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Neurological manifestations of COVID-19 infection in acute and late phases: A case-control study

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Abstract

Background & Objective: The late-term neurological effects of COVID-19 are not fully understood yet. Herein, we aimed to determine if COVID-19-related acute and late-term neurological symptoms exist in the patient group that differs from the general population during the pandemic period. *Methods:* Two hundred fifty patients with a history of COVID-19, whose treatments were completed at least one month before enrollment, were examined together with a control group consisting of 150 individuals that lived in the same socio-cultural environment during the same period. A survey that included questions about possible neurological symptoms that might be related to the COVID-19 infection was completed in both groups. *Results:* The patient and control groups were mostly similar regarding the neurological symptoms in the pre-pandemic period. The control group did not report any new symptoms except ageusia during the pandemic period. Whereas a number of neurological symptoms such as headache, ageusia and anosmia, difficulty in thinking and planning, forgetfulness, clumsiness of one or both hands, dizziness, unsteadiness, numbness in both hands and feet, and neuropathic pain occurred during the infection. Neurological symptoms, except headache and unsteadiness, prolonged to the late-term with a decreased prevalence.
Conclusion: The emergence of new neurological symptoms during the pandemic in those with COVID-19 disease, unlike the control group, suggested that these symptoms are related to the infection itself.

Keywords: COVID-19, Coronavirus, Pandemic, Neurological symptoms, SARS-CoV-2

INTRODUCTION

Coronavirus disease 2019 (COVID-19) was recognized as a new form of virus disease, causing 'Severe Acute Respiratory Syndrome (SARS)' at the end of 2019 and was defined as a pandemic by the World Health Organization (WHO) in the following weeks. Recently, WHO recommended the establishment of national and international groups to investigate the neurological abnormalities caused by COVID-19 to understand the whole aspects of the disease and the possible late-term effects.[1]

The late-term effects of COVID-19 concerning any organ or system involvement are not clear yet. However, the fact that neurological diseases occurred in some previous coronavirus outbreaks, such as SARS-CoV-1 and MERS, indicates the possibility that COVID-19 may cause similar complications.[2]

This study aims to investigate COVID-19-related neurological symptoms during the pandemic period by comparing the patients who had COVID-19 infection with controls.

METHODS

Two hundred and fifty adult patients diagnosed with COVID-19 by current tests and whose treatment was completed at least one month before the study were examined with a control group consisting of 150 adult individuals who did not have COVID-19 and were living in the same socio-cultural environment during the same period. A

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history of COVID-19 contact was defined as confirmation of COVID-19 infection or close contact following the World Health Organization (WHO) definition (spending 15 minutes or more within 2 meters of an infected individual)[3] while not wearing a mask.

The patient group were enrolled from two reference hospitals in Gaziantep by referring to the medical records that were completed in COVID-19 inpatient or outpatient clinics. Following the approval of Clinical Studies Ethics Committee the consecutive cases were invited to the present study and all cases accepted to participate were enrolled into the study. No additional inclusion or exclution criteria were applied.

The socioeconomic status and medical history of the patient and control groups were recorded. Patients' self-assessments about the severity of the disease, and their current health status, were recorded.

According to our previous follow-up experiences with COVID-19 patients, the symptoms that attracted our attention were considered possible neurological symptoms that might be related to the COVID-19 infection. Therefore, the presence of headache, ageusia and anosmia, difficulty in thinking and planning, forgetfulness, clumsiness of one hand or both hands, dizziness, unsteadiness, numbness in both hands and feet, and neuropathic pain were questioned separately for pre-pandemic and pandemic periods in both groups. Unsteadiness, dizziness, and clumsiness were questioned separately because the patients described them differently. Unsteadiness is defined as one being unstable in regard to the environment with a feeling of almost falling and need help for walking; dizziness is defined as having a whirling sensation in the head with a feeling of falling without any objective unsteadiness; and clumsiness is defined as physical incoordination during voluntary movements, especially in the upper limbs.

The status of the symptoms was recorded in 4 subgroups according to the variation of the time of occurrence during the course of COVID-19 infection as followed: 1- absent, 2- existed before the pandemic, 3- occurred during COVID-19 infection and recovered, 4- started during COVID-19 infection and ongoing. In the control group, the status of the symptoms was recorded in 3 subgroups according to their varying with time as the following: 1- none, 2- existed before the pandemic and continued, 3- emerged during the pandemic period. The relationship between all the symptoms detected in the patient and the control groups during the COVID-19 pandemic period was compared. Whether some symptoms continued together in the late period (at least one month after the completion of treatment) and, if so, which ones were related were also investigated. Sleep characteristics of these participants were also questioned, but these data are planned to be discussed in another article.

