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The value of MUNIX as an objective electrophysiological biomarker of disease progression in CIDP

Short Title: MUNIX in CIDP follow-up

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Abstract

Introduction/Aims: Objective outcome measures to monitor treatment response and guide treatment are lacking in chronic inflammatory demyelinating polyneuropathy (CIDP). We aimed to evaluate the motor unit number index (MUNIX) as an outcome measurement in patients with CIDP and investigate the correlation of MUNIX with functional and standard electrodiagnostic tests in a single follow-up study.

Methods: We evaluated MUNIX of the abductor pollicis brevis (APB), abductor digiti minimi (ADM), and tibialis anterior (TA) muslces bilaterally. Muscle force was assessed by Medical Research Council sumscores (MRCSS). Functional measures used were the Overall Neuropathy Limitation Score (ONLS) and the Rasch-built Overall Disability Scale (R-ODS) at baseline and after six months of treatment. Standard electrophysiology was evaluated by the Nerve Conduction Study Score (NCSS).

Results: Twenty patients were included at baseline, and 16 completed the follow-up study. Significant correlations were found between the MUNIX sumscore and both MRCSS and NCSS at baseline, between both the pinch strength and grip and upper limb MUNIX at baseline and follow-up, and between MUNIX of TA and both lower limb MRCSS with lower limb ONLS at baseline and follow-up. Significant correlations also were found between MUNIX sumscore change and MRCSS change, R-ODS change, and ONLS change.

Discussion: MUNIX changes correlated with strength and electrophysiological improvements in CIDP patients. This suggests that MUNIX may represent a useful objective biomarker for patient follow-up.

Introduction

Chronic inflammatory demyelinating polyneuropathy (CIDP) includes a spectrum of well-defined autoimmune disorders with different presentations, potentially responsive to immunomodulatory treatment.[1]

Objective outcome measures to monitor treatment response and guide treatment are lacking in CIDP.[2] Different outcomes have been used in research studies, including Neuropathy Disability Score (NDS),[3] Medical Research Council sumscore (MRCSS), Inflammatory Neuropathy Cause and Treatment (INCAT) scale,[4] Overall Neuropathy Limitation Score (ONLS),[5,6] and Rasch-built Overall Disability Scale (R-ODS).[7] All of these outcome measurements have limitations influenced by patients or physicians. Nerve conduction studies (NCS) have been used as an outcome measure for follow-up of CIDP patients.[8] Compound muscle action potential (CMAP) amplitude has been shown to correlate with clinical improvement.[9] Other parameters of NCS, including distal motor latency (DML), motor conduction velocity, CMAP area, and CMAP duration, have not been consistently correlated with clinical outcomes.[10]

Motor unit number index (MUNIX) is a relatively new electrophysiological index developed by Nandedkar and colleagues to estimate the size and number of functional motor units using a mathematical model.[11] The method has proved reliable, rapid, and minimally uncomfortable for patients.[11,12] Since its introduction, this index has been studied in patients with motor neuron disorders, especially amyotrophic lateral sclerosis.[11] More recently, studies have demonstrated MUNIX improvement following CIDP treatment.[13,14] In the latest study, a rapid MUNIX improvement after intravenous immunoglobulin (IVIg) treatment has introduced it as a possible IVIg response indicator in a short course of two weeks.[10]

This study was designed to examine the MUNIX in a six-month follow-up of CIDP patients and also study the correlations of MUNIX with several clinical and electrodiagnostic measures.

Methods

Study design

This prospective study was conducted in the neuromuscular clinic of Shariati hospital (affiliated with the Tehran University of Medical Sciences). Patients with CIDP were selected between October 2018 and December 2019. Patients were included with a definite diagnosis of CIDP, according to the 2010 EFNS/PNS criteria (updated in 2021).[15]

The ethics committee of Tehran University of Medical Sciences approved this study.

Participants

Consecutive subjects (≥ 18 years old) with definite CIDP were enrolled in the study. Patients were excluded if they had any other diseases that could affect results except diabetes mellitus since, in some cases, diabetes mellitus and CIDP can occur concurrently.[16] The patients were eligible if they were newly (treatment-naïve) or previously diagnosed (in the relapse phase). All patients received the same treatment protocol, consisting of a combination of IVIg (2 g/kg for the first month, then by 1g/kg monthly) and prednisolone (1 mg/kg/day followed by gradual tapering). All research participants provided informed consent.

