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Research paper

The additional diagnostic value of motor nerve excitability testing in chronic axonal neuropathy

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ABSTRACT

Objective: To explore potential differences in motor nerve excitability testing (NET) variables at group levels between patients with a clinical diagnosis of polyneuropathy (PNP), which did not fulfil diagnostic criteria of conventional nerve conduction studies (NCS) and patients without polyneuropathy. Such differences could support a role for NET in increasing the diagnostic sensitivity of NCS in chronic axonal PNP.
Methods: Motor NET was performed using the median nerve in patients with a clinical suspicion of PNP in addition to conventional NCS, skin biopsies, corneal confocal microscopy and structured clinical evaluation including scoring of neuropathy symptoms and signs.
Results: Of the 57 patients included, 32 had PNP, half of which had NCS, which fulfilled criteria for PNP (NCS+ PNP). There were no significant differences for any of the NET variables between PNP patients with non-diagnostic conventional NCS (NCS− PNP) and patients without PNP. Rheobase was increased, and Ted (undershoot) and subexcitability were decreased in NCS+ PNP. Sural amplitude, peroneal nerve F-wave latency and tibial nerve F-wave-latency were correlated with subexcitability, and tibial nerve motor amplitude was correlated with rheobase.
Conclusions: NET was correlated with conventional NCS and no differences were found between NCS− PNP patients and patients without PNP.
Significance: NET does not seem to offer any additional diagnostic value in chronic mixed etiology neuropathy.
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1. Introduction

Conventional nerve conduction studies (NCS) have a relatively low sensitivity for chronic axonal neuropathy (Tankisi et al., 2019). Neuropathy can be associated with a wide range of conditions such as diabetes, alcohol abuse, rheumatological or renal diseases, and often causes neuropathic pain. Diagnosis therefore has implications for further diagnostic work up strategy and pain management. The highest proportions of abnormal findings are found in tibial nerve recordings and sural nerve recordings with near-nerve-technique at 75% and 66%, respectively (Tankisi et al., 2019). Surface recordings of sural nerves are abnormal in only 49% of polyneuropathy patients. Combined with the high prevalence of this condition, ranging from 1 to 3 % with an increase to 7% in the elderly (Hanewinckel et al., 2016), there is a need to improve diagnostic sensitivity in neurophysiological testing. Attempts to increase sensitivity include examination of distal sensory nerve segments such as the dorsal sural and the medial plantar nerves (Sullivan et al., 2008; Uluc et al., 2008; Kural et al., 2017) and the sural/radial amplitude ratio (Sullivan et al., 2008). However, in a large cohort of patients with and without polyneuropathy (Vrancken et al., 2008), no sensory nerve action potential was elicited from the dorsal sural nerve in between 21% and 38% of patients without polyneuropathy, possibly limiting the value of this measure in clinical practice.

Nerve excitability testing (NET) provides information about the properties of axonal membranes through repeated stimulation with variation of stimulus intensity, duration and interval (Krarup and Moldovan, 2009). Axonal dysfunction has been demonstrated in polyneuropathy of different aetiology including diabetic neuropathy (Krishnan and Kiernan, 2005; Kristensen et al, 2021), chemotherapy-induced neuropathy (Park et al.,

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Table 1
Clinical characteristics.

	NCS+ PNP (n = 16)	NCS− PNP (n = 16)	No PNP (n = 25)
Age, median (range)	67 (48–76)	52 (39–74)	66 (47–83)
Sex, m/f	12/4	4/12	9/16
Duration of symptoms, months, median (range)	12 (3–180)	24 (4–120)	18 (3–140)
Neuropathy scores			
NIS, median (range)	19 (6–46)	7 (0–22)	
NSS, median (range)	4 (1–4)	3 (1–4)	
UENS, median (range)	17 (6–24)	7 (0–15)	
TNS, median (range)	16 (4–22)	5 (2–8)	
NPSI, median (range)	14 (0–64)	33 (0–82)	
Skin biopsy abnormal	3/16	6/16	0/25
CCM abnormal	5/16	3/16	0/25
CDT abnormal	8/16	7/16	9/25
MDT abnormal	8/16	6/16	8/25
VDT abnormal	11/16	10/16	14/25
MPT abnormal	8/16	4/16	10/25
Aetiology			
Unknown	5	7	
Diabetes	5	4	
Alcohol	0	2	
Chemotherapy	6	0	
Hypothyroidism	0	2	
Rheumatic disease	0	1	

CDT: Cold detection threshold; CCM: Confocal corneal microscopy; MDT: Mechanical detection threshold; MPT: Mechanical pain threshold; NIS: Neuropathy impairment score; NPSI: Neuropathic pain symptom inventory NSS: Neuropathy symptom score; TNS: Total neuropathy scale; UENS: Utah early neuropathy score; VDT: Vibration detection threshold.

