



Autonomic dysfunction in patients with COVID-19

Yuksel Erdal¹ · Arife Cimen Atalar¹ · Taskin Gunes² · Tugba Okluoglu¹ · Nurettin Yavuz¹ · Ufuk Emre¹

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Abstract

Purpose Autonomic dysfunction in patients with viral infections has been described before. In this study, we aimed to evaluate autonomic functions in patients with the coronavirus infectious disease 2019 (COVID-19).

Methods In this cross-sectional study, we compared 112 patients who had recovered from COVID-19 and 106 healthy controls. Symptoms of autonomic dysfunction were assessed with the SCOPA-AUT scale.

Results Pupillomotor, urinary and sudomotor subscores of SCOPA-AUT scale were significantly higher in the COVID-19 patient group ($p=0.03$, $p=0.006$, $p=0.0001$, respectively). There were no significant difference in terms of gastrointestinal, cardiovascular, sexual subscores and total SCOPA-AUT scores between the patient and control groups. The presence of fatigue symptom in the acute phase of COVID-19 increased the total SCOPA-AUT score by 2.2 points ($p=0.04$) whereas the presence of smell loss (OR = 5.82, $p=0.01$) and dyspnea (OR = 5.8, $p=0.03$) were significant risk factors for pupillomotor dysfunction. The urinary, cardiovascular, sexual subscores and the total score of SCOPA-AUT scale were positively correlated with the age of the patient group.

Conclusion Our study suggests that many patients might have prolonged symptoms of autonomic dysfunction after the acute phase of COVID-19 that might worsen the clinical recovery.

Keywords COVID-19 · Autonomic dysfunction · SCOPA-AUT · Sudomotor

Introduction

The coronavirus infectious disease 2019 (COVID-19), caused by novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), rapidly spread throughout the world leading to a pandemic disaster, and causing a serious mortality and morbidity especially for risky groups [1]. Although the most common clinical features of the disease are fever, dry cough and dyspnea, neurological manifestations are also very common and even might be the initial symptoms of the disease [2, 3]. In non-severe COVID-19 patients, the presented neurological symptoms are similar to the ones in other common respiratory virus infections (etc.; influenza) such as fatigue, headache, vertigo and nonspecific symptoms like anosmia and

ageusia. A proportion of critically ill patients develop central nervous system involvement such as encephalitis, encephalomyelitis, ischemic stroke and peripheral nervous system disorders like Guillain-Barre syndrome that might cause additional complications for the patients suffering from COVID-19 [4–7]. Although evidence of dysautonomia in COVID-19 infection is limited, a body of data is accumulating and studies focusing on autonomic system involvement suggest that, autonomic dysfunction is not a rare comorbidity in these patients and might exacerbate COVID-19 mortality [7].

Patients with autonomic nervous system dysfunction can present with a wide-range of symptoms including abnormalities in heart rate, blood pressure, thermoregulation, sexual functions, and bowel and bladder functions [8, 9]. Autonomic dysfunction have been reported in many of the viral infections, such as retroviruses (human immune deficiency virus (HIV)), herpes viruses, flavivirus, enterovirus and lyssavirus [10]. The 2009 pandemic of Influenza A (H1N1) is one of these viruses that have been reported to cause cardiac autonomic dysfunction in infants older than 1 year of age. [11]. Although the pathophysiological

✉ Yuksel Erdal
erdalyuksel_355@hotmail.com

¹ Department of Neurology, Health Sciences University, Istanbul Training and Research Hospital, Istanbul, Turkey

² Department of Neurology, Bahcesehir University, VM Maltepe Medical Park Hospital, Istanbul, Turkey

mechanisms underlying the autonomic system involvement in viral infections are scarce, direct invasion of the central nervous system, peripheral nervous system invasion and immune-mediated disorders are some of the proposed mechanisms [10, 12].

Autonomic dysfunction in cases of Guillain Barre syndrome related to COVID-19 [13] and acute motor axonal neuropathy (AMAN) presenting with dysautonomia symptoms were reported before [14]. Postural tachycardia syndrome (POTS) were also observed as a postinfectious complication of COVID-19 [15–17]. The American Autonomic Association has released an extensive paper recently, implying the importance of autonomic functioning and recommended further testing in patients with COVID-19 [18], but there is still a gap in this area and prospective studies are needed to further investigate the spectrum of autonomic dysfunction related to COVID-19. In this study, we aimed to evaluate the autonomic functions of patients recovered from COVID-19 at the post-infectious stage of the disease.