Functional measures

MUNIX, electrodiagnostic studies (EDX), clinical outcome measures, including MRCSS, ONLS, R-ODS, Jamar hand-grip dynamometry, Timed 10-Meter Walk Test (10MWT), pinch power test, and nine-hole peg test (NHPT) were performed at baseline and after six months, according to previously validated and published protocols.[17–19]

Manual muscle testing was used to measure the muscle strength bilaterally according to the MRCSS (ranging from 0 to 60 points) for shoulder abduction, elbow flexion, wrist extension in upper extremities and hip flexion, knee extension, and ankle dorsiflexion in lower extremities.

A hydraulic pinch gauge (SAEHAN Corporation, Changwon, South Korea) was used. The measurement was repeated three times, and the average was calculated.

Electrodiagnostic study

NCSs were performed with standard methods using a Nicolet EDX electromyography (EMG) machine (software: Synergy version 22.0.2.146, 2013 Natus, Pleasanton, CA). CMAPs were recorded with stimulation of the median, ulnar, tibial, and peroneal nerves on both sides. Sensory nerve action potentials (SNAPs) were recorded for bilateral sural and ulnar nerves. NCS data were quantified using a previously described scoring system.[20] Each abnormal motor nerve conduction study was scored with a maximum of 3 points: i) 1 point was allocated for reduced conduction velocity (CV), distal motor latency, prolonged F-wave latency, or possible conduction block, ii) 1 additional point was added if these motor nerve conduction study values reached percentages proposed by EFNS/PNS guidelines, and iii) 1 further point was added for reduced CMAP amplitude with distal stimulation. An unrecordably small CMAP was scored with a maximum of 3 points. Each abnormal SNAP was scored with a maximum of 2 points: i) 1 point for CV reduction and ii) 1 point for SNAP amplitude reduction. 2 points were calculated if no SNAP was recorded. The sum of all points yields the NCSS, with a maximum total score of 32 (16 points for each side). After six months, the change of NCSS was evaluated.

MUNIX

CIDP patients underwent MUNIX using a Nicolet EMG machine on both sides (software: Synergy version 22.0.2.146, 2013 Natus). The method of obtaining MUNIX was based on previous studies.[21–23] Each subject was positioned supine, and skin temperature was maintained above 34 ± 2°C during the procedure. The high-pass and low-pass filters were set to 5 Hz and 3 kHz, respectively. MUNIX measurements were performed recording over the ADM, APB, and TA muscles on both sides, as previously reported.[24–26] Ulnar, median, and peroneal nerves

were supramaximally stimulated using a tendon-belly surface electrode montage to obtain a CMAP for ADM, APB, and TA muscles according to published guideline.[27] Then, the tested muscles were assessed at five distinct force levels (about 10%, 25%, 50%, 75%, and 100% of maximal force) for a few seconds each, and the related surface interference pattern (SIP) was recorded for 300 milliseconds. Finally, at least 10 SIP epochs were imported to the Synergy software to calculate the MUNIX score. Motor unit size index (MUSIX) was calculated according to the following formula: (CMAP amplitude/MUNIX) × 1000

Statistical analysis

Statistical analyses were performed using the RStudio (R version: R-3.6.1). The compliance of variables with a normal distribution was tested with the Shapiro-Wilk test and probability graphics. For data with non-normal distributions, results are presented as median (25 - 75 percentile), whereas data with normal distributions are provided as mean (SD).

The Wilcoxon signed-rank test was used to compare the clinical and electrodiagnostic baseline to results at six months; for MUNIX, the paired t-test was used because the data followed a normal distribution. The Spearman's test wasused to calculate the correlations between MUNIX parameters and clinical and electrodiagnostic parameters.

For correlation analysis in upper limbs, we calculated MUNIX sumscores of APB and ADM (APB+ADM) and functional scores of upper limb MRCSS, upper limb ONLS, pinch, NHPT, and grip at baseline and follow-up. Likewise, for the lower limbs, the correlation was calculated between MUNIX of TA and lower limb MRCSS, 10MWT, and lower limb ONLS.

Finally, change in each score was defined (follow-up score – baseline score) as Δscores.

P-values < 0.05 were considered statistically significant.

