Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Myopathic changes in patients with long-term fatigue after COVID-19

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HIGHLIGHTS

- 20 patients with persistent neuromuscular symptoms including fatigue, 77–255 (median: 216) days after acute COVID-19 were examined.
- Nerve conduction studies did not show signs of neuropathy but 11 patients (55%) had myopathic changes with quantitative electromyography.
- Myopathy may be an important cause of physical fatigue and myalgia in long-term COVID-19 even in non-hospitalized patients.

ABSTRACT

Objective: To investigate the peripheral nerve and muscle function electrophysiologically in patients with persistent neuromuscular symptoms following Coronavirus disease 2019 (COVID-19).
Methods: Twenty consecutive patients from a Long-term COVID-19 Clinic referred to electrophysiological examination with the suspicion of mono- or polyneuropathy were included. Examinations were performed from 77 to 255 (median: 216) days after acute COVID-19. None of the patients had received treatment at the intensive care unit. Of these, 10 patients were not even hospitalized. Conventional nerve conduction studies (NCS) and quantitative electromyography (qEMG) findings from three muscles were compared with 20 age- and sex-matched healthy controls.
Results: qEMG showed myopathic changes in one or more muscles in 11 patients (55%). Motor unit potential duration was shorter in patients compared to healthy controls in biceps brachii (10.02 ± 0.28 vs 11.75 ± 0.21), vastus medialis (10.86 ± 0.37 vs 12.52 ± 0.19) and anterior tibial (11.76 ± 0.31 vs 13.2 6 ± 0.21) muscles. All patients with myopathic qEMG reported about physical fatigue and 8 patients about myalgia while 3 patients without myopathic changes complained about physical fatigue.
Conclusions: Long-term COVID-19 does not cause large fibre neuropathy, but myopathic changes are seen.
Significance: Myopathy may be an important cause of physical fatigue in long-term COVID-19 even in non-hospitalized patients.

1. Introduction

Severe Acute Respiratory Syndrome 2 (SARS-CoV-2), causing the new coronavirus disease 2019 (COVID-19), has become a life-threating pandemic. It has infected millions of individuals and caused more than 2.5 million deaths globally during one year of

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pandemic. In addition to the pulmonary system, COVID-19 is affecting multiple organs including nervous system (Varatharaj et al., 2020; Ahmed et al., 2020; Ellul et al., 2020; Zubair et al., 2020), cardiovascular system (Puntmann et al., 2020), and the kidneys (Werion et al., 2020). Among neurological manifestations, headache, confusion, Guillain Barre Syndrome, critical illness myopathy, stroke, cerebral perfusion abnormalities and leptomeningeal enhancement have been described during the acute infection (Arnaud et al., 2020; Cabañes-Martínez et al., 2020; Tankisi et al., 2020; Varatharaj et al., 2020; Ahmed et al., 2020; Ellul et al., 2020). Varatharaj and coworkers described peripheral nervous system complications in 5% of 153 patients in a UK-wide surveillance study (Varatharaj et al., 2020). Additionally, in two recent studies in China (Huang et al., 2020; Wang et al., 2020), and one study in Europe (Lechien et al., 2020), myalgia or fatigue affected 44–70% of the patients, suggesting muscle involvement during the acute infection.

The COVID-19 disease severity has been variable, differing from asymptomatic cases to patients requiring intensive care unit (ICU) treatment. While we expect long-term symptoms in patients recovering from severe COVID-19, particularly those who have had ICU treatment, a worrying number of reports demonstrate long term health issues after COVID-19 (Carfi et al., 2020; Huang et al, 2021), also in non-hospitalized patients (Logue et al., 2021). However, duration of persistent symptoms following COVID-19, and the causes and underlying mechanisms remain unknown. Accordingly, long-term neurological manifestations in long-term COVID-19 remain to be determined. In a large cohort of 1655 long-term COVID-19 patients at 6th month follow-up, fatigue and muscle weakness have been reported in 63% of patients, while joint pain was seen in 9% and myalgia in 2% (Huang et al., 2021). In a smaller cohort of 157 patients at a mean of 60 days follow-up, fatigue was seen in 53.1% of patients and muscle pain in around 5% (Carfi et al., 2020). Sensory disturbances have yet not been reported systematically. In a recent study, we found 13 of 49 (27%) patients reporting paresthesia 12 weeks after discharge from hospital (Leth et al., 2021). The present study aimed to further explore the sensory disturbances as long-term neurological manifestation following COVID-19.

We aimed in this study to investigate peripheral nerve and muscle function electrophysiologically in patients with persistent neuromuscular symptoms following COVID-19.

