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Modeling Nerve Conduction Criteria for Diagnosis of Diabetic Polyneuropathy

Peter J. Dyck, MD¹, Rickey E. Carter, Ph.D², and William J. Litchy, MD¹

¹Peripheral Neuropathy Research Laboratory, Department of Neurology, Mayo Clinic, 200 First Street SW, Rochester, Minnesota, USA 55905

²Division of Biomedical Statistics and Informatics, Mayo Clinic, 200 First Street SW, Rochester, Minnesota, USA 55905

Abstract

Objective—Which criteria are valid for nerve conduction (NC) diagnosis of typical diabetic sensorimotor polyneuropathy (DSPN)?

Methods—Eight criteria were assessed in diabetes databases (RDNS, n = 456) and healthy subjects (RDNS-HS, n = 330).

Results—In RDNS, the most frequent abnormal attributes ($\leq 2.5^{\text{th}}$ / $\geq 97.5^{\text{th}}$ percentile) are: fibular MNCV (26.3%); sural SNAP (25.4%); tibial MNCV (24.8%); ulnar MNCV (21.3%); fib F latency (16.9%); and ulnar F latency (16.0%). Normal deviate (from percentiles) composite scores of NC were: representative of neurophysiologic abnormalities, sensitive and specific for diagnosis and useful for epidemiologic surveys, randomized trials and medical practice. By contrast, abnormality of one or more attributes in any nerve or abnormally of two most sensitive attributes performed poorly.

Discussion—Composite sum scores of normal deviates (from percentiles corrected for applicable variables) of sensitive NC attributes and with modifications RDNS and AAN criteria performed acceptably for diagnosis of DSPN.

Keywords

composite scores of nerve conduction; diabetic sensorimotor polyneuropathy (DSPN); diagnostic criteria; nerve conduction; sensitivity, specificity of nerve test

INTRODUCTION

From previous studies, abnormality of nerve conduction (NC) is known to be a sensitive, objective and quantitative indication typical of diabetic sensorimotor polyneuropathy (DSPN).^{1–5} To be such an indication the NC procedures must be done proficiently; attributes must be compared to reference values corrected for applicable variables (e.g., age, gender, height and weight); and criteria used for diagnosis must be exactly defined (pre-specified) and representative of neurophysiologic abnormalities found in DSPN and be shown to be both sensitive and specific for the diagnosis of DSPN based on study of healthy subject and diabetes (DM) cohorts. In this study we tested eight specific criteria for the NC diagnosis of DSPN.

The performances of the eight NC criteria were assessed in previously studied cohort databases of population-representative healthy subject (RDNS-HS) and DM cohorts (RDNS).⁶⁻⁸

The first group of criteria (1–4) use defined percentile ($\leq 1\text{st} / \geq 99\text{th}$, $\leq 2.5\text{th} / \geq 97.5\text{th}$ or $\leq 5\text{th} / \geq 99\text{th}$) threshold abnormalities of individual or multiple attributes of NC in single or multiple nerves for diagnosis. The second group (Criteria 5–8) use a summated normal deviate (from percentiles) scores with the percentile value of the composite score based on study of the RDNS-HS cohort.

The different criteria were compared by the degree of exact pre-specification of abnormalities assessed, whether attribute abnormalities are representative of neurophysiologic abnormalities in DSPN, and by the degree of specificity obtained in study of a healthy subject cohort and sensitivity in a DM cohort.⁹

METHODS

The eight diagnostic NC criteria for DSPN are compared in databases of a population-based healthy subject cohort (RDNS-HS)^{8,10} and diabetes mellitus cohort (RDNS)⁷ – both at first evaluation.

The Healthy Subject (HS) and Diabetes Mellitus (DM) Cohorts and Description of Availability of NC Data

This study was possible because we had previously made measurements of 14 NC attributes in population-based studies of a cohort of persons without neurologic disease or medical conditions predisposing them to polyneuropathy in Olmsted County, MN, USA (RDNS-HS cohort)^{8,10} and of persons with diabetes mellitus (DM) in the same community (RDNS).⁷ The protocol for study was approved by Mayo Clinic IRB. The methods of testing attributes of nerve conduction are standard ones employed at Mayo Clinic and are extensively described previously.^{7,8,10} The RDNS-HS cohort values were used to set percentiles specific for applicable variables of age, gender, height, and weight.^{8,10} The nerve conduction values at prevalence of a population-representative group of patients with DM and as corrected for applicable variables has also been extensively described previously.^{6,7}

We use data from these two cohorts, making the assumption that the RDNS-HS cohort should have abnormality in only 5%, 2.5% or 1% – the pre-specified criteria for abnormality. Using these specificity levels in the DM cohort (RDNS), we assessed for percent sensitivity – a large difference of NC abnormality expected between RDNS-HS and RDNS.