Results

Demographic Data

Twenty patients were enrolled in this study. Nine patients were new (treatment-naïve). Clinical and electrodiagnostic studies were conducted for all patients at baseline;. Sixteen patients completed the follow-up study (two patients died during follow-up, and two patients declined to come for follow-up). No significant difference in clinical and electrodiagnostic data was found at baseline between treatment-naïve patients and those in the relapse phase (Table 1).

The mean age of patients was 43.9 years (SD: 13.5). Fourteen (70%) subjects were male, and the mean disease duration was 2.9 years (SD.: 3.0). Five patients (25%) had diabetes mellitus.

Change between Baseline and Follow-up MUNIX Parameters

APB, ADM, and TA MUNIX all improved significantly from baseline to the 6-month assessment; likewise, the mean MUNIX sum score also increased significantly (Table 1).

Change between Baseline and Follow-up Clinical and electrodiagnostic Parameters

Clinical, electrodiagnostic, and MUNIX parameters at baseline and follow-up are shown in Table 1. Upper, lower, and total MRCSS, Jamar grip, total ONLS, R-ODS, NHPT, and 10MWT significantly improved at six months. NCSS and CMAP amplitudes did not change significantly at six months. The effect size (ES) of the change in MUNIX parameters was larger than most other parameters. The MUNIX sumscore demonstrated the highest ES. Changes of MUSIX scores are shown in Supplementary Table 1.

Correlation between clinical and MUNIX parameters at baseline and Follow-up

The association between clinical and MUNIX parameters at baseline is presented in Tables 2 and 3. At 6-month follow-up, the MUNIX sumscore correlated with ONLS, R-ODS, and NCSS

(Table 2). Correlation between measurement tools and MUSIX sumscores at baseline and follow-up are shown in Supplementary Table 2.

Significant correlations were found between the MUNIX sumscore and both MRCSS and NCSS at baseline, between both the pinch strength and grip and upper limb MUNIX at baseline and follow-up, and between MUNIX of TA and both lower limb MRCSS with lower limb ONLS at baseline and follow-up. (Tables 2 and 3).

Correlation between MUNIX sumscore change and outcome measurement tools change

Significant correlations between MUNIX sumscore change (ΔMUNIX sumscore) and ΔMRCSS, ΔR-ODS, and ΔONLS were found (Figure 1).

Discussion

This study demonstrated that MUNIX parameters significantly improved six months after treatment, in agreement with the improvements in clinical scores. Notably, MUNIX parameters showed the most remarkable changes compared to other clinical and paraclinical parameters indicating the highest sensitivity (greater ES) for 6-month follow-up.

Improvement in MUNIX parameters following treatment was detected in previous studies despite a short-duration follow-up.[10,14,28,29] In one study, MUNIX sumscores were lower in CIDP patients than healthy subjects and correlated with ONLS and R-ODS scores.[10] A rapid, measurable improvement was seen in MUNIX parameters on repeat testing (average 15 days) following IVIg treatment.[10]

A double-blind, randomized study evaluated 23 patients with CIDP after 12 weeks of treatment with either subcutaneous immunoglobulin (11 patients) or placebo (12 patients).[14] Proximally evoked CMAP amplitudes and MUNIX tended to be better preserved in treated patients. However, changes in other parameters did not differ between groups.

A decrease in MUNIX is explained by axonal loss or conduction block, both seen in CIDP.[30] The rapid improvement in MUNIX parameters in previous studies suggests improvement of conduction block in multifocal motor neuropathy (MMN).[30] Long-term improvement in MUNIX has also been studied in dysimmune neuropathies like MMN and anti-myelin associated glycoprotein (MAG) neuropathy.[30,31] Philibert et al. assessed the MUNIX parameters longitudinally in the APB and ADM muscles of 7 MMN patients after IVIg infusion and 17 healthy controls. MMN patients were evaluated on the first day of IVIg infusion, 5 MMN patients were evaluated 22 days after the infusion, and 3 patients were assessed 1 month after two IVIg infusions. MUNIX was significantly lower in MMN patients than in healthy controls. The MUNIX sumscore improved in three of the five patients about three weeks after IVIg infusion and in two of the three patients one month after IVIg infusions.[30] In another study,[31] six anti-MAG neuropathy patients were evaluated one year after rituximab treatment. MUNIX sumscore was significantly correlated with ONLS, grip strength in the dominant hand, MRC testing, and CMAP sumscore. One year after rituximab, four patients improved on the ONLS score, and five patients improved on MUNIX sumscore.

