Pittsburgh Epidemiology of Diabetes Complications Study

Measuring Diabetic Neuropathy Follow-up Study Results

RAELENE E. MASER, PHD
DOROTHY J. BECKER, MBBCH
ALLAN L. DRASH, MD
DEMETRIUS ELLIS, MD
LEWIS H. KULLER, MD
DOUGLAS A. GREENE, MD
TREVOR J. ORCHARD, MBBCH

OBJECTIVE — This project evaluated the utility of quantitative sensory techniques in predicting the development of neuropathy for subjects participating in a prospective study.

RESEARCH DESIGN AND METHODS — Distal symmetric polyneuropathy was evaluated in 77 insulin-dependent diabetes mellitus individuals via quantitative sensory testing, nerve conduction studies, and clinical examination.

RESULTS — Although the specificity and positive predictive value were low for the quantitative sensory techniques as predictors of neuropathy diagnosed on clinical exam ~2 yr later, the sensitivity for vibratory thresholds was high (100%). Variability over the 2-yr interval was shown on follow-up testing for each of the objective assessment modalities and it was not explained by differences for potential risk factors measured at baseline.

CONCLUSION — Despite a cross-sectional relationship between the assessment modalities and clinically overt neuropathy at baseline, these follow-up data suggest that the potential for the objective modalities as predictors of clinically diagnosed neuropathy may be limited.

The assessment modalities used in the determination of distal symmetric polyneuropathy (DSP) may include both objective (e.g., electrophysiological and/or quantitative sensory testing [QST]) and subjective (e.g., clinical exam) techniques. We have previously shown in a cross-sectional study that QST modalities (e.g., elevated vibratory [VT] and thermal [TT] thresholds) are associated with the presence of clinically overt neuropathy (CON) (1). In addition, many individuals were identified who had threshold levels outside the normal range but who had no clinical evidence of neuropathy. This report evaluates over a 2-yr follow-up period the variability of these techniques and their sensitivity, specificity, and positive predictive value (PPV) for CON in a cohort of individuals with insulin-dependent diabetes mellitus (IDDM).

RESEARCH DESIGN AND METHODS

— The study population, described previously (1), comprised 25- to 34-yr-old participants of the Epidemiology of Diabetes Complications Study who took part in a special neuropathy study at baseline (n = 168) and who attended follow-up. All participants without CON (n = 110) at baseline were asked to take part in the follow-up study. Seventy-seven individuals (42 men, 35 women) have participated (i.e., 70% response rate). The follow-up clinical exam and QST were not always performed at the same clinic visit, and thus the mean time interval between baseline and follow-up for the exam and for QST was 1.7 ± 0.4 and 1.9 ± 0.5 yr, respectively.

Clinical evaluation

CON was based on the clinical examination protocol used for the Diabetes Control and Complications Trial (2) and defined as having two of three criteria: symptoms, signs, or reduced reflexes. Blood pressure was measured according to a standard protocol (3), with hypertension defined as taking antihypertensive medication and/or a blood pressure >140/90 mmHg. Overt nephropathy was defined as an albumin excretion rate >200 μg/min in at least two of three urine collections. Details of the clinical evaluation have been previously reported (1,4).

FROM THE SCHOOL OF LIFE AND HEALTH SCIENCES, UNIVERSITY OF DELAWARE, NEWARK, DELAWARE; THE DIVISIONS OF ENDOCRINOLOGY AND NEPHROLOGY, DEPARTMENT OF PEDIATRICS, CHILDREN'S HOSPITAL OF PITTSBURGH, PITTSBURGH; THE DEPARTMENT OF EPIDEMIOLOGY, UNIVERSITY OF PITTSBURGH, PITTSBURGH, PENNSYLVANIA; AND THE DEPARTMENT OF INTERNAL MEDICINE, UNIVERSITY OF MICHIGAN, ANN ARBOR, MICHIGAN.

ADDRESS CORRESPONDENCE AND REPRINT REQUESTS TO RAELENE E. MASER, PHD, SCHOOL OF LIFE AND HEALTH SCIENCES, UNIVERSITY OF DELAWARE, NEWARK, DE 19716.

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Table 1—*Comparison of the efficacy of vibratory and thermal sensory threshold testing as predictors of clinically overt diabetic neuropathy*

	Follow-up		Sensitivity (%)	Specificity (%)	Predictive value (%)	Youden index
	Normal	Abnormal				
Baseline						
Vibratory threshold						
Normal	30	0	100	43	15	0.43
Abnormal	40	7				
Baseline						
Thermal threshold						
Normal	53	4	43	76	15	0.19
Abnormal	17	3				

Vibratory threshold (normal ≤2.20 vibration U, abnormal >2.20 vibration U. Thermal threshold (normal ≤2.23°C, abnormal >2.23°C).

Metabolic investigation

Details with regard to the methods used to determine HbA_1 and all lipid parameters have been reported (4).

Sensory threshold and nerve conduction studies (NCS)

VT (assessment modality of large sensory fibers) and TT (assessment modality of small sensory fibers) were measured with the Vibratron II and the Thermal Sensitivity Tester NTE-2 (Physitemp, Clifton, NJ), respectively. The forced-choice procedures for the determination of the thresholds and results with regard to repeat testing have been reported previously in detail (1,5). Interobserver variation performed for control subjects for VT (n = 5) and TT (n = 4) was 6 and 19% (based on log-transformed data), respectively. Cutoff points were determined with a reference range provided by the manufacturer of the QST instrumentation of a normal population of 18- to 65-yr-old individuals. NCS included peroneal motor conduction velocity (PMCV) and sural sensory conduction velocity (SSCV) (6). Only subjects who consented to have NCS performed at baseline were asked to have the procedure performed at follow-up (n = 34).