COVID-19 PCR test was performed as follows; Coronex-COVID-19 Ver. 2.0 Multiplex Real-Time qPCR kit (Gensutek Health Technologies, Ankara, Turkey) targeting ORF1ab (opening reading frame 1ab), nucleocapsid protein (N) gene, and a human gene region (RNP) as an internal control were used to study SARS-CoV-2 RT-PCR from nasopharyngeal swab samples of patients. Amplification was performed on a Rotor-Gene Q 5plex instrument (Qiagen, Germany) in accordance with the manufacturer's recommendations. Samples with a cycle threshold (Ct) of <38 were considered positive, while those with a Ct value of ≥38 were negative.

The study was conducted under the Principles of the Declaration of Helsinki, and approval was obtained from the local ethics committee before the study period.

Statistical analysis

IBM SPSS Statistics v.23.0 package program was used for the data analysis. As descriptive statistics, mean and standard deviation values were given for quantitative data, and number and percentage values were given for qualitative data. In group comparisons, the chi-square test was used for the qualitative data, Fisher's exact chi-square test was used for expected values below 5, the Chi-Square test with continuity correction was used for observed values below 25, and the McNemar test was used for the comparison of the repeated evaluations. In the 3-group comparisons of the qualitative data, the Bonferroni-corrected p-value of 0.017 was taken into account by using the appropriate chi-square test to determine the group that caused the difference. The relationship between qualitative data was evaluated with the Phi coefficient. A p-value of <0.05 was considered statistically significant.

RESULTS

Sociodemographic and clinical characteristics

The patient group consisted of 250 patients (98 male,152 female) aged between 19 and 80 years (mean ± SD; 38.4 ± 13.2). The control group

included 150 individuals (53 male, 97 female) between the ages of 19 and 79 years (mean ± SD; 34.0 ± 13.3) (Table 1).

According to the patients' statements; 28 people (11.2%) had severe, 133 people (53.2%) had moderate, 89 people (35.6%) had mild symptoms. None of the patients with COVID-19 infection had any known neurological complications such as a cerebrovascular event, encephalopathy, meningitis, encephalitis, epileptic seizure, acute polyneuropathy, myasthenia gravis in the acute period. At the time of the survey, 216 patients stated their health status as good (86.4%), 33 people as moderate (13.2%), and one as bad (0.4%).

Ninety-four patients (62.7%) in the control group had a real-time polymerase chain reaction (RT-PCR) test for COVID-19 that resulted in negative. Sixty-seven people (44.7%) in the control group had at least one close contact who had COVID-19.

Comorbid chronic diseases were reported more commonly in patients with COVID-19 infection than the control group (p=0.003). Neuropathic pain and bilateral numbness of the hands and feet were reported more frequently in patients with chronic diseases before (p=0.003, p=0.002, respectively), during (p<0.001, p<0.001, respectively), and after (p<0.001, p<0.001, respectively) the pandemic than those without comorbid chronic diseases. There was no statistical differences for other symptoms between cases with and without comorbid diseases in the patient group.

Comparison of patient and control groups regarding neurological symptoms reported before the pandemic

The control group had a higher rate of forgetfulness before the pandemic than the patient group (p<0.001). In addition, pre-pandemic neuropathic pain was more common in the patient group than in the control group (p=0.036). Apart from these, all the questioned symptoms were similar in both the control and patient groups before the pandemic (Table 2).

Comparison of the control group's data regarding neurological symptoms before and during the pandemic

Ageusia and anosmia were the only symptoms reported more frequently in the control group

Table 1: Sociodemographic data of groups with and without COVID-19

	Cases with COVID-19 (n=250)		Cases without COVID-19 (n=150)	
Demographic characteristics	**n**	**%**	**n**	**%**
Gender				
Male	98	39,2	53	35,3
Female	152	60,8	97	64,7
Marital status				
Married	171	68,4	90	60
Single	79	31,6	60	40
Educational status				
No	7	2,8	2	1,3
Literate	4	1,6	1	0,7
Primary school	33	13,2	5	3,3
Middle school	18	7,2	3	2
High School	41	16,4	33	22
University	147	58,8	106	70,7
Comorbid disease				
No	158	63,2	116	77,3
Yes	92	36,8	34	22,7

