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Original Article

The Sensitivity and Specificity of Split-Hand Index Using Muscle Sonography

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ABSTRACT: ***Background:*** The split-hand index (SHI) (first dorsal interosseous (FDI) × abductor pollicis brevis (APB)/abductor digiti minimi muscle (ADM)) has been suggested as a useful measure for amyotrophic lateral sclerosis (ALS) diagnosis, using electrophysiological and sonographic indices. In the present study, we aimed to explore the specificity of SHI derived by muscle ultrasound (MUS) for the diagnosis of ALS and spinal muscular atrophy (SMA). ***Methods:*** Healthy controls ($n = 65$) were prospectively recruited at the Prosserman Family Neuromuscular clinic at Toronto General Hospital, from October to December 2018. In addition, 181 patients with ALS ($n = 91$), SMA ($n = 33$), polyneuropathy ($n = 35$), and myopathy ($n = 22$) were prospectively recruited at the neuromuscular clinic at Tel Aviv Sourasky Medical Center, from December 2018 to December 2020. All subjects underwent quantitative sonographic evaluation of muscle thickness, including the right APB, FDI, and ADM muscles. Area under curve (AUC), sensitivity, and specificity were determined for differentiating between groups. ***Results:*** Although SHI showed good to excellent accuracy for differentiating each patient subgroup from controls (AUC 0.83–0.92), poorer diagnostic accuracy was shown for differentiating between different patient subgroups (AUC 0.54–0.74). ***Conclusions:*** Sonographic SHI is useful for differentiating patients from healthy controls, but might be not specific for motor neuron disease.

RÉSUMÉ : La sensibilité et la spécificité de l'indice de la main divisée au moyen d'examens d'échographie musculaire. ***Contexte :*** L'indice de la main divisée (*split-hand index* ou « SHI » ; premier interosseux dorsal ou PID ; muscle court abducteur du pouce ou MCAP ; muscle abducteur de l'auriculaire ou MAA) a été suggéré comme une mesure utile permettant le diagnostic de la sclérose latérale amyotrophique (SLA), et ce, en utilisant des données électro-physiologiques et échographiques. Dans la présente étude, nous avons cherché à explorer la spécificité du « SHI » dérivé d'examens d'échographie musculaire pour le diagnostic de la SLA et de l'atrophie musculaire spinale (AMS). ***Méthodes :*** D'octobre à décembre 2018, des témoins en santé ($n = 65$) ont été recrutés de manière prospective au sein de la clinique neuromusculaire de la famille Prosserman de l'Hôpital général de Toronto. En outre, notons que 181 patients atteints de SLA ($n = 91$), d'AMS ($n = 33$), de polyneuropathie ($n = 35$) et de myopathie ($n = 22$) ont été recrutés de manière prospective de décembre 2018 à décembre 2020 au sein d'une clinique neuromusculaire du *Tel Aviv Sourasky Medical Center*. Tous les sujets à l'étude ont subi une évaluation échographique quantitative de l'épaisseur de leurs muscles, y compris les muscles PID, MCAP et MAA droits. Enfin, l'aire sous la courbe (ASC), de même que la sensibilité et la spécificité, ont été déterminées en vue de différencier les groupes. ***Résultats :*** Alors que le « SHI » a montré une précision allant de bonne à excellente pour différencier chaque sous-groupe de patients des témoins (ASC 0,83–0,92), une moins bonne précision diagnostique a été établie lorsqu'il s'agit de différencier entre eux les différents sous-groupes de patients (ASC 0,54–0,74). ***Conclusions :*** Le « SHI » obtenu par échographie est certes utile pour différencier les patients des témoins en santé ; cela dit, il pourrait ne pas être assez spécifique dans le cas de maladies du motoneurone.

