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Editorial

Clinical neurophysiological tests as objective measures for acute and long-term COVID-19

The world suffered tremendously from the worldwide SARS-CoV-2 pandemic, officially declared as such the 11.3.2020 by the WHO, and its toll affected our economy, our socio-professional life and our physical and mental well-being. Sadly, the burden still endures, including the medical consequences. At the time of writing of this editorial, fortunately, subsequent mutations of the original virus appear to be related to less severe diseases. However, this may not last and they were and probably will always be severe clinical cases, requiring medical interventions. Most importantly, an increasing number of long COVID cases particularly after mild-moderate acute COVID-19 suggests that less severe acute disease as a consequence of less pathogenic new variants or vaccination could still have the ability to cause serious long-term disabilities. While initial descriptions stemmed mainly from internal medicine and intensive care due to predominant suffering of the respiratory system, it became soon evident that the disease affects also both the central and peripheral system, which are best probed with neurophysiological methods.

In the current volume of *Clinical Neurophysiology Practice*, Menkes and Haykal summarized the scope of diagnostic studies and their results, which were requested to determine the acute and long-term consequences of COVID-19. They provide us with an excellent survey of which body part is affected most in the acute or chronic phase, or also in relation to complication of SARS-CoV-2 -vaccination (Menkes and Haykal, 2022).

Regarding the acute phase, most of the evidence points to critical illness myopathy in intensive care unit patients (Tankisi et al., 2020; Rodriguez et al., 2022), Guillain-Barré syndrome (Uncini et al., 2021) and encephalopathy (Canham et al., 2020), while in patients with long COVID, small fiber neuropathies are often at the origin of peripheral dysesthesia and may result in dysautonomic alterations (Shouman et al., 2021). Thus, neurophysiologists may add electroencephalography (EEG), quantitative sensory and autonomic testing, standard nerve conduction studies (NCS) and electromyography (EMG) to the diagnostic work-up of acute or long-term COVID-19 manifestations.

In the central nervous system, it appears that COVID-19 leads to two major pathologies: an endothelitis due to a major tropism of the virus for endothelial cells (Varga et al., 2020) and meningoencephalitis. Endothelial affection is not limited to the brain, associated to intravascular coagulopathy (Wichmann et al., 2020) and in some cases antiphospholipid antibodies (Zhang et al., 2020). Viral infections in general increase the risk of stroke, which includes the SARS-CoV-virus (Bahouth et al., 2021), resulting in slowing of blood flow as visualized with transcranial doppler ultrasound (TCD). However, the formation of autoantibodies to the CNS may turn out as the bigger – diagnostic and therapeutic – problem of long COVID as well as some cases of post-vaccination complications.

It appears that long COVID may be an equally difficult challenge for our health care system as the acute COVID-19 disease. “Brain fog” is a frequent complaint of patients suffering from long COVID. Predominantly extensive small vessel emboli could be a possible mechanism, but there is little evidence from autopsy or TCD studies. In contrast, breakdown of the blood–brain barrier and as a consequence, infection of the astrocytes, has been reported as significant mechanism of neuronal distress (Crunfli et al., 2022), through changes in the energy metabolism and indirectly to neuronal dysfunction of death. These insults are not seen in the MRI, but in positron-emission tomography (PET) or EEG. In the acute phase, PET showed that the fronto-parietal and temporal cortex is affected predominantly (Hosp et al., 2021). The recovery process in longitudinal PET-studies shows a more complex picture: while the hypometabolism recovers by 5–6 months, hypermetabolic areas in the hippocampus, amygdala, cerebellum and brainstem persists (Martini et al., 2022) and would explain subjective feelings such as “brain fog”. Additionally, transcranial magnetic stimulation (TMS) studies showed altered GABAergic and cholinergic neurotransmission in long COVID patients with cognitive deficit and brain fog (Versace et al., 2021; Ortelli et al., 2022). Fatigue is among the most prevalent described long COVID symptoms (Nasserie et al., 2021). While fatigue has a central origin also described as brain fog, its close association with myalgia and muscle weakness suggests an additional peripheral origin. The myopathic EMG changes that were reported as a cause of fatigue (Agergaard et al., 2021) has recently been confirmed with histopathological evidence of fiber atrophy, mitochondrial changes, inflammation, and capillary injury in muscle biopsies (Hejbol et al., 2022). Recent literature highlights the similarities between long COVID and myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) (Sukocheva et al., 2022), and gives hope to turning a corner in ME/CFS research which has been a conundrum for decades.

Regarding temporal lobe structures, EEG could be helpful in this regard, while the brainstem is best evaluated with evoked poten-

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tials (EP). Regarding the latter, not enough or large enough studies have been done to define the role of EPs in the acute and chronic work-up of COVID-19, as identified by the authors. However, EPs deserve a second look, also beyond the "traditional" EPs. Despite the fact that smell and taste were impaired in the majority of patients, and the deficits were long lasting, there is no study on olfactory EP.

EEG studies showed pattern of encephalopathy with focal or multifocal slowing. Interestingly a study of patients before and after COVID-19 infection and initial olfactory symptoms showed grey matter damage in the orbitofrontal cortex and parahippocampal gyrus, indicating degeneration through spread of the disease through olfactory pathways (Douaud et al., 2022). With 25 scalp electrode EEGs (Seeck et al., 2017), temporal alterations should be reliably picked up and monitored over time (Bernard-Valnet et al., 2021). Such studies, including high-density EEG studies for better spatial precision, are missing so far.

Minor or major infectious diseases are known to elicit autoantibodies in a small number of patients, including COVID-19, which can lead to dramatic neurological and psychiatric symptoms in adults and younger patients. In the CSF of three teenagers with new onset neuropsychiatric symptoms like psychosis, suicidal ideation and personality changes, no signs of significant inflammation but anti–SARS-CoV-2 antibodies with positive immunostaining of cortical and cerebellar cells were found. An EEG montage covering the temporal lobes might have noted abnormalities or even epileptogenic discharges in the left temporal lobe of patient 1 who presented an enlarged hippocampus in the MRI (figure 1 in Cabral-Marques et al., 2022). EEG can be helpful to identify focal abnormalities, which justify follow-up exams and extend pathological findings in COVID-19, like microbleeds, which would go otherwise unnoticed (De Stefano et al., 2020).

The question is not so much if a neurophysiological test is pathognomonic for COVID-19, this is best obtained with immunological and other blood tests as well as accessory exams. However, with the increase of long COVID cases, we need cost-effective algorithms to objectivate the patients' complaints and monitor their evolution. These should include neurophysiological tools, perhaps using more and longer measurements or more sensors to avoid misdiagnosis of "unrelated" neurological and psychiatric dysfunctions. In that sense, the review of Menkes and Haykal is stimulating, in that it shows us where the areas of future neurophysiological research in COVID-19 could be.

Conflict of interest statement

None.

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