2. Material and methods

2.1. Patients and healthy controls

In this study, 23 consecutive patients recovering from COVID-19 were examined. In all patients, prior infection with SARS-CoV-2 were demonstrated with a polymerase chain reaction (PCR) test or presence of antibodies. All patients were referred with the suspicion of neuropathy from the Long-term COVID-19 Clinic at the Department of Infectious Diseases, Aarhus University Hospital. Examinations were performed at the Department of Clinical Neurophysiology, Aarhus University Hospital in September-December 2020. Of these, 2 patients had ICU treatment during the acute COVID-19, and 1 patient was previously diagnosed for diabetic polyneuropathy. When these 3 patients with potential causes of myopathy and polyneuropathy were excluded, this left us with 20 patients. Their findings were compared with 20 age- and sex-matched healthy controls. Around 100 patients with long-term symptoms were evaluated in the Long-term COVID-19 Clinic during the time period in which patients were referred for neurophysiological examination. Long-term symptoms were registered in the patientś medical records.

Patient data was registered in a secure REDCap database hosted at Clinical Trial Unit, Aarhus University. Data collection was approved by Central Denmark Region (reference 1–45-70–5-20). The registry- and questionnaire-based design did not require ethics approval (Danish Committee Act, Section 14, Subsection 2), which was confirmed by the Regional Ethics Committee (reference 1–10-72–181-20). The Ethics Committee of the Central Denmark Region approved the recruitment of healthy controls (reference 1–10-72–53-17). Written informed consent was obtained from all healthy participants.

2.2. Clinical examination

All patients and healthy controls underwent a detailed clinical evaluation and neurological examination on the day of neurophysiological examination including force measurement, deep tendon reflexes and sensory testing. Additionally, three standard neuropathy scores were obtained for each patient. 1) The Michigan Neuropathy Screening Instrument (MNSI), 2) Utah Early Neuropathy Score (UENS) and 3) Neuropathy impairment score (NIS).

The MNSI is a screening instrument for diabetic polyneuropathy including 15 questions about sensory disturbances. UENS is a valid measure of early neuropathy with focus on sensory involvement divided into subgroups testing motor function, small fiber sensation, large fiber sensation and Achilles reflex (Singleton et al., 2008). The range of total UENS score is 0–42, giving 0 with normal neurological examination on all parameters, and the maximum score for small fiber function is 26. NIS is a standardized examination of muscle strength for all muscle groups both in upper and lower extremities, deep tendon reflexes and sensory testing. It has been used as an endpoint measure in clinical trials with scores ranging from 0 to 280.

Additionally, all patients were asked about the following: 1) physical fatigue, in particular whether they get tired quickly and feel physically exhausted, 2) myalgia, 3) joint pain, and 4) muscle cramps.

2.3. Electrophysiological examinations

NCS and EMG were performed using Keypoint.Net EMG equipment (Dantec, Skovlunde, Denmark) with conventional methods (Stålberg et al, 2019; Tankisi et al., 2019). Skin temperature was maintained over 32 °C using a heating lamp.

2.3.1. Nerve conduction studies (NCS)

NCS were performed using disposable pre-gelled surface electrodes (Ag/AgCl) with a recording area of 15 mm × 20 mm. In patients, median and ulnar nerves were examined while in healthy controls only ulnar NCS were performed. Peroneal, tibial motor NCS and sural and dorsal sural cutaneous sensory NCS were performed both in patients and healthy control, but bilaterally in patients and in healthy controls on the dominant side. Median and ulnar sensory and motor NCS were performed bilaterally if the symptoms were asymmetrical or more pronounced in the upper extremities. Additionally, sensory and motor NCS were performed in the relevant nerves in patients with symptoms corresponding to these nerves.

For median sensory NCS, the nerve was stimulated at the wrist and antidromic sensory nerve action potential (SNAP) was recorded from digit II, and for the ulnar nerve from the fifth digit. For median motor NCS, the stimulation sites were wrist and elbow, and compound muscle action potential (CMAP) was recorded from abductor pollicis brevis. For ulnar motor NCS, the nerve was stimulated at the wrist and below and above the elbow, and CMAP was recorded from abductor digiti minimi.

For peroneal nerve, the nerve was stimulated at the ankle, capitulum fibulae and fossa poplitea and the CMAP was recorded from extensor digitorum brevis. For the tibial nerve, the stimulation sites were medial malleolus and fossa poplitea and recording site was the abductor hallucis muscle.

For the sural NCS, the nerve was stimulated at the sura lateral to the edge of the Achilles tendon and antidromic SNAPs were recorded from behind the lateral malleolus at a distance of 13 cm. For dorsal sural cutaneous NCS (Kural et al., 2017; Tankisi et al., 2019), the recordings were done from the mid-portion of the fifth metatarsal bone, just lateral to the extensor digitorum longus tendon of the fifth toe and stimulation site was posterior to the lateral malleolus at a distance of approximately 12 cm.

The evaluated motor NCS parameters were distal motor latency, motor and sensory conduction velocity (CV), CMAP and SNAP amplitude and minimum F-wave latency. The CMAP amplitudes and sural and dorsal sural cutaneous nerve SNAPs were measured peak-to peak while, base-to-peak amplitude was used for median and ulnar sensory NCS measurements.