Nerve Conduction Criteria for DSPN

NC criteria for typical DPN (distal symmetric length-dependent sensorimotor polyneuropathy (DSPN)) are listed in Table 1, but are described here in greater detail. Criterion 1 is abnormality (by a pre-specified percentile value) of any one or more attribute of NC of any anatomical nerve tested. Criterion 2 (used in early RDNS cohort studies^{6,11}) is abnormality of one or more attributes in 2 or more separate nerves. Criterion 3 (AAN+) is like criterion 2, but one of the attributes must be sural SNAP, with both $\leq 1\text{st}$ percentile (for our purposes here ignoring the clinical features required in the criterion).¹² Criterion 4 is abnormality of each of the two most sensitive (for DSPN) attributes of NC identified here (i.e., fibular MNCV and sural SNAP). Criteria 5, 6, 7 and 8 are composite normal deviate (from percentiles corrected for applicable variables) scores of pre-specified NC attributes with abnormality of the composite score set at a defined percentile level.^{9,13}

Description of Composite Normal Deviate Scores of NC

As discussed in our previous publications, composite scores of NC cannot be derived without availability of reference values of a prospectively studied healthy subject cohort with values corrected for the influence of age, gender, height and weight.⁸⁻¹⁰ We described the methodology and reference values for the derivation of composite scores of neurophysiologic tests in previous publications.⁸⁻¹⁰ We have also extensively described their utility in studies of diabetic cohorts.^{14,15}

A brief description of the derivation of composite scores 5–8 follows. First, the percentile values of the studied attributes are corrected for applicable variables of age, gender, height, weight or other anthropomorphic variables.^{8,16} Percentile abnormality of all attributes used in the composite score are expressed in the same tail of the normal distribution (e.g., in our Criteria 5–8) in the upper tail, but lower tail would also be suitable. This is done by simple conversion of lower to upper tail values (e.g., $\leq 1\text{st}$ to $\geq 99\text{th}$ or 45th to 55th). All percentile values are expressed as normal deviate values from percentiles. The mean normal deviate value of the measurable attributes is multiplied by the number of attributes of the composite score (i.e., $\times 2$ in Criterion 5 and 6, $\times 4$ in Criterion 7, and $\times 6$ in Criterion 8). This mathematical manipulation is needed when some attributes may be unmeasurable, for example, when amplitude is 0 (a measurable value) conduction velocity and distal latency usually cannot be estimated. The percentile value of the derived composite nd score is then determined from estimated percentiles of the composite score assessed in a healthy subject cohort (in this case the RDNS-HS).

The 14 attributes of NC measured included: amplitude (CMAP), velocity (MNCV) and distal latency (MNDL) of motor fibers of ulnar, fibular and tibial nerves; F latency of ulnar, fibular and tibial nerves; and amplitude of ulnar and sural nerve (SNAP).

Description of the Healthy Subject (RDNS-HS) and DM (RDNS) Cohorts

Population-based cohort studies of the Olmsted County, MN, USA population are possible, because essentially all patients in this county receive their medical care either from Mayo Clinic or Olmsted Medical Center who share a common registry of diagnoses and laboratory test results; approximately 70% of inhabitants are medically evaluated in a 3-year period and most allow their medical records to be used for research purposes. From this disease and laboratory test registry, we randomly identified 15 men and 15 women volunteers per hemi-decade between 18–74 years of age who were without medical record diagnosis of inherited, neurologic, metabolic or neoplastic disease and who were without neurologic signs or symptoms by examination (330 HS from 407 persons clinically evaluated). The values from the 330 subjects (at a later time added to by a subset of even older subjects) were used to set percentile values of attributes of nerve conduction as corrected for age, gender, height or weight.⁸⁻¹⁰

Using similar approaches we identified a cohort of volunteers with DM (initially by NDDG and later by ADA criteria).⁷ Attributes of NC at prevalence were used in this analysis. Attributes of NC were expressed as nds from percentiles corrected for applicable variables and as sum scores of defined composite attribute scores (the same approach as was used in the RDNS-HS).

