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Demonstrating new-onset or worsened sudomotor function post-COVID-19 on comparative analysis of autonomic function pre-and post-SARS-CoV-2 infection

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ABSTRACT

Background: Autonomic dysfunction including sudomotor abnormalities have been reported in association with SARS-CoV-2 infection.

Objective: There are no previous studies that have compared autonomic function objectively in patients pre- and post- SARS-CoV-2 infection.

We aimed to identify if SARS-CoV-2 virus is triggering and/or worsening dysautonomia by comparing autonomic function tests in a group of patients pre-and post-SARS-CoV-2 infection.

Design/methods: Six participants were enrolled and divided into two groups. The first group of 4 participants reported worsened autonomic symptoms post-SARS-CoV-2 infection. These individuals had their first autonomic test prior to COVID-19 pandemic outbreak (July 2019–December 2019). Autonomic function testing was repeated in these participants, 6 months to 1-year post-SARS-CoV-2 infection (June 2021).

The second group of 2 participants reported new-onset autonomic symptoms post-COVID-19 infection and were also tested within 6 months post-SARS-CoV-2 infection.

All participants had mild COVID-19 infection per WHO criteria. They had no evidence of large fiber neuropathy as demonstrated by normal neurophysiological studies (EMG/NCS). They were all screened for known causes of autonomic dysfunction and without risk factors of hypertension/hyperlipidemia, thyroid dysfunction, diabetes/prediabetes, vitamin deficiencies, history of HIV, hepatitis, or syphilis, prior radiation or chemical exposure or evidence of monoclonal gammopathy, or autoimmune condition.

Results: Participants were female (age: 21-37y) and all endorsed orthostatic intolerance (6/6). Gastrointestinal symptoms ($^{5}/_{6}$), new-onset paresthesias, (3/6), and sexual dysfunction (2/6) were reported. Parasympathetic autonomic function remained stable 6-months to 1-year post-COVID-19 infection and no parasympathetic dysfunction was demonstrated in participants with new-onset dysautonomia symptoms. Postural orthostatic tachycardia was noted in half of the patients, being observed in one patient pre- SARS-CoV-2 infection and persisting post-SARS-CoV-2 infection; while new-onset postural tachycardia was observed in 1/3rd of patients. Sympathetic cholinergic (sudomotor) dysfunction was demonstrated in ALL participants. Worsened, or new-onset, sudomotor dysfunction was demonstrated in those with mild or normal sudomotor function on pre-COVID-19 autonomic testing.

Conclusions: Sympathetic adrenergic and cholinergic dysautonomia probably account for some of the symptoms of Long COVID-19. Sudomotor dysfunction was demonstrated as consistently worsened or new-sequelae to COVID-19 infection. COVID-19 may be responsible for triggering new-onset or worsened small-fiber neuropathy

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in this sample, supporting previously reported studies with similar findings. However, the findings in our study are preliminary, and studies with larger sample size are needed to confirm these observations.

1. Introduction

Autonomic dysfunction is implicated in post-COVID-19 syndromes [1–8], attributed to direct viral-invasion of central and peripheral autonomic nervous structures and/or immune-mediated processes [1–3]. Parasympathetic dysfunction with continued dysautonomia is observed [7]. Sympathetic adrenergic abnormalities such as hyperadrenergic postural tachycardia and blood pressure lability [6–10], and sympathetic cholinergic abnormalities in form of small fiber neuropathy have been noted [1–4].

While temporal association of autonomic dysfunction and exacerbation of underlying conditions is considerable [5], a growing body of reports suggests possible association of SARS-CoV-2 infection and dysautonomia. We conducted a single-center retrospective and prospective study to compare autonomic function pre- and post- SARS-CoV-2 infection in patients with worsened orthostatic intolerance and neuropathic symptoms post SARS-CoV-2 infection. A prospective analysis of autonomic function in patients with only new-onset autonomic symptoms post-SARS-CoV-2 infection was also conducted for comparison.

2. Methods

This study was approved by the Louisiana State University Health Sciences Center (LSUHSC) IRB. We conducted a retrospective review of patients who underwent autonomic testing 6 months prior to entry of SARS-COV-2 virus in the United States (July 2019–December 2019). From this cohort, patients who met inclusion criteria were enrolled for repeat autonomic testing. We also prospectively reviewed patients with new-onset dysautonomia symptoms post-COVID-19 from time period January 2020–May 2021. Table 1 describes inclusion criteria for patients selected for our study.

All patients provided voluntary informed consent. A structured survey reviewing medical history, neurological, autonomic and COVID-19 symptoms was conducted. All patients underwent a full clinical neurological examination.

