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Original Scientific Paper

NEUROLOGICAL SYMPTOMS COMMON IN COVID-19 PATIENTS: A RETROSPECTIVE OBSERVATIONAL STUDY

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SUMMARY – In December 2019, a novel coronavirus outbreak spread rapidly all over the world. The virus is known to be neuroinvasive, but much is still unknown. In this study, we aimed to present the main neurologic symptoms in patients who were diagnosed with coronavirus disease 2019 (COVID-19). The study was conducted retrospectively by phoning 156 patients in Turkey diagnosed with COVID-19 through real-time polymerase chain reaction; only 100 patients could be reached. Data about their demographics, initial symptoms, neurological symptoms, and sleeping habits were collected. During the disease process, 66% had at least one neurological symptom, 55% had central nervous system symptoms, 42% had peripheral nervous system symptoms, and 64% had sleep disturbances and myalgia. Impaired consciousness, smell and taste impairments, and sleep disturbances were significantly higher in patients with positive chest computed tomography imaging ($p < 0.05$). Neurological symptoms were observed in COVID-19, as in other coronaviruses. Headache in particular was the most common symptom in our population. In patients with respiratory system findings, the detection of certain neurological symptoms such as smell-taste impairments, impaired consciousness, and sleep disorders were more common. We concluded that COVID-19 patients should be approached in a more holistic way, taking the nervous system into account.

Key words: *COVID-19; SARS-CoV-2; neurology; neurological symptoms*

Introduction

Coronaviruses are neuroinvasive viruses that primarily affects the human respiratory system and have the ability to spread from the respiratory system to the central nervous system (CNS). For 50 years, coronaviruses have caused respiratory infections that have led to mild to severe clinical outcomes in humans[1]. In November 2002, a coronavirus infection that was first seen in Southern China spread to other countries, causing an epidemic with a mortality rate of ~9.6%; this virus was named SARS-CoV[2]. In June 2012, an agent causing a SARS-like respiratory infection was identified in Saudi Arabia and was named MERS-CoV. Both in 2012 in Saudi Arabia and in 2015 in South Korea, it caused two outbreaks with a mortality of about 35%[3].

The first coronavirus was detected in 1937 causing a respiratory disease in chickens before it was found in humans; it was defined as infectious bronchitis virus (IBV). Then, in 1965, the first human coronavirus was detected in an organ culture of a human embryonic trachea taken from a boy with a cold[4]. When the struc-

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ture of this virus was examined by an electron microscope, it was found to be similar to IBV. It is known that coronaviruses in humans also emerge from a wide variety of animal species, with the largest reservoir of these being bats[5].

In December 2019, a novel coronavirus, SARS-CoV-2, was identified in a patient working at a local indoor seafood market in Wuhan, China[6]. The World Health Organization (WHO) announced on January 31, 2020 that this infection was an alarming international epidemic[7].

The incubation period of SARS-CoV-2 has been shown in various studies to be between four and five days, and in one family of five patients, it extended from one to nineteen days[7]. Clinical findings range from asymptomatic infection to critical disease. The most common clinical findings are known to include the upper respiratory tract system, with fever, cough, sore throat, and fatigue. However, there have also been clinical findings related to other systems, such as hematological, gastrointestinal, urinary, and neurological systems[8]. Neurological symptoms are also very diverse, and there are findings that include both the CNS and the peripheral system. Among these, the symptoms are frequent dizziness, headaches, and smell and taste disorders[9].

In this study, we aimed to identify neurological symptoms and sleep disturbances in the disease process in patients diagnosed with coronavirus disease 2019 (COVID-19) who had been discharged or were followed up at home.

Methods

Our study included patients who had been hospitalized or followed up at home with COVID-19 and who were treated at the University Faculty of Medicine Hospital in the Department of Infectious Diseases and Pulmonology, between March 13 and April 27, 2020. Phone numbers were obtained from the primary physicians of 156 patients. All patients had been positively diagnosed with COVID-19 using a real-time polymerase chain reaction of the swab samples taken from the nasopharynx. In cases of clinical necessity, radiological evaluations and laboratory tests were performed on the patients.

We reached 100 patients in total, since some phone numbers were incorrect, and some patients did not respond. We noted the patients' age, gender, job, comorbidities, drug use, smoking habits, and initial symptoms. We asked about the patients' neurological symptoms in the disease process retrospectively, dividing the questions into three groups. In the first group, with symptoms related to the central nervous system (CNS), we asked about the presence of headache, dizziness, acute cerebrovascular disease, seizure, and ataxia. In the second group, we asked about symptoms involving the peripheral nervous system (PNS): smell, taste, vision impairment, facial paralysis, and neuropathy. For the final group, we inquired about sleep disturbances (increased sleep time or insomnia) and myalgia.