RESULTS

Frequency of Individual Attributes of NC Abnormality in the RDNS Cohort and Other Performance Characteristics

In decreasing order the following frequencies of individual attributes of NC abnormality at $\leq 2.5^{\text{th}}$ / $\geq 97.5^{\text{th}}$ percentile were obtained in the RDNS cohort at prevalence: fibular MNCV (26.3%); sural SNAP (25.4%); tibial MNCV (24.8%); ulnar MNCV (21.3%); tibial F latency (16.9%); ulnar F latency (16.0%); and then in lesser frequencies the other attributes. Among these six attributes, abnormality of a single NC attribute only in DM patients was observed in the following numbers and percentages: fibular MNCV 14 (3.1%); sural SNAP 22 (4.8%); tibial MNCV 17 (3.7%); ulnar MNCV 11 (2.4%); tibial F-wave latency 6 (1.3%) and ulnar F-wave latency 7 (1.5%). However, none of these patients with abnormality of only one attribute was judged to have a clinical mononeuropathy of that nerve.

Agreement between Pairs of NC Attributes for the Diagnosis of Polyneuropathy (DSPN)

We tested for agreement between pairs of NC attributes for the diagnosis of DSPN using the Kappa coefficient (Table 2). Note that there was a highly significant association for all but one pair of NC attributes tested. For many attribute pairs, there was good agreement for the diagnosis of DSPN. For the two most frequently abnormal attributes (fibular MNCV and sural SNAP), the agreement was not as good (a Kappa coefficient of 0.29) as it was for fibular MNCV and tibial MNCV (Kappa, 0.57). Because high Kappa scores indicate that the two attributes are measuring the same dysfunction, their use in a composite score may not increase sensitivity as much as other pairs (e.g., fibular MNCV and sural SNAP) (Table 1).

Performance of Different Criteria for DSPN

Criterion 1 – ≥ 1 abnormality of any one attribute of NC from among all 14 attributes evaluated (the criterion used by some electromyographers). This criterion uses an inexact pre-specification of abnormalities; any one of many attributes of several nerves could be abnormal. The abnormalities found may or may not be representative of DSPN. Use of this criterion results in a large type 1 error (i.e., over estimating disease due to multiple measurements – i.e., 37.3%, 17.3% and 9.1% from use of $\leq 5^{\text{th}}$ / $\geq 95^{\text{th}}$; $\leq 2.5^{\text{th}}$ / $\geq 97.5^{\text{th}}$ or $\leq 1^{\text{st}}$ / $\geq 99^{\text{th}}$ criteria) (Table 1).

Criterion 2 – “ ≥ 1 abnormal attributes in ≥ 2 separate nerves tested” (an early RDNS criterion^{6,17-19}). Like Criterion 1, different NC attribute abnormalities might be identified. In healthy subjects, the frequency of abnormality is overestimated using the $\leq 5^{\text{th}}$ / $\geq 95^{\text{th}}$ criterion (11.2%) (Table 1). Sensitivity in the RDNS cohort is high (i.e., 34.6% and 22.1% for $\leq 2.5^{\text{th}}$ / $\geq 97.5^{\text{th}}$ and $\leq 1^{\text{st}}$ / $\geq 99^{\text{th}}$ percentile).

Criterion 3 – “an abnormality ($\leq 1^{\text{st}}$ or $\geq 99^{\text{th}}$ percentile of any attributes of nerve conduction of two separate nerves, one of which must be the sural nerve” – abnormality of signs and symptoms were not considered in this analysis (AAN, AANEM and AAPMR consensus criteria¹²). One of the two criteria is precisely defined. In the HS cohort, there was an overestimate of affected persons using $\leq 5^{\text{th}}$ / $\geq 95^{\text{th}}$ criteria (7.3%) in RDNS-HS. In the DM cohort, sensitivity for $\leq 1^{\text{st}}$ / $\geq 99^{\text{th}}$ was low (15.6%) when compared to composite scores 4–8.

Criterion 4 – Abnormality of each of the two most sensitive attributes of NC observed in the RDNS cohort (i.e., fibular MNCV and sural SNAP) and at defined percentile abnormalities. Use of this criterion results in low specificity values in the healthy subjects and low sensitivity in the DM cohort.

