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SHORT COMMUNICATION

Sudomotor dysfunction in patients recovered from COVID-19

Anand Hinduja[a,*], **Abdul Moutairou**[b], **Jean-Henri Calvet**[b]

[a] *Aarti Clinic, Kharghar, Navi Mumbai, India*
[b] *Impeto Medical, Paris, France*

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Abstract Dysautonomia has been reported in COVID-19. Sweat function testing has been proposed to assess autonomic neuropathy. Fifty Indian patients consulting for neurological symptoms participated in this observational study. The NHS questionnaire for neurological symptoms was completed and electrochemical skin conductance was measured using Sudoscan. The 26% of patients with sweat dysfunction i) were older ($p = 0.001$), ii) were more frequently treated at home ($p = 0.008$), iii) were more likely to have received antiviral treatment ($p = 0.0006$), and iv) more frequently reported at least one motor, sensory or autonomic symptom ($p = 0.04$). This preliminary study suggests that patients with COVID-19 should be screened for dysautonomia.

Introduction

Since the beginning of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, several neurological manifestations have been reported in afflicted patients, ranging from mild symptoms, such as anosmia, hypogeusia, and headaches, to more severe manifestations, including acute encephalitis, cerebrovascular stroke, and peripheral neuropathy [5,13]. Additionally, Guillain Barré syndrome has been described by several teams [11]. An explanation for peripheral nervous system involvement could be ''molecular mimicry,'' the cross-reactivity of natural immunoglobulins—formed in response to a bacterial or viral antigen—with specific proteins on the myelin, axon, or neuromuscular junction [3]. Dysautonomia symptoms have also been observed in COVID-19 patients, including diarrhea and sweat dysfunction [10]. This is similar to dysautonomia reported with other viral infections such as mumps, HIV, Hepatitis C, Epstein-Barr, and Coxsackie B. Presence of dysautonomia in COVID-19 patients should be further studied in order to appropriately diagnose and manage post-COVID patients.

Sudomotor dysfunction is considered one of the earlier manifestations of distal small fiber neuropathies. Sweat glands are innervated by postganglionic unmyelinated sudomotor cholinergic sympathetic C-fibers, and several skin biopsy studies have shown a decrease in epidermal C-fibers

* Corresponding author at: Aarti Clinic, 10, Monarch Fortune CHS, Sector 18, Kharghar, Navi Mumbai, 410210, India.
E-mail address: dranand01@gmail.com (A. Hinduja).

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in patients with various diseases including diabetes, amyloidosis, or viral infections [9]. Therefore, assessment of sudomotor function is an attractive method to evaluate and follow small fiber neuropathy. Several methods have been developed to assess structure or function of small C-fibers, but these are lengthy, invasive, subjective, or non-quantitative and thus cannot be used for screening or follow-up of neuropathies [2]. Sudoscan is a rapid, non-invasive, objective and quantitative method of assessing sudomotor function by providing measures of electrochemical skin conductance (ESC); its performance (diagnostic value, accuracy, reproducibility) in peripheral small fiber neuropathy has been evaluated in several clinical studies, particularly in patients with diabetes, amyloidosis, Sjögren's syndrome, Hepatitis C, or receiving chemotherapy [8,12,15].

This study aimed to evaluate the potential impact of COVID-19 on autonomic small fibers using ESC measurements.

Methods

This observational study enrolled Indian patients who had recovered from COVID-19 and were seen within 3 months post-infection in an outpatient clinic for fatigue or various neurological symptoms. Written informed consent was obtained from all participants prior to any study procedure.

COVID-19 infection was confirmed from RT-PCR and/or antigen test reports. Daily smokers, pregnant patients, and patients with diabetes, thyroid dysfunction, coronary artery disease, previous stroke, chronic alcoholism or receiving drugs with significant anticholinergic effect were excluded from the study.

A complete questionnaire of symptoms of peripheral neuropathy, motor, sensory or autonomic: 15 questions in total; National Health Service (NHS), UK (https://www.nhs.uk/conditions/peripheral-neuropathy/symptoms/) was completed by the investigator during history taking by asking all the questions listed in the questionnaire. Regarding sensory and motor symptoms, these were recorded if they were present at least in lower limbs. In addition, COVID treatment modality (isolation at home for asymptomatic or mildly symptomatic cases, or compulsory hospital admission per standard of care for moderate and severe cases) and treatment received for SARS-CoV-2 (remdesivir or other antiviral treatment) were recorded. After clinical examination, including blood pressure recorded in supine position using a sphygmomanometer and heart rate recording using a pulse oximeter, sudomotor function testing was performed using the Sudoscan device (Impeto Medical, Paris, France) to measure electrochemical skin conductance of the hands and feet (HESC and FESC, respectively). This rapid non-invasive method is based on an electrochemical reaction between sweat chloride and stainless-steel electrodes after stimulation of sweat glands by a low voltage direct current (<4 Volts) for about 2 min. Patients are asked to stand for 2 min with the palms of their hands and soles of their feet in contact with the electrodes. ESC is a quantitative result (microSiemens, μS) obtained from the ratio between the measured current and the applied voltage. This method has been validated against reference methods in patients with various diseases [9].

