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Title Page

Title: Diagnostic characteristics of nerve conduction study parameters for vasculitic neuropathy.

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Running Title: Electrodiagnostic features of vasculitic neuropathy.

Ethical Statement:

We confirm that we have read the Journal's position on issues involved in ethical publication and

affirm that this report is consistent with those guidelines.

Abstract

Introduction/Aims: In vasculitic neuropathy (VN), a 50% side-to-side difference in the amplitude of compound muscle action potentials and sensory nerve action potentials is considered meaningful, but unequivocal evidence is lacking. The aim of this study is to characterize electrodiagnostic features that best distinguish VN from other axonal polyneuropathies.

Methods: We conducted a case-control study between January 2000 and April 2021. We reviewed the records of patients with VN who had bilateral nerve conduction studies (NCS) and evaluated different electrodiagnostic models to help distinguish VN from non-inflammatory axonal polyneuropathies.

Results: We identified 82 cases, and 174 controls with non-inflammatory axonal neuropathies. The amplitude percent difference Z-score model showed the best discriminatory capability between cases and controls (AUC 0.87; 95% CI 0.82, 0.93), and the number of nerves tested did not significantly influence the model. Individually, the ulnar motor nerve (AUC 0.86; 95% CI 0.77, 0.94) and median motor nerve (AUC 0.85; 95% CI 0.77, 0.94) showed the best discriminatory capability. A 50% amplitude difference between at least 2 bilateral nerves, either in the upper (AUC 0.85; 95% CI 0.77, 0.93) or lower (AUC 0.79; 95% CI 0.71, 0.87) extremity showed good discriminatory threshold for detecting VN.

Discussion: The best electrodiagnostic criteria for VN utilizes z-scores of percent differences in nerve amplitudes, but this approach may be difficult to implement at the bedside. Alternately, a 50% amplitude difference in at least 2 nerves is a reasonable approximation.

I.   **Introduction**

Vasculitic neuropathy (VN) is caused by ischemic injury to peripheral nerves due to destruction of nerve blood vessels by inflammatory cells. Patients present with acute to subacute painful sensory or sensorimotor symptoms.[1–3] VN may be clinically restricted to the peripheral nerves or occur as part of a systemic vasculitis. Timely diagnosis is crucial as immunosuppressive therapy improves patient outcomes.[4]

The diagnosis of VN relies on the clinical history, neurological examination, laboratory testing, electrodiagnostic testing, and nerve biopsy.[5] The classic electrodiagnostic features of VN are asymmetric axonal nerve injury in a pattern of multiple mononeuropathies, but a symmetric polyneuropathy pattern has also been described.[6]

A proposed approach to EDX includes side-to-side comparisons of the sural and superficial fibular sensory responses, as well any other sensory or motor nerve found to have a low amplitude. A side-to-side difference in amplitude of 50% has been considered meaningful,[1,7] but unequivocal evidence is lacking, and the number of nerves and the specific nerves that need to be tested to screen for asymmetry when VN is suspected is unknown. It also unknown whether a more nuanced, data-driven approach to nerve conduction studies (NCS) could improve the diagnostic capabilities of the test.

The aim of this study is to characterize electrodiagnostic features that best distinguish VN from other axonal polyneuropathies.

II.   **Methods**

This study and its methods were approved by the institutional review board of the University of Michigan.

We conducted a case-control, hospital-based study at the University of Michigan between January 2000 and April 2021. For the case subjects, we retrospectively identified all patients with a diagnosis of VN using the tenth revision of the International Classification of Diseases (ICD-10) codes G58.7 (mononeuritis multiplex), G63 (polyneuropathy in disease classified elsewhere) and I77.6 (arteritis). For these patients we reviewed the electronic medical records to confirm diagnosis based on PNS criteria as outlined below.