In our study, the MUNIX sumscore was correlated only with MRCSS and NCSS at baseline but not total ONLS or R-ODS. This finding contrasts with former studies.[13,30] Nevertheless, the lack of correlation between MUNIX and clinical measures has been reported by other studies. It may be due to the discrepancy between the muscle groups examined with MUNIX and those tested clinically.[14] However, when looking more specifically and repeating the calculations for upper limbs and lower limbs separately, we found that the upper limb MUNIX correlated with clinical tests that examined distal upper limbs (grip and pinch power test). Interestingly, similar results were found for lower limb MUNIX (TA) and lower limb ONLS. These associations persisted at a 6-month follow-up.

Moreover, associations between ΔMUNIX, ΔMRCSS, ΔR-ODS, and ΔONLS was found, indicating that MUNIX could be applied in parallel to clinical outcome measurements. A previous study found no similar correlations between ΔMUNIX and Δisokinetic muscle strength or Δgrip strength.[14] However, in this study, MUNIX was tested specifically in the APB muscle. In another analysis, the MUNIX sumscore correlated with total MRCSS, and the MUNIX score of individual muscles associated with the strength in the corresponding muscle.[13]

In our study, improvement in MUNIX after six months was probably due to a decrease in conduction block, improvement in disrupted nodal sodium-channel function [32], or changes in the paranodal region;[33] however, no correlation was found between ΔMUNIX and ΔNCSS. Furthermore, CMAP amplitudes did not change significantly in the observed interval, and the ES of CMAP amplitudes was considerably lower than ES of MUNIX parameters. Similar findings were demonstrated in previous studies in which NCS parameters did not change significantly despite clinical improvement.[34,35] These findings indicate higher sensitivity of MUNIX than conventional electrophysiology as an electrodiagnostic evaluation tool.

Our study had some limitations. It was performed in a single center and did not contain a group of healthy controls. We also used treatment modalities combining corticosteroid and immunoglobulin treatment which is not standard practice in many centers, where monotherapy is preferred, particularly in treatment-naïve patients. Also, the patients were non-homogeneous, with both treatment-naïve and treated patients enrolled in the study. Therefore further studies in larger, more homogeneouspopulations from multiple centers are needed to confirm our findings.

Conclusion

The identification of correlations between improvements in functional scales and changes in MUNIX suggests that MUNIX may potentially be an appropriate objective outcome measure for both research and clinical practice in subjects with CIDP.

Acknowledgment

Declaration of Competing Interest: None of the authors have potential conflicts of interest to be disclosed.