Methods

We enrolled 112 patients who had recovered from COVID-19 and 106 healthy controls in this study. Patients were recruited randomly from the neurology outpatient clinics, in Istanbul Training and Research Hospital between January and April 2021. For all patients, COVID-19 infection was confirmed from RT-PCR and/or antigen test reports. Demographic characteristics of the patients and clinical symptoms in the period following RT-PCR positivity were recorded. Patients with confirmed diagnoses of neurodegenerative diseases, polyneuropathy, metabolic diseases, heart diseases, using drugs with significant anticholinergic effects, chronic alcoholism and daily smokers were excluded from the study. Autonomic functions were measured using the SCOPA-AUT scale.

106 healthy individuals without clinical evidence of either previous or current COVID-19 were included as controls. The control group was randomly selected among the people and their relatives who applied to the neurology outpatient clinic and exclusion criteria were also similar for the control group. Local ethics committee approved the study (Decision number: 2578, Date: 13.11.2020). Written informed consent was obtained from all participants.

The SCOPA-AUT scale

The SCOPA-AUT scale determines the presence and frequency of autonomic symptoms [19]. The scale consists of a total of 23 items with the following 6 domains; gastrointestinal (7 items), urinary (6 items), cardiovascular (3 items), thermoregulator (4 items), pupillomotor (1 item), and sexual

(2 items for males and 2 items for females) dimensions. Responses for the frequency of each item are scored between 0 (never) and 3 (often), higher scores reflecting more severe autonomic dysfunction. The highest possible score is 99. All questions are based on experiences in the last month while the syncope query is based on the last 6 months. The Turkish validity and reliability study of the SCOPA-AUT scale was conducted by Yasar et al. [20].

Statistical analysis

Descriptive statistics are presented as frequencies, medians (with range), means (with standard deviations) or proportions, as appropriate. Normality was tested using $Q-Q$ plot and histogram. Continuous variables were analysed with independent samples t -test and Mann- U Whitney tests. Categorical variables were analysed by chi-square test. The relationship between acute clinical symptoms of COVID-19 and the final SCOPA-AUT score were further analysed by linear logistic regression analysis. The association of autonomic functions with disease duration and age were evaluated by Spearman correlation analysis. All statistical analysis were performed using Stata12 (Stata Corp LP, Texas, USA) software programme. A p value ≤ 0.05 was considered significant.

Results

Gender distribution of the patient and control groups were similar (F/M, 68/44 vs 64/42, $p=0.9$). The mean age of the control group was higher than the patient group (45.7 ± 12.5 and 40.3 ± 12.5 , respectively) ($p=0.001$).

Ten patients (9%) were hospitalized at the acute phase of COVID-19 infection. The time duration between the COVID-19 PCR test positivity and the application of the SCOPA-AUT test to the patients was 3.7 ± 1.7 (min–max 1–9) months. The most common symptom was fatigue (73.2%) at the acute phase of COVID-19. The distribution of the clinical symptoms of patients at the acute phase are summarized in Table 1.

The pupillomotor, urinary and sudomotor subscores of SCOPA-AUT scale of the patients were statistically higher than the control group ($p=0.03$, $p=0.006$ and $p=0.001$, respectively). There were no significant difference in terms of gastrointestinal, cardiovascular and sexual subscores ($p>0.05$). The total SCOPA-AUT scores were also similar between the patient and control groups ($p>0.05$) (Table 2).

In the linear regression analysis, we found that the presence of fatigue increased the total SCOPA-AUT scores by 2.2 folds [OR:2.2, $p=0.04$]. With regard to SCOPA-AUT subscores, having anosmia (OR = 5.82, $p=0.01$) and dyspnea ((OR = 5.8, $p=0.03$) could increase the pupillomotor

dysfunction risk at the post COVID phase. The presence of other clinical symptoms at the acute phase of the infection had no significant effect over the SCOPA-AUT scores. In addition, there was no significant difference between the SCOPA-AUT scores of the hospitalized or non-hospitalized patients (Table 3).