We included patient ages 18 years old or older who had NCS completed at our institution, including at least one nerve (sural, fibular motor, tibial motor, median sensory, median motor, ulnar sensory, ulnar motor or radial sensory) on both sides. We selected the first NCS performed after symptom onset. If there were 2 NCS within 12 months, we selected the NCS with the largest number of nerves that were studied bilaterally. A pathologist reviewed all the nerve biopsy reports and classified them as definite, probable, possible or no VN according to the PNS pathological criteria.[5] Patients had to meet criteria for pathologically definite VN or clinically probable VN established by the PNS. We classified the patients as systemic VN (SVN) and non-systemic VN (NSVN).[5]

For the control group, we used EMGPro, an institutional database of electrodiagnostic study results, to search for patients coded as 'axonal neuropathy' who had bilateral NCS and similar nerves tested to the cases, between January 2005 and April 2021. We reviewed their electronic medical records and selected the patients who had a clinical symmetric axonal polyneuropathy, with no concerns for vasculitic or another inflammatory etiology.

Statistical Analysis

Descriptive statistics were used to characterize patient demographic information and the distribution of bilateral nerve measurements stratified by VN status. We also identified the number of patients with bilateral measurements in common arm nerves (median sensory, ulnar sensory, median motor, ulnar motor) or common leg nerves (sural, fibular motor, tibial motor). We utilized Welch's t-tests to compare continuous covariates that were normally distributed, and Fisher's exact test to compare categorical covariates.

For each individual nerve, we separately calculated the within-participant side-to-side percent and absolute differences between amplitude, conduction velocity, and latency measurements. For the amplitude and latency comparisons, we utilized the distal stimulation values. To standardize differences (percent and absolute) across multiple nerves, z-scores of differences were calculated (using the whole control group as reference) for each nerve and measurement separately. Subsequently, z-scores were averaged across all available bilateral nerve measurements, for amplitude, conduction velocity (CV), and latency, separately to quantify each patient's overall asymmetry. For absent responses, we calculated a 95th percentile of the total observed data for CV and latency measurements, and we imputed an amplitude value of 0.1 for amplitude measurements, which allowed us to calculate side-to-side percent differences.

We fit a series of logistic regression models to determine the association between the above measures of asymmetry and VN. Specifically, we fit separate univariate logistic regression models for VN as a function of averaged z-scores for bilateral (1) amplitude percent differences, (2) amplitude absolute differences, (3) CV percent differences, (4) CV absolute differences, (5) latency percent differences, and (6) latency absolute differences. We also fit univariate logistic

regression models for VN as a function of the z-scores of bilateral amplitude percent differences for each of the 8 nerves separately.

To determine whether the number of bilateral nerves measured impacted discriminatory capability, we fit an additional multivariable logistic regression model as a function of the z-scores for bilateral amplitude percent differences, the number of bilateral nerves measured, and the interaction between the two. For the subsets of patients with bilateral measurements in all arm nerves and all leg nerves, we fit two additional multivariable logistic regression models (arm and leg separately) for VN as a function of z-scores for the percent differences in bilateral amplitude of each arm or leg nerve.

To assess the discriminatory capability of each model, we constructed receiver operating characteristic (ROC) curves. To summarize discriminatory capability for each model, we calculated the area under the ROC curve (AUC). We used Youden's J statistics to find the cutoff that optimized the sensitivity and specificity of each model, and found the optimal cutoffs while constraining either the sensitivity or specificity to be 95%. For each of these potential cutoffs, we also calculated positive likelihood ratios.

To compare the discriminatory capability of the primary models to more simplistic cutoffs, we fit six additional logistic regression models for VN as a function of whether patients had at least one or at least two bilateral amplitude differences of at least 30%, 40%, and 50%. To offer a fair predictive comparison, these 6 models were fit on the subsets of patients with bilateral measurements in all arm nerves and all leg nerves.

As a sensitivity analysis, we refit model (1) after excluding patients that met the criteria for carpal tunnel syndrome (CTS)[8–10] and patients diagnosed with fibular mononeuropathy at the knee, ulnar neuropathy at the elbow, C8 radiculopathy, T1 radiculopathy, L5 radiculopathy or S1

radiculopathy on electrodiagnostic testing. All analyses were completed using R software version 4.0.2.

