Approaches to Improve Epidemiological Studies of Diabetic Neuropathy

Insights from the Rochester Diabetic Neuropathy Study

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The quality of the epidemiological data on diabetic neuropathies remains poor for a variety of reasons. They include variability in *1*) ascertainment of diabetes, *2*) the clinical varieties of diabetic patients studied, *3*) characterization of neurological dysfunction, *4*) abnormal limits for neurological examinations and tests, *5*) minimal criteria for neuropathy, *6*) correct attribution of nondiabetic neurological disease, *7*) correct attribution of type of neuropathy, *8*) estimating neuropathy from use of multiple tests, and *9*) estimating severity of polyneuropathy. We have tried to remedy these shortcomings in the Rochester Diabetic Neuropathy Study (RDNS). It was not possible to adequately characterize and quantitate diabetic polyneuropathies using only one or two clinical or test abnormalities. To estimate severity of diabetic polyneuropathy, the results of the neurological examination and abnormalities of nerve conduction, quantitative sensory tests, and quantitative autonomic tests were combined into a composite score. One begins by scoring a standard test of neurological deficits (impairments) of the lower limbs (NIS[LL]) and adds to this transformed numbers for percentile abnormality of seven good functional tests. This NIS(LL)+7 tests score appears to provide a much more comprehensive and stable numeric score by which to diagnose and grade severity of diabetic polyneuropathy than does the use of individual clinical or test results. This test score should be useful as a measure of change in diabetic polyneuropathy for purposes of medical practice, epidemiology studies, and controlled clinical trials. The staging approach that we introduced previously continues to provide an important measure of overall severity of diabetic polyneuropathy, taking into account both symptoms and impairments. *Diabetes* 46 (Suppl. 2):S5–S8, 1997

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CMAP, compound muscle action potential; DCCT, the Diabetes Control and Complications Trial; DP, diabetic polyneuropathy; LL, lower limbs; MNCV, motor nerve conduction velocity; MNDL, motor nerve distal latency; NIS, Neuropathy Impairment Score; NSP, Neuropathy Symptoms Profile; RDNS, Rochester Diabetic Neuropathy Study.

Diabetic neuropathies undoubtedly represent major health problems for which improved prevention and treatment are needed. However, despite many scientific reports on diabetic neuropathies, much uncertainty, and even misinformation, exists about their frequency, classification, natural history, morbidity, mortality, and health and work outcomes, as well as the underlying mechanisms, risk factors, and optimal measures for prevention or treatment (1). The degree to which problematic degrees of polyneuropathy can be prevented is still unknown despite the recent convincing demonstration from the Diabetes Control and Complications Trial (DCCT) that with near euglycemia, fewer diabetic patients developed clinically evident polyneuropathy or nerve conduction abnormality than did the conventionally treated group (2–4). Because the severity of diabetic polyneuropathy was not estimated, the degree to which overt symptoms, neurological impairments, or poor outcomes were prevented was not estimated.

The reasons for the poor quality of epidemiological information about diabetic polyneuropathy (DP) are understood, at least in part, and can be remedied by well-designed and well-executed cross-sectional and longitudinal studies. The variability in the estimated frequency of diabetic neuropathies is attributable to at least nine reasons listed in the abstract and discussed below. Some of the most important reasons are lack of adequate characterization and quantitation of severity of neuropathic impairment using standardized instruments for which adequate reference values are available. To remedy this weakness, we have introduced several standardized questionnaires about symptoms: Neuropathy Symptoms Score (5), a tally of symptoms experienced by the patient from a standard list of symptoms and as abstracted from a physician's record that has questioned patients about these symptoms; Neuropathy Symptoms Profile (NSP; 6), a patient-completed standardized questionnaire read by optical reader and computer that converts responses into a series of scales of neuropathy (NSP-N), weakness (NSP-W), sensory (NSP-S), autonomic (NSP-A), and others and expresses each scale as a percentile based on study of a healthy subject cohort; and Neuropathy Symptoms and Change, a physician-completed standard questionnaire read by optical reader and computer that provides scores for number, severity, and change (as compared with a specific earlier date chosen by the physician) of symptoms. Analog scaling of pain from 1 to 10 is frequently used, but it reflects only one symptom—

