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Simplification of the Research Diagnosis of HIV-Associated Sensory Neuropathy

Scott R. Evans¹, David B. Clifford², Douglas W. Kitch¹, Karl Goodkin³, Giovanni Schifitto⁴, Justin C. McArthur⁵, and David M Simpson⁶

¹Harvard School of Public Health, Boston, Massachusetts, USA

²Washington University, St. Louis, Missouri, USA

³Cedars-Sinai Medical Center and the University of California at Los Angeles, California, USA

⁴University of Rochester, Rochester, New York, USA

⁵Johns Hopkins University, Baltimore, Maryland, USA

⁶Mount Sinai School of Medicine, New York, New York, USA

Abstract

Peripheral neuropathy (PN) is the most common neurological complication of HIV infection, affecting over one third of patients. The research diagnosis of PN is complicated by the need for expensive, time-consuming, and noxious diagnostic tests. We investigated whether nerve conduction studies (NSC) and quantitative sensory tests (QST) provide added value for the diagnosis of PN for research purposes or whether the easily obtainable clinical measures (sensory and motor symptoms, sensitivity to pain and vibration, tendon reflexes, motor function) are sufficient.

Keywords

nerve conduction; peripheral neuropathy; quantitative tests; sensory neuropathy

In the HAART era, sensory neuropathies (SN) have increased in prevalence to become the most common neurological disorders associated with HIV infection.^{1,2} The two most common types of SN in HIV-infected patients are HIV-associated distal sensory polyneuropathy (DSP) and antiretroviral toxic neuropathy (ATN), which together affect 30%–67% of subjects with advanced HIV disease.^{3–5} Risk factors in the HAART era have been investigated.^{6–10} The symptoms and signs of HIV-associated SN (HIV-SN) closely resemble some of the most common neuropathies encountered in clinical practice, including diabetic and alcohol associated neuropathy. Ellis et al. has reported the performance characteristics of a brief peripheral neuropathy screening instrument and Ebenezer et al. has investigated the use of epidermal nerve fiber density (ENFD) as a diagnostic tool.^{11,12} A case definition of DSP for clinical research has been proposed,¹³ although the definition was primarily based upon data obtained from studies of diabetic SN.

The research diagnosis of SN may be complicated by the use of expensive, noxious, and time-consuming diagnostic tests. To guide future research, we evaluated data from a clinical research study to identify an efficient battery of clinical measures and quantitative tests for use in

diagnoses of SN in clinical research. We address the degree to which quantitative investigations improve the clinical research diagnosis of HIV-SN.

Materials and Methods

ACTG A5117

AIDS Clinical Trials Group (ACTG) A5117 was a multicenter, prospective study of SN in HIV infection, performed at member sites of the Neurologic AIDS Research Consortium (NARC) and the ACTG with neurologic expertise. The methods and primary results have been previously reported.⁵ A5117 enrolled HIV-infected subjects with and without SN, age ≥ 18 years old, advanced immunologic progression of HIV-infection (CD4+ lymphocyte cell count of <300 cells/mm³), and prior antiretroviral (ARV) exposure of ≥ 15 weeks. Exclusion criteria included conditions, other than HIV or neurotoxic ARV therapy, which might confound the diagnosis of SN including diabetes mellitus, requiring oral hypoglycemic or insulin therapy; vitamin B12 level <200 pg/mL; alcoholism, defined by any alcohol-related medical complication within 6 months of study entry (a limited criterion for identifying the frequency of alcohol dependence); and treatment with neurotoxins other than ARV or potential neurotrophic agents, such as human growth hormone or acetyl carnitine derivatives.

A5117 collected information on each of the following measures at Weeks 0, 24, and 48 for each patient: sensory symptoms (SS), motor symptoms (MS), pin sensitivity (PS), vibration sensitivity (VS), motor function (MF), tendon reflexes (TR), quantitative sensory tests (QST) including cooling detection (CD), vibration detection (VD), heat, and pain, and nerve conduction studies (NCS), such as sural amplitude (SA), and peroneal amplitude (PA). The measures were graded on a 0–4 scale with a higher score indicating a higher level of abnormality (Table 1). ENFDs at the thigh (T) and distal leg (DL) were also quantified, with methods as previously described.¹⁴