Statistical analysis

Categorical data were expressed numerically and as percentages, while continuous variables with a normal distribution were expressed according to their arithmetic mean and standard deviation. For categorical variables, comparisons were made using Chi-square or Fisher's exact (for small numbers) tests. Student's *t*-tests for comparison of means were implemented for continuous variables with means that followed a normal distribution. Analysis of these parameters was done by comparing the baseline characteristics of subjects with FESC < 60 μS to those with FESC ≥ 60 μS. All tests performed are significant at $p < 0.05$ or $p < 0.01$ when multiple tests were performed. Data were analyzed using SAS software version 9.4.

Results

Fifty patients participated in the study from 67 consecutive selected patients presenting for outpatient consultation between September and November 2020. The 17 patients selected but not included had type 2 diabetes (12) or thyroid dysfunction (5). Sixteen asymptomatic or mildly symptomatic patients were isolated or treated at home, and 34 had been in hospital with moderate or severe infection. Presence of sweat dysfunction, defined as FESC < 60 μS, was observed in 13 (26%) patients, while 3 (6%) had severe sweat dysfunction (FESC < 40 μS). Demographic and clinical features of the whole study population and of patients with and without sweat dysfunction are displayed in Table 1. Patients with sweat dysfunction were older, were more frequently treated at home, had higher heart rate and were more likely to have received antiviral treatment (remdesivir or other). In addition, they were more likely to report at least one motor, sensory or autonomic symptom compared to patients without sweat dysfunction. Details of symptoms reported by the patients are displayed in Table 2.

Discussion

This observational study performed in 50 Indian patients consulting in an outpatient department evidenced that: i) 26% had sweat dysfunction and 6% had severe sweat dysfunction; ii) at least one autonomic symptom was more frequently reported than a sensory or motor symptom; and iii) patients with sweat dysfunction were older, were more likely to have been isolated/treated at home, had higher heart rates, were more likely to have received antiviral treatment, and more frequently reported at least one motor, one sensory or one autonomic symptom.

SARS-CoV-2 has potential for neurotropism, and physicians are increasingly seeing more patients with a spectrum of neurological manifestations including central and peripheral nervous system involvement associated with this infection [7]. High levels of neurological symptoms observed in our study can be explained by the inclusion criteria, since patients consulted for various neurological symp-

Table 1 Clinical characteristics of patients in the whole population and according to the presence (FESC <60 μS) or absence of sudomotor dysfunction (FESC ≥60 μS).

Parameters	Whole population (n = 50)	FESC < 60 μS (n = 13)	FESC ≥ 60 μS (n = 37)	p
Age (years)	40.6 ± 13.3	53.5 ± 12.5	36.0 ± 10.3	0.0001
BMI (kg/m^2)	25.8 ± 3.6	24.9 ± 2.8	26.1 ± 3.8	0.29
Female n, %	16 (32)	5 (38)	11 (30)	0.56
SBP (mm Hg)	122.6 ± 7.8	123.5 ± 8.1	122.2 ± 7.8	0.60
DBP (mm Hg)	78.7 ± 5.4	78.7 ± 4.4	78.7 ± 5.7	0.96
Heart rate (bpm)	87.7 ± 13.2	96.2 ± 12.7	84.8 ± 12.2	0.0061
HESC (μS)	71.2 ± 13.2	58.2 ± 16.8	75.7 ± 7.9	0.0001
Treated at home n, %	16 (32)	8 (62)	8 (22)	0.008
Treated in hospital n, %	34 (68)	5 (38)	29 (78)	
Antiviral treatment n %	30 (60)	13 (100)	17 (46)	0.0006
Remdesivir n, %	6 (12)	4 (67) &	2 (33) &	0.01
Other antiviral n, %	24 (48)	9 (69) &	15 (41) &	0.07
At least one motor symptom	(48) 24	(92) 12	(32) 12	0.0002
At least one sensory symptom	(78) 39	(100) 13	(70) 26	0.02
At least one autonomic symptom	(82) 41	(100) 13	(76) 28	0.04

&: percentages calculated only from patients having received remdesivir or another antiviral treatment.

Table 2 Details of symptoms (sensory, motor and autonomic) reported by the patients in the whole population and according to the presence (FESC <60 μS) or absence of sudomotor dysfunction (FESC ≥60 μS).

