

# Small fiber neuropathy in a patient with coronavirus disease 2019 (COVID-19)

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## Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel beta-coronavirus that causes a variety of symptoms in patients known as coronavirus disease (COVID-19). COVID-19 infection may cause complications involving the central nervous system (CNS), peripheral nervous system (PNS), muscles, or autonomic system (ANS). Compared with central and peripheral nervous system involvement in COVID-19 infection reports, the bibliography describing ANS manifestations is more limited. We report a patient with confirmed SARS-CoV-2, admitted to one of the tertiary hospitals in Singapore with small fiber neuropathy. Small fiber neuropathy as a neurological manifestation in COVID-19 infection is rare. Our case report adds to and supports this observation and also highlights how SFN in COVID-19 infection can be self-limited without requiring immunosuppressive treatment.

*Keywords:* COVID-19, Neurological complications, sudomotor dysautonomia, small fiber neuropathy, Sympathetic skin response

## INTRODUCTION

Small fiber neuropathy (SFN) is a neuropathy selectively involving small diameter myelinated and unmyelinated nerve fibers. Sudomotor dysautonomia is one of the earliest manifestations of distal SFN. The sweat function test has been proposed to assess autonomic neuropathy in many centers. Sweat glands are innervated by post-ganglionic unmyelinated sudomotor cholinergic C-fibers. Assessment of the sudomotor function is one of the most common methods to evaluate SFN. Recently, the COVID-19 pandemic has had an unprecedented impact on global health.<sup>1</sup> Here, we illustrate one of the less reported possible manifestations of the SARS-CoV-2 infection to bring further awareness to one of the probable neurological implications of this infection. Informed written consent was obtained from the patient for this publication.

## CASE REPORT

A 36-year-old, previously healthy, Asian man presented to our hospital with a two week history of cough. His nasopharyngeal swab performed to detect SARS-CoV-2 RNA was positive. His COVID-19 illness was mild: Respiratory

examination and chest X-ray were normal. His full blood count, C-reactive protein were normal, and he did not develop hypoxemia. He was admitted to our COVID-19 ward for close observation and isolation.

On Day-25 of his COVID-19 symptoms, he developed painful paraesthesia affecting the left upper limb, which started in the fingertips and then gradually ascended to the elbow. On Day-29 of his COVID-19 symptom, similar symptoms developed in his right hand. He also reported an 'ice-cold' sensation in both feet. There was no associated weakness or other neurological symptoms such as diplopia, vertigo, or urinary and bowel retention. He had no history of neck or back pain, trauma, or recent vaccinations. He did not complain of loss of taste and smell. He has no symptoms suggestive of autonomic dysfunction, such as abnormal sweating, postural giddiness, change in bowel habits, difficulty adjusting eyesight from light to dark, and vomiting. He did not have prior history of excessive alcohol use.

Neurological examination showed reduced pinprick and touch sensation over both feet. There was also reduced pinprick and touch sensation in an asymmetrical pattern in the upper limbs: the left upper limb was affected up to the elbow

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level, and the right upper limb was affected up to the level of the wrist. There was hyperesthesia to cold stimuli over both feet, the right hand, and the right forearm (both dorsal and ventral aspects). Proprioception was intact. The rest of the neurological examination, including the power, tone, deep tendon reflexes and Babinski reflexes responses, were normal. There was no cerebellar dysfunction and no cranial neuropathies. Olfactory and gustatory functions were intact. There was no skin or joint abnormalities. There was no resting or orthostatic tachycardia, orthostatic hypotension, and pupillary abnormality.

Blood investigations showed normal serum glycated hemoglobin (HbA1c), Vitamin B12 level, renal function and electrolytes, thyroid, and liver function tests were also normal.

His Electrodiagnostic studies were performed two weeks after his sensory symptom onset (Day-39 of COVID-19 symptom onset), after his demonstrated clearance of SARS-CoV-2 with a negative nasopharyngeal swab, showed normal upper and lower limb findings in his nerve conduction study, with no evidence of a large fiber polyneuropathy. The sympathetic skin response (SSR) study showed absent responses in both lower limbs and prolonged latencies in both upper limbs (Figure 1). Cardiovascular testing was not performed as it had been suspended in the institution to reduce the risk of COVID-19 transmission to healthcare staff during deep breathing maneuvers. Quantitative sudomotor axonal reflex testing (QSART) and skin biopsy to assess small nerve fiber density were not available at our institution. Lumbar puncture was performed, and cerebrospinal fluid (CSF) analysis showed normal white blood cell count, protein and glucose levels. All CSF microbiological studies, including CSF SARS-CoV-2 RNA, viral polymerase chain reaction (PCR) studies (including varicella zoster virus and cytomegalovirus), bacterial cultures and PCR, acid fast bacilli (AFB) cultures, tuberculosis (TB PCR), and fungal smears and cultures were also negative.

