Case Series – General Neurology

Small-Fiber Neuropathy Possibly Associated with COVID-19

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Abstract
COVID-19 has caused several neurological complications by affecting the central and peripheral nervous systems (PNS). Studies on the PNS involvement in COVID-19 are limited. These complications are likely unreported, given the difficulty of obtaining further diagnostic information, such as expert neurologist evaluation, electrodiagnostic testing, and skin biopsy. Herein, we report 2 cases of possible COVID-19-related small-fiber neuropathy (SFN). These cases are reported to increase awareness of a possible link between COVID-19 and SFN. Additional investigation, including neurology consultation, nerve conduction studies, and skin biopsy, should be considered in patients who develop paresthesia during and after COVID-19 infection. Further research is also needed to determine a possible underlying neuropathology mechanism and the role of immunomodulatory treatment, such as intravenous immunoglobulin, in COVID-19-related SFN.

Introduction

COVID-19 causes several neurological issues by affecting the central and peripheral nervous system (PNS). Its well-documented neurological complications include altered mental status and encephalopathy [1], encephalitis [1, 2], meningitis [1], postinfectious demyelination [1, 2], dizziness, headaches, acute ischemic stroke [1, 3–5], acute necrotizing hemorrhagic encephalopathy [6], cerebral venous sinus thrombosis [7], seizures [8–10],
Guillain-Barré syndrome [1, 11], critical illness polyneuropathy/myopathy [1], and olfactory neuropathy [12].

Studies on the PNS involvement in COVID-19 are limited [1, 13]. These complications are likely unreported, given the difficulty of obtaining further diagnostic information, such as expert neurologist evaluation, electrodiagnostic testing, and skin biopsy. Herein, we report 2 cases of possible COVID-19-related small-fiber neuropathy (SFN).

**Case Reports**

**Case 1**

A 49-year-old female with no significant medical history initially presented with dry cough, congestion, fever, and loss of taste and smell. She was quickly diagnosed with COVID-19, and she was isolated and given supportive treatment. Her initial symptoms were resolved within 7–10 days; however, she developed a burning and tingling sensation in the feet and hands 2 weeks after the initial presentation. She had not had similar symptoms. She was referred to neurology 2 months after the presentation due to the worsening of her symptoms. Her sense of taste returned, but she reported a tingling sensation in the tongue and a crawling feeling of tingling and/or shock-like sensation in the chest. Within 2 months, her symptoms had worsened such that they interfered with her daily activities. Neurological examination showed decreased temperature and light touch sensations with relatively intact vibration and proprioception sensations in the upper and lower limbs. The rest of the neurological examination was unremarkable.

The tests included detailed blood workup, nerve conduction study, and skin biopsy. Blood tests, including complete metabolic panel, cell blood count, sedimentation rate, hemoglobin A1c, vitamin B12, vitamin B6, vitamin D, vitamin C, serum electrophoresis, and human immunodeficiency virus were within normal limits. The nerve conduction studies of peroneal motor, tibial motor, sural sensory, and superficial peroneal nerves were negative for large-fiber neuropathy. The skin biopsy was performed on the foot, distal leg, and thigh, and it showed significantly decreased intraepidermal nerve fiber density (IENFD) in all three areas. The IENFD was 2.09 per millimeter (<8.3 per millimeter abnormal) in the thigh; 3.4 per millimeter (<4.5 per millimeter abnormal) at the distal part of the leg; and 1.61 per millimeter (<3 per millimeter abnormal) at the dorsal foot. Small-fiber damages were more significant in the foot and thigh areas. Analysis of the sudomotor nerves with skin biopsy showed that sweat glands were absent in the foot and thigh and significantly reduced in the distal leg (4.6 per millimeter [<36.5 per millimeter abnormal]).

The patient was placed on pregabalin for pain management, and it was effective in controlling her pain. She was diagnosed with non-length-dependent SFN. However, during her follow-up visit after 6 months, she still had a tingling and numbness sensation in the upper and lower limbs; there had been no significant changes.