When we performed a correlation analysis, we found a positive correlation between the urinary ($r=0.30$, $p=0.001$), cardiovascular ($r=0.22$, $p=0.01$) and sexual ($r=0.30$, $p=0.001$) subscores and the total SCOPA-AUT

scores ($r=0.27$, $p=0.03$), with the age of the patients. There was no correlation between the time duration after COVID-19 and SCOPA-AUT scores (Table 4).

Discussion

In this study, we found that symptoms of autonomic dysfunction are very common at the post-infectious period of COVID-19. The most common symptom at the acute phase was fatigue and the presence of fatigue increased the risk of autonomic dysfunction by 2.2 folds at the post-COVID period. Also, higher scores on SCOPA-AUT scale were found to be associated with older age. Our results could give clues for the management of autonomic symptoms at the post-infectious phase of COVID-19.

There are insufficient data to show that SARS-CoV-2 directly infects the brain [21]. However, serious neurological symptoms are seen in COVID-19 disease, one of which is autonomic dysfunction [7, 22]. There are several studies reporting the neurological system involvement in addition to the respiratory, cardiovascular and other systematic complications of the disease in the acute and later stages but data on the autonomic system involvement is still limited. We suggest that COVID-19 could lead to autonomic dysfunction symptoms at the post infectious stage of the disease in addition to its other neurological and systematic symptoms at the acute phase such as headache, anosmia, ageusia, myalgia and fatigue. We showed that sudomotor, pupillomotor and urinary dysfunction symptoms could emerge at the later stages which could complicate the recovery phase of the patient. We believe these autonomic dysfunction symptoms could be a part of the so called “long COVID” spectrum of the disease [23, 24].

Fatigue appears to be a very common presentation of the disease both at the acute and post infectious stages of COVID-19 [25]. It was reported to be directly related to autonomic dysfunction in some of the reported studies [26]

Table 1 Demographic and clinical characteristics of the COVID-19 patient and control groups

	COVID-19 (+) <i>n</i> = 112	Controls <i>n</i> = 106	<i>p</i>	
	Mean ± SD / <i>n</i> , %	Mean ± SD / <i>n</i> , %		
Age	40.3 ± 12.0	45.7 ± 12.5	0.001	<i>m</i>
Gender				
Female	68 (61%)	64 (60%)	0.9	χ^2
Male	44 (39%)	42 (40%)		
Hospitalization	10 (9%)			
During post-COVID time, (months)	3.7 ± 1.7			
Symptoms				
Headache	74 (66.0%)			
Myalgia	52 (46.4%)			
Fatigue	82 (73.2%)			
Loss of smell	73 (65.1%)			
Loss of taste	67 (59.8%)			
Diarrhea	24 (21.8%)			
Pharyngitis	53 (47.4%)			
Rhinitis	29 (25.9%)			
Fever	66 (58.9%)			
Cough	54 (48.2%)			
Dyspnoea	32 (29.0%)			

Boldface values indicate significant results ($p < 0.05$)

m Mann-Whitney *U* test; χ^2 Chi square test,

Table 2 Comparison of the SCOPA-AUT scale parameters between COVID-19 patients and controls

	Patients (<i>n</i> = 112)		Controls (<i>n</i> = 106)		<i>p</i>
	Mean ± SD	Median	Mean ± SD	Median	
SCOPA-AUT scale					
Pupillomotor	0.4 ± 0.7	0.3	0.6 ± 0.7	0.5	0.03
Sudomotor	3.1 ± 2.5	3.0	1.7 ± 1.8	1.0	0.0001
Gastrointestinal	2.9 ± 2.1	2.0	2.5 ± 2.1	2.0	0.7
Cardiovascular	1.8 ± 1.6	2.0	1.9 ± 2.4	1.0	0.2
Urinary	3.6 ± 3.2	3.0	2.5 ± 2.2	2.0	0.006
Sexual	0.7 ± 1.1	0.6	0.9 ± 1.2	0.1	0.1
Total points	12.7 ± 9.6	10.0	10.4 ± 7.7	8.0	0.06

Boldface values indicate significant results ($p < 0.05$)

m Mann-Whitney *u* test,

Table 3 Linear logistic regression analysis of association between acute symptoms of COVID-19 infection, post-COVID duration time and SCOPA-AUT parameters