2.3.2. Quantitative electromyography (qEMG)

EMG of biceps brachii, vastus medialis and anterior tibial muscles was performed in all healthy controls while in patients, biceps brachii was examined in all patients, vastus medialis in 9 and anterior tibial muscle in 10. Additionally, EMG of the other muscles was performed in patients with relevant symptoms.

EMG was performed using a concentric 35 mm Dantec needle electrode and the Departmenťs standard filter settings of 20 Hz–10 kHz, gain (100 mV/division) and sweep speed (10 ms/division).

The presence of spontaneous activity (fibrillation potentials, positive sharp waves and fasciculations) was assessed at 10 separate sites, and spontaneous activity at more than two sites was required for abnormality (Tankisi et al., 2007). Quantitative motor unit potential (MUP) analysis (Stålberg et al., 2019) was done by sampling at least 20 MUPs during weak voluntary contraction. Mean duration, amplitude, and percentage of polyphasic potentials were evaluated. A MUP has been described as polyphasic if number of phases were ≥ 5 (Stålberg et al., 2019). The mean MUP duration was calculated for the simple potentials. A mean MUP duration lower than the 95% confidence interval of healthy controls was considered as myopathic.

2.4. Laboratory tests

In all patients, routine blood tests including vitamin B12, hemoglobin A1c (HbA1c) and thyroid-stimulating hormone (TSH) levels were performed. Additionally, erythrocyte sedimentation rate (ESR), creatinine kinases (CK), myoglobin and lactic dehydrogenases (LDH) levels in long-term COVID-19 period were examined in most patients.

2.5. Data analysis

The QtracP component of the QtracW software (© University College London, London, UK) was used for the statistical analyses and for generating figures for the electrophysiological data. Variables were tested with students' t-test or Mann-Whitney U-test depending on whether the data was normally distributed using Lilliefors test. Peroneal, tibial and ulnar motor CVs, CMAP amplitudes and minimum F-wave latencies, and ulnar, sural and dorsal cutaneous sural sensory CVs and SNAP amplitudes, and qEMG results were compared between patients and healthy controls. Additionally, sensory and motor NCS results in patients were compared with laboratorýs larger control material and values outside 2SD were defined abnormal (Tankisi et al., 2005).

Baseline characteristics and long-term symptoms were compared between patients with vs without myopathic changes using one sides Fishers exact test and Stata Intercooled version 11.

Bonferroni's correction was performed to minimize type I errors with the formula of significance level = 0.05/number of tests performed. We had 3 MUP parameters, 3 motor and 2 sensory NCS parameters tested. Therefore, a p-value of < 0.016 was required for MUP analyses and motor NCS and a p-value of < 0.02 was required for sensory NCS.

3. Results

3.1. Participant demographics

There was no significant difference in age between healthy controls (mean: 52.6 ± 1.86) and patients (mean: 53.05 ± 1.86) ($p = 0.84$) or concerning sex (healthy controls and patients: 4 males, 16 females) ($p = 1$). Ten patients were hospitalized between 2–9 days while 10 patients had mild symptoms and hospitalisation was not necessary. Neurophysiological examination was performed from 77 to 255 (median: 216) days after initial symptoms of acute COVID-19 (Table 1).

3.2. Clinical characteristics

Sensory and muscle related symptoms and clinical scores are summarized in Table 1. Four patients had sensory disturbances localized to specific nerves, and in two patients the symptoms were bilateral. The remaining 17 patients had distal symmetrical sensory symptoms either in both hands or feet or both in hands and feet (Table 1). MNSI scores ranged from 0 to 3. The UENSs ranged between 0 and 2 in 18 patients while in 3 patients the UENS was 8, 10 and 16 with higher scores for large fiber function. NIS scores ranged between 0 and 14, and in the patients with higher scores there was usually weakness in the proximal muscles. Six of the 11 patients with myopathic qEMG had decreased force both in upper and lower limb proximal muscles, 2 had weakness only in lower limb proximal muscles while 3 patients had normal force (Table 1). All patients with myopathic qEMG had physical fatigue and 8 patients had myalgia. Additionally, 3 more patients without myopathic changes had physical fatigue. All patients complaining about physical fatigue were previously physically active and did not regain physical strength despite persistent attempt of physical rehabilitation.

3.3. Neurophysiological examinations

3.3.1. Nerve conduction studies

NCS results are summarized in Table 2. There was no significant difference in motor CV, CMAP amplitudes or minimum F-wave latencies of the ulnar, peroneal and tibial nerves comparing healthy controls and patients. Similarly, ulnar, sural and dorsal cutaneous sural sensory CVs and SNAP amplitudes did not show any significant differences between the two groups.

Additionally, the NCS results including the nerves that were not examined in healthy controls were compared with laboratory control material. In one patient (Patient #12), we identified carpal tunnel syndrome. None of the other patients had abnormal NCS in any of the nerves examined.