On autonomic testing, parasympathetic function was assessed by heart rate variability during deep breathing and Valsalva maneuvers. Continuous blood-pressure monitoring was performed throughout 10-min head-up tilt table (HUT) test. Catecholamine levels at baseline and tilt were recorded. Quantitative sudomotor axonal reflex testing was performed to assess sudomotor function.

Six participants were enrolled and divided into two groups.

The first group of 4 participants reported worsened autonomic symptoms post-SARS-CoV-2 infection. These patients had previous symptoms of dysautonomia, and their clinical presentation comprised of symptoms of lightheadedness, dizziness, and syncope. These symptoms were noted to have worsened post-SARS-CoV-2 infection. Table 2b describes initial symptom presentation prior to SARS-CoV-2 infection and symptoms post-SARS-CoV-2 infection. These individuals had initial autonomic test prior to COVID-19 pandemic outbreak (July 2019–December 2019) and repeat autonomic testing 6 months to 1-year [June 2021] post-infection.

The second group of 2 participants reported new-onset autonomic symptoms post-SARS-CoV-2 infection and were tested within 6-months post infection [March/May 2021].

Table 1
Inclusion criteria of study participants.

Inclusion criteria
1) Age > 18 years
2) SFN symptoms of paresthesia/dysesthesias OR autonomic symptoms/orthostatic intolerance
3) Normal routine NCSs
4) Positive* COVID-19
5) Stable risk factors including normal blood pressure, normal/stable thyroid function, Hba1c < 5.7 or if between 5.7 and 6.2 then no change >0.2 points, normal B vitamin levels, RPR negative, Hepatitis panel negative, no evidence of monoclonal gammopathy, and/or autoimmune condition; all testing within the past 6 months

* A positive COVID-19 antigen or PCR test was considered as positive COVID-19.

3. Results

All 6 participants were female (age: 21-37y) and endorsed new or worsened orthostatic intolerance post SARS-CoV-2 infection (6/6). Pupillary dysfunction with difficulties in accommodation was reported in one patient (1/6). Gastrointestinal symptoms including lack of appetite, bloating, nausea, and diarrhea/constipation were reported in most patients (5/6). Urinary leakage, urinary frequency (2/6) and sexual dysfunction/decreased libido (2/6) was reported in one-third of patients. Sweating abnormalities and new-onset paresthesias were reported in half of the patients (3/6).

All patients had mild COVID-19 infection per WHO criteria. Anosmia and dysgeusia were reported in half of the patients (3/6).

On neurological examination, cranial nerve abnormalities as mild anisocoria in one-third of patients (2/6), abnormal Rinne test in 1 patient (1/6) and abnormal Weber test in half the patients (3/6) were seen. Subjective sensory deficits (large/small-fiber) were observed in only one patient (1/6). Motor, cerebellar and gait examination was normal in all patients. Myotatic reflexes were normal in all except in ⅙ patients with bilaterally symmetric reduced ankle jerks. Table 2a outlines the clinical presentation of patients in this study.

On autonomic testing, cardiovascular indices (heart-rate variability to deep breathing and Valsalva) were normal in both patients with new-onset symptoms post-COVID-19 and stable/unchanged in patients who had repeat testing post-COVID-19.

Neurogenic postural orthostatic tachycardia with exaggerated norepinephrine response on tilt-testing was seen in half the patients (1/2) with new-onset dysautonomia.

In patients with worsened dysautonomia symptoms post-COVID-19, new-onset neurogenic postural orthostatic tachycardia with incipient neurally-mediated syncope was seen in 1 patient and persistent postural tachycardia in 1 patient (total: 2/4 patients who reported worsened dysautonomia post-COVID-19). Blood pressure responses to Valsalva maneuver showed mild to moderate abnormalities in these same patients. There was a significant decrease of blood pressure in Phase II Valsalva, which can indicate reduced preload states. The drop in blood pressure was accompanied by bradycardia indicating a predisposition to neurally mediated syncope.

Sudomotor dysfunction was demonstrated in all participants. In patients with new-onset symptoms, sudomotor indices were abnormal in all patients. In patients with worsened dysautonomia, worsened sudomotor indices in 3/4 patients and persistent abnormal score in the fourth patient was noted. Skin biopsies performed in 3 patients, demonstrated decreased intraepidermal nerve fiber density (IENFD) in 2/3 patients.

4. Discussion

Dysautonomia symptoms including postural orthostatic tachycardia, orthostatic intolerance and sudomotor dysfunction/small-fiber neuropathy have been observed post COVID-19 [1–10].

There are no previous studies comparing objective findings of

Table 2a
Clinical presentation of patients.