	Pupillomotor	Sudomotor	GIS	Cardiovascular	Urinary	Sexual	Total
Headache							
OR	1.21	1.57	1.23	1.40	1.14	1.08	1.02
<i>p</i>	0.7	0.2	0.5	0.3	0.7	0.8	0.2
Myalgia							
OR	2.43	1.26	0.80	0.55	0.96	2.02	1.01
<i>p</i>	0.1	0.5	0.5	0.1	0.9	0.1	0.4
Fatigue							
OR	0.36	0.65	1.22	1.20	0.65	0.55	2.2
<i>p</i>	0.1	0.3	0.6	0.6	0.3	0.2	0.04
Loss of smell							
OR	5.82	1.56	1.44	2.96	0.61	1.38	1.02
<i>p</i>	0.01	0.4	0.5	0.08	0.4	0.6	0.2
Loss of taste							
OR	0.32	0.83	0.69	0.44	2.43	0.60	1.01
<i>p</i>	0.08	0.7	0.4	0.1	0.1	0.4	0.4
Dyspnea							
OR	3.05	1.84	1.98	2.00	1.08	1.68	1.01
<i>p</i>	0.03	0.1	0.09	0.1	0.8	0.2	0.5
Diarrhea							
OR	0.80	0.96	0.72	1.51	1.22	0.45	1.03
<i>p</i>	0.6	0.9	0.4	0.3	0.6	0.1	0.07
Duration (months)							
OR	1.3	1.5	0.9	1.1	1.0	0.6	1.03
<i>p</i>	0.4	0.4	0.9	0.5	0.3	0.3	0.9

Boldface values indicate significant results ($p < 0.05$)

OR odds ratio

Table 4 Correlation analyses of patients with post-COVID-19 duration, age and SCOPA-AUT parameters

	Pupillomotor	Sudomotor	GIS	Cardiovascular	Urinary	Sexual	Total MOCI score
Age							
<i>r</i>	0.09	0.18	0.13	0.22	0.30	0.30	0.27
<i>p</i>	0.3	0.05	0.1	0.01	0.001	0.001	0.003
Duration (month)							
<i>r</i>	0.12	0.12	0.10	0.12	0.05	0.14	0.10
<i>p</i>	0.2	0.1	0.3	0.2	0.6	0.1	0.3

Spearman correlation

GIS gastrointestinal

and the relationship of fatigue with autonomic dysfunction in some other neurological diseases such as multiple sclerosis [27], Parkinson's disease [28], sleep disorders [29] and chronic hepatitis [30] is also well known. Although Townsend et al. reported that there was no difference in terms of autonomic dysfunction symptoms between patients with fatigue and non-fatigue [31], our results show that the presence of fatigue at the acute stage of SARS-CoV-2 infection increases the risk of autonomic dysfunction by 2.2 folds at the post

COVID phase. Fatigue could be a risk factor for more severe neurological symptoms related to autonomic dysfunction at the later stages of the disease that will impair quality of life with an impact on the individuals' personal and professional life.

The mechanisms underlying the association between COVID-19 and autonomic dysfunction is still uncovered. The invasion of the virus and the inflammatory cytokines to the median eminencia of the hypothalamus, could result

with the activation of the autonomic nervous system and the release of adrenal catecholamines and steroids [2]. Also, entry of the virus and/or proinflammatory molecules through the subfornical organ and the area postrema could also affect brainstem autonomic pathways that are controlling blood pressure and breathing [32]. Alternatively, COVID-19-related autonomic dysfunction could be mediated by the virus itself [33]. Another hypothesis is that an underlying autoimmune mechanism can be responsible from the infection-related autonomic dysfunction. In certain autonomic syndromes such as orthostatic hypotension (OH) and POTS, the presence of autoantibodies against α -/ β -adrenoceptors and muscarinic receptors is already shown [34]. The cytokine storming induced by the autonomic nervous system and neurohumoral effect could lead to end-organ damage at the older individuals with comorbid diseases which could result with a vicious circle that could be life-threatening [35].