n: Number

Table 2: Comparison of data of groups with and without COVID-19

	Cases with COVID-19 (n=250)	Cases without COVID-19 (n=150)	p
Headache n(%)			
Before	54 (21.6%)	45 (30%)	0,059
During	165 (66%)	54 (36%)	<0,001
Continues	67 (26.8%)	35 (23.3%)	0,441
Ageusia n(%)			
Before	8 (3.2%)	1 (0.7%)	0,162
During	142 (56.8%)	9 (6%)	<0,001
Continues	20 (8%)	2 (1.3%)	0,009
Anosmia n(%)			
Before	8 (3.2%)	4 (2,7%)	1,000
During	147 (58.8%)	9 (6%)	<0,001
Continues	28 (11.2%)	3 (2%)	0,002
Difficulty in thinking and planning n(%)			
Before	6 (2.4%)	8 (5.3%)	0,206
During	60 (24%)	10 (6,7%)	<0,001
Continues	38 (15,2%)	6 (4%)	0,001
Forgetfulness n(%)			
Before	27 (10.8%)	38 (25.3%)	<0,001
During	87 (34,8%)	29 (19.3%)	0,001
Continues	73 (29.2%)	25 (16.7%)	0,005
Clumsiness of one hand n(%)			
Before	4 (1.6%)	0 (0%)	0,302
During	18 (7.2%)	3 (2%)	0,043
Continues	14 (5.6%)	1 (0.7%)	0,025
Clumsiness of both hands n(%)			
Before	2 (0,8%)	1 (0.7%)	1,000
During	12 (4.8%)	1 (0.7%)	0,037
Continues	7 (2.8%)	0 (0%)	0,049
Dizziness n(%)			
Before	21 (8.4%)	8 (5.3%)	0,344
During	81 (32.4%)	13 (8.7%)	<0,001
Continues	40 (16%)	8 (5.3%)	0,003
Unsteadiness n(%)			
Before	1 (0.4%)	3 (2%)	0,150
During	27 (10.8%)	3 (2%)	0,002
Continues	11 (4.4%)	3 (2%)	0,325
Numbness in both hands and feet n(%)			
Before	14 (5.6%)	2 (1.3%)	0,065
During	33 (13.2%)	2 (1.3%)	<0,001
Continues	25 (10%)	2 (1.3%)	0,002
Neuropathic pain n(%)			
Before	26 (10.4%)	6 (4%)	0,036
During	64 (25.6%)	7 (4.7%)	<0,001
Continues	47 (18.8%)	8 (5.3%)	<0,001

n (%); number (p<0.05 significant)

during the pandemic period (p=0.008). The other questioned neurological symptoms did not reveal any statistical significance regarding the pre-pandemic and the pandemic periods in the control group (Table 3).

Comparison of the data of the patient group regarding neurological symptoms before the pandemic, during the disease period, and in the late period

Contrary to the control group, several symptoms in the patient group were significantly higher both during the infection and in the long term compared to the pre-pandemic period (Table 3). Headache and unsteadiness were higher in the patient group only during the disease period compared to both the pre-pandemic period and the control group (p<0.001, p=0.002, respectively). However, after the treatment was completed, both symptoms regressed to similar rates with the controls as in the pre-pandemic period (p=0.441, p=0.325, respectively) (Table 2).

It was determined that the symptoms of difficulty in thinking and planning, ageusia and anosmia, numbness in both hands and feet, dizziness and clumsiness of a hand or both hands, which increased significantly during the infection period, remained significantly higher in the late-term period (p=0.001, p=0.002, p=0.002, p=0.003, p=0.009, p=0.025, p=0.049, respectively).

Neuropathic pain in the extremities was reported more frequently in the patient group than in the control group before the pandemic (p=0.036). The difference was also significant during the infection and in the late-term (p<0.001, p<0.001, respectively) (Table 2).

Evaluation of the relationship between the symptoms during COVID-19 infection and the disease severity

During COVID-19 infection, ageusia, and anosmia (p=0.01), neuropathic pain (p=0.001), unsteadiness (p<0.001), dizziness (p=0.006), and forgetfulness (p<0.001) were significantly higher in patients who had a severe infection than patients with a mild infection. Dizziness (p=0.006) and forgetfulness (p=0.013) were significantly higher in patients with moderate infection than patients with mild infection.

Evaluation of the relationship between the symptoms that persist in the late-term and the severity of the disease

Difficulty in thinking and planning (p<0.001 and p=0.005, respectively), forgetfulness (p<0.001 and p= 0.014, respectively), and unsteadiness (p=0.011 and 0.012, respectively) persisted significantly more in patients who stated to have the moderate or severe disease than patients who stated mild severity. The patients who stated moderate and mild disease were similar regarding neuropathic pain (p=0.460). However, neuropathic pain tended to persist in patients who stated that they had severe disease compared to moderate and mild patients (p<0.001 and p=0.007).