III.   Results

From January 1, 2000 through April 30, 2021, we identified 98 patients with a diagnosis of VN, out of which 82 had bilateral NCS. Forty patients met pathologically definite criteria and 42 met clinically probable criteria (16 probable pathologically, 4 possible pathologically, and 22 confirmed systemic vasculitis with no nerve biopsy). We identified 174 controls: 74 (42.5%) type 2 diabetes, 35 (20%) prediabetes, 33 (19%) idiopathic, 13 (7.5%) chemotherapy toxicity, 9 (5.2%) alcohol toxicity, 6 (3.5%) type 1 diabetes, 2 (1.1%) critical illness neuropathy, 1 (0.6%) vitamin B12 deficiency and 1 (0.6%) copper deficiency. Demographic information and clinical characteristics for the cases are displayed in Table 1.

Of the 82 patients with VN, 62 (76%) were SVN and 20 (24%) were NSVN. The etiologies of the SVN cases were: 58 connective tissue disorders (30 ANCA-associated vasculitis, 8 Sjogren disease, 6 systemic lupus erythematous, 5 rheumatoid arthritis, 3 polyarteritis nodosa, 2 livedoid vasculitis, 1 systemic scleroderma, 1 eosinophilic vasculitis, 1 temporal arteritis, 1 undifferentiated connective tissue disorder), 2 mixed cryoglobulin and 2 active cancers. Ten patients with NSVN had positive inflammatory markers (1 had a positive c-ANCA 1:20 but negative PR3 and MPO antibodies, 8 had elevated erythrocyte sedimentation rate less than 100 mm/h and 1 had a low complement C4 level).

Clinical presentation

All the VN patients presented with distal predominant symptoms, 77 (94%) reported pain, 76 (93%) had predominant lower limb symptoms and findings, 73 (89%) had asymmetric or multifocal features, 70 (85%) had a non-length dependent presentation and 80 (97.5%) had one or more acute attacks during the course of the disease. Sixty-nine (84%) patients had a sensorimotor presentation while 13 (16%) patients had pure sensory manifestations. Nine (10.8%) patients had symmetric distal symptoms and decreased symmetric distal sensation on exam at onset, 2 (2.5%) of which had a slowly progressive, length-dependent, distal symmetric polyneuropathy phenotype after presentation.

NCS models

The first NCS from symptom onset was selected in 77 (94%) cases. The number of bilateral nerves tested per patient is described in (Supplemental Table 1). All models are summarized in (Supplemental Table 2). Model 1, 2 and 3 assessed the amplitude, CV, and latency respectively, utilizing percent differences, out of which model 1 had the highest AUC (Figure 1A). Model 4, 5 and 6 the assessed the amplitude, CV, and latency respectively, utilizing absolute differences, out of which model 4 showed the best AUC. Out of these 6 models, the amplitude percent difference (Model 1) showed the best discriminatory capability between cases and controls. Constraining Model 1 to have a 95% sensitivity, corresponded to a specificity of 0.16, based on the average Z-score cutoff of greater than -0.51. Alternatively, constraining Model 1 to have 95% specificity corresponded to a sensitivity of 0.70, using an average Z-score cutoff of 0.80. Lastly, using Youden's J, we found that using a Z-score cutoff of 0.44 resulted in a sensitivity of 0.80 and specificity of 0.85. In a sensitivity analysis, Model 1 had similar characteristics after excluding patients with median mononeuropathy at the wrist (11 cases, 2

controls), fibular mononeuropathy at the knee (2 controls), ulnar neuropathy at the elbow (1 case, 2 controls), L5 radiculopathy (4 controls) and S1 radiculopathy (1 case, 1 control) (AUC 0.87; 95% CI 0.81, 0.92). None of the patients had a C8 or T1 radiculopathy on electrodiagnostic testing.