pain. We have introduced the Neuropathy Disability (now called Impairment) score (NIS; 5) to provide an overall single number of neuropathic impairments as judged from a neurological examination of a standard group of muscles, reflexes, and sensory evaluations. A more limited evaluation of lower limbs (NIS[LL]) appears to be especially useful for study of DP. In a subsequent section, we describe how transformed numeric values of various functional tests can be added to NIS or NIS(LL) to obtain a composite score of DP (e.g., NIS[LL]+7 tests). Finally, we have proposed a staging approach (7) for severity of DP: N0, no polyneuropathy; N1, asymptomatic polyneuropathy; 2a, symptomatic polyneuropathy—the patient can carry his or her weight on heels; 2b, symptomatic polyneuropathy—the patient cannot carry his or her weight on heels; and 3, symptomatic polyneuropathy that is disabling.

REASONS FOR THE POOR QUALITY OF EPIDEMIOLOGICAL DATA

Variability in ascertainment of diabetes in the population studied. The incidence (number developing neuropathy per 100,000 population or per 1,000 diabetic patients) or prevalence (number who have neuropathy on a given date per 1,000 population or per 100 diabetic patients) depends on reliable estimates of the number of people in the population with diabetes and with various diabetic neuropathies. This is a major source of error. Patients with IDDM, because they are insulin deficient and require insulin for survival, need to see physicians and obtain insulin from pharmacies; therefore, their disease condition is known to health providers. Clinical recognition of patients with NIDDM, on the other hand, is a huge problem. The tests used to make the diagnosis (fasting plasma glucose, glycated hemoglobin, glucose tolerance test, under what conditions, and how often repeated) and the specific criteria that are adopted have a large effect on epidemiological results. Thus, only 84% of Rochester, Minnesota, residents considered to have diabetes at the Mayo Clinic in 1945–1969 met more recent National Diabetes Data Group (National Diabetes Data Group 1979) criteria for diabetes (8,9). This change to more stringent diagnostic criteria reduced the number of diabetic patients and would likely have increased the relative frequency of DP. Conversely, inclusion of milder degrees of glucose intolerance would have the opposite effect. In many studies, the criteria for diabetes are not even provided.

Variability in the clinical spectrum of diabetic varieties studied. Differences in diagnostic criteria for diabetes also influence the resulting clinical spectrum. In the example above, the change to more stringent National Diabetes Data Group criteria, by deleting the mild or borderline cases, caused the median fasting blood glucose value at the time of diagnosis to rise from 150 to 169 mg/dl and the proportion of patients on insulin treatment to increase from 20 to 24% (8). Even in a population-based study with fixed diagnostic criteria, there are substantial differences in the characteristics of patients at the onset of diabetes (incidence cases) and those who survive to a later time (prevalence cases). For example, at the time of first diagnosis of diabetes, only 6.3% of patients had some evidence of microvascular disease, compared with 26% of all patients assessed later (9). The situation is even worse when patients are systematically sampled from different clinical settings. Compared to the 26% prevalence of microvascular disease among diabetic community residents generally, the prevalence was 34% among those who were attended in the diabetes clinic and 40% among the subset of patients who were hospitalized in the previous year (10). All of these trends are exaggerated among diabetic patients attending tertiary referral centers. Groups of patients reported from accession cases referred to diabetes centers or evaluated in transplant centers, dialysis units, ophthalmology clinics, or neuromuscular clinics represent highly biased patient series.

Variability in assessment of DP. In most prevalence studies, investigators based the diagnosis of neuropathy on one (or a few) endpoint measurements, e.g., decreased or absent ankle reflex, decreased vibration sensation, or abnormal nerve conduction. Unfortunately, none of these markers is an adequate representation of DP, which is the sum of the symptoms, dysfunctions, and impairments of sensory, autonomic, and motor nerve fibers. Use of different neuropathy assessments having different and unknown sensitivities, specificities, reproducibilities, or accuracies makes it difficult to compare the results of one series of diabetic patients with other series.

Variability in abnormal limits for tests. There may be large differences in the adequacy of the healthy subject cohort used for estimating normal limits, the methodology of setting abnormal limits, and the limits chosen as abnormal (11,12). These choices have a large influence on the frequency of the different types of diabetic neuropathy. As we discuss in the publications cited above, it is not correct to set an abnormal limit based on a given (e.g., 2) standard deviation from the mean, particularly when a small sample of unrepresentative healthy people is used as a reference population.