Symptoms	Whole population (n = 50)	FESC < 60 μS (n = 13)	FESC ≥ 60 μS (n = 37)	p
Sensory symptoms				
Pins and needles	19 (38)	8 (61.5)	11 (29.7)	0.04
Numbness and less ability to feel pain or changes in temperature	17 (34)	4 (30.7)	13 (35.1)	0.77
Burning or sharp pain	17 (34)	11 (84.6)	6 (16.2)	<0.0001
Feeling pain from something that should not be painful at all, such as a very light touch	18 (36)	9 (69.2)	9 (24.3)	0.0037
Loss of balance or coordination caused by less ability to tell the position of the limb	1 (2)	1 (7.7)	0 (0)	0.08
Motor symptoms				
Twitching and muscle cramps	22 (44)	10 (76.9)	12 (32.4)	0.005
Muscle weakness or paralysis affecting one or more muscles	7 (14)	6 (46.2)	1 (2.7)	0.0001
Thinning (wasting) of muscles	1 (2)	1 (7.7)	0 (0)	0.08
Foot drop, particularly noticeable when walking	0 (0)	0 (0)	0 (0)	
Autonomic symptoms				
Constipation or diarrhea	5 (10)	2 (15.4)	3 (8.1)	0.45
Feeling sick, bloating, or belching	14 (28)	5 (38.5)	9 (24.3)	0.32
Low blood pressure, which can make you feel faint or dizzy when you stand up	11 (22)	5 (38.5)	6 (16.2)	0.09
Rapid heartbeat	15 (30)	10 (76.9)	5 (13.5)	<0.0001
Excessive sweating or a lack of sweating	12 (24)	2 (15.4)	10 (27.1)	0.39
Problems with sexual function, such as erectile dysfunction in men	4 (8)	1 (7.7)	3 (8.1)	0.96
Difficulty emptying your bladder of urine, or loss of bowel control	0 (0)	0 (0)	0 (0)	

toms. It must be emphasized that in this study, FESC decrease is more linked to motor and sensory symptoms than specifically to autonomic symptoms (see Tables 1 and 2), suggesting that FESC reduction reflects overall PNS damage and is a good marker of peripheral neuropathy in COVID patients.

Dysautonomia has been reported by multiple groups treating COVID patients. In particular, a patient was shown

to have developed acute onset dysautonomia preceding acute motor axonal neuropathy during SARS-CoV-2 infection [4]. Others reported that a patient had acute hyperhidrosis and symptomatic orthostatic tachycardia while three other patients had various pupillary abnormalities suggesting patchy dysautonomia [14]. Yet another group reported on a patient with highly fluctuating blood pressure that could be explained by acute dysautonomia through afferent baroreflex failure, a syndrome characterized by highly labile blood pressures with hypertensive crises alternating with hypotensive episodes; the mechanism involves damage to the afferent baroreceptor pathway, ending in the nucleus tractus solitarius [1]. Finally, many patients with extremely low blood oxygenation have no sensation of dyspnea, a phenomenon referred to as ''happy hypoxemia'' because these patients have no conscious awareness of hypoxia. This could be explained by possible damage to the afferent hypoxia-sensing C-fiber neurons that play a prominent role in the genesis of dyspnea and its subjective perception, due to the intense cytokine storm or direct damage from SARS-CoV-2 on mitochondria or the nerve fiber [6]. Direct damage to C-fibers innervating sweat glands or in other parts of the body could explain the decrease in ESC and autonomic symptoms observed in our study.

In terms of the factors associated with sweat dysfunction in our study, these patients were older, even although sweat function and ESC are known not to decrease with age [15]. Secondly, they appear to have had a less severe course of disease, when considering where patients were treated (in hospital or at home): this finding might be affected by selection bias due to small sample size, but neurological symptoms should be assessed whatever the severity of the disease. Thirdly, they had received more antiviral treatment: this suggests that a potential decrease in the initial viral load did not prevent the occurrence of dysautonomia.

Strengths of this study include the fact that it is the first report of sweat dysfunction in COVID-19. Our findings are in keeping with increasing recognition of neurological manifestations in COVID-19 but this is only the second report of objectively measured sweat dysfunction in viral disease, as evidenced in a recent publication reporting ESC decrease in patients with hepatitis C [12].

However, this study presents several weaknesses: i) the number of patients included was limited; ii) no ESC measurement captured prior to infection was available for comparison, although only patients with no obvious causes to explain low ESC values were included; iii) no concurrent neurological examination was performed, especially for PNS assessment; and iv) there was no other test performed for sweat function.

This preliminary observational study reveals that more than 25 % of patients who recovered from COVID-19 and seen in an outpatient clinic, had sweat dysfunction generally reflecting dysautonomia, which could have severe consequences and must be monitored during follow-up. These findings must be confirmed in a larger population with additional testing but underline the necessity of enhancing screening of dysautonomia in this population.

Conflicts of interest

A Hinduja has no conflict of interest to declare for this study. A Moutairou and JH Calvet are employees of Impeto Medical.

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