Keywords: SHI; muscle ultrasound; ALS; SMA; polyneuropathy; myopathy

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Introduction

Patients with amyotrophic lateral sclerosis (ALS) may present with disproportional wasting and weakness of the abductor pollicis brevis (APB) and first dorsal interosseous (FDI) muscles, with relative sparing of the abductor digiti minimi muscle (ADM), which is known as the split-hand syndrome.[1] Consequently, the split-hand index (SHI) ((FDI × APB)/ADM) has been suggested as a useful measure for ALS diagnosis, using electrophysiological indices such as the compound muscle action potential (CMAP) amplitudes,[2–4] F-waves,[4,5] and motor unit number index (MUNIX),[3,6] and recently also by using sonographic indices including muscle echointensity[7] and thickness.[8] In addition, split hand was

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recently demonstrated also in patients with spinal muscular atrophy (SMA) using MUNIX[6] and muscle ultrasound (MUS).[8] However, the sensitivity and specificity of split hand are somewhat limited, as split hand can be found in 20% of disease controls,[2,9] and at a higher rates of 30% in patients with inflammatory polyneuropathies.[9]

We have previously shown that SHI can be determined by quantitative sonographic assessment of hand muscle thickness, with excellent diagnostic accuracy for differentiating healthy controls from patients with ALS, and with good diagnostic accuracy for differentiating healthy controls from patients with SMA.[8] In the present study, we aimed to explore the specificity of SHI derived by MUS for differentiating ALS and SMA from patients with other neuromuscular disorders.

Materials and Methods

Healthy controls were prospectively recruited at the Prosserman Family Neuromuscular clinic, Toronto General Hospital, University Health Network, from October to December 2018, as part of a study aimed to determine normative values for muscle thickness measured by US, including subjects from the clinic and hospital staff, and family members accompanying patients to the neuromuscular clinic.[10] The Research Ethics Board of the University Health Network approved the study protocol and all subjects signed an informed consent. In addition, patients with ALS, SMA, polyneuropathy, and myopathy were prospectively recruited at the neuromuscular clinic at Tel Aviv Sourasky Medical Center, Tel Aviv, Israel, from December 2018 to December 2020. The Institutional Review Board of Tel Aviv Sourasky Medical Center approved the study protocol and all subjects signed an informed consent. Clinical scales applied to assess disease severity included ALS Functional Rating Scale Revised (ALSFRS-R)[11] in patients with ALS and SMA, Hammersmith Functional Rating Scale Expanded (HFMSE)[12] in patients with SMA, and the Overall Neuropathy Limitations Scale (ONLS)[13] in patients with polyneuropathy and myopathy. All healthy controls and patients underwent quantitative sonographic evaluation of muscle thickness, including the right APB, FDI, and ADM muscles, except for patients with significantly greater weakness in their left hand that underwent sonographic evaluation of their left hand. All subjects underwent MUS examination by a single examiner experienced with neuromuscular US (AA), in the supine position. MUS was performed in healthy controls using General Electric ultrasound device (LOGIQ S7 Expert, Toronto, Canada), and a transducer with a frequency of 15 Hz (ML6-15),[10] while MUS in all patients was performed using Mindray M7 ultrasound device (Mindray, Shenzen, China), with a linear array transducer (L14-6Ns, Mindray, Shenzen, China). Muscle compression apart from the weight of the probe, was avoided, and the mean value of two to three consecutive thickness measurements was calculated to improve reliability.[10] All muscles were imaged at their short axis, with electronic calipers placed online to measure muscle thickness at the location of maximum thickness. For FDI imaging, the probe was placed with a hand at semipronation perpendicular to the axis of the second metacarpal at the level of the first metacarpophalyngeal joint,[14] for the APB with the hand at supination perpendicular to the axis of the first metacarpal slightly proximal to its center, and for the ADM with the hand at supination laterally and perpendicular to the axis of the fifth metacarpal slightly proximal to its center (Figure 1).

Statistical Analysis

Statistical analysis was performed using statistical package for social sciences (SPSS) software version 25 (IBM Corp., Armonk, NY, USA). Comparisons of demographics, clinical characteristics, between healthy controls and patients were performed using the Kruskal–Wallis one-way analysis of variance, Mann–Whitney U test, or the $\chi 2$-test, as appropriate. Comparisons of muscle thickness and SHI between healthy controls and each patient subgroup were performed using the Kruskal–Wallis one-way analysis of variance. Pairwise comparisons have been adjusted by the Bonferroni correction for multiple tests. Diagnostic accuracy for differentiating between healthy controls and each patient subgroup and between different patient subgroups was performed using the area under curve (AUC) calculated from the receiver operating characteristics curves formed using sensitivity and (1-specificity). Optimal cut-off point for SHI maximizing sensitivity and specificity was determined using Youden index. P values <0.05 were considered as significant.

