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LETTER TO THE EDITORS

Autonomic dysfunction in long-COVID syndrome: a neurophysiological and neurosonology study

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Dear Sirs,

A significant proportion of patients infected from SARS-CoV-2 experience new, recurring, or ongoing symptoms usually 3 months after infection that may last for weeks or months and comprise the so-called Long-COVID Syndrome (LCS). Most frequent neurological symptoms include fatigue, memory/attention deficits, sleep disorders, myalgias and hyposmia [1]. The occurrence of LCS is not associated with the severity of foregoing acute COVID-19 nor have specific predisposing factors been identified so far. LCS shares common features with two other diseases, Fibromyalgia (FM) and Chronic Fatigue Syndrome (CFS): young women are predominantly affected, the etiology is unknown, although a previous viral infection is suspected, and both conditions have symptoms similar to those of LCS. Autonomic Nervous System (ANS) maladaptation has been proposed as a possible pathogenetic underlying mechanism. [2, 3]

Hence, a case–control study was conducted to investigate if ANS dysfunction may contribute to LCS. Consecutive, adult patients, with history of laboratory-confirmed COVID-19 without hospitalization, presenting with persistent LCS symptoms for > 3 months from COVID-19 onset, including fatigue, cognitive impairment (brain fog), orthostatic dizziness, palpitations, breathlessness or gastrointestinal symptoms, were evaluated at a referral center in Athens, Greece ("Attikon" University Hospital) between September 2021 and December 2021. LCS patients with cardiovascular complications or diabetes were excluded. Controls included colleagues, nursing staff and volunteers without history of SARS-COV-2 infection, cardiovascular diseases, diabetes and ANS disorders. Evaluation of ANS function was performed by Sympathetic Skin Response (SSR) to investigate the Sympathetic Nervous System (SNS), and the cross-sectional area (CSA) of the Vagus Nerve (VN) was assessed by ultrasound to investigate the Parasympathetic Nervous System (PNS) [4]. A detailed description of the methods is available in the online-only supplement. The study was approved by the Institutional Research Bioethics. Informed consent was obtained by all participants. Statistical analysis was performed using the Statistical Package for Social Science (SPSS Inc., version 24.0 for Windows; IBM, Armonk, NY, USA). Descriptive statistics are given as the mean and standard deviation, frequency, and percentage. Statistical comparisons between different groups were performed using the chi-square test (or exact test) for binary outcomes, and Student's *t* test or Mann–Whitney *U* test for continuous variables as appropriate.

A total of 44 healthy subjects (25 women, 19 men) and 11 LCS patients (9 women, 2 men) were included. The mean age of controls and LCS was 43 years (23–65 years) and

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40 years (21–66 years), respectively. The two groups did not differ in age (p = 0.828, unpaired *t* test) and sex ($p = 0.174$, Fisher's exact *t* test). SSR were elicited in all subjects. Amplitudes did not differ between groups. Latencies were significantly longer in patients compared to controls. SSR latencies were in the upper limb (mean ± standard deviation): 1.28 ± 0.24 s vs. 1.49 ± 0.19 s, $p = 0.010$ in controls and patients, respectively; in the lower limb (mean ± standard deviation): 1.8 ± 0.31 s vs. 2.09 ± 0.34 s, $p = 0.014$. CSA of both the right and the left VN were significantly smaller in patients compared to controls: CSA of the right VN (mean ± standard deviation): 2.07 ± 0.54 mm^2 vs. 2.94 ± 0.84 mm^2, $p = 0.002$ in patients and controls, respectively; CSA of the left VN (mean ± standard deviation): 1.41 ± 0.35 mm^2 vs. 2.36 ± 0.92 mm^2, $p < 0.001$ (Figs. 1, 2 in Supplement). A strong negative correlation was observed between SSR latencies from palm and sole and CSA of both VN [between palm latency and CSA ($r = -0.41$, $p = 0.004$; for right VN & $r = -0.340$, $p = 0.021$; for left VN); plantar latency and CSA ($r = -0.498$, $p = 0.001$; for right VN & $r = -0.340$; $p = 0.026$; for left VN).

This study provides evidence that autonomic dysfunction may contribute to LCS symptoms that persist for several months beyond the resolution of acute COVID-19. It was demonstrated that LCS patients show vagus atrophy accounting for parasympathetic implication and prolonged SSR latencies, accounting for sympathetic implication.

Dysautonomia in acute COVID-19 has been involved in the development of acute respiratory distress syndrome and is attributed to either direct neuronal injury, or to immune-induced mechanisms [5]. In LCS, postural orthostatic tachycardia syndrome and inappropriate sinus tachycardia have been reported and are similar to previous post-viral dysautonomia syndromes [6].

The pathophysiology of neuropsychiatric complications in LCS remains unclear [7]. In similar conditions, such as FM and CFS, ANS involvement has been suggested, but results remain controversial regarding the involvement of each ANS component. Most studies suggest hypersympathetic predominance and fewer a parasympathetic. A recent study has demonstrated an association between fatigue in LCS patients and sympathovagal imbalance [8], but could not evaluate separately SNS and PNS.

Certain limitations of the present study should be highlighted, including the small sample size, the case–control design, the lack of standardized clinical assessment of autonomic dysfunction and the lack of long-term follow-up on the evolution of neuropsychiatric symptoms. Furthermore, we aim to evaluate the ANS function in a third group of patients, with history of SARS-CoV-2 infection and absence of obvious LCS-related symptoms, in a future study. This may allow us to detect subclinical dysautonomia in subjects who recovered from COVID-19 without developing LCS-related symptoms. In conclusion, our preliminary observations lend support to the hypothesis that autonomic dysfunction may contribute to LCS pathogenesis and warrant independent confirmation by larger, prospective cohorts.

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Data availability Anonymized data used in this article will be made available on reasonable request from the corresponding author.

Declarations

Conflicts of interest None of the contributing authors has any conflict of interest to declare.

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