

Small fiber neuropathy associated with SARS-CoV-2 infection

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Abstract

Introduction/Aims: The development and persistence of neurological symptoms following severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is referred to as “long-haul” syndrome. We aimed to determine whether small fiber neuropathy (SFN) was associated with SARS-CoV-2 infection.

Methods: We retrospectively studied the clinical features and outcomes of patients who were referred to us between May 2020 and May 2021 for painful paresthesia and numbness that developed during or after SARS-CoV-2 infection and who had nerve conduction studies showing no evidence of a large fiber polyneuropathy.

Results: We identified 13 patients, Eight women and five men with age ranging from 38–67 y. Follow-up duration ranged from 8 to 12 mo. All patients developed new-onset paresthesias within 2 mo following SARS-CoV-2 infection, with an acute onset in seven and co-existing autonomic symptoms in seven. Three patients had pre-existing but controlled neuropathy risk factors. Skin biopsy confirmed SFN in six, all of whom showed both neuropathy symptoms and signs, and two also showed autonomic dysfunction by autonomic function testing (AFT). Of the remaining seven patients who had normal skin biopsies, six showed no clinical neuropathy signs and one exhibited signs and had abnormal AFT. Two patients with markedly reduced intraepidermal nerve fiber densities and one with normal skin biopsy had severe and moderate coronavirus disease 2019 (COVID-19); the remainder experienced mild COVID-19 symptoms. Nine patients received symptomatic neuropathy treatment with paresthesias controlled in seven (77.8%).

Discussion: Our findings suggest that symptoms of SFN may develop during or shortly after COVID-19. SFN may underlie the paresthesias associated with long-haul post-COVID-19 symptoms.

KEYWORDS

long-haul COVID-19 symptoms, neurological complications, post-acute COVID-19 syndrome, SARS-CoV-2, small fiber neuropathy

Abbreviations: AFT, autonomic function test; ANA, antinuclear antibodies; COVID-19, coronavirus disease 2019; HbA1c, hemoglobin A1c; IENFD, intraepidermal nerve fiber density; MRI, magnetic resonance imaging; NCS, nerve conduction studies; PCR, polymerase chain reaction; QSART, quantitative sudomotor axon reflex test; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SFN, small fiber neuropathy; TSH, thyroid stimulating hormone.

1 | INTRODUCTION

Chronic fatigue, brain fog, sleep disturbances, and paresthesias may become significant “long-haul” symptoms of the post-acute coronavirus disease 2019 (COVID-19) syndrome.^{1,2} Some of these symptoms overlap

with those of small fiber neuropathy (SFN). The SFN associated with COVID-19 has not been well studied. COVID-19 can exacerbate SFN symptoms, but to date, de novo SFN associated with COVID-19 appears to be very rare.³ Autonomic dysfunction has been described in association with COVID-19, which can occur during or several months after the infection.³⁻⁵ Herein, we retrospectively studied the demographics, clinical features, test findings, and outcomes of 13 patients with new-onset paresthesias suggestive of SFN that developed during or after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.

2 | METHODS

We searched our skin biopsy database and identified 13 patients with confirmed SARS-CoV-2 infection, who were referred to our neuromuscular clinic by the Center for Post-COVID Care at The Mount Sinai Hospital between May 2020 and May 2021 for evaluation of paresthesia. All these patients received routine nerve conduction

studies (NCS) and electromyography, which showed no evidence of a large fiber polyneuropathy. They also underwent clinical evaluation and skin biopsy to confirm SFN by one of the authors. Three-millimeter punch skin biopsies were performed at the distal leg and proximal thigh of each patient after appropriate consent was obtained. Biopsy specimens were processed and immunostained using PGP9.5 antibody for intraepidermal nerve fiber density (IENFD) evaluation by either Boston University Medical Center or Johns Hopkins University Cutaneous Nerve Laboratory. These two laboratories use the same methodology and follow the same published guidelines.⁶ Four patients also underwent standardized autonomic function testing (AFT) with quantitative sudomotor axon reflex testing (QSART), heart rate responses to deep breathing, Valsalva maneuver, assessment of blood pressure changes in response to passive head-up tilt. The demographics, clinical features, test results, and outcomes of these patients were retrospectively studied by electronic chart review. This study was approved by the Institutional Review Board of the Icahn School of Medicine at Mount Sinai.