Variability in minimal criteria for diabetic neuropathies. One of the major sources of variability in the reported frequency of diabetic neuropathies relates to variability in the criteria used to diagnose each variety of diabetic neuropathy. Pirart (13), for example, used absent ankle reflexes and decreased vibratory perception as the diagnostic criteria for DP, without reference to control subjects or correction for age. This probably led to overestimation of polyneuropathy, since a sizable number of healthy people lose ankle reflexes and vibration sensation in old age. Quite different results may be obtained if abnormality of nerve conduction decrease, variability of heartbeat with deep breathing, or increased vibratory detection threshold is used. In the Diabetes Control and Complications Trial, neurologists judged whether "evident polyneuropathy" was present, absent, or questionably present. This judgment by neurologists was sufficiently accurate to recognize a difference between intensively and conventionally treated patients. Unfortunately, it is unclear what severity of polyneuropathy the term "evident polyneuropathy" encompasses, since this is a dichotomous, not a continuous, quantitative assessment of severity.

Variability in correct attribution of nondiabetic neurological disease or neuropathies. If all, or most, concurrent neurological disease is tallied as DP, its frequency would be spuriously increased. Undoubtedly, this is a further reason for inaccurate epidemiological data. A confounding neurological disease occurred in 2% of IDDM and 7% of NIDDM patients in the RDNS (14). In these patients, it was not possible to determine the extent to which the polyneuropathy was attributable to the coexisting disease. If these coex-

isting neurological abnormalities had been spuriously attributed to DP, the prevalence of DP would have been erroneously increased by about 5%.

Variability of assignment into varieties of diabetic neuropathy. There is considerable heterogeneity of peripheral nerve involvement in diabetes (1). This heterogeneity probably represents different disorders, perhaps involving different underlying mechanisms. It seems reasonable to divide diabetic neuropathies into the following varieties: DP, proximal diabetic neuropathy, truncal radiculopathy, diabetic mononeuropathies (e.g., carpal tunnel syndrome and tardy ulnar palsy), diabetic oculomotor neuropathy, and perhaps others (e.g., diabetic autonomia, a painful sensorimotor neuropathy associated with weight loss, and hypoglycemic neuropathy). Inclusion of different types of diabetic neuropathy with DP, for example, results in a variable estimate of the frequency of DP.

Variability due to estimating frequency from any abnormality of multiple measurements. Just by chance alone, a spuriously high percentage of a cohort would be declared to have polyneuropathy if any abnormality of multiple measurements were used for diagnosing diabetes. If one measurement is used and ≥95th percentile is used for abnormality, 5% would be declared abnormal by chance. This percentage increases to 20% if any abnormality of 5 multiple tests is the basis of abnormality and to 36% if any of 25 tests are the basis of abnormality. This error is common in previously reported series of diabetic patients.

Variability in estimating overall severity of DP. Failure to assess the severity of DP is a major shortcoming in most of the published cohorts of diabetic patients. It is not sufficient to simply tally the number of diabetes patients with neuropathy; what is needed is the spectrum of patients with different degrees of symptoms (by kind and severity) and of dysfunction and impairment of sensory, autonomic, and motor neurons. It is simply not sufficient to equate one patient's polyneuropathy (diagnosed by one abnormal attribute of nerve conduction) with another patient's polyneuropathy consisting of severe symptoms, neuropathic impairments, and bad outcome. This subject will be discussed in greater detail below.

THE RDNS

Design issues. We have attempted to circumvent the problems summarized in the preceding section by performing a cross-sectional and longitudinal study (RDNS) of diabetic patients who were willing to participate from Rochester, Minnesota (15). We used the resources of the Rochester Epidemiology Project to identify every clinically recognized case of diabetes among the residents of Rochester, Minnesota. For reasons that we have outlined elsewhere, we believe we have been able to identify most of the diabetic patients in this town. We approached all 870 Rochester, Minnesota, residents who met National Diabetes Data Group criteria for diabetes on January 1, 1986, but we obtained complete study data on only 44% because many subjects did not want to spend the necessary time to be evaluated and some were in poor health or unable to provide informed consent. Compared with those who participated in the study, the nonresponders were older and more likely to have cardiovascular disease, dementia, or cerebrovascular disease (16). Fortunately, based on comparable medical record review of the two groups, the respondents and nonrespondents less than 70 years old had a similar co-morbidity.