2009; Heide et al., 2018), hereditary neuropathy (Nodera et al., 2004), and immune-mediated neuropathy (Cappelen-Smith et al., 2001), mainly focusing on pathophysiological mechanisms. The potential diagnostic value of nerve excitability testing in chronic axonal polyneuropathy of mixed and unknown aetiology has not been examined.

The aim of this study was to compare NET in patients with and without a clinical diagnosis of chronic axonal polyneuropathy following extensive diagnostic work up in which conventional NCS did not fulfil criteria for polyneuropathy. We hypothesised that there would be differences between these patients at group levels. Such a finding could support the role of NET for increasing the sensitivity of NCS. Patients with polyneuropathy confirmed by conventional NCS were examined for comparison. In a secondary analysis, correlations between NET and NCS variables and clinical neuropathy scores in patients with clinically confirmed polyneuropathy were examined to determine whether there was an association between NET and NCS abnormalities.

2. Methods

2.1. Recruitment of patients

Participants in an ongoing study on diagnosis and classification of chronic axonal polyneuropathy at the Department of Neurology at Odense University Hospital were invited to participate in the present study. This is a comprehensive study of an unselected population of subjects referred to the department due to a clinical suspicion of polyneuropathy, which could only be confirmed in approximately half of the patients (unpublished data).

2.2. Study procedures

Neuropathy symptoms and signs were systematically assessed using the Neurological Symptoms Score (NSS) (Dyck et al., 1980), The Neuropathy Impairment Score (NIS) (Dyck et al., 2005), the Utah Early Neuropathy Score (UENS) (Singleton et al., 2008), the Total Neuropathy Scale (TNS) (Cavaletti et al., 2003) and the Neuropathic Pain Symptom Inventory (NPSI) (Bouhassira et al., 2004).

Neuropathy examinations included standard NCS of the median and ulnar nerves unilaterally and the peroneal, tibial and sural

Table 2
Conventional nerve conduction studies.

	NCS+ PNP (n = 16)	NCS− PNP (n = 16)	No PNP (n = 25)
Median nerve			
Motor amplitude (mV)	11.9 (3.3)	12.5 (4.2)	11.1 (2.3)
Motor CV (m/s)	54.1 (3.1)	56.5 (3.3)	55.5 (2.6)
Sensory amplitude (μV)	3.9 (2.0)***,††	11.5 (6.4)	9.2 (4.7)
Sensory CV (m/s)	52.3 (4.1) †	56.0 (5.6)	58.4 (7.7)
F wave latency (ms)	31.5 (2.5)**	27.5 (1.7)	28.2 (2.9)
Ulnar nerve			
Motor amplitude (mV)	12.1 (3.6) *	16.7 (2.1)	12.5 (2.4)
Motor CV (m/s)	54.8 (4.6) *	62.3 (1.9)	57.1 (5.6)
Sensory amplitude (μV)	2.1 (1.2) ***,†††	9.1 (2.7)	6.9 (3.8)
Sensory CV (m/s)	50.4 (6.4)*, ††	56.0 (3.4)	57.8 (6.5)
F wave latency (ms)	31.6 (1.9) **	28.0 (1.6)	29.2 (3.8)
Peroneal nerve			
Motor amplitude (mV)	2.9 (3.1) **,†††	7.1 (3.1)	7.4 (2.6)
Motor CV (m/s)	37.7 (5.2) **,†††	45.4 (4.6)	45.5 (5.3)
F wave latency (ms)	59.6 (7.6) *,†	51.8 (6.9)	50.5 (5.3)
Tibial nerve			
Motor amplitude (mV)	4.6 (4.5) ***,†††	17.5 (5.7)	18.4 (8.9)
F wave latency (ms)	61.2 (9.0) *,†	52.2 (7.9)	52.6 (6.3)
Sural nerve			
Sensory amplitude (μV)	2.1 (2.0) *,†††	8.3 (5.4)	11.3 (8.9)
Sensory CV (m/s)	42.3 (15.3) *,†	52.2 (6.6)	52.9 (4.1)