Results

Sixty-five controls, 91 patients with ALS, 33 with SMA, 35 with polyneuropathy, and 22 patients with myopathy were included (Tables 1S and 2S). There were significant differences between subgroups. While SMA patients were the youngest with longest disease duration, ALS patients were the oldest with shortest disease duration. ALS patients had a more severe disease compared with SMA patients as captured by the ALSFRS-R, while there was no difference in disease severity between patients with polyneuropathy and myopathy as captured by the ONLS (Table 1). Compared with healthy controls, FDI muscle thickness was lower in all patients, APB in all patients except those with myopathy, and ADM only in patients with ALS and SMA. The SHI was lower in all patient subgroups compared with controls, most prominently in ALS (Figure 2). Although SHI showed excellent accuracy for differentiating ALS patients from controls (AUC – 0.92), and good accuracy for differentiating other patient subgroups from controls (AUC 0.83–0.87), poorer diagnostic accuracy was shown for differentiating between different patient subgroups (AUC 0.54–0.74), with the lowest diagnostic accuracy shown for differentiating SMA from polyneuropathy (AUC 0.54) (Table 2).

Discussion

We have previously shown that the SHI determined by quantitative sonographic evaluation of hand muscle thickness has excellent diagnostic accuracy for differentiating patients with ALS from healthy controls (AUC – 0.92), and good diagnostic accuracy for differentiating patients with SMA from healthy controls (AUC – 0.87).[8] The ability of the sonographic SHI to differentiate between patients with motor neuron disease and healthy controls is in line with previous studies using electrophysiological and sonographic indices.[3,4,6,7] However, our current study results suggest that sonographic SHI cannot differentiate between motor neuron diseases, and other neuromuscular disorders, including polyneuropathy or myopathy (AUC 0.54–0.74). The sonographic SHI showed good to excellent accuracy for differentiating all patient subgroups from controls (AUC – 0.83–0.92), especially in ALS (AUC – 0.92), but had inferior performance for differentiating between various neuromuscular disorders, including between

