensory tests are highly reproducible and complementary to each other.[2–4] However, the role of quantitative sensory tests in the diagnosis of distal neuropathy requires further study.[1] 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.[5] 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 the identification of possible peripheral neuropathy in the feet. The analysis for the assessment was carried out in a population of dental professionals.

METHODS

Subjects were recruited during the Michigan Dental Association (MDA) annual conventions held in 2009 ($n = 232$) and 2010 ($n = 283$). Participants were comprised of a convenience sample of dental professionals who attended the conventions and were recruited for a gene–environment study that investigated the relationship between nerve conduction tests and urinary and hair mercury biomarkers. Each participant signed a written informed consent document approved by the institutional review board of University of Michigan (HUM00027621).

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.[4] A TECA Synergy device (Oxford Instruments, Hawthorne, New York)

Abbreviations: BDS, body diagram symptom; MDA, Michigan Dental Association; MF, monofilament; Sx, symptom

Key words: agreement, monofilament, nerve conduction, sural nerve, symptom

Additional Supporting Information may be found in the online version of this article.

Correspondence to: A. Franzblau; e-mail: afranz@umich.edu

Published online 18 November 2011 in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/mus.23238

was used to record the amplitude and peak latency after stimulation was applied to the posterior aspect of the right calf, 14 cm 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 <32°C. The peak latency (milliseconds) was defined as the time required for an electrical stimulus to reach peak deflection from baseline of an action potential waveform. The amplitude (microvolts) 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.[6]

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: at <6 weeks; at 6–12 weeks; or at >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 >1 week in the previous 6 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.

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, Illinois).[7] 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.[8] 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 attempts.

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 >4.1 ms (20–60 years old) or >5 ms (>60 years old); and (2) age-adjusted amplitude ≤ 6 μV (20–60 years old) or ≤ 5 μV (>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: $\text{latency}_{\text{corrected}} = \text{latency}_{\text{initial}} - 0.3 \text{ ms} \cdot (32\text{-T})^{\circ}\text{C}$.[9] 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.

Because nerve conduction and monofilament tests were conducted only on the right foot, the analyses describe only those results for the right foot. All analyses were performed using SAS software, version 9.2 (SAS Institute, Inc., Cary, North Carolina). 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), or poor (<0.40).[10] 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

Table 1. Demographic characteristics of study 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^2)		26.41	29.15†	26.29†	26.91

*$P < 0.05$;
†$P < 0.005$.

Table 2. Neuropathy definitions from results of body diagram scores and symptom questionnaire.

Symptom consistent with neuropathy	Abbreviation	Definition
Definition a: Body diagram score	BDS	Probable or possible body diagram score for neuropathy
Definition b: Body diagram score and numbness and/or tingling in feet	BDS and 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

function stratified by various combinations of the clinical tests just noted. Normality tests showed that 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.

RESULTS

The prevalence of self-reported diabetes was approximately 4% (Table 1). Diabetic subjects were significantly older and had higher body mass index (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 higher than that of abnormal monofilament results.

The main results are 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 having kappa values that were among the highest. In Tables S1–S3 (see Supplementary Material), 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.

Table 3. Prevalence of subjects with positive findings among all subjects and for diabetic and non-diabetic subjects.

	Total subjects	Diabetic subjects	Total subjects w/ findings	Percent	Diabetic subjects w/ findings	Percent	Non-diabetic subjects w/ findings	Percent
Temperature and age-adjusted nerve conduction test								
Peak latency >4.1 ms (or 5 ms)	453	19	85	18.76	3	15.79	82	18.89
Amplitude ≤6 μV (or 5 μV)	491	20	50	10.18	4	20.00	46	9.77
Peak latency >4.1 ms (or 5 ms) *and* amplitude ≤6 μV (or 5 μV)	453	19	16	3.53	2	10.53	14	3.23
Peak latency >4.1 ms (or 5 ms) *or* amplitude ≤6 μV (or 5 μV)	491	20	119	24.24	5	25.00	114	24.20
Symptom consistent with neuropathy in feet								
BDS	515	23	35	6.80	4	17.39	31	6.30
BDS and 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
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.