Mean (SD); *: $p < 0.05$ (NCS+ PNP vs. NCS− PNP); **: $p < 0.01$ (NCS+ vs. NCS− PNP); ***: $p < 0.001$ (NCS+ PNP vs. NCS− PNP); †: $p < 0.05$ (NCS+ PNP vs. no PNP); ††: $p < 0.01$ (NCS+ PNP vs. no PNP); †††: $p < 0.001$ (NCS+ PNP vs. no PNP).

Table 3
Motor nerve excitability testing.

	NCS+ PNP (n = 16)	NCS− PNP (n = 16)	No PNP (n = 25)
Latency (ms)	8.0 (1.4)	7.3 (1.4)	7.5 (1.2)
Stimulus-response and strength-duration properties			
Stimulus (mA): 50% max CMAP	9.0 (4.2) **,†	5.7 (1.6)	6.8 (2.7)
SDTC (ms)	0.42 (0.07)	0.48 (0.13)	0.42 (0.06)
Rheobase (mA)	6.2 (3.1) **,†	3.8 (1.22)	4.4 (1.8)
Current-threshold relationship			
Resting I/V slope	0.56 (0.07)	0.55 (0.11)	0.57 (0.08)
Minimum I/V slope	0.27 (0.07)	0.28 (0.09)	0.25 (0.05)
Threshold electrotonus			
TEd (10–20 ms)	66.4 (6.5)	69.2 (7.2)	67.2 (7.5)
TEd (peak)	69.0 (9.8)	69.2 (5.6)	68.4 (8.7)
TEd (40–60 ms)	53.0 (3.9)	51.3 (5.3)	49.3 (5.5)
TEd (90–100 ms)	50.4 (13.3)	47.7 (7.1)	46.4 (12.3)
S2 accommodation	18.7 (6.3)	21.5 (7.1)	21.9 (5.7)
TEd^{20} (peak)	37.8 (4.4)	41.7 (6.7)	38.2 (4.2)
TEd (undershoot)	−14.8 (7.5) *,†	−20.1 (4.1)	−18.5 (7.0)
TEd (overshoot)	14.8 (4.7)	17.9 (3.9)	16.6 (5.1)
TEh (10–20 ms)	−75.0 (10.2)	−79.6 (9.0)	−76.8 (10.7)
TEh (20–40 ms)	−94.4 (11.6)	−100.2 (13.9)	−97.8 (13.8)
TEh (90–100 ms)	−122.6 (22.1)	−128.8 (28.0)	−129.0 (23.8)
Accommodation half-time (ms)	42.1 (9.6)	41.8 (16.9)	38.8 (8.5)
Recovery cycle			
Relative refractory period (ms)	3.1 (0.4)	3.0 (0.4)	3.1 (0.4)
Superexcitability (%)	−22.8 (7.1)	−25.7 (8.2)	−22.0 (5.3)
Subexcitability (%)	10.9 (3.6) **,††	16.2 (5.1)	15.5 (4.4)
Refractoriness at 2.5 ms (%)	23.0 (14.6)	24.8 (20.4)	24.3 (20.4)

Mean (SD); *: p < 0.05 (NCS+ PNP vs. NCS− PNP); **: p < 0.01 (NCS+ PNP vs. NCS− PNP); †: p < 0.05 (NCS+ PNP vs. no PNP); ††: p < 0.01 (NCS+ PNP vs. no PNP).

