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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Letter to the Editor

Is myopathy part of long-Covid?

Acute infections with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causing coronavirus disease 2019 (Covid-19) are known to affect multiple organ systems including the nervous system. There is now a growing body of research literature addressing long-term sequelae of apparently mild Covid-19 infections, so called cases of "long-Covid" or "post-Covid (fatigue) syndrome". However, the underlying pathology thereof is largely unknown. The main symptoms of long-Covid are fatigue, loss of smell and taste, arthralgias, exercise intolerance and cognitive changes ("brain fog"). Muscle deconditioning, dysautonomia, immune- or virus-mediated neuropathy and exercise hyperventilation have been hypothesized to play an important role in the development of these disabling symptoms (Mendelson et al., 2020). Here we describe a patient who experienced persistent fatigue and muscle weakness after a mild Covid-19 infection without the need of hospitalization.

A 26-year-old female patient with no past medical history developed intermittent fever, fatigue, headache and muscle pain on August 8th, 2020. Reverse transcription polymerase chain reaction assay (RT-PCR) of nasal swab was done the next day and returned positive for SARS-CoV-2 on August 11th. Two days after symptom onset the patient developed chest pain and 5 days after symptom onset, she experienced loss of smell and taste for 3 consecutive days. During the whole acute disease, the patient did not experience any respiratory symptoms. However, after the acute phase she experienced prolonged shortness of breath, fatigue, headaches, muscle weakness and exercise intolerance.

The presented patient previously participated in a study investigating muscle excitability in a healthy population using the technique of recording multi-fiber muscle velocity recovery cycles (MVRC). The examination took place on December 18th, 2019 and was performed as previously described in detail (Boerio et al., 2012). MVRC recordings were made from the left tibialis anterior muscle and showed results within known normal limits for the patient's sex and age group. When the patient reported "feeling very unfit" to us and was still experiencing profound muscle fatigue and exercise intolerance 3 weeks after symptom onset, we decided to repeat the previously done muscle excitability examination on August 26th, 2020. The post-Covid examination showed a marked decrease of early supernormality compared to the previous measurement, indicating muscle membrane depolarization. Fig. 1 illustrates the technique of MVRC measurements and the patient's data. Nerve conduction studies from the median and peroneal nerve and EMG from the tibialis anterior muscle were done on the same day and showed normal results. With the patient's consent, we then performed a fine needle muscle biopsy from the left tibialis anterior muscle using a 16 Gauge soft tissue semi-automated biopsy disposable needle instrument (Temno Evolution®). The biopsy was immediately frozen (-80 °C). Biochemical analysis showed a reduced myosin:actin ratio of 0.957, comparable to values that have been published in patients with moderate critical illness myopathy (CIM) (Marrero et al., 2020).

The number of reported neurological complications of SARS-CoV-2 virus infections is rapidly increasing. There are reports of probable direct neuro-invasive as well as parainfectious neurological complications. The spectrum of associated acute neurological diseases includes smell and taste alterations, headache, encephalopathy or encephalitis and meningitis. Additionally, there are several reports of cranial or peripheral nerve diseases such as Miller-Fisher and Guillain-Barré syndrome. Far more common are reports of thromboembolic complications due to SARS-CoV-2 virus infections such as stroke and sinus venous thrombosis. Direct muscle involvement, e.g., myositis or myopathy has not yet been shown. To our knowledge, the only muscular complication in Covid-19 published is the occurrence of CIM in patients treated on intensive care units (Tankisi et al., 2020). CIM is a primary and acquired myopathy that can develop as a sequelae of intensive care treatment (Z'Graggen and Tankisi, 2020). Although the exact etiology is not known in detail, it is well accepted that CIM does not have an infectious cause. One diagnostic hall mark of CIM is a preferential loss of myosin filaments.

The patient here described had a mild disease course involving fever, fatigue, headache, and loss of smell and taste over a period of 8 days, without the need of hospitalization at any time. Nevertheless, as a consequence she developed prominent muscle fatigue and exercise intolerance, which only gradually improved to normal levels. MVRC recordings 3 weeks after the onset of Covid-19 symptoms showed compared to an earlier recording a marked reduction of early supernormality as a sign of muscle membrane depolarization. Similar MVRC changes have been described e.g., in CIM and uremic myopathy (Z'Graggen and Tankisi, 2020). EMG and nerve conduction studies were within normal limits. Muscle biopsy revealed a low myosin:actin ratio as a sign of an underlying loss of myosin filaments, confirming a primary myopathy as the probable cause of her complaints. Although there are obvious parallels between the reported findings in this patient and those typical of CIM, the patient never suffered from severe acute illness and did not require intensive care treatment. Consequently, the findings have to be attributed to different pathophysiological mechanisms than those suggested in CIM. We hypothesize that the observed muscle membrane potential change and the loss of myosin as a sign of concomitant structural alterations in a patient with an apparently mild disease course of Covid-19 may be attributed to