Statistical analyses

Univariate analyses for potential baseline risk factor differences included the χ^2 test, Student's t test, and analysis of variance, where appropriate. Youden's index was used as an estimate of the overall accuracy of each assessment modality to the clinical examination (7). Multiple logistic regression was used to examine the relationship between the binary dependent variable (CON) and the independent variables. Each full model was analyzed with backward stepping, in which nonsignificant variables leave the model and the coefficients for the remaining variables are recomputed.

RESULTS — During the 1.7-yr interval, 9% (n = 7) developed CON. Table 1 shows that the sensitivity, specificity, and PPV were low, with the exception of VT sensitivity. Similar results, with regard to sensitivity, specificity, and PPV, were obtained when comparing the VT and components of DSP (i.e., symptoms: sensitivity 67%, specificity 36%, PPV 5%; signs: 75, 45, and 17%, respectively; reduced reflexes: 83, 46, and 16%, respectively). Given the distribution of the data, a VT of 4 vibration U would appear to be a better predictive cutoff for the progression to CON with better screening characteristics (sensitivity 100%, specificity 73%, PPV 27%) than current normal-range cutoffs. Continued prospective follow-up of this cohort is needed to further examine this issue. The resulting Youden index of accuracy was better for the VT (0.43) than for the TT (0.19). Although ~50% of the cohort also had NCS performed, only two of such individuals developed CON, thus the sensitivity, specificity, and PPV are not presented.

Comparisons of those that developed CON (n = 7) with those who did not (n = 70) for potential differences in risk factors (e.g., age, duration, gender, HbA_1, lipids, smoking, and nephropathy status) measured at baseline, revealed diastolic blood pressure (82 vs. 72 mmHg, $P < 0.05$) and nephropathy status (71 vs. 17%, $P < 0.01$) to be statistically different between the two groups. Because nephropathy is associated with elevated blood pressure, the difference seen in blood pressure may simply be a reflection of the presence of nephropathy (there was no significant difference in blood pressure for those with nephropathy who had developed CON compared to those with nephropathy who had not developed CON [84 vs. 77 mmHg]). With multivariate analyses, nephropathy status (coefficient = 1.95, coefficient/SE = 1.998, $P < 0.05$) and VT (coefficient = 0.716, coefficient/SE = 2.503, $P < 0.01$) were statistically significant independent determinants of DSP.

Potential risk-factor differences were examined for those with progression of their thresholds or reduced conduction velocity (defined as >1SD of the group mean baseline measure), those whose thresholds or conduction velocity remained within ± 1SD of the group mean baseline value and those with regression (e.g., threshold value on follow-up was lower by >1SD from the group mean baseline measure). Essentially no risk-factor differences (e.g., blood pressure, lipids, HbA_1) were seen between the groups for any testing modality. However, 54% of those that showed regression of thermal thresholds (and 1 of 2 that showed progression) had nephropathy at baseline compared to only 12% of those with threshold values that remained within ±1SD of the group mean.

The highest rate of progression, based on the definition given above, was seen with SSCV (88%), whereas PMCV, VT, and TT showed rates of 18, 13, and 3%, respectively. Although there appeared to be no regression of disease as assessed by the SSCV, there appeared to be some regression as assessed by the other techniques (i.e., TT 16%, VT 9%, and PMCV 9%).

CONCLUSIONS — This follow-up study of an IDDM cohort aged 25–34 yr at baseline provided the opportunity to examine the sensitivity, specificity, and PPV of two assessment modalities and investigate potential risk-factor differences between those that did and did not develop CON. Although the poor PPV may reflect the short follow-up time, it appears that the VT is a better indicator of subsequent clinical neuropathy than TT. The low sensitivity for TT may reflect some of the difficulties that previously have been encountered with its use (e.g., high coefficient of variation on repeat testing) (1). Comparison of the VT and TT in terms of the Youden index, which assumes that a false negative and false positive result are equally important, revealed that the VT gave a more accurate estimate than TT.

In terms of the natural history of diabetic neuropathy, over half of the subjects that developed CON during the follow-up had overt nephropathy at baseline, and therefore it could indicate that nephropathy might be an underlying determinant in some subjects for the development of CON. A fairly high degree of variability (i.e., progression and regression) was seen for both QST and nerve conduction assessment modalities but the variability of these measures does not appear to be associated with potential risk factors measured at baseline. However, changes in unmeasured risk factors over time cannot be ruled out. Thus, the variability is likely to be a combination of measurement and biological variability that may limit the PV of these modalities. The QST measures and NCS, obtained at both baseline and follow-up, however, used the same type of instrumentation and were performed by personnel carefully standardized to each other. Until the components of this variability of QST techniques and NCS are better understood and controlled, the recommendation of using multiple modalities in the assessment of neuropathy is still warranted (8), and the place of TT and NCS as predictors of clinical disease remains uncertain.

Our conclusions are based on small numbers. Nonetheless, there is sufficient power to demonstrate an affect (e.g., 80% power to demonstrate a 5-fold risk for those with an abnormal VT). Therefore, the continued follow-up of this study cohort offers a unique opportunity to describe the natural history of diabetic neuropathy and the predictive power of these assessment modalities.

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