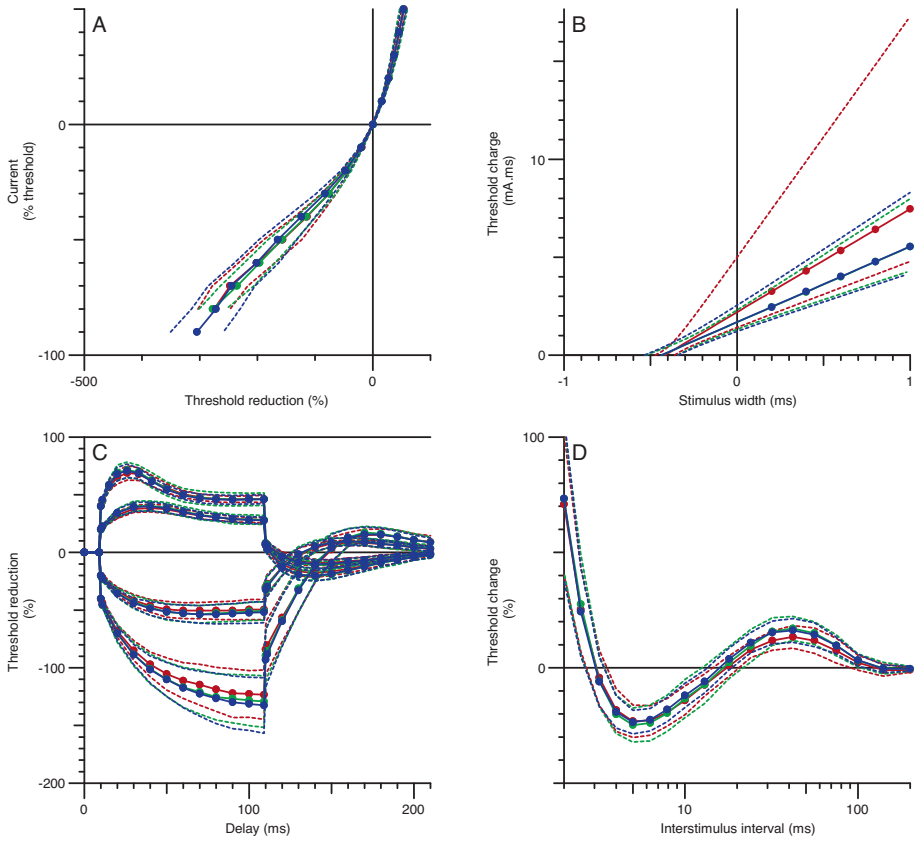

Fig. 1. Motor nerve excitability measures including A: current-threshold relationship, B: strength-duration properties, C: threshold electrotonus, and D recovery cycle. Red: NCS+ PNP, green: NCS− PNP, blue: No polyneuropathy. Data shown as mean ± SD. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

