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.

Clinical Neurophysiology 147 (2023) 58–59

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Letter to the Editor

Long-COVID and myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS): Potential neurophysiological biomarkers for these enigmatic entities

Since early in the pandemic, fatigue has been recognized as one of the most common persistent complaints in individuals infected with SARS-CoV-2, and constitutes one main symptom of the so-called long-COVID syndrome. The term fatigue refers to a sustained feeling of tiredness, which can be present at rest; it is not directly related to physical activity, but can be exacerbated disproportionally by exertion.

Survivors of other recent coronavirus outbreaks, such as severe acute respiratory syndrome (SARS) in 2002 and Middle East respiratory syndrome (MERS) in 2012 also developed chronic fatigue. These 'post-infectious' fatigue syndromes, including long-COVID, resemble myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), a chronic disorder of unknown physiopathology characterized by fatigue, post-exertional malaise, chronic muscle or skeletal pain, and cognitive impairment ('brain fog').

Despite it being an extremely disabling symptom, the results of routine examinations are often normal in patients complaining of lingering fatigue, a phenomenon that has also led the medical-scientific community to view this condition with skepticism.

In physiology, fatigue is defined as a decrease in the maximal force-generating capacity of a muscle during exercise. It may result from peripheral processes distal to the neuromuscular junction and from central processes controlling the discharge rate of motoneurons.

Physical fatigue related to both central and peripheral nervous system dysfunction can be assessed with neurophysiological techniques including transcranial magnetic stimulation (TMS) of the motor cortex, electrical stimulation of nerve trunks or intramuscular nerve fibers, and electromyography (EMG) recordings.

In August 2021, the first study showing myopathic changes in quantitative EMG (qEMG) in long-COVID patients with musculoskeletal symptoms was published (Agergaard et al., 2021). The same authors demonstrated myopathic qEMG features and histopathological changes in skeletal muscle biopsies in 16 patients with complaints of fatigue, myalgia, and/or weakness persisting for up to 14 months after mild to moderate COVID-19 (Hejbøl et al., 2022). The wide variety of histological changes in this study, including muscle fiber atrophy, mitochondrial changes, subsarcolemmal accumulation, inflammation, capillaries alteration, suggests that skeletal muscle may be a major target of SARS-CoV-2.

On the opposite side of the neuroaxis, dysfunction in the activity of the primary motor cortex and reduced corticomotor output may underlie fatigue.

The first TMS study on motor cortex physiology was conducted on 12 patients with long-term fatigue and 'brain fog' after severe COVID-19 (Ortelli et al., 2021). It showed disruption of the physiological mechanism of post-contraction depression, i.e., the transient decrease in the amplitude of motor evoked potentials and prolongation of the cortical silent period after a fatiguing motor task, which depends on cortical inhibitory mechanisms and has the protective purpose of preventing muscle overload. Impairment of intracortical GABAergic activity, as indicated by disrupted long-interval intracortical inhibition, together with reduced excitability of the primary motor cortex was subsequently demonstrated in 67 patients with fatigue and cognitive difficulties after mild COVID-19 (Ortelli et al., 2022). These patients also presented selective deficits in executive functions. Based on these findings, the authors proposed that fatigue depends on altered excitability and neurotransmission within the motor cortex at rest, and on abnormal reactivity to muscular exercise. In addition, reduced executive control may contribute to exacerbating poor physical performance and fatigue tolerance (Ortelli et al., 2022).

These objective neurophysiological and histopathological findings showed for the first time that fatigue may due both to pathological processes in the muscle (the effector of the motor command) and/or at the site of motor command processing. The mechanisms of chronic dysfunction of neural and muscle cells may be sustained by inflammation or dysimmunity, triggered by SARS-COV-2 in predisposed individuals.

Immune-inflammatory and neuroendocrine mechanisms have also been implicated in ME/CFS. In particular, increased production of autoantibodies against CNS and autonomic nervous system targets, such as the ß2 adrenergic receptor (ß2AdR), have been documented (Wirth et al., 2021). As ß2AdR are important vasodilators, their functional disturbance may result in vasoconstriction and hypoxemia with chronic muscular and cerebral hypoperfusion.

The COVID-19 pandemic is likely to greatly increase the incidence of ME/CFS, so that the intense research on the pathophysiological mechanisms of fatigue in long-COVID can help to shed light on a poorly understood and underestimated syndrome. Neurophysiological tests may be potential biomarkers for these enigmatic entities (Haykal and Menkes, 2023).

Conflict of Interest Statement

None of the authors have potential conflicts of interest to be disclosed.

References

Agergaard J, Leth S, Pedersen TH, Harbo T, Blicher JU, Karlsson P, et al. Myopathic changes in patients with long-term fatigue after COVID-19. Clin Neurophysiol 2021;132:1974–81.

Haykal MA, Menkes DL. The clinical neurophysiology of COVID-19-direct infection, long-term sequelae and para-immunization responses: A literature review. Clin

https://doi.org/10.1016/j.clinph.2023.01.001

Neurophysiol Pract 2023;8:3–11. https://doi.org/10.1016/j.cnp.2022.09.005. Epub 2022 Oct 17. PMID: 36275861; PMCID: PMC9574576.
Hejbøl EK, Harbo T, Agergaard J, Madsen LB, Pedersen TH, Østergaard LJ, et al. Myopathy as a cause of fatigue in long-term post-COVID-19 symptoms: Evidence of skeletal muscle histopathology. Eur J Neurol 2022;29:2832–41.
Ortelli P, Ferrazzoli D, Sebastianelli L, Engl M, Romanello R, Nardone R, et al. Neuropsychological and neurophysiological correlates of fatigue in post-acute patients with neurological manifestations of COVID-19: Insights into a challenging symptom. J Neurol Sci 2021;420 117271.
Ortelli P, Ferrazzoli D, Sebastianelli L, Maestri R, Dezi S, Spampinato D, et al. Altered motor cortex physiology and dysexecutive syndrome in patients with fatigue and cognitive difficulties after mild COVID-19. Eur J Neurol 2022;29:1652–62.
Wirth KJ, Scheibenbogen C, Paul F. An attempt to explain the neurological symptoms of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. J Transl Med 2021;19:471.

Viviana Versace *
Department of Neurorehabilitation, Hospital of Vipiteno (SABES-ASDAA), Vipiteno-Sterzing, Italy
Lehrkrankenhaus der Paracelsus Medizinischen Privatuniversität, Salzburg, Austria
* Corresponding author at: Department of Neurorehabilitation, Hospital of Vipiteno (SABES-ASDAA), Margarethenstraße 24, 39049 Vipiteno-Sterzing, BZ, Italy.
E-mail address: viviana.versace@sabes.it

Hatice Tankisi
Department of Clinical Neurophysiology, Aarhus University Hospital, Aarhus, Denmark
Accepted 2 January 2023

Available online 13 January 2023