TABLE 1 Summary of patients with abnormal skin biopsy

(patient no) age (y)/gender	COVID-19 severity ^a	Symptoms	Time from COVID-19 to onset of neuropathy	Neuropath y signs	IENFD			Outcome at last follow-up
					DL	PT	AFT	
(1) 58 F	Severe	Acute onset generalized burning, shocking, tingling, itching deep aching joint pains orthostatic discomfort	3 wk	Distally decreased PP	↓↓↓	↓↓	NP	Poorly controlled on duloxetine and gabapentin at 8 mo
(2) 38 F	Moderate	Acute onset generalized burning, pins-and-needles in the hands and feet Skin hypersensitivity Heart palpitations Orthostatic discomfort	2 wk	Distally decreased PP	↓↓↓	↓↓	POTS ↓SF at FA	Poorly controlled on gabapentin at 11 mo
(3) 40 F	Mild	Acute onset generalized pins-and-needles Heart palpitations Orthostatic discomfort	1 mo	Distally decreased PP	↓↓	NL	NP	Improvement on gabapentin at 1 y
(4) 46 F	Mild	Tingling in the hands and feet Heart palpitations Orthostatic discomfort	1 mo	Distally decreased PP and vibration sense	↓	NL	POTS Absent SF at F; ↓ SF at DL	Moderate improvement on amitriptyline and gabapentin at 1 y
(5) 61 F	Mild	Painful pins-and-needles in the hands and feet Skin discoloration (redness) in the hands and feet	2 wk	Distally decreased PP	↓↓	NL	NP	Improvement on gabapentin at 1 y
(6) 46 F	Mild	Numbness, tingling, and burning in the toes Deep aching bilateral legs	Symptoms started during viral illness	Distally reduced PP	↓ [%]	NL [%]	NP	Improvement on pregabalin at 5 mo

Abbreviations: DL, distal leg; F, foot; FA, forearm; NL, normal; NP, not performed; POTS, postural orthostatic tachycardia syndrome; PP, pinprick; PT, proximal thigh; SF, sudomotor function.

Note: ↓: mildly reduced (<25% reduction); ↓↓: moderately reduced (25–75% reduction); ↓↓↓: severely reduced (>75% reduction). %: small axonal swelling on pathology.

^aClinical spectrum of SARS-CoV-2 Infection from National Institutes of Health COVID-19 Treatment Guideline.⁹

3 | RESULTS

Patient demographics, clinical features, test findings, therapy, and outcomes are detailed in Table 1 for those with abnormal skin biopsy and in Table 2 for those with normal biopsy results. Eight patients (61.5%) were females, and five were males (38.5%). Ages ranged from 38 to 67 y, with a median of 50 y. Ten patients had confirmed SARS-CoV-2 infection by nasopharyngeal polymerase chain reaction (PCR), and three patients were confirmed by antibody tests. COVID-19 was severe in one, moderate in two, mild in nine, and asymptomatic in one (Supporting Information Appendix S1, which is available online). Time from SARS-CoV-2 infection to paresthesia onset ranged from 0 to 2 mo. Seven patients had acute onset of sensory symptoms. Sensory symptoms included burning, tingling, electric shock-like sensation, squeezing pain, itching, and numbness. The symptoms mainly involved distal limbs in seven and were diffuse in six. Seven patients reported orthostatic discomfort and/or palpitations.

Most of the patients had brain (9/13) and/or spine (6/13) magnetic resonance imaging (MRI) scans, which were unrevealing. Skin biopsies in 6/13 (46.2%) patients showed reduced IENFD, confirming the diagnosis of SFN. The median age was 46 y (range 38 to 61) for the biopsy-positive group and 52 y (range 46 to 67) for the biopsy-negative group. The IENFD was reduced only at the distal leg in four and at both distal leg and proximal thigh with a distal-to-proximal gradient in two. The remaining 7/13 (53.8%) did not appear to have significant small fiber loss. QSART showed absent or reduced sweat output in the distal limbs in 2/6 biopsy-positive patients. AFT revealed

abnormalities in three out of four patients who felt orthostatic discomfort: two had orthostatic tachycardia and one had orthostatic hypotension. Time from symptom onset to biopsy ranged from 5 to 10 mo with a median of 8.5 mo in the biopsy-positive group, and 8–15 mo with a median of 10 mo in the biopsy-negative group. All six patients who had positive skin biopsies were females, and they also had SFN signs, while most of the biopsy-negative patients had no objective sensory findings. Patient 7, who had sensory signs but a normal skin biopsy of the leg, did show reduced sweat output at the proximal thigh by QSART and orthostatic hypotension by passive head-up tilt testing. All patients had negative exclusionary neuropathy blood profile including hemoglobin A1c (HbA1c), antinuclear antibodies (ANA), B12, thyroid stimulating hormone (TSH), free T4, and serum immunofixation. Only three patients with biopsy proven SFN had pre-existing risk factors for neuropathy. Patient 4 had long-standing, well-controlled hypothyroidism. Patient 5 had well-controlled diabetes mellitus with HbA1C of 5.1%. Patient 6 experienced a flare of her ulcerative colitis during the viral illness but was previously well-controlled on mesalamine and ustekinumab.