Criterion 5–8 – These are described together because of their similar performance in both the healthy subjects and DM cohort. Criterion 5 combines the two most sensitive attributes of NC into a composite score (i.e., fibular MNCV and sural SNAP). Criterion 6, is a composite score combining the two attributes with the highest agreement for the diagnosis of DSPN (i.e., fibular MNCV and tib MNCV). Criterion 7, is abnormality of a composite score of attributes of NC considered to be representative of DSPN (i.e., Σ 5 NC nds consists of fibular CMAP, MNCV and MNDL, tib MNDL and sural SNAP).⁹⁻¹⁴ Criterion 8 is a composite score of the 6 most sensitive attributes of NC abnormality observed in the RDNS cohort (i.e., fibular MNCV, sural SNAP, tibial MNCV, ulnar MNCV, tibial F-latency and ulnar F-latency).

All these composite scores (5–8) provided close estimates of the set specificities in the healthy subject cohort and high sensitivity in the DM cohort (Table 1). The highest sensitivity was achieved by Criterion 5, with values of 37.9 and 31.1% for $\leq 2.5^{\text{th}} / \geq 97.5^{\text{th}}$ and $\leq 1^{\text{st}} / \geq 99^{\text{th}}$.

DISCUSSION

This study assessed the databases of previously studied cross-sectional cohorts of population representative healthy subjects (RDNS-HS) and patients with diabetes mellitus (DM) (RDNS) and addressed three questions. One, at a given percentile level of abnormality (i.e., $\leq 2.5^{\text{th}} / \geq 97.5^{\text{th}}$), which are the most sensitive attributes of NC abnormality and useful for the diagnosis of DSPN? Two, what is the agreement between pairs of attributes of NC for the diagnosis of DSPN? Three, among eight NC criteria for the diagnosis of DSPN, which perform best by the criteria of being representative of NC abnormality characteristic of DSPN, avoidance of type 1 error from assessment of multiple measurements, obtaining high degrees of specificity in a healthy subject cohort, and high degrees of sensitivity in a diabetic cohort? The study focused on patients with typical DPN (i.e., DSPN), since atypical DPN (intercurrent small fiber sensory and autonomic neuropathies may not be detectable using NC approaches.²⁰

In this study, we found that the six most sensitive attributes of NC in the RDNS cohort in decreasing frequencies were fibular MNCV, sural SNAP, tibial MNCV, ulnar MNCV, tibial F-wave latency, and ulnar F-wave latency, using as the basis for comparison abnormality criteria at the $\leq 2.5^{\text{th}} / \geq 97.5^{\text{th}}$ percentile as estimated from study of the RDNS-HS cohort. We have previously studied the clinometric performance of attributes of NC verses that of other neurophysiologic and clinical tests in the diagnosis of DSPN.^{14·15·17·19·21·22}

This study of different criteria for DSPN provides several lines of useful information and finds that it provides objective and valid diagnostic information. First, it shows that not all attributes are equally sensitive for the diagnosis of DSPN. Second, rates of abnormality from use of any single attribute are below that of use of composite NC endpoints. These inferences, however, apply only to DSPN, not to atypical DPN or to focal or multifocal varieties.

The degree of agreement between pairs of NC tests, using the Kappa coefficient provides additional useful information on which attribute might be useful as components of composite NC scores for the diagnosis of DSPN. Although it was considered to be desirable that pairs of attributes should show significant agreement (thus indicative that both were an indication of DSPN), we found that high degrees of agreement did not necessarily improve their performance in composite scores. This is illustrated by comparison of fibular MNCV and tibial MNCV vs. fibular MNCV and sural SNAP – the first pair has a higher degree of agreement but when combined as a composite score lower sensitivity (Table 1 and 2).

The eight NC criteria for the diagnosis of DSPN provided quite different estimates of abnormality in both our healthy subject and DM cohorts. A critical examination of which are the most valid criteria is therefore justified. Criterion 1 is an unacceptable criterion for several reasons. The abnormality could be due to a mononeuropathy and not a polyneuropathy. Second, the abnormalities are not specifically defined. Many different outcomes could result from its use, therefore it is unsuitable for epidemiologic surveys or randomized clinical trials. An elevated false positive rate is expected and demonstrated in our RDNS-HS cohort due to the large number of attributes studied (a corollary to the elevated type 1 error rate that occurs when multiple hypothesis testing is performed). In particular, in a healthy subject cohort with values normally distributed and the attributes not linked to each other (i.e., statistically independent), 46%, 26% and 11% of patients would be classified as DSPN when only 5%, 2.5% and 1% would be expected to show abnormality. Empirical evaluation of the RDNS-HS cohort resulted in frequencies of 37%, 17% and 9% – somewhat lower values than the theoretical and suggestive of correlation, or clustering, of some of the 14 attributes (Table 1). These high false positive determinations of DSPN would be detrimental to diagnostic utility not only in research but also in medical practice. Because of this lack of specificity using this criterion, excessively high estimates of DSPN were found in RDNS (Table 1).