Clinical presentation	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Symptoms suggestive of Small fiber neuropathy	None	None	Electric shocks, burning in extremities	None	Non-length dependent Paresthesias	Non-length dependent Paresthesias
Orthostatic Intolerance	Stable from previous	Worsened lightheadedness	Worsened lightheadedness	None	Palpitations	None
Symptoms suggestive of pupillary dysfunction	None	Difficulty adjusting from light to dark, blurry vision	Worsened Difficulty adjusting from light to dark, blurry vision	None	Difficulty adjusting from light to dark, blurry vision	None
Gastrointestinal symptoms	None	Nausea, early satiety, bloating	Worsened Early satiety, bloating post meal, irregular bowel movements	Constipation	Early satiety, diarrhea, post meal bowel movements, nausea, vomiting	Bloating post-meal
Genitourinary symptoms	None	None	New onset urinary leakage	None	Increased urinary frequency	None
Sexual symptoms	None	None	Decreased libido	Decreased libido	None	None
Sweating abnormalities	Diffuse decreased sweating	None	New onset decreased sweating in extremities	None	None	Decreased sweating worse in extremities
Abnormalities on Neurological Exam	Cranial Nerve Exam: Weber lateralized to right	Cranial Nerve Exam:* Rinnes Exam: L > R	Cranial Nerve Exam: Weber lateralized to right	Cranial Nerve Exam: Weber Lateralized to Left	Cranial Nerve Exam: Normal	Cranial Nerve Exam:* Normal
	Motor: Normal	Motor: Normal	Motor: Normal	Motor: Normal	Motor: Normal	Motor: Normal
	Sensory: Normal	Sensory: Normal	Sensory: Decreased pin prick and temperature distally in extremities Decreased vibration/ proprioception: L Toe	Sensory: Normal	Sensory: Normal	Sensory: Normal
	DTRs: 2+ throughout	DTRs: 2+ throughout	DTRs: 2+ throughout except bilateral 1+ ankle	DTRs: 2+ throughout	DTRs: 2+ throughout	DTRs: 2+ throughout
	Cerebellar and Gait: normal	Cerebellar and Gait: normal	Cerebellar and Gait: normal	Cerebellar and Gait: normal	Cerebellar and Gait: normal	Cerebellar and Gait: normal

* Anisocoria was noted in Patient 2, and Patient 6; however pupillary reaction was brisk bilaterally in both patients.

autonomic function pre-and post-SARS-CoV-2 infection. Our study provides comparative analysis of autonomic function pre-and post-SARS-CoV-2 infection in a group of patients without any known risk factors of autonomic dysfunction.

On neurological exam, detailed cranial nerve exam was performed to determine any association with dysautonomia and cranial nerve dysfunction. Direct neural invasion via cranial nerves affecting central autonomic structures, with viral affinity to ACE-II receptors in baroreflex-arc have been implicated in orthostatic intolerance post-COVID-19 [9,11].Although anosmia and dysgeusia was reported in half of our study patients, it was not evident on exam. Abnormalities in Weber and Rinne tests were noted in a small subset; a formal audiological evaluation was not performed in these patients. As the inner-ear structures have ACE2, TMPRSS2, and FURIN receptors facilitating entry of SARS-CoV-2 [11], we suggest that vestibulo-auditory evaluations as part of evaluation of dizziness post-COVID-19 as it could overlap and exacerbate features of orthostatic intolerance.

In our study, parasympathetic function remained stable pre- and post-COVID-19. In patients with new-symptom onset post COVID-19, no parasympathetic abnormalities were noted. Similarly, in another retrospective study of fourteen patients with long COVID-19, patients who complained of orthostatic intolerance had normal cardiovagal function [10].

Hyperadrenergic states from infection, hypovolemia, and deconditioning are implicated in development of orthostatic intolerance post-pandemic. In a retrospective review of 20 patients, 75% had postural tachycardia, with residual dysfunction noted 6–8 months post infection [6]. Exacerbation of pre-existing conditions may provoke dysautonomia in patients [5]. In our study, hyperadrenergic postural orthostatic tachycardia syndrome (POTS) was noted in half of the patients in the study group, with new-onset POTS in 1/3rd of patient sample.

On sympathetic cholinergic/sudomotor testing, all participants demonstrated worsened sudomotor indices post COVID-19 infection, and in some patients, was not present on pre COVID-19 testing. This observation supports previous studies [1–4] that suggest small fiber neuropathy may be triggered by SARS-CoV-2 infection.

Neurotropism of SARS-CoV-2 virus via ACE-2 receptors in peripheral nerve and dorsal receptor ganglia axons as virion entry point has been proposed and non-length dependent neuropathy reported [12]. Small fiber neurons/axons have intra-neuronal reflex mechanisms to control local inflammatory processes, but cytokine-induced damage post COVID-19 has been observed [13]. Deficits in sweat production have also been observed post COVID-19 [14].