Duration of follow-up ranged from 8 to 12 mo from onset of neuropathy symptoms. Nine patients received symptomatic therapy, of which seven (77.8%) had paresthesias relatively well-controlled. Among six patients with biopsy proven SFN, paresthesias were controlled in four (66.7%). Symptoms were not well-controlled in two patients who had IENFD severely reduced at the distal leg and moderately reduced at the proximal thigh. Four patients with intermittent paresthesias and normal skin biopsy declined therapies. Three patients

TABLE 2 Summary of patients with Normal skin biopsy

(Patient no) age (y)/gender	COVID-19 severity ^a	Symptoms	Time from COVID-19 to onset of neuropathy	Neurologic exam	AFT	Outcome at last follow-up
(7) 43 M	Mild	Acute onset generalized itching, burning, “fizzing” electric shocks Heart palpitations Orthostatic discomfort	6 wk	Hyperesthesia to PP in the hands Distally decreased PP	OH ↓SF at PT	Improvement on nortriptyline at 1 y
(8) 56 M	Asymptomatic	Acute onset generalized pins-and- needles Sensation of muscle twitching	2 mo	Normal	NP	Asymptomatic at 1 y
(9) 50 M	Moderate	Tingling in hands and feet Left facial numbness Persistent anosmia	2 mo	Normal	NP	Moderate improvement on gabapentin at 1 y
(10) 46 F	Mild	Pins-and-needles on soles of feet Heart palpitations	2 wk	Normal	NP	Intermittent paresthesias off-medication at 1 y
(11) 56 M	Mild	Acute onset right arm numbness followed by numbness and pain in both feet Occasional orthostatic discomfort	1 mo	Normal	NL	Improvement on duloxetine at 1 y
(12) 67 M	Mild	Acute onset generalized burning in both feet, hands, and perioral region	1 mo	Normal	NP	Intermittent paresthesias off-medication at 1 y
(13) 52 F	Mild	Generalized numbness Deep squeezing pain	2 wk	Variable, non- reproducible PP	NP	Improvement off medications at 1 y

Abbreviations: NL, normal; NP, not performed; OH, orthostatic hypotension; PP, pinprick; PT, proximal thigh; SF, sudomotor function.

^aClinical spectrum of SARS-CoV-2 Infection from National Institutes of Health COVID-19 Treatment Guideline.⁹

with positive AFT had resolution of autonomic symptoms by the last clinic visit without medical intervention.

4 | DISCUSSION

Our findings suggest that symptoms of SFN may develop following SARS-CoV-2 infection regardless of the severity of COVID-19, and paresthesias may underlie long-haul post-COVID-19 symptoms. Sensory symptoms following COVID-19 are not uncommon. SFN should be suspected when patients show both small fiber sensory symptoms and signs despite normal NCS. A majority (7/13) of patients in our cohort who showed reduced pinprick sensation in the distal limbs had abnormal skin biopsy (six patients) or AFT/QSART (Patient 7), confirming the diagnosis of SFN, while none of the six patients without neuropathy signs on clinical exam had abnormal skin biopsy or AFT. The causes of paresthesias in these six patients are not entirely clear, but they could still be due to small fiber dysfunction, as a central cause was ruled out by imaging studies. The delay to performing the biopsies was typically the result of restrictions to clinical care during the peak of the pandemic in New York City or patient hesitancy. This temporal delay may have allowed time for small fiber recovery and resulted in false-negative results in the normal biopsy group.

Although causality cannot be proven, it appears that SFN in our patients is strongly associated with COVID-19. None had neurological symptoms prior to the viral infection. Our findings differ from those of Shouman et al.,³ who observed that autonomic dysfunction following COVID-19 infection may have been due to unmasking or exacerbation of a preexisting condition, while our SFN cases are all de novo. Except for the patient who developed paresthesias during the infection, the others developed sensory symptoms 2 wk to 2 mo after the infection, which makes direct viral invasion of small nerve fibers or ganglia unlikely. This acuity may suggest a small fiber-restricted form of post-infectious acute neuropathy or post-viral autoimmune phenomenon.

Symptoms of SFN can occur regardless of COVID-19 severity. All but three of our patients had mild or asymptomatic COVID-19 symptoms. It is intriguing that in six biopsy-proven SFN cases, the reduction of IENFD was length-dependent with the distal leg being solely or more affected than the proximal thigh, despite that the SFN symptoms were diffuse and appeared non-length-dependent in three of six. The sensory deficits on examination were also length-dependent in these patients. Although non-length-dependent SFN is more likely to be associated with an immune-mediated process than length-dependent SFN, an immune-mediated process can also cause length-dependent SFN.^{7,8}

None of these patients received immunotherapy specifically for their SFN symptoms, and nine received symptomatic treatment with mixed results. While most of our patients responded to symptomatic treatment for neuropathic pain, the symptoms were not well controlled in two who had IENFD severely reduced at the distal leg and moderately reduced at the proximal thigh (Patient 1 and Patient 2). Further studies are required to determine if there is any role for immunotherapy in this setting. Such clinical studies to test these treatments will assess efficacy and ultimately may help post-COVID survivors with lingering chronic painful paresthesias.

This study has several limitations. It is retrospective and the cohort is small. Given that most patients in this study developed COVID-19 during the initial New York City peak of the pandemic in March–April 2020, it is possible that patients with milder neuropathy symptoms may have recovered and were never assessed with a skin biopsy at the peak of their post-infectious symptoms. Increased and earlier recognition of SFN is crucial to address what is clearly an under-recognized source of morbidity.

CONFLICT OF INTEREST

None of the other authors has 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

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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