Criterion 2 criterion performed considerably better than Criterion 1. Use of this criterion ensures that a mononeuropathy is highly unlikely to explain the abnormality. Like Criterion 1, specificity is higher than it should be in RDNS-HS using the 5 percentile abnormality criterion. This criterion is more stringent than Criterion 1, so it is expected to provide greater control of the false positive rate. Using $\leq 2.5\text{th} / \geq 97.5\text{th}$ or $\leq 1\text{st} / \geq 99\text{th}$ percentile as the threshold for abnormality, very low rates of abnormality were observed in the healthy subject cohort; however, the criteria produce estimates of the prevalence of DSPN that are highly sensitive to the threshold selected. In particular, shifting from $\leq 2.5\text{th} / \geq 97.5\text{th}$ to the more stringent $\leq 1\text{st} / \geq 99\text{th}$ decreases the estimated frequency of DSPN from 34.7% to 22.1% (Table 1).

Criterion 3 did not perform well if it is followed strictly. As compared to Criterion 2, there is pre-specification of one attribute (sural SNAP), and percentile abnormality is set at $\leq 1\text{st}$ percentile but there is failure to exactly pre-specify other attributes. In the RDNS-HS cohort, abnormality using this criterion occurs in less than 1% of patients (0.6%) and results in low (too low considering frequencies reported in the medical literature and composite score estimates) of the prevalence of DSPN (e.g., using the AAN criteria 15.6% in the RDNS cohort). If the $\leq 2.5\text{th}$ or $\geq 97.5\text{th}$ percentile thresholds were used, the estimated frequency of DSPN in RDNS increases to 26.3% – a more reasonable estimate. As for Criterion 2, which percentile cut-off is used (i.e., $\leq 2.5\text{th} / \geq 97.5\text{th}$ or $\leq 1\text{st} / \geq 99\text{th}$) has a large effect on frequency of DSPN in the RDNS cohort.

Criterion 4 has exact pre-specification of criteria and of percentile abnormality, but this criterion performed poorly. In RDNS-HS it results in an insufficiently low frequency of abnormality (false positive rates of 0.6% and 0.3%) for $\leq 2.5\text{th}$ and $\leq 1\text{st}$ percentiles. For the DSPN cohort, the criterion results in too low an estimate of DSPN (i.e., sensitivity of 11.8% and 3.9%) – well below expected frequencies of DSPN in a population-based cohort of patients with DM and also well below the figures obtained using composite scores 5–8.

The four composite scores of NC (Criterion 5–8) performed excellently in both the RDNS-HS and RDNS cohorts. All four composite scores were highly specific in the healthy subject cohort with a frequency of abnormality near the specificity criteria of $\leq 5\text{th} / \geq 95\text{th}$, $\leq 2.5\text{th} / \geq 97.5\text{th}$ or $\leq 1\text{st} / \geq 99\text{th}$ percentiles. In the RDNS cohort, however, sensitivity in the strict diagnostic accuracy meaning was not assessable. Assuming that specificity is the same

for the RDNS as it was shown to be in the RDNS-HS cohort (not an unreasonable assumption, since the technique of testing and the criteria for abnormality are exactly alike), sensitivity can be assessed in the RDNS. The results, therefore, support the idea that these four composite scores are both specific and sensitive for the accurate detection of DSPN. As anticipated, their use did not over diagnose DSPN in the HS cohort; they provided abnormalities very near the set pre-specified percentile levels. Also of importance, the attributes chosen for composite scores 5–8 are all thought to be representative of nerve dysfunction in DSPN (i.e., leg nerves) and inclusive of different functional neurophysiologic abnormalities. The use of composite scores allows inclusion of disparate functional attributes, avoids identification of false positives, and, because they are continuous measurements, allows estimates of function and dysfunction through the range of normality and abnormality. Therefore, composite scores may be used to assess latent neuropathic dysfunction and severity of DSPN, a clear advantage over dichotomous judgments.¹⁵ The good quality of composite scores makes them especially useful for epidemiologic surveys and randomized controlled trials, a subject we have previously discussed.^{15,22–25}

Considering their good qualities, why are composite scores not more widely used? Possibly the reasons are that the needed reference values as corrected for by the applicable variables are not generally available in a readily usable form, and some degree of mathematical manipulation of data is needed. Such reference databases and computational facilities could be made available for some ethnic and geographic cohorts and probably should be used more widely. Software programs could be made available by a medical institution, a governmental agency or by an equipment manufacturer.