Abbreviations

10MWT: Timed 10-Meter Walk Test

ADM: Abductor Digiti Minimi

Anti-MAG neuropathy: Anti-Myelin Associated Glycoprotein

APB: Abductor Pollicis Brevis

CIDP: Chronic Inflammatory Demyelinating Polyneuropathy

CMAP: Compound motor action potential

CV: Conduction Velocity

DML: Distal Motor Latency

EDX: Electrodiagnostic Studies

EMG: Electromyography

ES: Effect Size

INCAT: Inflammatory Neuropathy Cause and Treatment

IVIg: intravenous immunoglobulin

MMN: Multifocal Motor Neuropathy

MUSIX: Motor Unit Size Index

MRCSS: Medical Research Council Sumscore

MUNIX: Motor unit number index

NCSS: Nerve Conduction Study Score

NDS: Neuropathy Disability Score

NHPT: Nine-Hole Peg Test

ONLS: Overall Neuropathy Limitation Score

R-ODS: Rasch-built Overall Disability Scale

SD: Standard Deviation

SIP: Surface Interference Pattern

SNAP: Sensory Nerve Action Potential

TA: Tibialis Anterior

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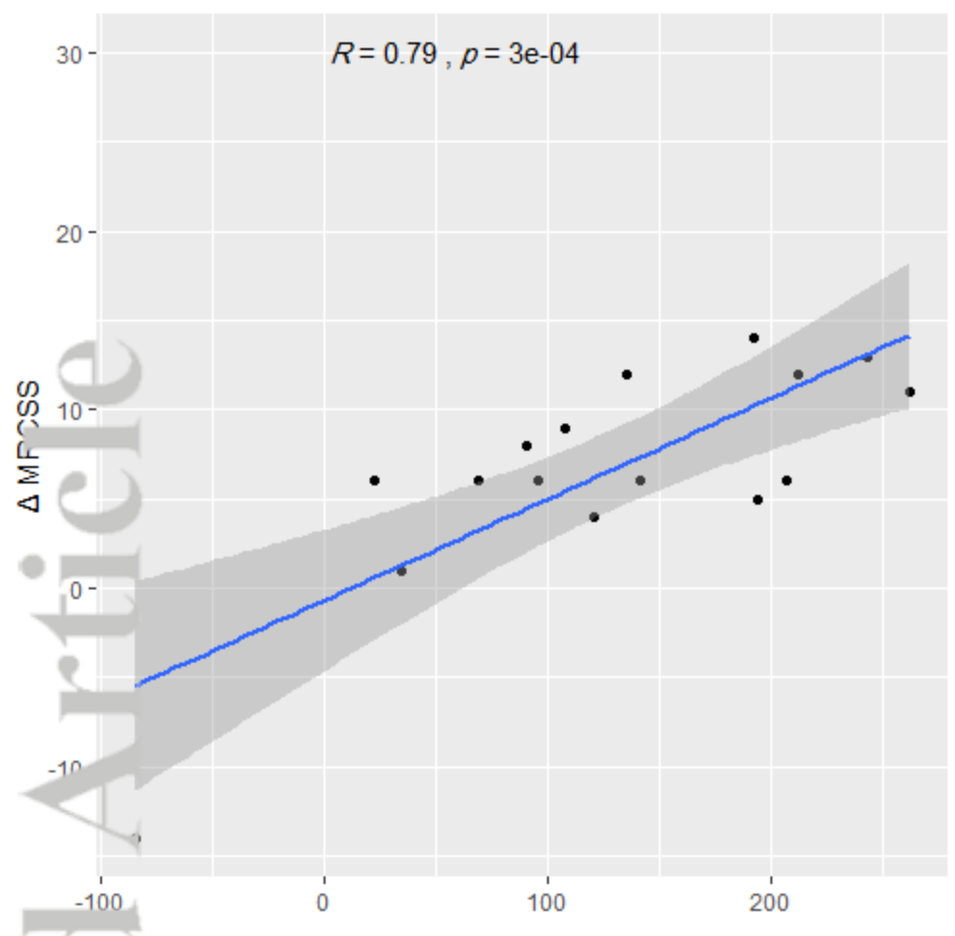
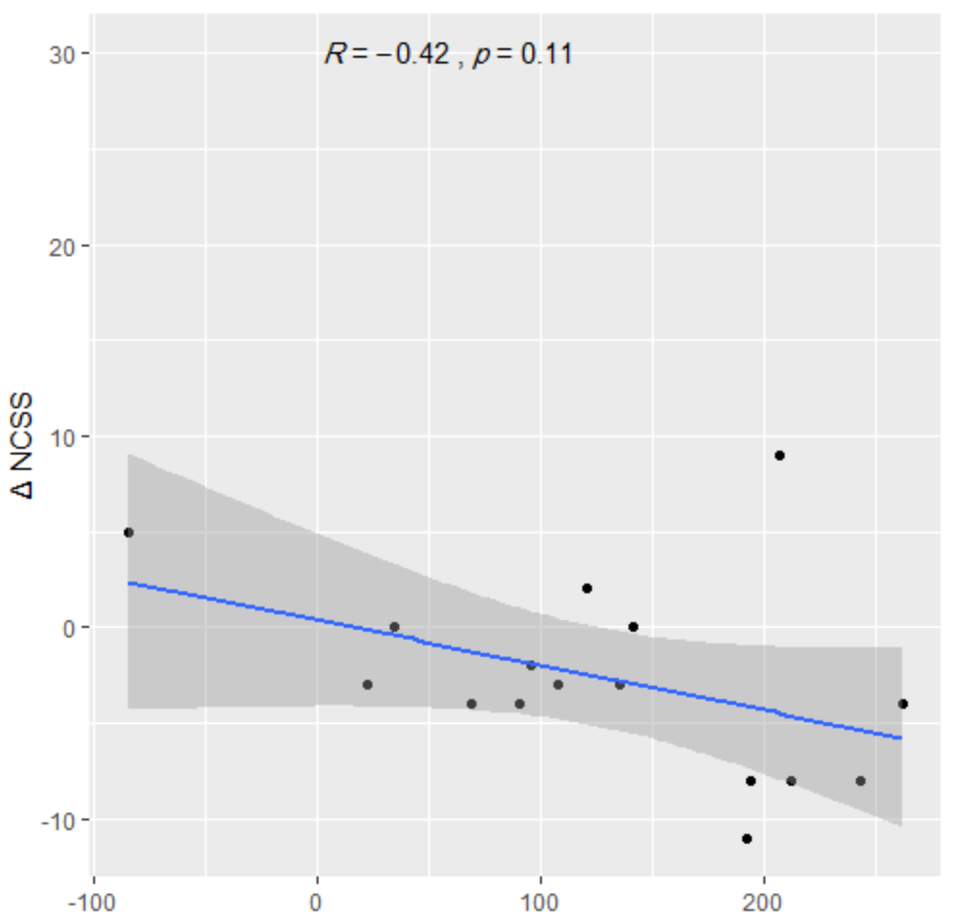
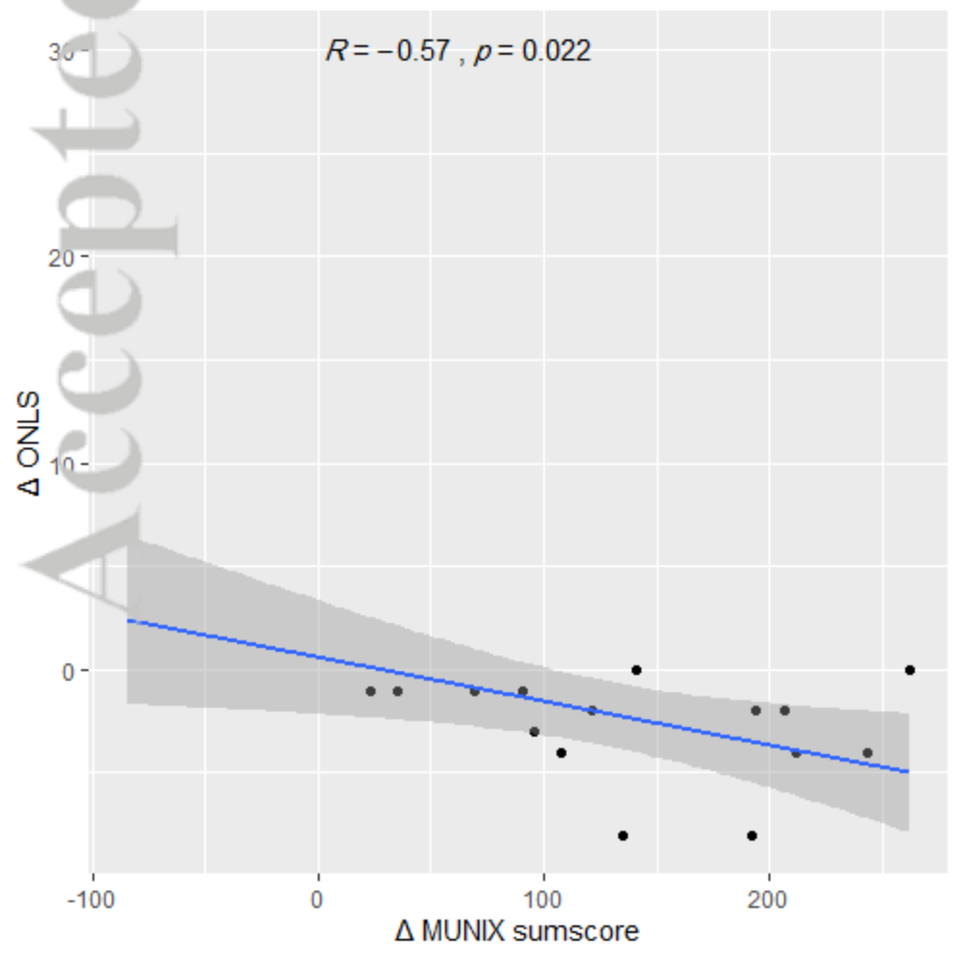
Figure Legend