3.3.2. Electromyography

None of the patients showed fibrillation potentials or positive sharp waves in any of the examined muscles. In 11 patients (55%), MUP analysis showed myopathic changes with shortened MUP duration with or without decreased amplitude or increased

Table 1
Patient demographics and clinical score and quantitative electromyography (qEMG) results.

ID	Age/ Sex	Hospitalisation (days)	Time to NCS/EMG (days)	Sensory symptoms	Clinical scores					Muscle symptoms	EMG
					MNSI	UENS Total	UENS SFN	UENS LFN	NIS		
1	68/M	7	189	Burning sensation and allodynia at medial side of forearm, hand and fingers (Bilateral)	0	8	0	8	8	None	N
2	59/F	6	162	Paresthesia in fingers	0	2	0	2	2	None	N
3	56/F	None	174	Paresthesia at radial side of forearm and hand (Bilateral)	0	0	0	0	2[1]	Myalgia, physical fatigue	M
4	52/F	8	180	Paresthesia in fingertips and walking on cotton wool sensation	2	0	0	0	4[1]	Myalgia, physical fatigue	M
5	68/F	9	210	Paresthesia in fingertips	0	0	0	0	12[2]	Physical fatigue	M
6	54/F	None	236	Paresthesia at medial side of left overarm and forearm	1	0	0	0	0	Physical fatigue	N
7	50/M	4	230	Short bursts of pain in arms	1	0	0	0	0	Muscle cramps	N
8	55/F	None	228	Burning sensation in fingertips	0	0	0	0	2	None	N
9	40/F	None	230	Paresthesia in feet	2	2	2	0	8[2]	Myalgia, physical fatigue	M
10	43/F	None	184	Paresthesia in fingers	0	0	0	0	0	None	N
11	54/F	None	219	Short bursts of pain in the whole body, burning sensation in feet and walking on cotton wool sensation	3	0	0	0	0	Physical fatigue	N
12	51/F	None	223	Paresthesia in fingertips and toes	3	10	4	6	14	Physical fatigue	N
13	57/F	8	224	Paresthesia in hands and feet	1	2	2	0	4	None	N
14	35/F	3	233	Paresthesia in feet	2	4	0	4	12[2]	Myalgia, physical fatigue, cramps	M
15	50/F	None	255	Paresthesia in feet	2	0	0	0	14[2]	Myalgia, physical fatigue, joint pain	M
16	64/F	3	77	Paresthesia in right lateral femoral cutaneous nerve innervation	0	0	0	0	10[2]	Physical fatigue	M
17	55/M	3	98	Paresthesia in fingertips and toes	1	0	0	0	0	Myalgia, physical fatigue	M
18	46/F	None	255	Paresthesia in fingertips and toes	1	0	0	0	0	Myalgia, physical fatigue, joint pain	M
19	53/M	2	110	Paresthesia in hands and feet	1	0	0	0	0	Physical fatigue	M
20	51/F	None	212	Paresthesia in hands and feet	2	0	0	0	12[2]	Myalgia, physical fatigue	M

MNSI: Michigan neuropathy screening instrument, UENS: Utah early neuropathy score, NIS: Neuropathy impairment score, M; Male, F; Female, N: Normal, M; Myopathic qEMG. In the first two patients included (Patients #1 and #2), vastus medialis and anterior tibial muscles were not examined. Additionally, in Patient #13, vastus medialis was not examined due to discomfort.
[1] indicates patients with decreased force in lower limbs.
[2] indicates patients with decreased force both in upper and lower limbs.

number of polyphasic potentials in one or more muscles and the results were interpreted as being consistent with myopathy (Table 1). In all patients with myopathic MUP analysis, interference pattern was also myopathic with full pattern and low amplitude. In Fig. 1, an example from a patient and healthy control is shown.

MUP duration was reduced in biceps brachii, vastus medialis and anterior tibial muscles in patients compared with age- and sex-matched healthy controls ($p < 0.0001$) (Table 2, Fig. 2a). Eleven (55%) patients had shortened duration in biceps brachii, 8 (45%) in vastus medialis and 10 (50%) in tibialis anterior (Fig. 2a). MUP amplitude in biceps brachii muscle was lower in patients than in healthy controls ($p < 0.05$) while there was no significant difference for vastus medialis and anterior tibial muscles (Table 2, Fig. 2b). There was a tendency for lower MUP amplitudes in patients than healthy controls, but this was not significant for any of the muscles. Additionally, MUP amplitude was not outside the 95% confidence interval in any of the patients (Table 2, Fig. 2b). The incidence of polyphasic potentials was higher in patients than in healthy controls for only anterior tibial muscle ($p = 0.008$) (Table 2).

