dysfunction, changes in skin, hair, and nails, or abnormalities of sweating. Studies that may be performed to assess ANS involvement are a contrast-enhanced magnetic resonance imaging (MRI) of the pituitary gland, determination of releasing factors, pituitary stimulating hormones, and hormones of peripheral endocrine organs, and diagnostic testing for involvement of the peripheral ANS. Several of the latter tests are not widely available and their sensitivity and specificity may be low if portions of the peripheral ANS are tested that are not affected.

Not addressed was the role of anti-COVID-19 drugs in the development of SFN. There is increasing evidence that some of the compounds administered to infected patients are neurotoxic and can be responsible for polyneuropathy. Some of these compounds, such as lopinavir, ritonavir, daptomycin, and linezolid, may also damage autonomic fibers.

I agree that there is a need to investigate the involvement of the central and peripheral ANS in some patients with acute SARS-CoV-2 infections or long-COVID syndrome. Such patients should be investigated not only by use of questionnaires and the Quantitative Sudomotor Axon Reflex Test (QSART) but particularly by quantitative sensory testing (QST), micro-neurography of C-fibers of the superficial peroneal nerve, sensory stimulation tests, the deep breathing test, the Valsalva maneuver, tilt testing, cerebral blood flow velocity measurements, pain-related evoked potentials (PREP), laser speckle contact analysis (LASCA), laser Doppler flowmetry, laser Doppler imaging, contact heat-evoked potentials (CHEP), corneal confocal microscopy (CCM), and proximal or distal skin biopsy stained with protein gene product (PGP) 9.5. Furthermore, hormone levels should be determined and autopsy of COVID-19 patients should include histological investigations of central and peripheral autonomic pathways.

KEYWORDS

adverse reactions, COVID-19, SARS-CoV-2, side effects, vaccination

CONFLICTS OF INTEREST

None.

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AUTHOR CONTRIBUTION

JF: design, literature search, discussion, first draft, critical comments, final approval.

ETHICAL PUBLICATION STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

DATA AVAILABILITY STATEMENT

All data are available form the correspndong author

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Comment on small fiber neuropathy associated with SARS-CoV-2 infection: Author response

We appreciate Dr Finsterer's letter to the editor regarding our recent work,[1] as well as Dr Gemignani's editorial.[2] We have several responses.[1]

According to the US Centers for Disease Control and Prevention,[3] post-COVID conditions are new, recurring, or ongoing symptoms and clinical findings present 4 or more weeks after infection, and are

referred to by different names, including post-acute COVID syndrome and long COVID. The patients in our study developed new-onset paresthesia with or without autonomic symptoms 2 weeks to 2 months after the onset of COVID-19. The long-term follow-up of these patients showed persistence of painful small fiber neuropathy symptoms for at least 5 to 12 months. Therefore, our study patients have post-COVID syndrome, and they are COVID long haulers.

Multiple studies have shown that Guillain-Barré syndrome (GBS) may be seen in association with SARS-CoV-2 infection,[4,5] and dysautonomia can be present in GBS patients. However, our patients showed no evidence of conventional GBS by history, examination findings, or nerve conduction study/electromyography (NCS/EMG) findings. All had NCS/EMG studies that showed no evidence of a large fiber polyneuropathy, but all had paresthesia that prompted skin biopsy evaluation for small fiber neuropathy. We agree and discussed in our work that post-infectious autoimmune neuropathy limited to small fibers appears the likely mechanism.[1]

Dr Finsterer raised the interesting possibility that the autonomic dysfunction may be caused by hypothalamic-pituitary axis dysfunction due to SARS-CoV-2 infection. Nine of 13 patients had brain imaging showing no abnormality in the hypothalamus or pituitary gland. Although autonomic symptoms were present in 7 of 13 patients, none of these patients had pure dysautonomia and 4 had biopsy-proven small fiber neuropathy.

Some of the antiviral therapies mentioned by Dr Finsterer have the potential for neurotoxicity. At the time of assessment (May 2020 to May 2021), antiviral therapies specific for SARS-CoV-2 were not available for the cohort of patients in our study. These medications are currently approved only for patients with severe disease or those likely to progress to severe disease. Although they may be associated with adverse neurotoxic drug effects, the use of these drugs is only short term, and the treatment may in fact limit the development of post-COVID conditions by suppressing acute SARS-CoV-2 infection.

CONFLICT OF INTEREST

None of the authors have any conflict of interest to disclose.

ETHICAL PUBLICATION STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm this report is consistent with those guidelines.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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