Figure 1: Correlation between ΔMUNIX and ΔMRCSS, ΔR-ODS, ΔONLS, and ΔNCSS. The blue line indicates the best-fit line of data points expressing the most optimal relationship between them. The gray zone around the blue line denotes the 95% confidence interval around the best-fit line.







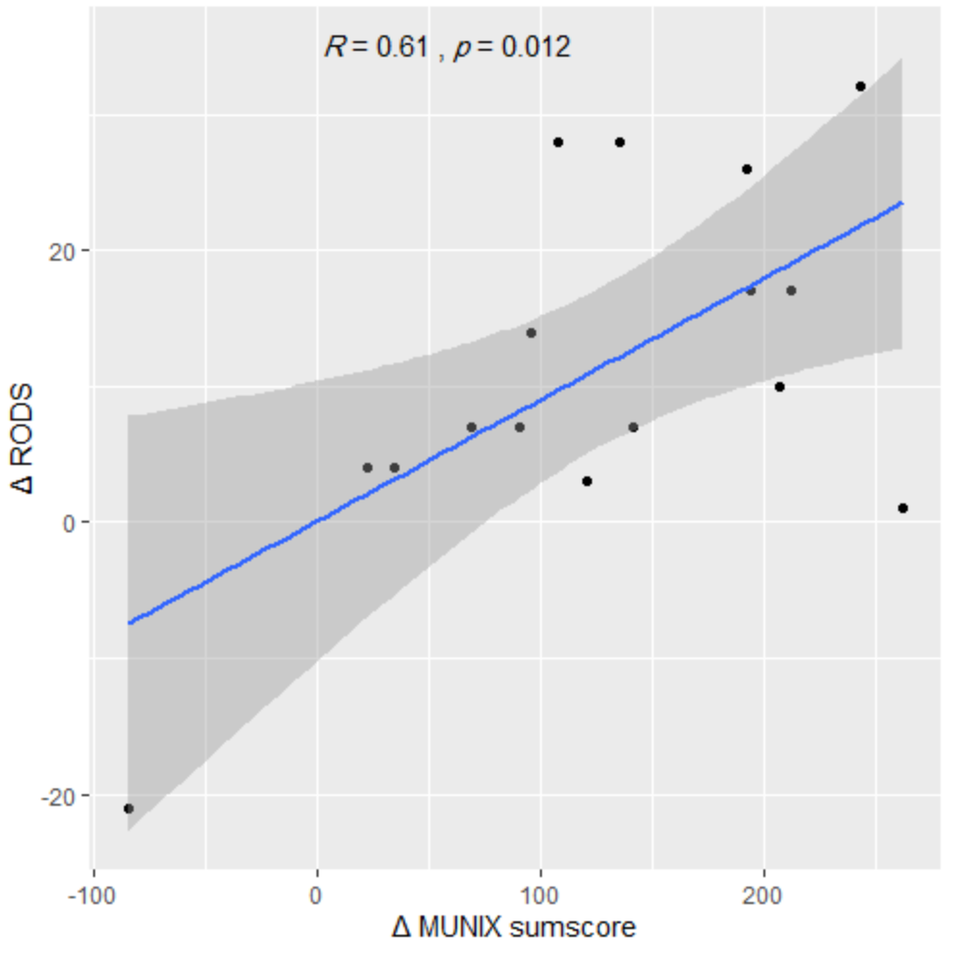


Table 1. Changes in clinical, electrodiagnostic, and MUNIX scales						
	Parameter	Baseline (IQR)	P*	After 6 months (IQR)	ES	P**
Clinical Scales	Upper MRC Sum score	27 (24 - 28)	0.69	30 (30 – 30)	0.68	0.010
	Lower MRC Sum score	22 (19.8 - 24)	0.67	28 (24 – 29)	1.00	0.004
	Total MRC Sum score	48 (44.8 - 50.5)	0.97	57.5 (53.5 - 59)	1.00	0.007
	Handgrip (kg)	19.5 (12.8 – 25)	0.76	26.5 (22 – 31.8)	0.60	0.007
	Pinch (kg)	3.4 (2.3 - 3.9)	1	4.5 (3.8 - 7)	0.54	0.065
	NHPT	37 (30.1 - 42.1)	0.77	23.8 (22.4 - 30.9)	0.67	0.002
	10MWT(seconds)	8.2 (5.5 - 10.4)	0.36	4.7 (4 - 7.8)	0.73	<0.001
	RODS	25 (18.8 - 31.2)	0.88	39.5 (33.8 - 44)	0.86	0.004
	ONLS (upper)	2 (2 - 3.2)	0.56	0.5 (0 - 2)	0.68	0.022
	ONLS (lower)	2 (2 - 3.2)	0.75	1 (0.8 - 2)	0.50	0.047
	ONLS (total)	4.5 (3 - 6.2)	0.91	2 (1 - 4)	0.62	0.01
NCSS	NCS sum score	24 (20.5 - 28)	0.22	22.5 (15.8 - 26)	0.51	0.073
Distal CMAP Amplitude	Median Nerve	4.8 (3.2 – 6.6)	0.97	5.2 (2.8 – 8.2)	0.36	0.18
	Ulnar Nerve	5.0 (3.4 – 7.3)	0.45	5.4 (3.2 – 8.3)	0.21	0.31
	Common Peroneal Nerve	1.3 (0.4 – 2.6)	0.48	1.2 (0.7 – 3.8)	0.41	0.15
MUNIX	APB MUNIX	58 (34.2 - 90)	0.27	109 (67.8 - 164.2)	1.01	0.004
	ADM MUNIX	58 (47 - 77.8)	0.88	121 (72.8 - 169.8)	0.96	0.003
	TA MUNIX	35.5 (26.8 - 58)	0.25	80.5 (49 - 100)	1.35	0.001
	MUNIX sum score	169 (129 - 215.2)	0.13	309.5 (195.8 - 432.2)	1.41	<0.001