We confirmed the patients' clinical information using the hospital software with the consent of the hospital, and, because of the infectiousness of hospitals, verbal consent was also obtained from the patients before the interview. The participants' information was kept completely confidential, and their names were not stated at any stage of the study. The study was performed in accordance with the principles of the Declaration of Helsinki and was approved by the Ethics Committee of the University with the number of 60116787-020/29689.

This study was a descriptive study in which patients who were followed up with a diagnosis of COVID-19 (SARS-CoV-2) at Pamukkale University Faculty of Medicine Hospital were interviewed by phone about their demographic data and clinical symptoms. Continuous variables were expressed as mean ± standard deviation and median (minimum-maximum values), and categorical variables as number and percent. Statistical analysis of the data was performed using the SPSS 22.0 (SPSS Inc., Chicago, IL, USA) program. The relationships between continuous variables were analyzed by Pearson correlation analysis, and the differences between categorical variables were examined by Chi-square analysis.

Results

Of the 156 patients with a COVID-19 diagnosis, 100 patients could be reached by telephone. The mean age was 41.2 ± 16.4 years, and 55 (55%) were men and 45 (45%) were women. The demographic and clinical findings of the patients are shown in Table 1. Fifty-three (53%) patients had at least one comorbidity, and 47 (47%) did not have any underlying disorder. Among those with comorbidities, 15% had respiratory system disease, 13% had diabetes mellitus (DM), 12% had hypertension (HT), 10% had heart disease, 4% had a malignancy, and 32% had other diseases

Table 1. Demographic-clinical findings and comorbidities of patients

	Total (n=100)	
Age, Mean ± SD, years	41.2 ± 16.4	
Sex		
Female	45(45%)	
Male	55(55%)	
Onset clinic severity		
Good	95(95%)	
Bad	5 (5%)	
	+ (%)	**- (%)**
Healthcare proffesionals	36%	64%
Smoking	27%	73%
Comorbities	53%	47%
Any	32%	68%
Respiratuar system disease	15%	85%
Diabetes Mellitus	13%	87%
Hypertension	12%	88%
Cardiac Disease	10%	90%
Malignancy	4%	96%
Initial Symptoms	79%	21%
Cough	62%	38%
Sore Throat	56%	44%
Fever	39%	61%
Dyspnea	27%	73%
Diarrhea	8%	92%
Stomache	7%	93%
Neurological Symptoms	66%	34%
CNS	55%	45%
Headache	49%	51%
Dizziness	18%	82%
Ataxia	4%	96%
Impaired consciousness	4%	96%
Seizure	1%	99%
Acute cerebrovascular disease	-	100%
PNS	42%	58%
Smell impairment	33%	67%
Taste impairment	28%	72%
Neuropathic pain	10%	90%
Vision changes	3%	97%
Fasial paralysis	-	100%
Other	64%	36%
Myalgia	47%	53%
Sleep disturbances	41%	59%
- Increased sleep time	22%	78%
- Decreased sleep time	19%	81%
Positive Chest CT findings	37%	73%