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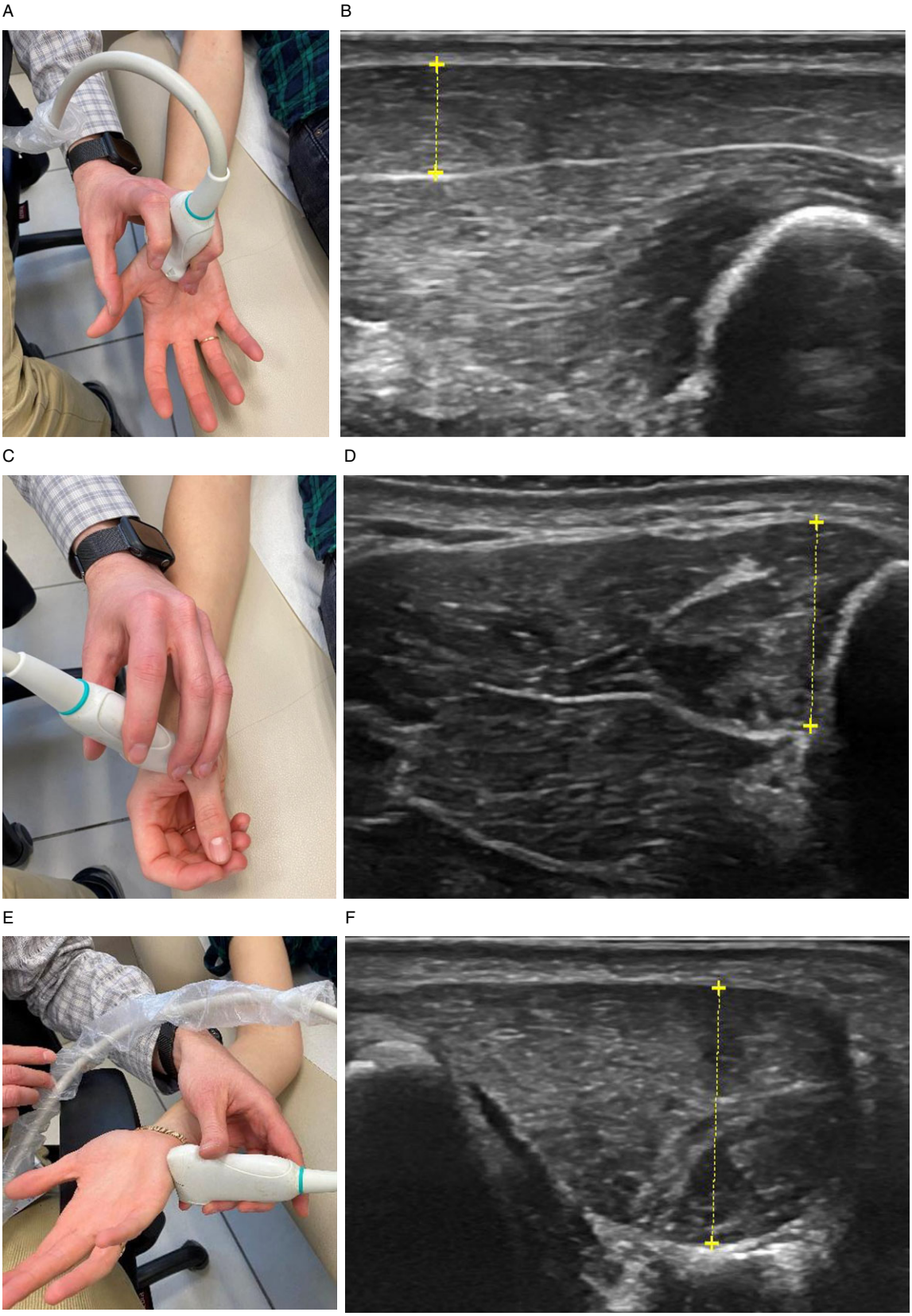

Figure 1: Ultrasound probe position and images of APB (A and B), FDI (C and D), and ADM (E and F) muscles in a healthy subject.

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Table 1: Comparisons of demographics and clinical characteristics between 65 healthy controls and 181 patients with various neuromuscular disorders

	Controls	ALS	SMA	PNP	MYO	*P*-value
N	65	91	33	35	22	
Females (%)	63	44	56	60	59	0.159
Age (years)	47 [32,60]	66 [54,72]	32 [25,45]	54 [40,68]	52 [41,72]	**<0.001**
BMI	24 [21.9,28.6]	24.2 [21.9,27.3]	24.5 [22,28.9]	26.9 [22.1,30.7]	24.3 [21.5,27.9]	0.583
Disease duration (months)	–	30 [18,47]	366 [240, 456]	60 [15,120]	168 [30,315]	**<0.001**
Right hand dominance, n (%)	63 (97)	87 (96)	29 (88)	29 (85)	21 (95)	0.112
ALSFRS-R (0–48)	–	32 [24,37]	38 [31,43]	–	–	**0.001**
HFMSE (0–69)	–	–	15 [5,37]	–	–	–
ONLS (0–10)	–	–	–	3 [2,4]	3 [2,6]	0.407

PNP: peripheral neuropathies; MYO: Myopathies; ALS: Amyotrophic Lateral Sclerosis; SMA: Spinal Muscular Atrophy; BMI: Body mass index; ALSFRS-R: ALS functional rating scale-revised; HFMSE: Hammersmith functional rating scale Expended. Data are presented as median [interquartile range] unless indicated otherwise. Significant p-values (<0.05) are bolded.