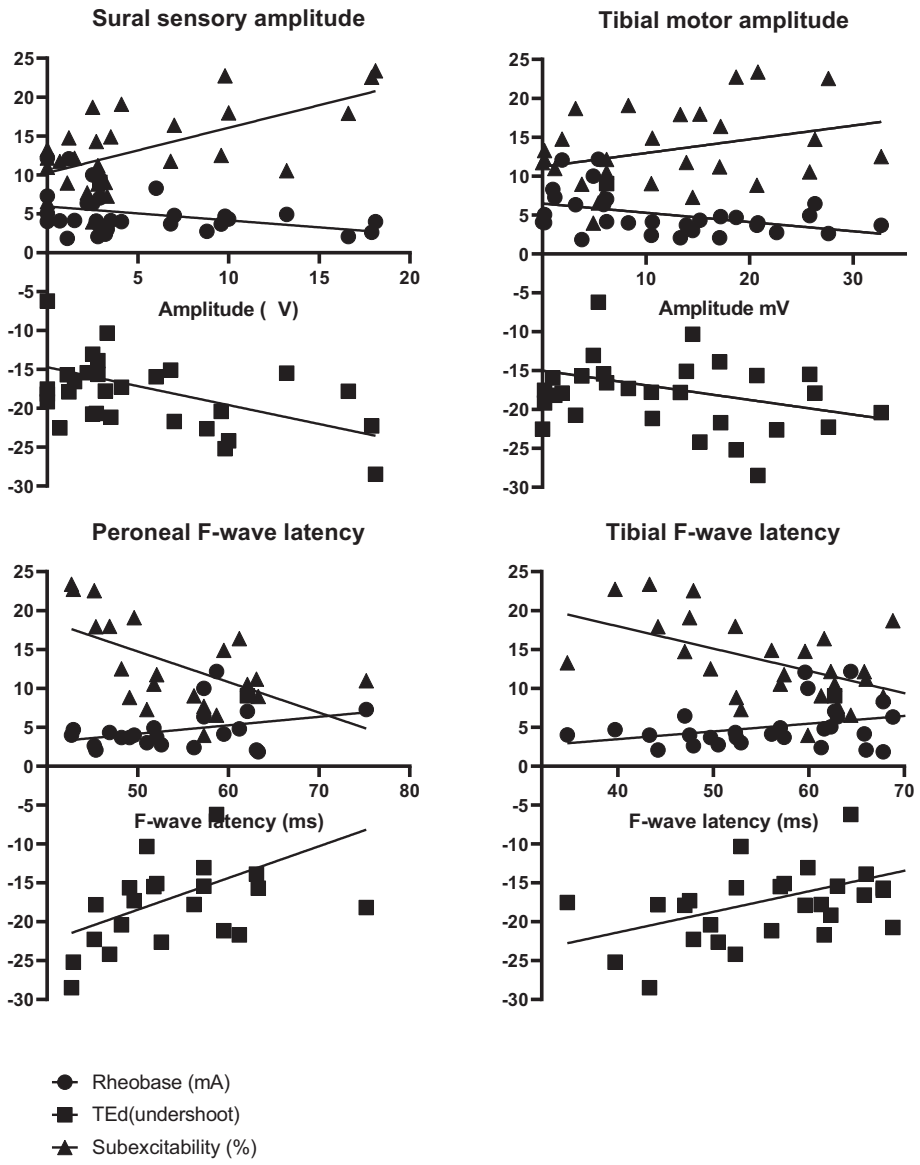

Fig. 2. Correlations between NET and conventional NCS. Sural nerve amplitude and subexcitability (r = 0.6309; p = 0.018), tibial nerve motor amplitude and rheobase (r = −0.4139; p = 0.044), peroneal nerve F-wave latency and subexcitability (r = −0.5525; p = 0.010) and tibial nerve F-wave-latency and subexcitability (r = −0.5408; p = 0.004) were significantly correlated.

nerves bilaterally using conventional methods previously described (Stålberg et al., 2019; Tankisi et al., 2019). Further, small fibre diagnostic work up including skin biopsies, quantitative sensory testing (QST), and corneal confocal microscopy (CCM) was performed.

Skin biopsies from 10 cm proximal to the lateral malleolus were processed according to EFNS standards (European Federation of Neurological Societies/Peripheral Nerve Society, 2010). QST, which comprised cold, warm, cold pain, mechanical, vibration, and pain detection thresholds, was performed in accordance with the German Research Network on Neuropathic Pain (DFNS) standards (Rolke et al., 2006). CCM was performed as previously described (Tavakoli and Malik, 2011).

The diagnosis of polyneuropathy was made by experienced neuromuscular specialists. It was based on clinical examination and large and small fibre diagnostic work up. Patients with a diagnosis of polyneuropathy had either 1) typical symptoms and signs of polyneuropathy and abnormal NCS or skin biopsies or 2) typical symptoms and signs of polyneuropathy and relevant additional diagnostic work up e.g. lumbar MRI to exclude lumbar root compression.

NET was performed on the right median nerve following exclusion of carpal tunnel syndrome. Compound muscle action potentials were recorded from thenar muscles over the abductor pollicis brevis muscle using surface electrodes. Stimulation was carried out according to the standard TRONDNF protocol as previously described (Kiernan et al., 2000). Data were analysed using the QTRAC software (© Prof Hugh Bostock, UCL). Strength duration time constant and rheobase were calculated based on the duration–charge curve, threshold electrotonus and current–threshold relationship based on sequential sub-threshold currents, and recovery cycle variables based on paired supra-threshold stimulations.

Patients were divided into three groups based on the results of the comprehensive polyneuropathy study as described above: (1) Patients with polyneuropathy confirmed by conventional NCS (NCS+ PNP), (2) patients with polyneuropathy and normal NCS (NCS− PNP), and (3) patients without polyneuropathy (no PNP).