3.4. Comparison of clinical characteristics between patients with and without myopathic changes

Physical fatigue and myalgia were significantly more common in patients with myopathic qEMG compared to patients without myopathic changes ($p < 0.05$). Age, sex, body mass index (BMI), hospitalization or treatment with oxygen during acute COVID-19, long lasting dyspnea, chest pain, palpitations, headache, difficulties in concentrating or memory problems were not different between patients with and without myopathic changes (Table 3). Additionally, there was no difference in the number of days from acute infection to neurophysiological examination between patients with and without myopathic changes.

None of the patients received hydroxychloroquine during the acute infection or later. None of the patients received corticosteroids during the acute infection. In the myopathy group, one patient was taking methotrexate for rheumatoid arthritis. In the non-myopathy group, one patient was taking methotrexate and prednisolone for sarcoidosis and another patient was taking simvastatin (Table 3).

Table 2
Quantitative electromyography (qEMG) and nerve conduction studies (NCS) results.

	Mean (±SE) or Median (25%,75% IQR)		Controls vs patients p-value
	Healthy controls (n = 20)	Patients (n = 20)	
MUP duration (ms) (BB)	11.8 ± 0.2	10.0 ± 0.3	**2.3^{-5}**
MUP amplitude (μV) (BB)	261.5 ± 16.1	214.1 ± 10.4	0.017
Polyphasia % (BB)§	2.1 (0, 4.8)	6.8 (0, 19.2)	0.043
MUP duration (ms) (VM)	12.5 ± 0.2	10.9 ± 0.4	**2.4^{-4}**
MUP amplitude (μV) (VM)	300.2 ± 14.8	263.5 ± 14.4	0.08
Polyphasia % (VM)§	0 (0, 4.5)	4.5 (0, 10.0)	0.042
MUP duration (ms) (TA)	13.3 ± 0.2	11.8 ± 0.3	**3.1^{-4}**
MUP amplitude (μV) (TA)	356.6 ± 19.4	321.0 ± 9.04	0.11
Polyphasia % (TA)§	8.7 (4.8, 11.9)	15.9 (10.4, 21.7)	**0.008**
Ulnar SCV (m/sec)	59.2 ± 0.9	59.1 ± 1.2	0.89
Ulnar SNAP amplitude (μV)	24.7 ± 3.0	22.3 ± 2.3	0.54
Ulnar MCV (m/sec)	62.8 ± 1.1	62.3 ± 1.0	0.74
Ulnar CMAP amplitude (mV)§	13.9 (12.8, 16.8)	13.3 (12.5, 17.2)	0.86
Ulnar minimum F-wave latency (ms)§	25.5 (24.9, 26.8)	25.7 (25.3, 27.4)	0.53
Peroneal MCV (m/sec)	46.8 ± 0.9	45.8 ± 0.8	0.41
Peroneal CMAP amplitude (mV)	7.9 ± 0.7	6.9 ± 0.5	0.22
Peroneal minimum F-wave latency (ms)§	46.2 (44.2, 47.5)	49.3 (44.3, 52)	0.11
Tibial MCV (m/sec)	51.1 ± 1.1	49.74 ± 0.99	0.36
Tibial CMAP amplitude (mV)	20.16 ± 1.36	21.7 ± 1.9	0.53
Tibial minimum F-wave latency (ms)§	47.0 (45.1, 49.1)	48.5 (46.0, 53.2)	0.34
Sural SCV (m/sec)	57.3 ± 1.0	54.9 ± 1.3	0.17
Sural SNAP amplitude (μV)	14.2 ± 1.8	16.6 ± 2.0	0.37
Dorsal sural cutaneous SCV (m/sec)	47.1 ± 1.0	46.1 ± 0.8	0.49
Dorsal sural cutaneous SNAP amplitude (μV)	4.8 ± 0.5	4.7 ± 0.4	0.82

SE: Standard error, IQR: Interquartile range, MUP: Motor unit potential, BB: Biceps brachii, VM: Vastus medialis, TA: Tibialis anterior, SCV: Sensory conduction velocity, SNAP: Sensory nerve action potential, MCV: Motor conduction velocity, CMAP: Compound muscle action potential, ms: millisecond, μV: microvolt, m/sec: meter per second, mV: millivolt.
§ indicates median (25%, 75% IQR) due to non-normally distributed data.

3.5. Laboratory tests

None of the patients showed abnormalities in routine blood tests including vitamin B12, HbA1c and TSH levels. One patient with myopathic qEMG had an ESR of 36 (normal range: 0–30 mm) and 14 had normal levels. CK was examined in 12 patients, myoglobin in 12 and LDH in 18 patients. None of the patients had increased CK or myoglobin except for 1 patient with myopathic qEMG with slightly elevated CK of 204 U/l (normal range: 50–150 U/l). LDH was slightly above normal level in 3 of 9 with and 1 of 9 without myopathic changes (up to 241 U/l, normal level 105–205 U/l). There were no signs of rhabdomyolysis in available biochemical analyses in none of the patients.

