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Letter to the Editor

Neurology of long- and post-COVID-syndrome

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We read with interest the review article by Franke *et al.* about the diagnostic and therapeutic management of neurological manifestations of long-COVID syndrome (LCS) and of post-COVID-syndrome (PCS) [1]. It was concluded that COVID-19 patients with residual symptoms should undergo extensive examinations, preferentially by a multidisciplinary team [1]. In patients with LCS/PCS in whom immunologic compromise is evident, immune-suppressive treatment should be considered [1]. The study is promising but raises concerns that should be discussed.

A pathophysiological mechanism not addressed in the review is the affection of the hypothalamic, pituitary, and adrenal axis. Because COVID-19 patients can experience hypophysitis or pituitary apoplexy [2], it should be considered that long-term disturbance of hormonal balances may ensue after a COVID-19 infection and could be responsible at least some of the manifestations of LCS/PCS [3]. Cortisol, thyroxin and growth hormone levels have been shown reduced in patients with LCS [3]. Another pathophysiological mechanism that should not be neglected is the affection of the autonomous nervous system [4]. Not only autonomic fibers of the peripheral autonomic nervous system (PANS) may be affected but also components of the central autonomic nervous system (CANS). Because the autonomic system governs the entire body, including brain and heart, it is essential to consider ANS impairment as an explanation for manifestations of LCS and PCS. Under-innervation by the cardiac autonomic fibers may result in cardiac dysfunction, which could contribute to several clinical manifestations including fatigue [4]. PANS involvement mainly occurs in the context of small fiber neuropathy [5].

In neurological examinations, we recommend distinguishing between LCS/PCS patients with and without abnormalities. Patients with structural or functional lesions visible on neurological examinations will have less difficulty in being accepted by health authorities and health insurance companies with a diagnosis LCS or PCS than patients without these lesions. Patients without structural or functional lesions on blood exams, MRI, electrophysiology, ultrasound, or electroencephalography (EEG), should undergo high resolution MRI (e.g., 7T), FDG-PET, cerebrospinal fluid (CSF) studies, and neuropsychological testing. If these investigations remain non-informative, a consultation with a psychological service should be ordered.

The spectrum of neurological diseases complicating COVID-19 infections includes, in addition to what has been listed in the review, also autoimmune encephalitis, acute, disseminated encephalomyelitis (ADEM), acute, hemorrhagic, necrotising encephalopathy (AHNE), multiple sclerosis, neuromyelitis optica spectrum disorder (NMO-SD), opsoclonus myoclonus syndrome, hypophysitis, apoplexy of the pituitary gland, cerebellitis, reversible, cerebral vasoconstriction syndrome (RCVS), cerebral vasculitis, Bickerstaff encephalitis, and myasthenia.

We disagree with the statement that "neuropathy" is a neurological complaint [1]. Diagnosing neuropathy requires extensive work-up and should not be classified as a symptom.

Overall, the interesting study has limitations that call the results and their interpretation into question. Clarifying these weaknesses would strengthen the conclusions and could improve the study. Patients with neurological symptoms or signs after COVID-19 persisting for more than 3 months should undergo extensive work-up, including history, clinical exam, MRI, MRA, carotid ultrasound, neuropsychological testing, and EEG, and if informative high-resolution MRI and FDG-PET.

Declarations

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