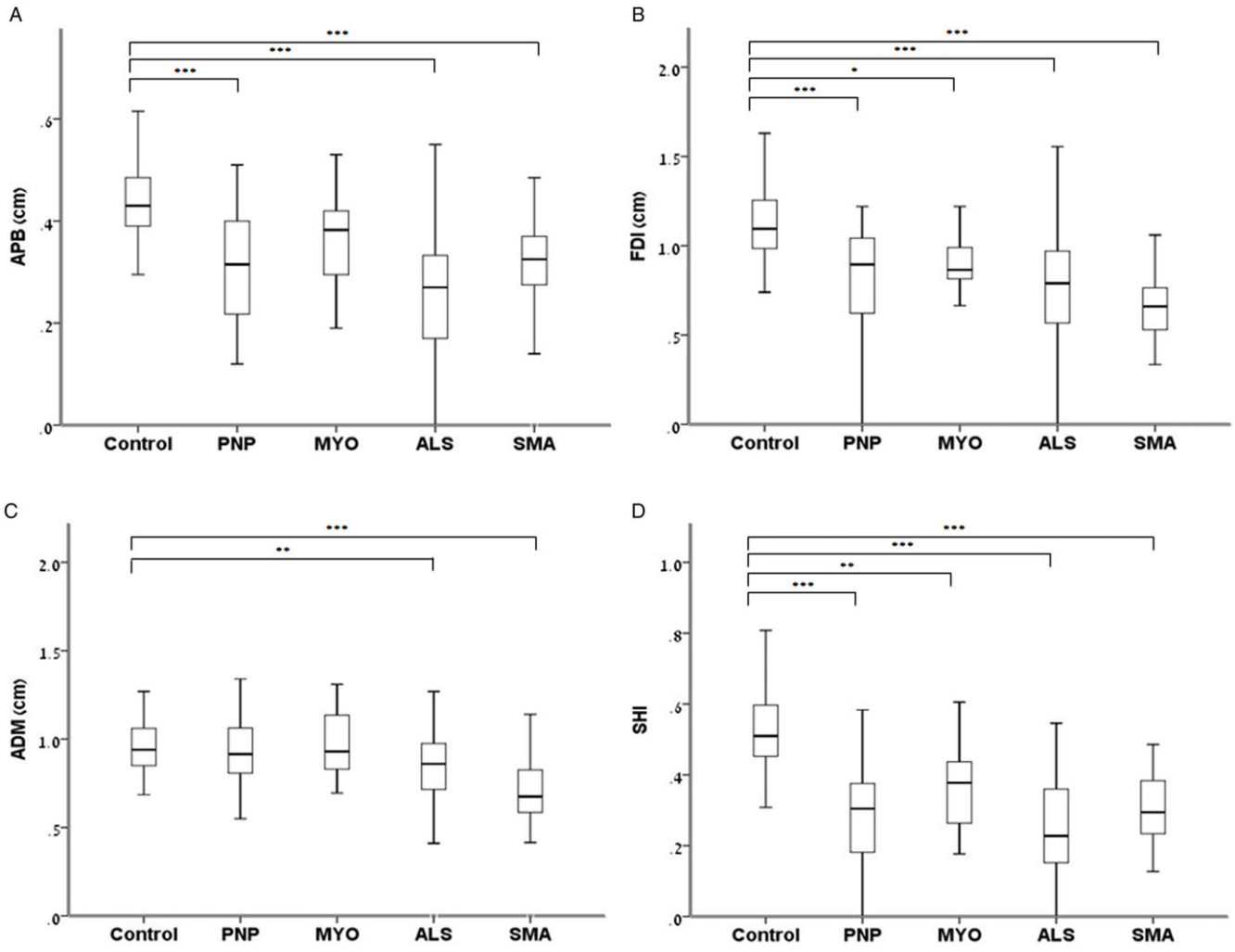

Figure 2: Comparisons of hand muscle thickness and SHI between healthy controls and patients with various neuromuscular disorders.

motor neuron diseases and other neuromuscular disorders. These findings are in contrast to previous studies suggesting that the SHI is a specific measure, which can differentiate between ALS and other neuromuscular diseases.[2,5,7] However, only one study showed sonographic SHI specificity for motor neuron disease using echointensity, and had a limited number of nine patients with other neuromuscular conditions.[7] The discrepancy of SHI performance regarding specificity between electrophysiological and sonographic findings is surprising in light of the correlation between CMAP amplitude and muscle thickness.[15] However,