Evaluation of the interrelationship of ongoing symptoms in those who had COVID-19

In the late-term, the highest correlation was found between anosmia and ageusia (Phi coefficient: 0.643 p<0.001). Difficulty in thinking and planning was associated with many symptoms. Difficulty in thinking and planning were significantly correlated with forgetfulness (Phi coefficient: 0.610 p<0.001), clumsiness of a hand (Phi coefficient: 0.236 p<0.001), dizziness (Phi coefficient: 0.393 p<0.001), clumsiness of both hands (Phi coefficient: 0.131 p=0.039), neuropathic pain (Phi coefficient: 0.167 p=0.008) and unsteadiness (Phi coefficient: 0.344 p<0.001).

The correlations between ageusia and anosmia, thinking and planning difficulties and forgetfulness, numbness in both hands and feet (Phi coefficient: 0.556 p<0.001), and neuropathic pain were found as moderate-high or high.

DISCUSSION

The results of this study revealed that, in the pre-pandemic period, there was no difference in neurological symptoms between the patient and control groups (except for forgetfulness in the control group and neuropathic pain in the patient group), while many neurological symptoms emerged during the infection in those who had COVID-19, and some of the symptoms persisted into the late-term. Contrary to the patient group, the pandemic period did not cause a significant difference in any symptoms except the ageusia in the control group. Considering that the patient and the control groups in this study spent the pandemic period in the same city and a similar socio-cultural environment, our results suggest that the neurological symptoms that emerged in the patient group during the infection period and persisted in the late-term period may be related to the COVID-19 infection itself.

None of our participants in the patient group had any neurological complications during or after

Table 3: Intragroup comparisons of neurological symptoms in groups with and without COVID-19 infection

	CONTROL GROUP (n=150)			PATIENT GROUP (n=250)					
Symptoms:	**Pre-pandemic**	**During the pandemic**	**p**	**Pre-pandemic**	**During infection**	**Continues**	**p***	**p****	**p*****
Headache n(%)	45 (30%)	54 (36%)	0,175	54 (21.6%)	165 (66%)	67 (26.8%)	<0,001	0,154	0,001
Ageusia n(%)	1 (0.7%)	9 (6%)	0,008	8 (3.2%)	142 (56.8%)	20 (8%)	<0,001	0,023	<0,001
Anosmia n(%)	4 (2,7%)	9 (6%)	0,180	8 (3.2%)	147 (58.8%)	28 (11.2%)	<0,001	0,001	<0,001
Difficulty in thinking and planning n(%)	8 (5.3%)	10 (6,7%)	0,754	6 (2.4%)	60 (24%)	38 (15,2%)	<0,001	<0,001	<0,001
Forgetfulness n(%)	38 (25.3%)	29 (19.3%)	0,093	27 (10.8%)	87 (34,8%)	73 (29.2%)	<0,001	<0,001	0,024
Clumsiness of one hand n(%)	0 (0%)	3 (2%)	-	4 (1.6%)	18 (7.2%)	14 (5.6%)	0,001	0,013	0,289
Clumsiness of both hands n(%)	1 (0.7%)	1 (0.7%)	1,000	2 (0,8%)	12 (4.8%)	7 (2.8%)	0,006	0,125	0,125
Dizziness n(%)	8 (5.3%)	13 (8.7%)	0,180	21 (8.4%)	81 (32.4%)	40 (16%)	<0,001	0,003	<0,001
Unsteadiness n(%)	3 (2%)	3 (2%)	1,000	1 (0.4%)	27 (10.8%)	11 (4.4%)	<0,001	0,002	<0,001
Numbness in both hands and feet n(%)	2 (1.3%)	2 (1.3%)	1,000	14 (5.6%)	33 (13.2%)	25 (10%)	<0,001	0,001	0,057
Neuropathic pain n(%)	6 (4%)	7 (4.7%)	1,000	26 (10.4%)	64 (25.6%)	47 (18.8%)	<0,001	<0,001	0,006

* Comparison between pre-pandemic and during infection in the patient group ** Comparison between pre-pandemic and ongoing in the patient group *** Comparison of those who continued during the infection in the patient group n: Number ($p<0.05$ significant)

the acute phase of the disease. However, when questioned individually, they mentioned various neurological symptoms that appeared during the infection and persisted into the late periods. Symptoms such as clumsiness of a hand or hands, numbness in both hands and feet, dizziness, and unsteadiness were significantly more common in patients with COVID-19 compared to the pre-pandemic period, as previously reported.[4] Nevertheless, such neurological symptoms were only be revealed when the patients are questioned individually. Ageusia and anosmia were among the most common findings in the acute phase of the disease in our patient group, as previously reported.[5] Although they decreased significantly in the late-term compared to the acute period of the disease, they persisted at a significantly higher rate than the pre-pandemic period and showed the highest correlation in terms of co-existence with each other.