p* indicates the comparison between treatment-naïve patients and the patients with relapse at baseline, p** indicates the comparison between 6-month follow-up and baseline in the patients, ADM: Abductor Digiti Minimi, APB: Abductor Pollicis Brevis, CMAP: Compound Muscle Action Potential, ES: Effect Size between 6-month follow-up and baseline, IQR: Interquartile Range, NHPT: Nine-Hole Peg Test, 10MWT: Timed 10-Meter Walk Test, MRC: Medical Research Council, MUNIX: Motor unit number index, NCS: Nerve Conduction Study, NCSS: Nerve Conduction Study Sum score, ONLS: Overall Neuropathy Limitation Score, RODS: Rasch-built Overall Disability Scale, TA: Tibialis Anterior.

Table 2. Correlation between measurement tools and MUNIX sum scores (APB+ADM+TA) at baseline and follow-up				
MUNIX parameters / Clinical & EDX Parameters	Baseline		6-month Follow-up	
	MUNIX sum scores		MUNIX sum scores	
	r	p	r	p
MRCSS	**0.58**	**0.01**	**0.62**	**0.01**
ONLS	-0.44	0.053	**-0.65**	**0.007**
RODS	0.24	0.30	**0.64**	**0.007**
NCSS	**-0.50**	**0.025**	**-0.58**	**0.018**

ADM: abductor digiti minimi, APB: abductor pollicis brevis, MRCSS: Medical research council sum score, MUNIX: Motor unit number index, NCSS: Nerve Conduction Study sumscore, ONLS: Overall Neuropathy Limitation Score, RODS: Rasch-built Overall Disability Scale, TA: tibialis anterior.

Table 3. Correlation between upper and lower limb measurement tools and MUNIX sum scores of upper limbs (APB+ADM) and lower limbs (TA) at baseline and follow-up

	Measurement tools	Baseline MUNIX		6-month Follow-up MUNIX	
		r	p	r	p
Upper	**MRCSS (upper)**	0.44	0.05	**0.58**	**0.02**
	ONLS (upper)	-0.26	0.27	-0.47	0.07
	Pinch	**0.51**	**0.02**	**0.72**	**0.0001**
	NHPT	-0.21	0.38	**-0.59**	**0.02**
	Handgrip	**0.46**	**0.04**	**0.56**	**0.02**
Lower	**Lower MRCSS**	**0.62**	**<0.001**	**0.57**	**0.02**
	ONLS (Lower)	**-0.55**	**0.01**	**-0.56**	**0.03**
	10MWT	-0.29	0.26	-0.09	0.76

10MWT: 10-meter walking test, ADM: abductor digiti minimi, APB: abductor pollicis brevis,, NHPT: nine-hole peg test, MRCSS: Medical research council sum score, MUNIX: Motor unit number index, ONLS: Overall Neuropathy Limitation Score, TA: Tibialis Anterior.