Motor nerves showed a better discriminatory capability in comparison to sensory nerves in Model 1 (Supplemental Table 2). Model 7 and 8 assessed the amplitude percent difference in the lower extremity and upper extremity nerves respectively (Figure 1B and Figure 1C). The amplitude percent difference in the upper extremity (Model 8) showed the best discriminatory capability. Model 9 showed that the number of bilateral nerves measured did not impact the discriminatory capability. We corroborated this lack of impact of number nerves by re-fitting Model 1 on different subsets of patients with varying numbers of nerves as shown in Table 2 and Figure 1D. After evaluating each individual nerve, the ulnar motor nerve and the median motor nerve showed the best discriminatory capability (Supplemental Table 2). The individual nerves with the worst discriminatory capability were the ulnar sensory and radial sensory.

Greater amplitude percent differences performed better than smaller differences regardless of the number of nerves or limbs studied. Likewise, amplitude percent differences in 2 nerves showed a better discriminatory capability compared to differences in only 1 nerve, regardless of the amplitude percent difference value or the limb studied. A 50% amplitude difference between bilateral nerves in at least 2 nerves either at the upper or lower extremities showed the best discriminatory threshold for detecting VN (Table 3). The number of patients with 50% or higher side-to side amplitude difference per individual nerve is described in Table 4.

IV.   Discussion

Our study showed that the percentage difference in nerve amplitudes had the best discriminatory capability to detect VN, compared to the absolute difference in amplitudes or differences in CV or distal latency. Since VN predominantly causes axonal changes, it is not surprising that amplitude parameters were superior to speed parameters.[1,5,11] The percent difference in amplitudes using z-scores can be used with different cut-off values which maximize the sensitivity, specificity or both. Selecting the value with the highest sensitivity is not ideal, as the specificity is too low and the number of false positives is high. The value with the highest specificity limits the number of false positive cases, but may also not identify true positive cases. The Youden's J statistic cut-off maximizes the sensitivity and specificity. The advantage of using this method is that the z-score obtained will clearly indicate which cut-off it has reached, thus providing more information on the likelihood of a VN diagnosis. One way to implement this approach would be to program NCS software to calculate these z-scores.

If this calculation is not feasible, a more practical approach would be focusing on the amplitude difference between nerves. It is common practice to consider a 50% side-to-side difference in amplitudes recorded from the same nerve as a meaningful difference,[1,6,11] which derives from NCS performed in healthy subjects.[12,13] Although not validated for VN, multiple studies have described an asymmetric NCS pattern in a high proportion of VN cases utilizing the 50% amplitude difference cutoff, which is why this difference has been generally accepted as a supportive finding to identify VN.[1,2,6,11,14,15] Our findings validate the use of this 50% difference in at least 2 nerves to support the diagnosis of VN.

The assessment of 6-9 bilateral nerves did not perform better than 1-3 or 4-5 nerves indicating that the number of bilateral nerves tested did not influence the diagnostic

characteristics of NCS. VN tends to cause axonal injury in a pattern of multiple mononeuropathies, but the distribution of nerve infarction is not random, as some nerves are more likely to be involved than others.[16] Thus, selecting the nerves that need to have bilateral NCS based on clinical findings and low amplitude recordings on EDX studies is more important and less time consuming than randomly assessing a high number of bilateral nerves.

Our results suggest that the best electrodiagnostic approach to discriminate VN from other axonal polyneuropathies includes an evaluation of motor nerves and upper extremity nerves. This is interesting as studies have shown that lower extremity nerves (fibular motor and sural) are preferentially targeted over the upper extremity nerves in VN, and if the upper extremity is involved, the ulnar nerve tends to be primarily affected.[16–18] Furthermore, the sural and superficial fibular sensory nerves have been preferentially targeted as nerves that should be studied bilaterally when performing EDX.[1,7] This discrepancy between our findings and prior studies may be explained by our control group. Non-inflammatory axonal polyneuropathies preferentially impact lower extremity nerves and sensory nerves.[19,20] Once there is a significant reduction in the amplitude, a small absolute side-to-side difference can result in a higher side-to-side percentage difference. This is reflected in the high proportion of patients in the control group with 50% amplitude asymmetries in the fibular and tibial motor nerves. Likewise, non-inflammatory axonal neuropathies can affect the upper extremities once they progress and become more severe.[19,20]