	Overall					Diabetic subjects				
Symptom consistent with neuropathy in feet	Simple kappa coefficient (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	Pearson chi-square	Chi-square *P*-value	Simple kappa coefficient (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	Fisher exact (one-tailed) *P*-value	Fisher exact (two-tailed) *P*-value
BDS	0.10 (–0.05, 0.24)	18.75% (0, 0.38)	94.28% (0.92, 0.96)	4.52	**0.03**	0.44 (–0.21, 1)	50.00% (0, 1)	94.12% (0.83, 1)	0.20	0.20
BDS and Sx	0.12 (–0.04, 0.27)	18.75% (0, 0.38)	95.42% (0.93, 0.97)	—	**0.04***	0.44 (–0.21, 1)	50.00% (0, 1)	94.12% (0.83, 1)	0.20	0.20
BDS or Sx	0.04 (–0.04, 0.13)	25.00% (0.04, 0.46)	85.81% (0.82, 0.89)	—	0.27*	0.07 (–0.28, 0.42)	50.00% (0, 1)	64.71% (0.42, 0.87)	0.49	1
Monofilament test (MF)	0.16 (–0.03, 0.34)	18.75% (0, 0.38)	97.02% (0.95, 0.99)	—	**0.02***	–0.12 (–0.23, –0.003)	NA	88.24% (0.73, 1)	0.79	1
BDS and MF	0.09 (–0.09, 0.27)	6.25% (0, 0.18)	99.31% (0.98, 1)	—	0.13*	—	NA	NA	—	—
BDS and Sx and MF	0.10 (–0.09, 0.28)	6.25% (0, 0.18)	99.54% (0.99, 1)	—	0.10*	—	NA	NA	—	—
BDS or Sx and MF	0.16 (–0.05, 0.37)	12.50% (0, 0.29)	98.86% (0.98, 1)	—	**0.02***	–0.08 (–0.18, 0.03)	NA	94.12% (0.83, 1)	0.89	1

	Non-diabetic subjects				
Symptom consistent with neuropathy in feet	Simple kappa coefficient (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	Fisher exact (one-tailed) *P*-value	Fisher exact (two-tailed) *P*-value
BDS	0.06 (–0.07, 0.19)	14.29% (0, 0.33)	94.29% (0.92, 0.96)	0.16	0.20
BDS and Sx	0.08 (–0.07, 0.23)	14.29% (0, 0.33)	95.48% (0.94, 0.97)	0.12	0.14
BDS or Sx	0.03 (–0.05, 0.12)	21.43% (0, 0.43)	86.67% (0.84, 0.90)	0.19	0.41
Monofilament test (MF)	0.19 (–0.02, 0.30)	21.43% (0, 0.43)	97.37% (0.96, 0.99)	**0.007**	**0.008**
BDS and MF	0.10 (–0.10, 0.30)	7.14% (0, 0.21)	99.29% (0.98, 1)	0.12	0.12
BDS and Sx and MF	0.11 (–0.10, 0.32)	5.56% (0, 0.16)	99.52% (0.99, 1)	0.09	0.09
BDS or Sx and MF	0.18 (–0.05, 0.42)	14.29% (0, 0.33)	99.05% (0.98, 1)	0.01	**0.01**

Pearson chi-square is reported instead because the expected number of subjects in all chi-square 2 × 2 table cells is >5. Bold values indicate statistical significance. "—" denotes the expected number of subjects in at least one of chi-square 2 × 2 table cells is zero. "NA" indicates that the expected number of subjects needed to calculate sensitivity or specificity is zero. CI, confidence interval.
**Fisher exact P-value is reported instead because the expected number of subjects in at least one of chi-square 2 × 2 table cells is <5.*

Comparisons of means of nerve function between screening test strata were performed using Mann–Whitney tests (see Tables S4 and S5 in Supplementary Material). 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 μV) was significantly lower than among those with a negative monofilament test (mean = 13.12 μV; $P < 0.0001$). Despite these differences, the overlap of the distributions of nerve test results when stratified by screening test outcome was considerable (see Fig. S1 in Supplementary Material).