In a recent observational study, 50 patients were evaluated with the National Health Service (NHS) questionnaire for neurological symptoms and electrochemical skin conductance test. Sudomotor dysfunction was shown in 26% of the patients revealing that sweat dysfunction reflecting dysautonomia is very common at the recovery phase of COVID-19 [36]. Similarly, in another retrospective study, Shouman et al. reported that 26% of their patients with COVID-19 showed sudomotor dysfunction symptoms [37]. There are also several case reports revealing the presence of sudomotor dysfunction after COVID-19 [38–40]. Peripheral nervous system involvement and related neurological symptoms in COVID-19 suggest that small demyelinated nerve fibers might be involved but the role of central nervous system (CNS) in autonomic dysfunction could not be ruled out. Unlike CNS, there is no evidence that the virus could directly invade the peripheral nervous system (PNS) but rather damage the PNS by a cytokine storming or dysimmune mechanism [36]. Stella et al. performed a questionnaire-based study on a large sample of long-COVID patients with and without neurological symptoms, using the COMPASS-31 questionnaire, and found that orthostatic intolerance, sudomotor, gastrointestinal and pupillomotor dysfunction were the most affected domains of the autonomic nervous system in these patients. In addition, COMPASS-31 scores were higher in patients with neurological symptoms due to more severe orthostatic intolerance whereas sudomotor, gastrointestinal and pupillomotor functions were more severely affected in patients without neurological symptoms [41]. In our study, the most significant difference was found in sudomotor subscore of SCOPA-AUT scale in the patient group comparing to the other subscores or the total score which suggest that there could be an underlying small fibre neuropathy. Small fibre neuropathies were reported after several viral infections before [42] but the causative relationship of the neuropathy and the viral infection is still unclear and

yet to be proven. We believe further studies performed with quantitative autonomic testing methods in larger cohorts are needed to highlight the nature of autonomic dysfunction in these patients.

Autonomic nervous system have been traditionally composed of sympathetic nervous system, parasympathetic nervous system, and the enteric nervous system, however neuroendocrine and neuroimmune systems have recently been identified and expanded the concept of “autonomic” [43]. Hightened sympathetic nervous system activity accompanies chronic cardiovascular and endocrine diseases such as hypertension, cardiac failure, type 2 diabetes mellitus and chronic renal failure and contributes to the progression of these diseases [44]. Recent epidemiological studies report that COVID-19 patients with these comorbid diseases are more prone to mortal complications and mortality [35, 45].

Although we excluded patients with comorbid diseases such as diabetes mellitus, multiple sclerosis, neurodegenerative disease etc. that might have severe autonomic system involvement, we observed that our patients with COVID-19 had prominent autonomic dysfunction symptoms. Moreover, despite the older age of the control group, the presence of autonomic symptoms were lower than the patients supporting that COVID-19 might lead to autonomic dysfunction independent from the age of the patient.

Cardiovascular complications such as arrhythmia, myocarditis, cardiac failure, and myocardial infarction have been widely reported before. It is hypothesised that COVID-19 could induce sympathetic nervous system over activity and worsen the prognosis [46]. Recently American Autonomic Society provided a statement to guide physicians, health systems and researchers about the impact of long-COVID POTS which occurs when the commonly described symptoms of long-COVID are accompanied by excessive orthostatic tachycardia [47]. We did not have any significant difference in terms of cardiac parameters between patient and control groups which could be related to the exclusion of patients with severe metabolic and vascular comorbid diseases.

Our study has some limitations of note. First, we did not perform quantitative standardized autonomic function tests such as thermoregulatory sweat test, quantitative sudomotor axon reflex test and heart rate variability test to the patient and control groups. As a second limitation, our patients were referred from our neurology outpatient clinics which could be a selection bias for this study therefore further studies performed with larger cohorts are needed to support our results. Also, we assessed the autonomic functions with an extensive range (1–9 months), so that means that the patients were not uniformly evaluated at the same time.

In conclusion, COVID-19 is associated with a high burden of symptoms of autonomic dysfunction especially in sudomotor, urinary and pupillomotor systems. Autonomic dysfunction should be questioned as a part of the standard

neurological examination alongside the other neurological symptoms. Early diagnosis of autonomic dysfunction in patients with COVID-19 may help planning the management and limit the progression of the disease. Further studies with larger populations are needed to support our findings.

Author contributions YE: Conceptualization; investigation; methodology; writing original draft. TO and NY: Methodology; resources; data curation; formal analysis. ACA: Writing-review and editing. TG: Data curation; formal analysis. UE: Data supervision and editing.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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