Total Neuropathy Score-Based Diagnosis

A standardized neurological history and examination were performed as part of A5117, with a focus on features most relevant to HIV-SN.⁵ A team of experienced HIV neurologists constructed an algorithm for SN given the available quantitative and clinical information. This algorithm was adapted from the Total Neuropathy Score, developed and validated in other neuropathic pain states.¹⁵ The SA and PA components were combined to form a single “electrophysiology” component. Similarly, a “sensory function” (SF) component was defined based in part upon the PS and VS components. The SS component score was abnormal if at least one of the following symptoms were reported: paresthesias, numbness, or neuropathic pain (burning, aching, or stabbing). In order for the SF component to have an abnormal score, examination abnormalities in sensation had to be present for either the PS or VS subcomponent. The QST and electrophysiology components were abnormal if any subcomponents were abnormal. For the TR component to be considered abnormal, the ankle subcomponent had to have an abnormal score. A subject was categorized as having SN if either: (1) the QST component score was abnormal (score >0) and at least one of electrophysiology (SA or PA), SF, and TR was abnormal; or (2) the SA score was abnormal and at least one of QST, SF, and TR was abnormal. Otherwise a subject was classified as neuropathy free.

Objective

The objective was to investigate whether the more costly and time-consuming quantitative tests (QST, electrophysiology, and ENFD) were necessary for the research diagnoses of SN or whether the more easily obtainable (clinical) and less-expensive measures (SS, MS, PS, VS, MF, and TR) could be sufficient in providing a reliable research diagnosis.

Statistical Methods

Logistic regression modeling using generalized estimating equations (GEE) was conducted using the TNS-based diagnosis as the dependent variable and the clinical and quantitative measures (i.e., component scores) as the independent variables (allowing use of data at all time points for each subject). The statistical modeling strategy proceeded in three steps. In Step 1, a model containing only the clinical measures was fit. In Step 2, we sought to examine whether adding one or more of the quantitative measures (QST, SA, PA, ENFD-T, and ENFD-DL) would provide a significant improvement to the clinical-based diagnoses. In Step 3, once quantitative measures were identified for inclusion into the model, we sought to identify clinical or quantitative measures (or respective subcomponents) that could be deleted without significantly decreasing the diagnostic accuracy of the model. For each model considered, the probability of SN as a function of the independent variables was calculated. Various cutoff probabilities were examined to identify a decision algorithm to diagnose SN, with each cutoff resulting in a particular sensitivity/specificity pairing. Receiver operating characteristic (ROC) curves were used to display the relationship between sensitivity versus specificity as cutoff values are varied.

Results

One hundred and one subjects enrolled in A5117 (90% male, 60% white, median age = 45 years, median baseline CD4+ 169 cells/mm³, median baseline log HIV-1 RNA 2.95 copies/mL). The ROC curves from Step 2 of the analyses indicate that QST provides significant improvement to the model containing only clinical measures (Figure 1). Electrophysiological measures (SA and PA) and ENFDs (T and DL) do not appear to add significant diagnostic value. Step 2 of the analyses revealed that a model containing only QST, TR, and PS (with a cutoff probability of 0.77) provides 88% sensitivity and 82% specificity. Other clinical measures did not add diagnostic value.

Step 3 of the analyses revealed that a model containing only QST cooling detection (CD), TR, and PS (with a cutoff probability of 0.76) provides 85% sensitivity and 80% specificity. QST subcomponents other than CD did not add diagnostic value. Assuming prevalences of SN of 30%, 20%, or 10%, the positive predictive values (PPV) generated by the algorithm are 65%, 52%, or 32%, respectively. The following decision algorithm was derived from the model. If the sum of the scores (as per Table 1) for QST CD, TR subcomponent, and PS is 4 or greater, then SN is diagnosed. If the sum of the component scores is 2 or fewer, then the patient is classified as neuropathy free. If the sum of the component scores is 3, then SN is diagnosed if either the QST CD is ≥ 1 or QST CD = 0 and PS ≥ 2 .

Discussion

Our results suggest that a simplified battery of clinical and quantitative studies may provide a reliable diagnosis of neuropathy in the research setting. The QST CD appears to add significant diagnostic value in the diagnosis of HIV-SN. A model containing TR, PS, and QST CD resulted in 85% sensitivity and 80% specificity relative to a TNS-based algorithm that incorporated neurological examination, nerve conduction studies, and quantitative sensory testing. Limitations of this model include that the model results are a function of the TNS-defined decision algorithm and that the PPV may be low in cohorts with low prevalence. NCS, ENFDs, and other QST subcomponents do not appear to add significant diagnostic value in the research diagnosis of DSP beyond the clinical measures. This study does not necessarily imply limited utility of ENFD, NCS, or other QST subcomponents. It is possible that the measures providing value in this study are mediated by ENFD, NCS, or other QST subcomponents. For example, nerve conduction studies reflect large nerve fiber function, which mediate tendon reflexes, while ENFD reflect primarily small fiber function, which also mediate pin sensitivity.