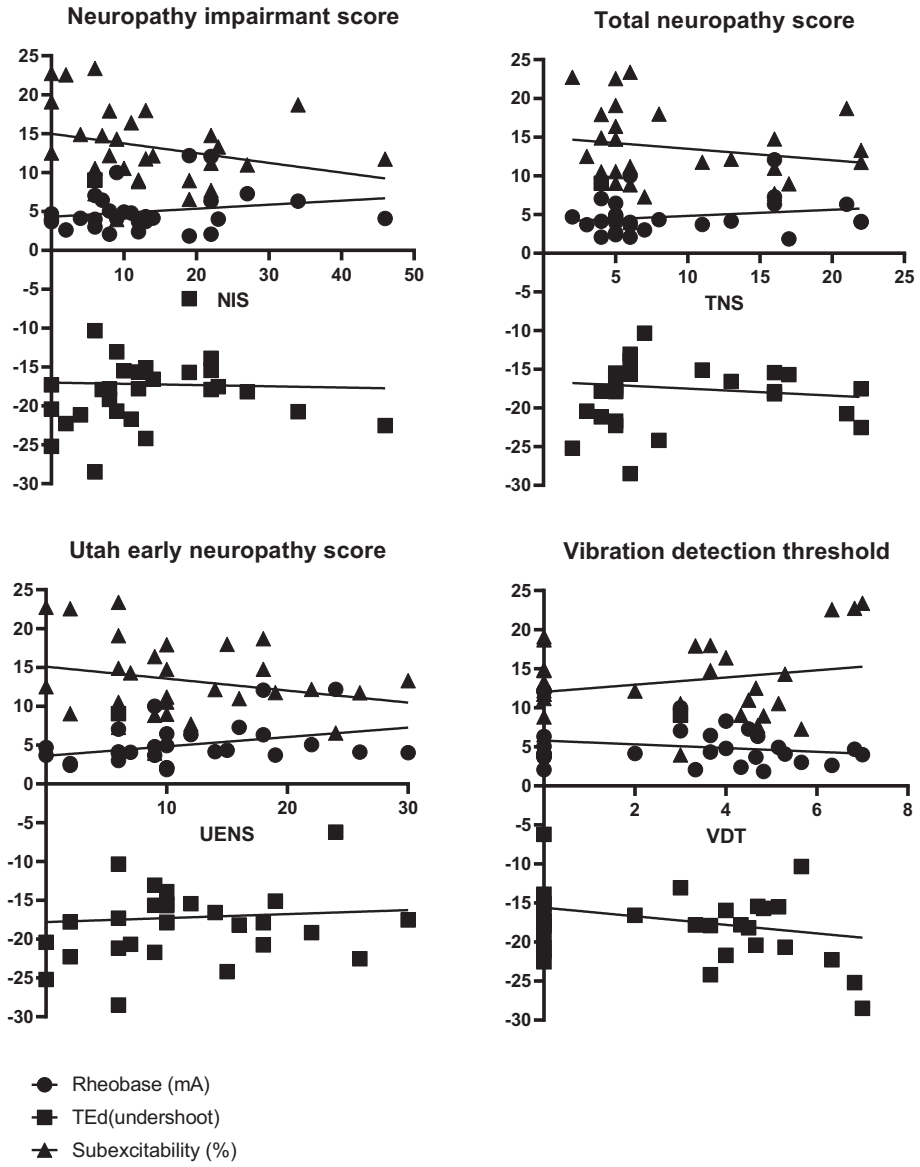

Fig. 3. Correlations between NET and clinical neuropathy scores and vibration detection threshold (VDT). Correlations were not statistically significant.

NCS criteria for polyneuropathy were at least one abnormal variable (amplitude, conduction velocity, distal motor latency or F-wave latency) in at least two nerves, one of which must be the sural nerve (England et al., 2005).

2.3. Data analysis

Groups of patients were compared using one-way ANOVA analysis followed by Tukey's test for post-hoc analysis. Correlations between all NET variables and conventional NCS and clinical neuropathy scores were examined using multiple linear regression including age and sex to adjust for these background variables. Analyses were performed using GraphPad Prism version 7.0, GraphPad Software, San Diego, California USA, www.graphpad.com.