Based on expert opinion, a proposed approach to EDX includes evaluating the sural, superficial fibular, median, ulnar, and radial sensory nerves and the fibular, tibial, median, and ulnar motor nerves unilaterally. The next step should be side-to-side comparisons of the sural and superficial fibular sensory responses, and any other sensory or motor nerve that shows a low

amplitude on NCS.[1,7] Based on our results, we suggest evaluating at least 2 different nerves side-to-side, one of which should include an upper extremity nerve (ulnar motor preferentially), and any other nerves showing a low amplitude. Analyzing the data with the z-score approach would be ideal, but a 50% side-to-side difference in amplitudes in at least 2 nerves is easier to calculate at the bedside and has a good discriminatory capability for VN. If a z-score approach is chosen, the clinician should determine which cut-off to use. Both the EDX findings and the clinical presentation are important to determine the risk-benefit ratio of a nerve biopsy.

It is important to highlight that symmetric EDX findings do not rule out VN. Many cases in our cohort did not show a 50% side-to-side amplitude differences between nerves (Table 4). Once VN progresses, the clinical and EDX findings might resemble a distal symmetric polyneuropathy.[1] In these cases, the initial clinical presentation and examination are crucial to identify patients with possible VN and avoid treatment delays.

Limitations of this study include the retrospective and single-center study design. No standard NCS approach was used for included patients, which meant that not all patients had all nerves tested. As a result, we investigated patients with comprehensive upper extremity (median sensory, ulnar sensory, median motor, ulnar motor) and lower extremity (sural, fibular motor, tibial motor) data and found similar results. The fact that this study was performed in a large tertiary center may limit the generalizability of our findings. Further, the small sample size decreases the precision of our estimates. There were demographic differences between the cases and controls, but these would not be expected to impact side-to-side differences between amplitude, conduction velocity, and latency nerve measurements within the same subject. Another possible limitation of this study is that it assessed the diagnostic value of NCS data,

rather than the entire electrodiagnostic evaluation. It is unknown if including needle EMG data would have allowed us to better distinguish VN from other axonal polyneuropathies.

In conclusion, NCS are a valuable tool in the diagnosis of VN. An asymmetry in amplitude of ≥50% in at least 2 nerves, especially if there is electrodiagnostic involvement of the upper extremity nerves, should raise concern for the possibility of VN when evaluating for polyneuropathy. In addition, we have demonstrated that z-scores of percentage differences in amplitudes have the best diagnostic test characteristics and should be considered in laboratories that have the capacity to implement this approach.

List of abbreviations

- AUC: Area under the ROC curve

- CTS: Carpal tunnel syndrome

- CV: Conduction velocity

- EDX: Electrodiagnosis

- IQR: Interquartile range

- NCS: Nerve conduction studies

- NSVN: Nonsystemic vasculitic neuropathy

- PNS: Peripheral Nerve Society

- ROC: Receiver operating characteristic

- SVN: Systemic vasculitic neuropathy

- VN: Vasculitic neuronopathy

V. References

1. Gwathmey KG, Burns TM, Collins MP, Dyck PJB. Vasculitic neuropathies. Lancet Neurol. 2014 Jan;13(1):67–82.

2. Bennett DLH, Groves M, Blake J, Holton JL, King RHM, Orrell RW, et al. The use of nerve and muscle biopsy in the diagnosis of vasculitis: a 5 year retrospective study. J Neurol Neurosurg Psychiatry. 2008 Dec;79(12):1376–81.

3. Beachy N, Satkowiak K, Gwathmey KG. Vasculitic Neuropathies. Semin Neurol. 2019 Oct;39(5):608–19.

4. Stone JH, Merkel PA, Spiera R, Seo P, Langford CA, Hoffman GS, et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. N Engl J Med. 2010 Jul 15;363(3):221–32.

5. Collins MP, Dyck PJB, Gronseth GS, Guillevin L, Hadden RDM, Heuss D, et al. Peripheral Nerve Society Guideline on the classification, diagnosis, investigation, and immunosuppressive therapy of non-systemic vasculitic neuropathy: executive summary. J Peripher Nerv Syst. 2010 Sep;15(3):176–84.