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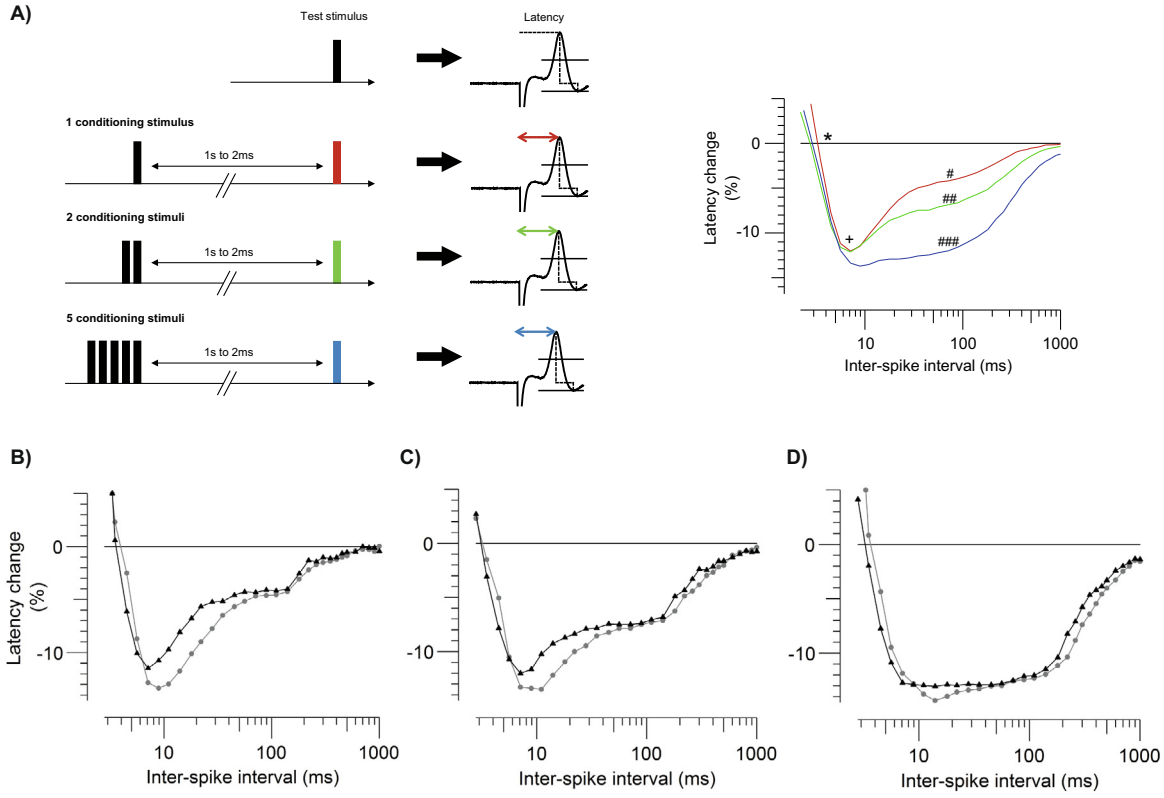

Fig. 1. (A) (left side) Illustration of the technique of recording multi-fiber muscle velocity recovery cycles (MVRC). The procedure is based on standard neurophysiological techniques and measures how one or several preceding conditioning stimuli change, depending on the interstimulus interval, the velocity of a second muscle action potential elicited by the test stimulus. These changes provide an indirect indication of the afterpotential following the muscle action potential. The afterpotential and consequently the recovery cycle is strongly dependent on membrane potential. (A) (right side) Illustration of a recovery cycle with percentage changes in latency due to 1 (red line), 2 (green) and 5 (blue) conditioning stimuli, plotted as a function of interstimulus interval. * muscle relative refractory period, + early supernormality, # late supernormality with one conditioning stimulus, ## late supernormality with 2 conditioning stimuli, ### late supernormality with 5 conditioning stimuli. (B) Illustration of the recorded MVRC in the presented patient with 1 conditioning stimulus before (grey dots) and after (black triangles) Covid-19. The same is shown in (C) for recordings with 2 and in (D) with 5 conditioning stimuli. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

either a direct muscular SARS-CoV-2 virus affection or a parainfectious muscular complication. Muscular involvement in Covid-19 may therefore play an important role for development of long-Covid. As the symptoms of long-Covid often have a considerable impact on the patients' quality of life and occupational performance, and often affect young people with an initially mild disease course, further research into the pathology of long-Covid is urgently needed to increase our understanding of this complex disease and ultimately improve treatment strategies.

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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Belén Rodriguez
Department of Neurosurgery, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland

Sandra Nansoz
David R. Cameron
Department of Intensive Care Medicine, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland

Werner J. Z'Graggen *
Department of Neurosurgery, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland
Department of Neurology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland
* Corresponding author at: Departments of Neurosurgery and Neurology University Hospital Bern, Freiburgstrasse 16, 3010 Bern, Switzerland.
E-mail address: werner.zgraggen@insel.ch
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