4. Discussion

This is to our knowledge the first study to examine the persistent neuromuscular symptoms, signs and electrophysiology in patients recovering from COVID-19. Although the patients were examined due to sensory symptoms with the suspicion of neuropathy, unexpectedly in 55% of the patients we found signs of myopathy in average 210 (range: 77–255) days after their initial symptoms, but no signs of large fiber mono- or polyneuropathy. With a more detailed questioning of the symptoms, all patients with myopathic qEMG did have physical fatigue and 73% had myalgia.

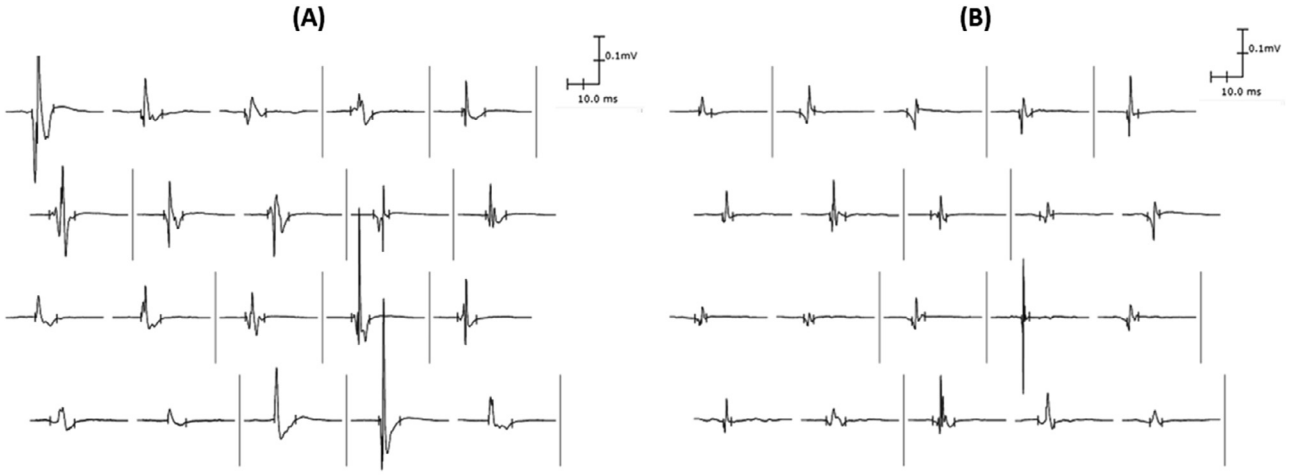

Fig. 1. Quantitative electromyography of the biceps brachii muscle in a healthy control (A) and in a patient with myopathic changes (B). There are myopathic motor unit potentials with decreased amplitude and short duration in the patient and normal motor unit potentials in the healthy control.