DISCUSSION

In this study 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 Tables S4 and S5 in Supplementary Material) 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 findings highlight the potential influence of nerve function cut-off values and the potential importance of using nerve function as a continuous versus dichotomous outcome in comparing test procedures. Unlike 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 may 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 shown in Figure S1 (Supplementary Material), 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.

In this study we 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.[11] The current results 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 highlights the challenge in 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 demonstrate a low discriminatory power between the screening procedures for identifying persons with impaired sural nerve function in a non-random convenience sample of volunteers.

This study was supported by a NIOSH training grant (T42 OH 008455-04) from the University of Michigan Center for Occupational Health and Safety Engineering and a grant (UL1RR024986) from the Michigan Institute for Clinical and Health Research. Y.W. was supported by the Michigan Risk Science Center Summer Fellowship and by funds from the Department of Environmental Health Sciences, School of Public Health, University of Michigan. J.G. was supported by a training grant (T32 007062) from the NIEHS Environmental Toxicology and Epidemiology. This research was approved by the institutional review board of the University of Michigan (HUM00027621).

REFERENCES

1. England JD, Gronseth GS, Franklin G, Miller RG, Asbury AK, Carter GT, et al. Distal symmetric polyneuropathy: a definition for clinical research: report of the American Academy of Neurology, the American Association of Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. Neurology 2005; 64:199–207.
2. Kincaid J, Price K, Jimenez M, Skljarevski V. Correlation of vibratory quantitative sensory testing and nerve conduction studies in patients with diabetes. Muscle Nerve 2007;36:821–827.
3. Bird S, Brown M, Spino C, Watling S, Foyt H. Value of repeated measures of nerve conduction and quantitative sensory testing in a diabetic neuropathy trial. Muscle Nerve 2006;34:214–224.
4. Salerno DF, Werner RA, Albers JW, Becker MP, Armstrong TJ, Franzblau A. Reliability of nerve conduction studies among active workers. Muscle Nerve 1999;22:1372.
5. Kimura J. Principles and pitfalls of nerve conduction studies. Ann Neurol 1984;16:415.
6. American Association of Electrodiagnostic Medicine. Practice parameter for electrodiagnostic studies in carpal tunnel syndrome: summary statement. Muscle Nerve 2002;25:918.

7. Herman W, Kennedy L. Underdiagnosis of peripheral neuropathy in type 2 diabetes. Diabetes Care 2005;28:1480–1481.
8. Feng Y, Schlsser F, Sumpio B. The Semmes Weinstein monofilament examination as a screening tool for diabetic peripheral neuropathy. J Vasc Surg 2009;50:675–682.
9. Tong H, Werner R, Franzblau A. Effect of aging on sensory nerve conduction study parameters. Muscle Nerve 2004;29:716–720.
10. Streiner D, Norman G. Health measurement scales: a practical guide to their development and use, 4th ed. London: Oxford University Press; 1994.
11. Homan MM, Franzblau A, Werner RA, Albers JW, Armstrong TJ, Bromberg MB. Agreement between symptom surveys, physical examination procedures and electrodiagnostic findings for the carpal tunnel syndrome. Scand J Work Environ Health 1999;25: 115–124.

APPENDIX

The criteria for defining neuropathy in the feet are as follows:

2—Probable
- If both feet are entirely shaded.
- If a large portion of both feet, including all toes, is shaded.
- If all toes are shaded in both feet.

1—Possible
- If shaded areas include one or more but not all of the toes.
- If shaded areas include anywhere in the foot but not toes.
- If shaded areas include anywhere in the foot including toes.
- If one foot is fully shaded but the other foot has only partial shading.

0—Unlikely
- If no shading anywhere on feet below ankle.
- If other non-lateral parts of foot are shaded; toes are not shaded.
- If no shading anywhere on toes regardless of shading elsewhere.
- If shading is present on only one foot.