Table 1 & Figure 1: Sympathetic skin reflex (SSR) study performed 2 weeks after onset of neurological symptoms, on Day 39 of COVID-19 infection onset.

In the context of the patient's symptoms and lack of other autonomic symptoms, the abnormal SSRs were interpreted as being due to small fiber neuropathy secondary to COVID-19 infection. Further investigations to identify other known etiologies of SFN, such as antinuclear antibody, anti-extractable nuclear antigen profile,

anti-double-stranded DNA and antineutrophil cytoplasmic antibodies, HIV, hepatitis B, hepatitis C, serum triglycerides, serum and urine protein immunofixation, were all negative.

As no other etiology could be identified, his SFN was deemed to likely be related to his COVID-19 infection, given the temporal relation. He was treated symptomatically with oral gabapentin 300mg once daily with good relief of his pain. His sensory symptoms subsequently resolved a week after neurological symptom onset (Day-32 of COVID-19 illness). A repeat SSR study (Figure 2) four weeks after the initial study (69 days after onset of his COVID-19 infection) showed normalization of the responses in all limbs. The nerve conduction study remained normal. A neurological examination performed on the same day demonstrated corresponding resolution of his previous neurological deficits - sensation to pinprick, touch and cold stimuli were now intact.

Table 2 & Figure 2: Sympathetic skin reflex (SSR) study performed 4 weeks after the first SSR study.

## DISCUSSION

COVID-19 infection may cause complications involving the central nervous system (CNS), peripheral nervous system (PNS), muscles, or autonomic system (ANS).<sup>2</sup> Compared with CNS and PNS in COVID-19 infection reports, the bibliography describing ANS and muscle pathology is more limited. Reported neurological manifestations in COVID-19 affecting the PNS includes Guillain Barré syndrome, cranial neuropathies (causing ophthalmoparesis, or facial nerve palsy) are thought to be para-infectious phenomena rather than due to direct viral effects.<sup>3</sup>

We report this case with SFN associated with COVID-19 infection. Although we were unable to confirm the diagnosis with the gold standard of skin biopsy, which was not available during the COVID-19 pandemic, the character of his positive and negative sensory symptoms, together with evidence of abnormal small fiber nerve function on sympathetic skin reflex (SSR) study, and normal nerve conduction studies were nevertheless consistent with this disorder. The spontaneous resolution of his symptoms and electrophysiological abnormalities following the resolution of his COVID-19 illness further support the association between COVID-19 and his neurological condition.

Dysautonomia has been reported as a PNS complication, and some of the CNS complications,

in COVID-19 infection. Further surveillance and observing for overlap with SFN would be of interest for COVID-19 patients during this COVID-19 pandemic. SFN has a poorly understood pathology with numerous associated causative aetiologies.<sup>3</sup> Unlike Guillain-Barré syndrome, it is not an established post-infectious inflammatory condition resulting from molecular mimicry, with only occasional case reports of SFN developing following viral infections such as Coxsackie B3, Coxsackie B5, and Influenza A, H3N2 viruses.<sup>4</sup> While proposed mechanisms by which viruses can induce pain include direct infection of neurons or nerve fibers, evidence of direct viral neuro-invasion in COVID-19 has been limited to date in reported CSF analyses and pathological studies. On the other hand, COVID-19 has also been associated with immune dysregulation affecting various organ systems and is proposed to be one of the mechanisms of neurological manifestations. SFN has established an association with autoimmune disorders, such as Sjogren syndrome.<sup>5</sup> As such, we believed it is not entirely inconceivable for SFN to be an immune-mediated manifestation of COVID-19.

Our case report adds to the spectrum of reported autonomic manifestations in COVID-19 presentation and complications. Our patient's COVID-19 illness had been mild, and his neurological symptoms were well controlled with symptomatic medication and later resolved spontaneously. It is uncertain if SFN severity would correlate with COVID-19 severity. Recently a case report has been published by Mawuntu *et al.*<sup>6</sup> suggested numbness and prolonged anosmia can be related to small fibre neuropathy pathophysiologically. Further large studies would be required to elucidate this.

## DISCLOSURE

Conflict of interest: None

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