6. Zivković SA, Ascherman D, Lacomis D. Vasculitic neuropathy--electrodiagnostic findings and association with malignancies. Acta Neurol Scand. 2007 Jun;115(6):432–6.

7. Lacomis D, Zivković SA. Approach to vasculitic neuropathies. J Clin Neuromuscul Dis. 2007 Sep;9(1):265–76.

8. Werner RA, Andary M. Electrodiagnostic evaluation of carpal tunnel syndrome. Muscle Nerve. 2011 Oct;44(4):597–607.

9. Felsenthal G, Spindler H. Palmar conduction time of median and ulnar nerves of normal subjects and patients with carpal tunnel syndrome. Am J Phys Med. 1979 Jun;58(3):131–8.

10. Sander HW, Quinto C, Saadeh PB, Chokroverty S. Sensitive median-ulnar motor comparative techniques in carpal tunnel syndrome. Muscle Nerve. 1999 Jan;22(1):88–98.

11. Collins MP, Hadden RD. The nonsystemic vasculitic neuropathies. Nat Rev Neurol. 2017 Apr 27;13(5):302–16.

12. Bromberg MB, Jaros L. Symmetry of normal motor and sensory nerve conduction measurements. Muscle Nerve. 1998 Apr;21(4):498–503.

13. Kumbhare D, Robinson L, Buschbacher R. Buschbacher's Manual of Nerve Conduction Studies. 3rd ed. Demos medical; 2016.

14. Ramineni KK, Chandra SR, Mahadevan A, Kulkarni GB, Ramanujam CN. Clinical, electrophysiological and laboratory parameters, and outcome in patients with biopsy proven systemic and nonsystemic vasculitic neuropathy. Neurol India. 2019 Feb;67(Supplement):S62–70.

15. Vital C, Vital A, Canron MH, Jaffré A, Viallard JF, Ragnaud JM, et al. Combined nerve and muscle biopsy in the diagnosis of vasculitic neuropathy. A 16-year retrospective study of 202 cases. J Peripher Nerv Syst. 2006 Mar;11(1):20–9.

16. Olney RK. AAEM minimonograph #38: neuropathies in connective tissue disease. Muscle Nerve. 1992 May;15(5):531–42.

17. Chang RW, Bell CL, Hallett M. Clinical characteristics and prognosis of vasculitic mononeuropathy multiplex. Arch Neurol. 1984 Jun;41(6):618–21.

18. Said G, Lacroix-Ciaudo C, Fujimura H, Blas C, Faux N. The peripheral neuropathy of necrotizing arteritis: a clinicopathological study. Ann Neurol. 1988 May;23(5):461–5.

19. 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 Jan 25;64(2):199–207.

20. Dyck PJ, Carter RE, Litchy WJ. Modeling nerve conduction criteria for diagnosis of diabetic polyneuropathy. Muscle Nerve. 2011 Sep;44(3):340–5.