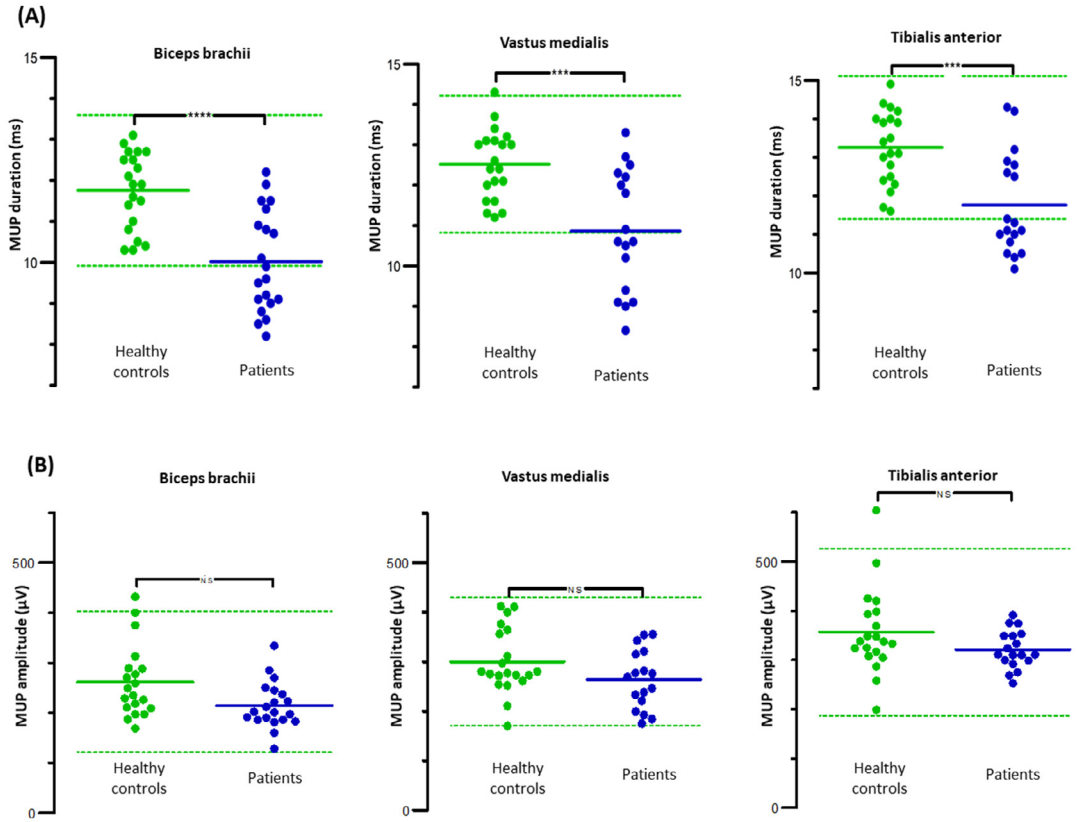

Fig. 2. Dot plots of quantitative electromyography measurements in patients compared with healthy controls. All muscles were examined in all healthy subjects. In patients, motor unit potential (MUP) analysis was performed in all patients in biceps brachii while in vastus medialis 17 and in anterior tibial muscle in 18 patients. (A) MUP duration and (B) MUP amplitude. Solid lines are the mean of the group, dashed lines are 95% confidence limits for the control group. Asterisks indicate level of significance (*** = $p < 0.001$, **** = $p < 0.0001$). MUP: Motor unit potential.

Table 3
Characteristics of patients with and without myopathic electromyography (EMG).

	All patients	Myopathy	No myopathy	Relative Risk (Confidence interval)	p
Age (median, IQR)	54 (49–57)	53 (46–56)	54 (50–58)		0.87[1]
Female (%)	16/20 (80)	9/11 (81)	7/9 (78)	1.05 (0.67–1.64)	0.62
BMI ≥ 25 (%)	9/20 (45)	4/11 (36)	5/9 (56)	0.65 (0.25–1.74)	0.34
Comorbidity (1 or 2)[2] (%)	7/20 (35)	4/11 (36)	3/9 (33)	1.09 (0.33–3.66)	0.63
Hospitalized (%)	10/20 (50)	6/11 (55)	4/9 (44)	1.23 (0.49–3.04)	0.50
Oxygen treatment during acute COVID-19 (1–3 l/min) (%)	6/20 (30)	3/11 (27)	3/9 (33)	0.82 (0.22–3.11)	0.57
Duration between acute COVID-19 and EMG (median number of days (IQR))	216 (176–230)	210 (110–233)	223 (187–229)	-	0.54
Long term symptoms					
Headaches[3] (%)	12/20 (60)	7/11 (63)	5/9 (56)	1.15 (0.55–2.39)	0.54
Difficulties in concentrating[3] (%)	11/20 (55)	6/11 (55)	5/9 (56)	0.98 (0.44–2.17)	0.65
Memory problems[3] (%)	10/10 (50)	6/11 (55)	4/9 (44)	1.23 (0.49–3.04)	0.50
Dyspnea[3] (%)	18/20 (90)	10/11 (91)	8/9 (89)	1.02 (0.76–1.38)	0.71
Chest pain[3] (%)	13/20 (65)	8/11 (72)	5/9 (56)	1.31 (0.66–2.60)	0.37
Palpitations[3] (%)	5/20 (25)	4/11 (36)	1/9 (11)	3.27 (0.44–24.34)	0.22
Physical fatigue[4] (%)	18/20 (90)	11/11 (100)	3/9 (33)	3.00 (1.19–7.56)	0.002
Myalgia[4] (%)	14/20 (70)	8/11 (73)	0/9 (0)		0.001

[1] Equality-of-medians test.
[2] Myopathy: 1 hypertension, 1 asthma/hypertension, 1 Crohńs disease in remission (no treatment after 2016), 1 Rheumatoid arthritis (methotrexate). No myopathy: 1 asthma, 1 sarcoidosis (methotrexate, prednisolone), 1 ischemic heart disease/hypertension.
[3] Symptom registered during investigations in Long-term COVID-19 Clinic
[4] at EMG investigation. IQR: Interquartile range, BMI: Body mass index.

4.1. Sensory disturbances in long-term COVID-19 illness

In contrast to the myopathic changes in most patients, we did not find electrophysiological signs of large fibre mono- or polyneuropathy in any of the patients despite primary sensory disturbances. The distribution of sensory symptoms varied considerably. While in 17 patients, there were symptoms that might be consistent with distal symmetric polyneuropathy, 4 patients

complained of paresthesias corresponding to one or two nerves on either one or both sides. All patients having focal symptoms had the corresponding nerves examined including comparison of NCS with the other side and EMG when necessary. In a recent case report, a pure sensory neuralgic amyotrophy was described, with symptoms and electrodiagnostic involvement of the lateral antebrachial cutaneous nerve (Cacciavillani et al., 2021). Infections are proposed to be triggers of an immune-mediated pathophysiologic mechanism for amyotrophic neuralgia, therefore it is likely that the four patients in our cohort might have had a form of mono-neuropathic brachial or lumbosacral neuritis with pure sensory or sensorimotor involvement that we could not confirm with NCS or EMG. However, none of the patients had severe pain early in the disease course suggesting neuralgic amyotrophy. Accordingly, patients with distal symmetric sensory disturbances had symptoms such as paresthesia and burning sensations that could suggest small fiber neuropathy, and further investigations are needed such as skin biopsy and quantitative sensory testing. However, the low clinical scores do not indicate a manifest of either small- or large fiber polyneuropathy. Additionally, we cannot exclude that symptoms were partly psychological.