Cognitive disorders have been observed in patients following the COVID-19 infection, and the term "brain fog" has been used for this situation.[6] A study evaluating the long-term symptoms of patients with COVID-19 infection reported that the loss of concentration continued one month after the infection in 59%.[7] Difficulty in thinking and planning was one of the most common symptoms in the late-term and showed a close relationship with some other ongoing symptoms in the present study. Our results suggest that patients with cognitive complaints should be followed up more closely in terms of accompanying neurological dysfunctions in the long term after the COVID-19 infection.

While the literature studies focused on muscle and joint pain[8-10], there is not enough information about neuropathic pain. Neuropathic pain was reported at a rate of 2.3% in one study.[11] One of the remarkable findings of our study is that neuropathic pain was detected in a significant part of the patients both at the time of the infection (25.6%) and in the late-term (18.8%). Further investigation of the characteristics of neuropathic pain in patients with COVID-19 may contribute to further knowledge on this subject.

Some complaints, such as headache, can be considered a nonspecific symptom that is reported in various viral infections during the acute period.[12] In a meta-analysis on headache in the acute and the subsequent periods in patients with COVID-19, it was reported that headache was present in approximately 50% of the patients during hospitalization and decreased to lower rates (8%-15%) 6 months after infection.[13] Similarly, in our study, 66% of the patient group complained of a headache during the infection, whereas it persisted in only 26.8% of the group in the late-term. This was not statistically different to the pre-pandemic period (21.6%).

Ageusia, anosmia, neuropathic pain, unsteadiness, dizziness, and forgetfulness were significantly higher in the group who self-reported severe illness during the disease period compared to those with mild disease course. Inconsistent with the previous studies[7,14,15], in the present study, no symptoms were detected significantly more frequently in the moderate or mild disease groups.

According to our results no new symptom arised in the later period. All the neurological symptoms which were reported to be persistent in the patient group were those that occurred in the acute period. The time course suggested that neurological symptoms did not occur due to the late-term effects of the virus or the immunological responses but instead developed in the acute period, while in some cases persisted for a longer period. Similarly, in a study in which neurological findings were periodically questioned during the post-infection period, it was reported that no new neurological findings occurred and that some existing findings tended to decrease.[7]

During the pandemic period, the socio-economic and psychological stress caused by the pandemic in society, in general, affected everyone regardless of being infected with the COVID-19 virus. Therefore, it may not be easy to interpret whether some symptoms which may be associated with the infection develop due to the general influence of the pandemic period. There are not many controlled studies in the literature comparing the multiple possible neurologic symptoms.[7] In the present study, the presence of a control group living in the same environment may be helpful to interpret that the findings detected in the patient group during the acute and late-terms were not related to the general effects of the pandemic only. Additionally, the symptoms were questioned in both the patient and the control groups in the same way by a doctor who explained in a way that the participants could understand, which is the strength of the present study.

There are limitations of our study. Firstly, the present study was a cross-sectional study. All cases were questioned only once that did not give an opportunity to evaluate the course of the neurological symptoms chronologically. Additionally, we could not able to designate the exact time that the symptoms first occurred.

Therefore we could not interpret if some of them existed from the very beginning of COVID-19 infection. Prospectively design studies that survey neurological symptoms of all included COVID-19 cases during and after the infection period may provide more accurate data. Sequential neurological examination records of the COVID-19 cases with neurological symptoms would enhance the strength of such a prospective study design. Also, a survey for pandemic course was thought to be reliable, but there may be a recall bias during completing a survey on behalf of the cases.

In conclusion, contrary to the controls, the emergence of neurological symptoms in the patient group suggested that these symptoms are related to the infection itself. Patients with COVID-19 infection should be examined in more detail in terms of different neurological symptoms during acute infection and in the late period.

DISCLOSURE

Financial support: None

Conflict of interest: None

Ethics: Approval was obtained from the SANKO University Clinical Studies Ethics Committee (date: 17/09/2020, session number: 2020/16, decision number: 02). Informed consent: Informed consent was obtained from all individual participants included in this study.

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