Figure 1. Receiver Operating Characteristic (ROC) curve for Vasculitic Neuropathy as a function of total percent amplitude asymmetry (Z-scores). A, Sensory and motor nerves in all patients. B, Lower extremity nerves (sural, fibular motor and tibial motor) in patients with NCS in all lower extremity nerves. C, Upper extremity nerves (ulnar sensory, ulnar motor, median sensory, median motor) in patients with NCS in all upper extremity nerves. D, Sensory and motor nerves in all patients, categorized by the number of nerves performed on NCS.
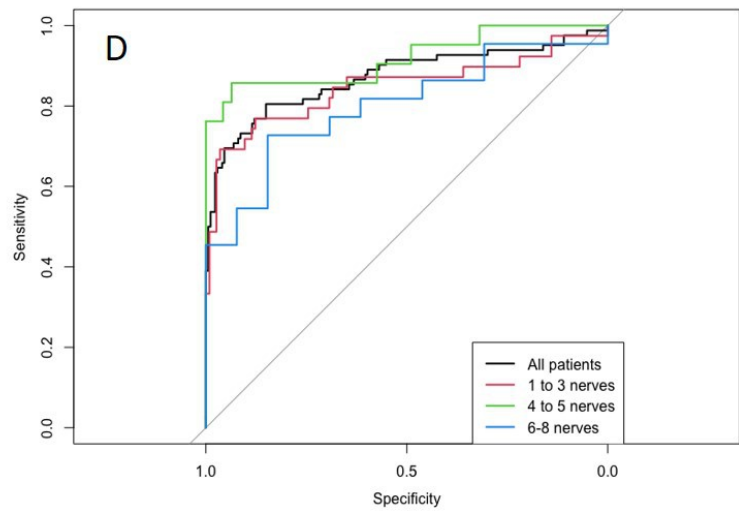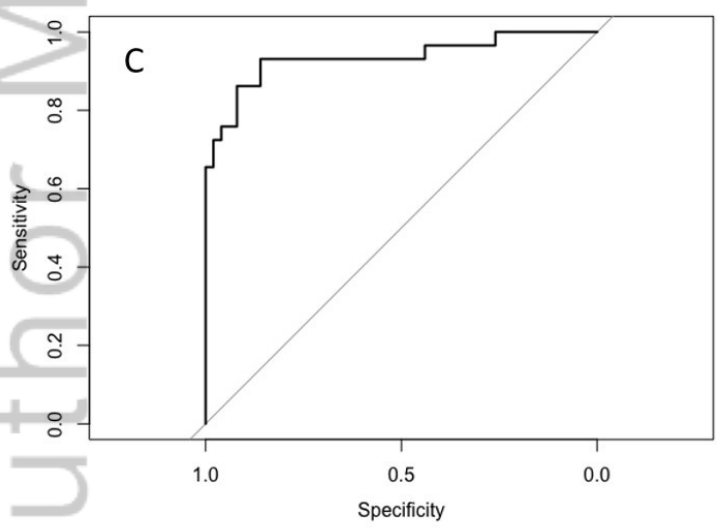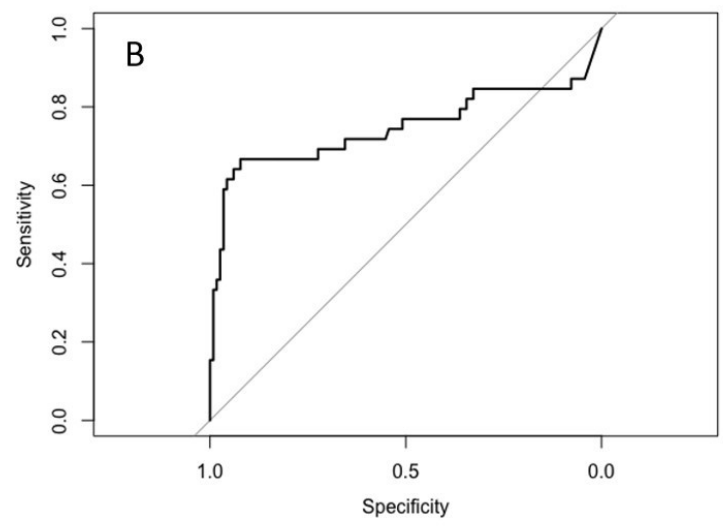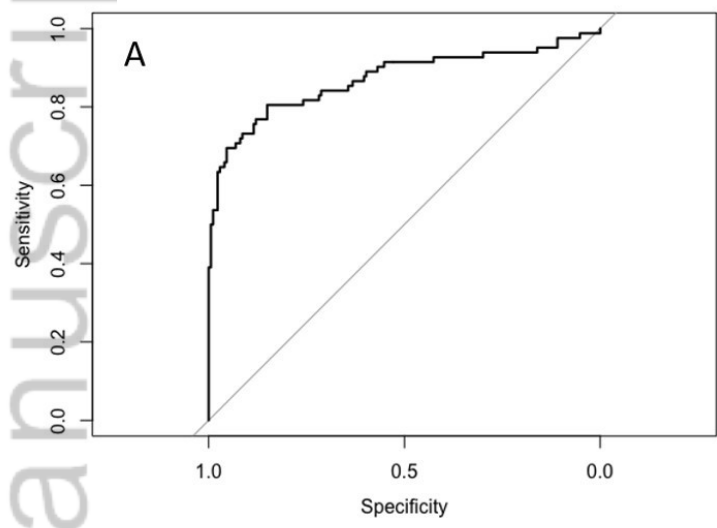
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Tables