3. Results

Fifty-seven patients were included. Thirty-two patients had a clinical diagnosis of polyneuropathy based on the comprehensive diagnostic evaluation. Sixteen of these patients had NCS which fulfilled the criteria for polyneuropathy. Clinical characteristics and the results of the small fibre tests consisting of skin biopsies and corneal confocal microscopy are presented in Table 1 along with the results of selected QST variables. Small fibre tests consisting of skin biopsies and corneal confocal microscopy were normal in most patients, both NCS+ PNP and NCS− PNP. Median clinical neuropathy scores were higher in NCS+ PNP patients than in NCS− PNP patients, except for the neuropathic pain symptom inventory (NPSI).

The results of conventional NCS are presented in Table 2. Significant differences were found between patients with NCS+ PNP and the other two group. There were no difference between patients with NCS− PNP and patients without polyneuropathy.

The results of NET are presented in Table 3 and Fig. 1. The stimulus required to obtain 50% of the CMAP, rheobase, Ted (undershoot) and subexcitability were significantly different in patients with NCS+ PNP compared to the other two groups, but as was the case for conventional NCS, no differences were found between patients NCS− PNP, and patients without PNP.

Correlations (adjusted for age and sex) between selected NCS variables and rheobase, Ted (undershoot) and subexcitability are presented in Fig. 2. Significant correlations were found between sural nerve amplitude and subexcitability ($r = 0.6309$; $p = 0.018$), tibial nerve motor amplitude and rheobase ($r = -0.4139$; $p = 0.044$), peroneal nerve F-wave latency and subexcitability ($r = -0.5525$; $p = 0.010$) and tibial nerve F-wave-latency and subexcitability ($r = -0.5408$; $p = 0.004$). There were no statistically significant correlation with other NET variables and no significant correlations between median or ulnar NCS and NET.

No significant correlation was found between clinical neuropathy scores or vibration detection thresholds (Fig. 3).

4. Discussion

The results indicate that nerve excitability studies will not be of additional value compared to conventional NCS for the diagnosis of large fibre polyneuropathy of mixed etiology. The only significant differences were found between patients with NCS+ PNP and both of the other two groups. The findings probably reflect that polyneuropathy is more severe in NCS+ PNP patients than in NCS− PNP patients, although no significant correlation was found between NET and clinical neuropathy scores. The proportion of patients with abnormal small fibre tests was relatively similar in patients with and without NCS which fulfilled criteria.

This is the first study of nerve excitability testing in polyneuropathy of mixed aetiology. We demonstrated significant differences in both the strength duration relationship (rheobase), threshold electrotonus (TEd undershoot) and the recovery cycle (subexcitability). Similar changes were previously demonstrated in diabetic polyneuropathy (Sung et al., 2012; Kwai et al., 2013; Kristensen et al., 2021). Nerve excitability testing has not been performed in idiopathic polyneuropathy, which comprised the largest proportion of the patients in the present study.

We found significant correlations between NET and conventional NCS, some of which were statistically marginal, which suggests that common pathophysiological changes are detected by the two methods. This finding supports the conclusion that NET will not be of additional diagnostic value in mixed aetiology polyneuropathy. On the other hand, we found no statistically significant correlation between NET and clinical severity of polyneuropathy.

It may be considered a limitation to the study, that patients with polyneuropathy were not compared to healthy controls. On the other hand, comparison with a group of patients, in which the diagnosis of polyneuropathy was ruled out following comprehensive diagnostic work up, which was the case in the present study, reflects a realistic clinical setting. Furthermore, mean values in patients without polyneuropathy are very close to those previously reported in studies of healthy subjects (Kiernan et al., 2020).

Another limitation is that only motor, and not sensory, NET was performed. It is possible that sensory NET would have resulted in significant differences. However, in diabetic neuropathy, changes in sensory NET were less pronounced than changes in motor NET despite significant affection of sensory nerves demonstrated by conventional NCS (Kristensen et al., 2021).

Regarding the risk that different pathologies caused by varying etiologies resulted in opposing excitability changes, which cancelled each other out; we are not able to exclude this possibility.

Finally, it must be considered that we examined the median nerve in chronic axonal neuropathy, which is typically length dependent. It is a potential limitation that the distal part of leg nerves, which are probably more severely affected, is not examined by NET.

In conclusion, nerve excitability testing does not seem to offer any additional diagnostic value in patients with polyneuropathy compared to conventional nerve conduction studies.

Declarations of interest

None.

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