In the RDNS, we base our judgment of whether the patient has DP on use of standard quantitative evaluations of symptoms, neuropathic impairments, nerve conduction, quantitative sensory tests, and quantitative autonomic tests and derive percentile responses specific for test, age, sex, and physical variables based on comparison to reference values from a healthy subject cohort (HS-RDNS) (12) drawn from the same geographic region but screened to exclude patients with neurological disease or neuropathy (11,12). In addition, we validated our criteria for the diagnosis of DP by comparison to neuropathological and morphometric study of sural nerve (17). The five evaluations used are the ones recommended by the San Antonio Conference (18).

The study has provided confirmation of many insights coming from surveys of diabetic patients of other investigators (19–28) and has provided some new insights. More than one-half of the cohort had evidence of neuropathy, with the most common variety being DP. Only 13% of patients with DP were symptomatic. The spectrum of stages of severity is more severe for IDDM than for NIDDM patients. Six percent of IDDM patients had stage 2b (unable to walk on heels) DP, whereas only 1% of NIDDM patients had this stage of abnormality.

Assessing the severity of DP. Because DP comprises sensory, autonomic, and motor symptoms and impairments, it is necessary to use standard and continuous measures of these manifestations, compare them with reference values, and summate all abnormalities into a composite score.

The NIS(LL)+7 composite score. For epidemiological and controlled clinical trials of DP, the NIS alone may not be a sufficiently robust measure of severity of polyneuropathy because electrophysiological dysfunction, quantitative sensory loss, and quantitative autonomic deficits are not included. In designing a composite score, we assume that *1*) most impairments in polyneuropathy are of the lower limb and that upper limb abnormality should not be included because of possible contamination from abnormalities due to carpal tunnel syndrome or cubital tunnel syndrome; *2*) suitable transformations to summate abnormality from different measurements will be needed; *3*) weighting of the contribution of the various tests to the composite score will be needed; and *4*) longitudinal data of a representative diabetic cohort, such as the RDNS, can provide information about the clinical evaluations and tests that provide the greatest monotone and magnitude of change for use in such a composite score. Below, we show how one derives an NIS(LL) + 7 tests score. If reference values are available, one can use similar composite scores for small-diameter function or for large-diameter function.

- Sum individual scores of the NIS for the lower limbs, NIS(LL).
- In NIS(LL), substitute transformed points for percentile abnormality (<95th = 0, ≥95th–99th = 1, ≥99th–99.9th = 2, and ≥99.9th = 3) of VPT (vibration perception threshold) for each great toe (obtained with CASE IV) for clinical vibration sensation of great toes.
- Add transformed points for percentile abnormality (<95th = 0, ≥95th–99th = 1, ≥99th–99.9th = 2, and ≥99.9th = 3) of heart beat deep breathing (HB DB) (1 × only).
- Add the summated (Σ) transformed points for percentile

abnormality (<95th = 0, ≥95th–99th = 1, ≥99th–99.9th = 2, and ≥99.9th = 3) of the five best attributes of nerve conduction of lower limb: peroneal nerve (compound muscle action potential [CMAP], motor nerve conduction velocity [MNCV], and motor nerve distal latency [MNDL]), tibial nerve (MNDL), and sural nerve (sural sensory nerve action potential [S SNAP]).
- Σ points (for percentile abnormalities) of 5 nerve conduction (NC) attributes divided by number of attributes with obtainable values (MNCV and MNDL cannot be estimated when CMAP is 0), times 5.

The use of composite scores such as the NIS(LL) + 7 in medical practice, epidemiology studies, and controlled clinical trials has several advantages over the use of disparate individual endpoint measurements. It provides one number for a comprehensive assessment of the neurological abnormalities and major test abnormalities. It can be used not only to set abnormality as a percentile (e.g., 95th, 97.5th, or 99th) considering reference values, but also to provide a broad range of values in the disease range to scale severity. It avoids overestimation of disease due to the error of multiple measurements. Compared with individual endpoints, this composite score shows a greater degree of monotone worsening with magnitude in longitudinal trials of diabetic patients. These favorable characteristics make it a useful measurement to use for studies of longitudinal change, for risk factor analysis, and for controlled clinical trials.

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