Our study demonstrates repeat testing post-COVID-19 showed worsened sudomotor indices in setting of otherwise stable risk factors in patients with previous SFN. In patients with new-onset symptoms, abnormal sudomotor indices was also seen. We conclude that there may be both trigger-effect and worsening of SFN from SARS-CoV-2 infection.

Our group of patients had mild COVID-19 infection per WHO criteria. Disease severity does not appear to have any relationship to SFN development [4].

5. Conclusion

Parasympathetic function on autonomic testing remained stable in patients pre and post SARS-CoV-2 infection. Postural orthostatic tachycardia was noted in half of our study's patients, persisting in one patient pre- and post-SARS-CoV-2 infection and new-onset in 1/3rd of patients. A consistent abnormality was noted in sudomotor/sympathetic cholinergic function in patients with new-onset and worsening

Table 2b
Autonomic function Pre-SARS-CoV-2 and Post-SARS CoV-2 infection (mild COVID-19 per WHO criteria) in group of healthy young adults.

Patient	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age/Sex	23/F	25/F	26/F	24/F	28/F	37/F
EMG/NCS	NORMAL	NORMAL	BL carpal tunnel syndrome	NORMAL		
Skin biopsy	Abnormal *Reduced IENFD	Abnormal *Reduced IENFD	NP	NP	NL	NP
PRE-COVID-19 AUTONOMIC TEST	CASS:2	CASS: 2	CASS:1	CASS: 3	NP (new-onset dysautonomia post COVID-19)	NP (new-onset dysautonomia post COVID-19)
	Cardiovascular: 0	Cardiovascular: 0	Cardiovascular: 1 *HR_DB mildly decreased	Cardiovascular: 0	–	–
	Adrenergic: 0	Adrenergic: 1* **POTS Decreased vasopressor response associated with bradycardia. Predisposition to neurally mediated syncope	Adrenergic: 0	Adrenergic:0	–	–
	Sudomotor: 2 Blunted norepinephrine response to tilt	Sudomotor:1 NL norepinephrine response to tilt	Sudomotor: 0 NL norepinephrine response to tilt	Sudomotor: 3 Blunted norepinephrine response to tilt	– –	– –
POST COVID-19 AUTONOMIC TEST	CASS: 4	CASS: 4	CASS: 3	CASS: 3	CASS: 3	CASS: 3
	Cardiovascular: 0	Cardiovascular: 0	Cardiovascular: 1 *HR_DB mildly decreased	Cardiovascular: 0	Cardiovascular: 0	Cardiovascular: 0
	Adrenergic: 1 POTS Decreased vasopressor response associated with bradycardia. Predisposition to neurally-mediated syncope	Adrenergic: 2 POTS Decreased vasopressor response associated with bradycardia. Predisposition to neurally-mediated syncope	Adrenergic: 0	Adrenergic: 0	Adrenergic: 1 POTS neurogenic	Adrenergic: 1
	Sudomotor: 3 Blunted norepinephrine response to tilt	Sudomotor: 2 NL norepinephrine response to tilt	Sudomotor: 2 Difficult venous access No catecholamines drawn	Sudomotor: 3 NL norepinephrine response to tilt** (Low baseline norepinephrine levels)	Sudomotor: 2 Exaggerated norepinephrine response to tilt c/w POTS	Sudomotor: 2 NL norepinephrine response to tilt

NP: Not performed.
NL: Normal.
CASS: Composite Autonomic Severity Score (CASS).
POTS: Postural orthostatic tachycardia, NCS: Neurocardiogenic syncope.
HR_DB: Heart Rate Variability to Deep Breathing.
IENFD: Intraepidermal nerve fiber density.

dysautonomia post-COVID-19 infection. Sympathetic adrenergic and cholinergic dysautonomia probably account for some of the symptoms of Long COVID-19. Whether these abnormalities are due to direct viral invasion or due to dysimmune mechanisms remain unknown. The findings in our study are preliminary, and studies with larger sample size are needed to confirm these observations.

Credit authorship contribution statement

Aditi Varma-Doyle: Conceptualization, Methodology, Investigation, Visualization, Funding acquisition, Writing – original draft. **Nicole R. Villemarette-Pittman:** Methodology, Project administration, Formal analysis, Data curation, Writing – review & editing. **Paul Lelorier:** Supervision, Conceptualization, Methodology, Investigation, Writing – review & editing, Writing – original draft. **John England:** Supervision, Conceptualization, Methodology, Investigation, Writing – review & editing, Writing – original draft.

Declaration of Competing Interest

There are no conflicts of interest, real or perceived in the preparation or submission of this manuscript for publication.

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