Of criteria 1–4, criteria 1 and 4 performed unacceptably. Despite some short-comings (i.e., some degree of false positives and lack of complete pre-specification), criteria 2 and 3 performed reasonably well but only when $\leq 2.5^{\text{th}}$ / $\geq 97.5^{\text{th}}$ percentile was used. Overall, the composite scores performed best!

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ABBREVIATIONS

AAN criteria	AAN, AANEM, AAPMR criteria for diagnosis of diabetic polyneuropathy
CMAP	compound muscle action potential
DM	diabetic mellitus
DSPN	diabetic sensorimotor polyneuropathy
F-wave	tibial or ulnar F-wave latency
MNCV	motor nerve conduction velocity
MNDL	motor nerve distal latency
NC	nerve conduction
nd	normal deviate from percentiles

RDNS	Rochester Diabetic Neuropathy Study, a cross-sectional and longitudinal study of patients with DM in Olmsted County, MN, USA
RDNS-HS	a healthy subject cohort
SNAP	sural nerve action potential

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Table 1
Nerve Conduction abnormality in the RDNS and RDNS-HS Cohorts Using Different Criteria

	RDNS-HS* (N=330) # (%) Abnormal			RDNS (N=456) Prevalence at First Visit	
	5 th /95 th	2.5 th / 97.5 th	1 st /99 th	2.5 th / 97.5 th	1 st /99 th
Criteria 1: ≥ 1 of 12 NC attributes abn. [†]	123 (37.3)	57 (17.3)	30 (9.1)	60.1	42.5
Criteria 2: ≥ 1 abn. in 2 separate nerves	37 (11.2)	8 (2.4)	3 (0.9)	34.6	22.1
Criteria 3: ≥ 1 abn. in 2 separate nerves (1 is sural)	24 (7.3)	7 (2.1)	2 (0.6)	26.3	15.6
Criteria 4: Fibular, CV abn. and Sural Amp abn.	2 (0.6)	2 (0.6)	1 (0.3)	11.8	3.9
Criteria 5: Σ 2 NC nds abn. (Fib, CV and Sur. Amp)	17 (5.2)	9 (2.7)	4 (1.2)	37.9	31.1
Criteria 6: Σ 2 NC nds abn. (Fib, CV and Tib, CV)	17 (5.2)	9 (2.7)	4 (1.2)	34.2	21.1
Criteria 7: Σ 5 NC nds abn.	17 (5.2)	9 (2.7)	1 (0.3)	28.3	17.5
Criteria 8: Σ 6 NC nds abn.	17 (5.2)	9 (2.7)	4 (1.2)	30.9	23.5

* Based on theoretical considerations (Bonferroni modelling) the following abnormal frequencies would be expected based on type 1 error and lack of linkage among attributes studies.

[†] Of $330 \times 12 = 3960$ nerve attributes tested, 197 (5.0%) are abnormal at the 95th, 75 (1.9%) at the 97.5th, and 36 (0.9%) at the 99th.

Table 2
Agreement between Different Criteria for Nerve Conduction Abnormality in RDNS-HS Cohorts

	RDNS-HS (N = 330)					
	Criteria 5: Σ 2 NC nds abn.					
	5 th / 95 th		2.5 th / 97.5 th		1 st / 99 th	
	Kappa	p ^A	Kappa	p ^A	Kappa	p ^A
Criteria 3: $\geq$ 1 abn. in 2 separate nerves (1 is sural)	0.56	<0.0001	0.49	<0.0001	0.33	<0.0001
Criteria 4: Fibular, CV abn. and Sural Amp abn.	0.20	<0.0001	0.36	<0.0001	0.40	<0.0001
Criteria 7: Σ 5 NC nds abn.	0.32	<0.0001	0.09	0.0596	0.40	<0.0001
Criteria 8: Σ 6 NC nds abn.	0.57	<0.0001	0.43	<0.0001	0.24	<0.0001