Furthermore, in the clinical and research settings, the value of these measures has been well-established in neuropathy associated with HIV, diabetes mellitus, and other disorders.^{16,17}

A case definition of DSP for clinical research has been proposed,¹⁸ however the definition was primarily based upon data obtained from studies of diabetic SN. These results provide an option of a simplified battery of clinical measures and quantitative tests for efficient use in clinical research of HIV-SN. Readers should be cautioned that these model results are not intended to replace the judgment of an experienced neurologist for individual patient diagnosis. The decision algorithm is obtained to optimize large-sample diagnostic probabilities. The application of the critical techniques in this case was performed by trained neurologists, and the techniques they use may be critical to its sensitivity and specificity. In the case of tendon reflexes, practice in the technique is important to become comfortable with performance of the measure, but the assessment of the relative function of distal versus more proximal reflexes is also factored into the assessment. Because the reflex loop required for ankle jerks is longer than that required for knee jerks, and because the neuropathy is a distal, dying back neuropathy, this comparison is rational and critical to correct diagnosis. Sometimes diminished ankle jerks alone have been assessed, and these may be misleading since normal reflexes may vary from brisk to barely obtainable in normal individuals. Similarly, skill in the interpretation of pin sensitivity testing may be important. Preparing the patient to report only significant differences is generally advised. The testing is again more sensitive when it finds a change in the sensory modality in the individual. For PS, this is achieved by applying the stimulus starting in the toes and ascending. If a clear demarcation of sensory loss is found, this is likely to reflect the distal loss of acuity in this modality. Because the loss is symmetric in this neuropathy, side to side differences are of no value; and because the change is most commonly a relative difference rather than absolute loss of PS, the spatial application of the test becomes critical to its sensitivity.

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Figure 1.

Receiver operating characteristic curves by step for evaluation of the gain in diagnostic accuracy by the addition of quantitative tests over clinical measures. SS = sensory symptoms; MS = motor symptoms; PS = pin sensitivity; VS = vibration sensitivity; TR = tendon reflexes; QST = quantitative sensory tests; SA = sural amplitude; PA = peroneal amplitude; T = thigh; DL = distal leg; CD = cooling detection; VD = vibration detection.

Table 1

Scoring of sensory neuropathies measures

Components	Subcomponents	0	1	2	3	4
Sensory symptoms [*]	Parathesia, numbness, neuropathic pain	None	Symptoms limited to fingers or toes	Symptoms extend to ankle or wrist	Symptoms extend to knee or elbow	Symptoms above knees or elbows, or functionally disabling
Motor symptoms [†]	Hands, feet, legs, arms	None	Slight difficulty	Moderate difficulty	Require help/assist	Paralysis
Pin sensitivity [‡]	Pin level	Normal	Reduced in fingers/toes	Reduced up to wrist/ankle	Reduced up to elbow/knee	Reduced above elbow/knee
Vibration sensitivity [‡]	Vibration level	Normal	Reduced in fingers/toes	Reduced up to wrist/ankle	Reduced up to elbow/knee	Reduced above elbow/knee
Motor function [‡]	Toe extension, toe flexion, ankle dorsiflexion, hip flexion, finger spread, thumb abduction, wrist extension, arm abduction	Normal	Mild weakness	Moderate weakness	Severe weakness	Paralysis
Tendon reflexes	Biceps, triceps, supinator/brachioradialis, knee, ankle	Normal/ brisk	Ankle reflex reduced	Ankle reflex absent	Ankle reflex absent, others reduced	All reflexes absent
QST [*]	Vibratory detection, cooling detection, heat pain detection, 0.5, heat pain detection, 5.0	<95 th percentile	95%–96%	97%–98%	99%	>99%
Sural amplitude [*]	Sural nerve	Normal/reduced to <5%	76%–95% of LLN	51%–75% of LLN	26%–50% of LLN	0%–25% of LLN
Peroneal amplitude [*]	Peroneal nerve	Normal/reduced to <5%	76%–95% of LLN	51%–75% of LLN	26%–50% of LLN	0%–25% of LLN

Note: QST = quantitative sensory tests; LLN = lower limits of normal.

^{*} The component score is the highest score for each individual subcomponent.

[†] The component score is the maximum of the subcomponent scores where the subcomponent score is the minimum of the left and right sides.

[‡] The component score is the minimum of the left and right scores for the respective single subcomponents.