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Table 2: Sensitivity, specificity, and area under the curve (AUC) calculated from the receiver operating characteristics curves for differentiating between different neurological conditions and healthy controls using the sonographic Split-Hand Index

		Control	PNP	MYO	ALS
PNP	AUC	0.86			
	SHI	0.45			
	Sensitivity (%)	86			
	Specificity (%)	83			
MYO	AUC	0.83	0.66		
	SHI	0.45	0.21		
	Sensitivity (%)	78	96		
	Specificity (%)	93	37		
ALS	AUC	0.92	0.58	0.74	
	SHI	0.44	0.30	0.21	
	Sensitivity (%)	78	54	96	
	Specificity (%)	93	33	47	
SMA	AUC	0.87	0.54	0.64	0.63
	SHI	0.42	0.21	0.32	0.24
	Sensitivity (%)	86	81	64	75
	Specificity (%)	84	37	66	54

Wang et al. found in patients with carpal tunnel syndrome and ulnar neuropathy association between neuropathy and sonographic hyper-echointensity in APB and FDI, but not in ADM,[16] in line with our study finding, showing more prominent muscle thickness loss in the APB and FDI compared with ADM across all patient subgroups. Furthermore, we found that ADM muscle thickness was reduced only in patients with ALS and SMA. These finding suggest possible discrepancy regarding the association between electrophysiology and MUS for ADM, possibly explaining the lack of sonographic SHI specificity. An additional contribution for the lack of specificity, which was most prominent for differentiating between polyneuropathy and motor neuron diseases, might be related to our cohort composition. It has been previously shown that 30% of patients with inflammatory polyneuropathies such as chronic inflammatory demyelinating disease (CIDP) show split hand characteristics, and indeed, 16 out of 35 patients with polyneuropathy in our cohort had CIDP.[9]

Our study has several limitations. We have not performed electrophysiological evaluations at the time of the MUS study, and therefore could not explore the specificity of SHI using electrophysiological indices, or assess for additional confounding factors such as median or ulnar entrapments which might affect muscle thickness. We recorded muscle thickness, but not cross sectional area (CSA), which might be a more robust measure. However, there is a very strong correlation between muscle thickness and CSA,[17] and in some muscles, such as the APB, CSA measurement might be more challenging compared with thickness measurement. In addition, the cross-sectional area have not recorded echointensity, as healthy controls and patients were studied using different ultrasound devices. However, while echointensity depends on device type and setting, and has to be analysed offline using an external computer and dedicated software, muscle thickness is expected to be similar across different devices and could be determined online or offline by the US device, and therefore might be a more practical parameter at clinic, and yielding more generalisable results. Although age was different between subgroups, we have not adjusted muscle thickness accordingly. However, our previous study showed that age had the most prominent effect on the quadriceps muscle, affecting much less small hand muscle thickness.[10] Finally, we have not restricted ultrasound studies only to patients with specific neuromuscular disorders such as multifocal motor neuropathy and inclusion body myositis, which has the potential to mimic motor neuron disease, due to the relative rarity of these diseases.

In conclusion, sonographic SHI is useful for differentiating patients with various neuromuscular disorders from healthy controls, but might be not specific for motor neuron disease.

Supplementary Material. To view supplementary material for this article, please visit https://doi.org/10.1017/cjn.2022.20

Disclosures. Reuven Avidan, Alon Abraham, and Yaara Fainmesser have no conflicts of interest to declare.

Vera Bril is a consultant to CSL Behring, Grifols, Union Chimique Belge, ArgenX Alexion, Alnylam, Akcea, Takeda, Octapharma, and Immunovant. She serves on international scientific advisory boards for the Myasthenia Gravis Foundation of America and Guillain-Barré Syndrome/Chronic Inflammatory Demyelinating Polyneuropathy (CIDP/GBS) Foundation International, and has received research support from CSL Behring, Grifols, Union Chimique Belge, ArgenX, Immnovant, Momenta, Talecris, Takeda, Octapharma, and Akcea.

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