4.2. Myopathy in long-term COVID-19

Myopathy in patients who had severe COVID-19 and required ICU treatment have been reported (Tankisi et al., 2020; Cabañes-Martínez et al., 2020), but this is not necessarily different from a critical illness myopathy of other etiologies (Z'Graggen and Tankisi, 2020; Tankisi et al., 2021. We excluded in our cohort the patients who had received ICU treatment. Surprisingly, we found a high incidence of myopathic qEMG following a mild to moderate COVID-19 where 50% of the patients were not even hospitalized. Although patients referred for neurophysiological evaluation for sensory disturbances as long-term symptoms, most patients had physical fatigue and myalgia when interviewed specifically for muscle symptoms. We, therefore, consider our findings to be of great importance as a possible explanation for fatigue which has been reported as a common symptom of both acute (Huang et al., 2020; Lechien et al., 2020; Wang et al., 2020) and long-term COVID-19 (Carfì et al., 2020, Huang et al., 2021), but until now has been difficult to explain.

Our data does not provide information on the causal link between the acute infection and myopathy, but we, however, suspect that myopathy and sensory disturbances may arise from disease-causing autoinflammatory process: An inflammatory response suggesting mitochondrial stress were seen more than 40 days after COVID-19 (Doykov et al., 2020), and microthrombi containing signs of immunoactivity (C5b-9) were found in pathologic analysis of hearts from 40 hospitalized patients succumbed to COVID-19 (Pellegrini et al., 2021). Leung et al. reported possible immune mediated focal myofiber necrosis from postmortem skeletal muscles of 8 consecutive patients who died of SARS in March 2003 (Leung et al., 2005).

In a recent case report, a patient with SARS-CoV-2 infection and myopathy who had a muscle-biopsy specimen showing evidence of virus-induced type I interferonopathy was described (Manzano et al., 2020). All our patients have had symptoms since the acute infection. Therefore, there might have been virus-induced myopathy during the acute infection in our patients. The high incidence of myalgia reported in previous studies (Huang et al., 2021; Wang et al., 2020) supports this hypothesis. Rhabdomyolysis during acute infection has also widely been reported, and associated with poor outcomes in different cohorts (Buckholz et al., 2020; Geng et al., 2021). Another possible explanation for our results could be the immobility of the patients since immobility can change MUP signals by itself (Fuglsang-Frederiksen and Scheel, 1978), however none of our patients was bedridden at any time for more than a few days during the acute infection and we do not believe this can explain our results. To explore the type of myopathy and underlying mechanisms further, studies examining muscle biopsies both during the acute infection and later in the disease course would be highly informative.

Interestingly, we had a female dominance in our cohort (16 females vs 4 males) that may be because of immunological, genetical or hormonal sex differences. A recent study proposed that sex differences in immune responses underlie COVID-19 disease outcomes, and a poor T cell response was predictive of worse disease outcome in males while higher levels of innate immune cytokines were associated with worse disease progression in female patients (Takahashi et al., 2020).

4.3. Limitations

Although, we could exclude any large fiber involvement in these patients, we cannot exclude small fiber neuropathy or central pathology causing sensory symptoms. We did not do magnetic resonance imaging because the distribution of sensory symptoms and signs were not consistent with central affection. However, magnetic resonance imaging of the medulla spinalis and muscles would be useful. Lack of small fiber neuropathy assessment with skin biopsies and quantitative sensory testing is a main limitation of this study. Another limitation is the lack of muscle biopsy. Additionally, the number of patients is small and not all patients had the full set of muscles investigated, but our results showed a clear differentiation of patients, and we do not believe including more patients would have changed the results. Furthermore, inclusion of patients primarily with muscle symptoms may have exhibited even more pronounced myopathic changes.

4.4. Conclusion

We have shown in patients with mild or moderate SARS-CoV-2 infection that myopathic qEMG is a common finding in long-term COVID-19. We propose that myopathy may be an important cause of physical fatigue in these patients. Our findings may guide identification of novel targets for treatment to facilitate recovery from COVID-19. Such treatments could alleviate the morbidity in millions of SARS-CoV-2 infected people and reduce the immense socioeconomics burden of the disease.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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