Table 1. Demographic information and clinical characteristics of population

	Cases (N= 82)	Controls (N= 174)	All patients (N= 256)	p-value
Age mean (SD), years	58.5 (13.9)	60.2 (11.6)	59.6 (12.4)	0.34
Female sex, N (%)	43 (52%)	56 (32%)	99 (39%)	0.003
Weight mean (SD), lbs	174.4 (44.9)	210 (49.5)	198.5 (50.77)	<0.001
Height mean (SD), inches	67.2 (4.5)	68.9 (4.0)	68.41 (4.25)	0.003
Comorbidities, N (%)				
Diabetes	11 (13%)	80 (46%)	91 (36%)	<0.001
Alcohol abuse	2 (2%)	20 (11%)	22 (9%)	0.015
Vitamin B12 deficiency	0 (0%)	5 (3%)	5 (2%)	0.18
Cervical stenosis	2 (2%)	9 (5%)	11 (4%)	0.51
Lumbosacral stenosis	3 (4%)	43 (25%)	46 (18%)	<0.001
Time between symptom onset and NCS, median (IQR), months	6 (2-12)			
Time between NCS and nerve biopsy, median (IQR), days	7 (3-34)			

Table 2. Refitting Model 1 with varying number of nerves allowed

Number of Nerves Allowed in Model 1	*AUC (95% CI)*
All Nerves (Model 1) Cases: 82, Controls: 174	0.87 (0.81, 0.92)
1-3 Nerves Cases: 39, Controls: 114	0.85 (0.76, 0.94)
4-5 Nerves Cases: 21, Controls: 47	0.92 (0.83, 1.0)
6-8 Nerves Cases: 22, Controls: 13	0.80 (0.65, 0.95)

Table 3. Specifying threshold of percentage difference between bilateral nerves

Model Description	*Complete Leg Models AUC (95% CI)*	*Complete Arm Models AUC (95% CI)*
At least **1** nerve with bilateral amplitude percent difference >= 30%	0.57 (0.53, 0.61)	0.58 (0.53, 0.63)
At least **2** nerves with bilateral amplitude percent difference >= 30%	0.70 (0.63, 0.78)	0.76 (0.69, 0.84)
At least **1** nerve with bilateral amplitude percent difference >= 40%	0.62 (0.57, 0.68)	0.72 (0.65, 0.79)
At least **2** nerves with bilateral amplitude percent difference >= 40%	0.74 (0.66, 0.82)	0.81 (0.73, 0.89)
At least **1** nerve with bilateral amplitude percent difference >= 50%	0.68 (0.62, 0.74)	0.78 (0.71, 0.86)
At least **2** nerves with bilateral amplitude percent difference >= 50%	0.79 (0.71, 0.87)	0.84 (0.76, 0.93)

Note: Median sensory and median motor nerve responses were counted as 1 nerve (median nerve). Ulnar sensory and ulnar motor nerve responses were counted as 1 nerve (ulnar nerve).

Table 4. Number of patients with 50% or higher side-to side amplitude difference per individual nerve.

Individual Nerve	Number of patients	
	Cases, N(%)	Controls, N(%)
Fibular motor Cases: 56, Controls: 120	33 (59%)	40 (33%)
Median motor Cases: 34, Controls: 51	18 (53%)	3 (6%)
Ulnar motor Cases: 36, Controls: 58	19 (53%)	1 (2%)
Tibial motor Cases: 48, Controls: 128	25 (52%)	29 (23%)
Sural sensory Cases: 58, Controls: 131	30 (52%)	17 (13%)
Median sensory Cases: 39, Controls: 56	18 (46%)	6 (11%)
Radial sensory Cases: 28, Controls: 28	10 (36%)	5 (18%)
Ulnar sensory Cases: 43, Controls: 57	14 (33%)	8 (14%)