**Case 2**

A 62-year-old female with a history of breast cancer (in remission for more than 5 years) and cervical disc degeneration initially developed COVID-19 infection that presented with fever, chills, shooting pain, diarrhea, and anorexia. Her initial COVID-19-related symptoms were resolved within 7–10 days with no significant residual problems. However, she noticed a tingling and numbness sensation 4 weeks after her COVID-19 infection. Her symptoms progressed quickly and led to a painful, disturbing, burning sensation in the feet and hands. She was seen by neurology 3–4 months after the COVID-19 onset. Her symptoms were persistent and had been affecting her daily activities.
The initial neurological exam showed decreased temperature and light touch sensation in the lower limbs up to the mid-thigh level and in the hands up to the wrist level. The rest of the neurological examination was unremarkable. The detailed neuropathy blood workup like in the case 1 was unremarkable. The nerve conduction studies of peroneal motor, tibial motor, sural sensory, and superficial peroneal nerves were negative for large-fiber neuropathy. The skin biopsy showed a statistically significantly reduced intraepidermal nerve density in the foot, distal leg, and thigh areas. The IENFD was 1.44 per millimeter (<8.3 per millimeter abnormal) in the thigh; 0.15 per millimeter (<4.5 per millimeter abnormal) at the distal part of the leg; and 0.58 per millimeter (<3 per millimeter abnormal) at the dorsal foot.

She was initially placed on nortriptyline, but she could not tolerate its side effects. She was thus placed on duloxetine, which was partially effective in controlling her pain. She wanted to try immunoglobulin therapy, but her insurance denied it. Due to lack of clinical studies and potential side effects, immunosuppressive treatments were not offered. On her 8th-month follow-up, she reported not experiencing any significant improvement in her symptoms.

**Discussion**

We report 2 cases of SFN that may be related to COVID-19. There are limited cases suggesting COVID-19-related SFN. In one recent study [13], Abrams et al. [13] retrospectively reviewed the clinical features and outcomes of patients for painful paresthesia and numbness that developed during or after COVID-19 infection. They identified 13 patients who developed new-onset paresthesia within 2 months of infection [13]. Among these cases, skin biopsy confirmed SFN in 6 patients with neuropathy symptoms and signs.

Similarly, in our cases, the patients developed paresthesia within 2 months of COVID-19 infection (the first case developed within 2 weeks, and the second case developed within 4 weeks). Neither case had previously diagnosed neuropathy and reported any neuropathy-related symptom before COVID-19 infection. Skin biopsy in both cases showed significantly reduced intraepidermal nerve fiber density.

It is difficult to determine if SFN is common in COVID-19. In our cases, skin biopsy findings were consistent with non-length-dependent neuropathy [14, 15] in the first case and with length-dependent neuropathy in the second case.

The underlying neuropathological mechanism of possible COVID-19-related SFN is unclear. However, further studies are needed to determine whether SARS-CoV-2 directly damages nerves or COVID-19 triggers an abnormal autoimmune response that causes nerve damage. The presence of other autoimmune-related neurological complications of COVID-19 infection, such as acute disseminated encephalomyelitis and acute inflammatory demyelinating polyneuropathy [11], and the delayed onset of their symptoms (a few weeks after the infection) support the idea of a possible abnormal autoimmune response that may be causing a postinfectious autoimmune damage mechanism of SFN in COVID-19 cases. Immunosuppressive treatments such as prednisone, mycophenolic acid, azathioprine, or immunomodulatory treatment such as intravenous immunoglobulin (IVIg) treatment [16] may be able to alleviate the symptoms of these patients. In our cases, the symptoms and signs were reported during the sixth- to eighth-month follow-up visits of the patients, who had to use duloxetine and pregabalin for pain control. Due to lack of clinical studies and potential side effects, immunosuppressive treatments were not offered in our case. No spontaneous improvements were observed in these cases; hence, IVIg-like immunomodulatory treatments or other immunosuppressive treatments may be administered to improve their clinical symptoms and signs.
Conclusion

COVID-19 continues to be a global health problem with new variants. This disease has a wide spectrum of clinical presentations affecting central nervous system and PNS with various symptoms [1, 17, 18]. These cases are reported to increase awareness of a possible link between COVID-19 and SNF. Additional investigation, including neurology consultation, nerve conduction studies, and skin biopsy, should be considered in patients who develop paresthesia during and after COVID-19 infection. Further research is also needed to determine a possible underlying neuropathology mechanism and the role of immunomodulatory treatment, such as IVIg, in COVID-19-related SNF.

Statement of Ethics

Written informed consent was obtained from both patients for publication of this case report and any accompanying images. Ethical approval is not required for this study in accordance with local or national guidelines.

Conflict of Interest Statement

The author has no conflicts of interest to declare.

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Author Contributions

Ahmet Z. Burakgazi was involved in data acquisition, case management, and manuscript preparation, editing, and review.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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