Abbreviations: CNS, central nervous system; PNS, peripheral nervous system

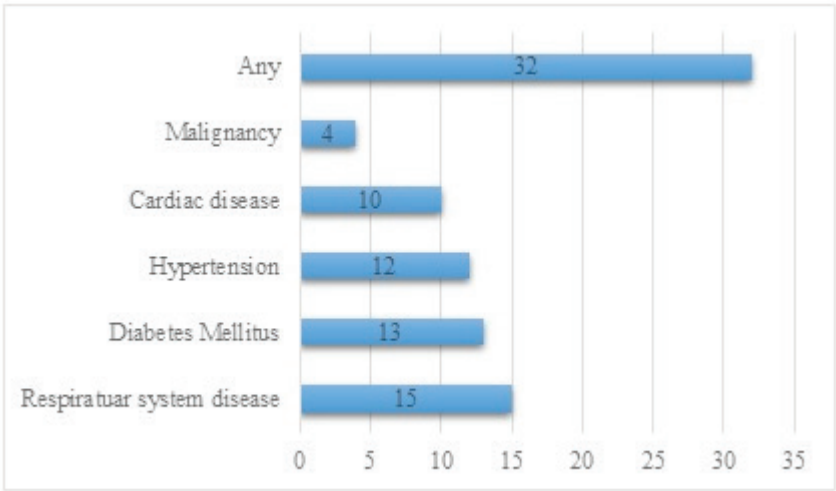

Figure 1. Comorbidities of COVID-19 patients

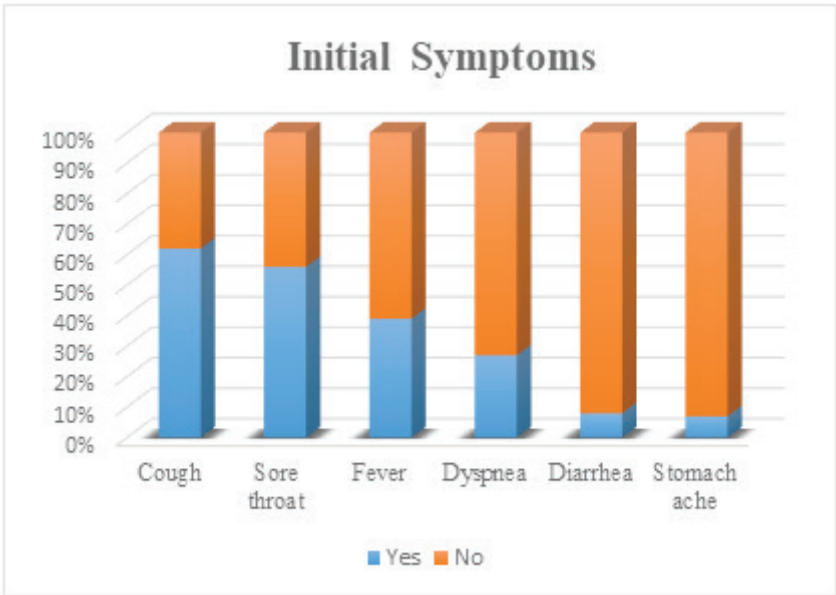

Figure 2. Initial symptoms of COVID-19 patients

(thyroid, psychiatric, etc.) (Fig. 1) Twenty-seven patients (27%) were cigarette smokers. Thirty-six of the patients (36%) were healthcare professionals, and 56 patients (56%) had a history of contact with known COVID-19 (+) patients.

At the onset of the disease, 95 patients (95%) had a good clinical picture, and five patients were hospitalized after intensive care unit follow-up. Thirty-seven (37%) patients had chest computed tomography (CT) image findings supporting COVID-19. At least one admission symptom was present in 79 (79%) of the patients who were followed up. The other 21 (21%) were asymptomatic and were examined after contact with a COVID-19-positive patient.

The most common initial symptoms were cough (62%), sore throat (56%), fever (39%), dyspnea (%27), diarrhea (8%), and stomachache (7%) (Fig. 2).

Sixty-six patients (66%) had at least one neurological symptom in the disease process. Fifty-five patients (55%) had CNS symptoms, 42 (42%) had PNS symptoms, and 64 patients (64%) had sleep disturbances and myalgia. The most common neurological symp-

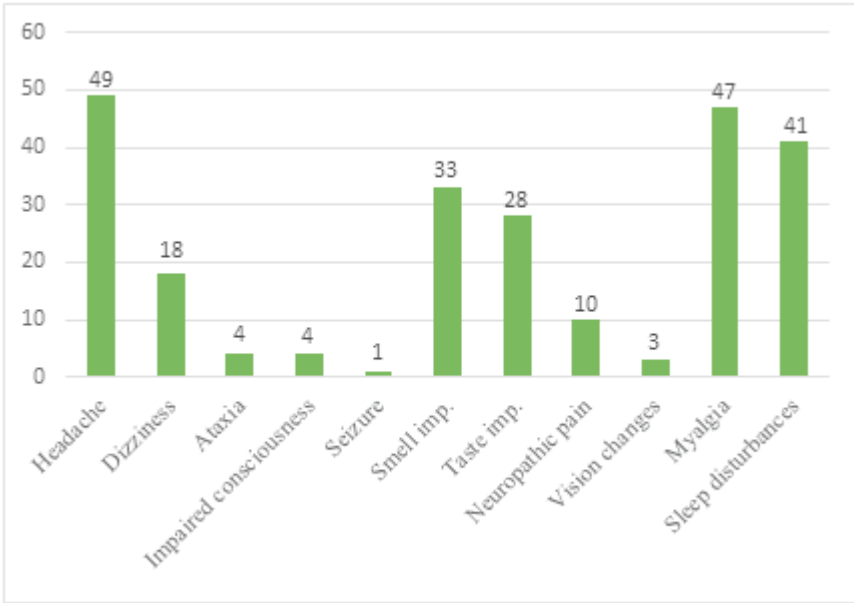

Figure 3. Neurological and other symptoms

tom was headache (49%); other symptoms were smell impairment (33%), taste impairment (28%), dizziness (18%), neuropathy (10%), ataxia (4%), impaired consciousness (4%), and vision impairment (3%). None had acute cerebrovascular disease or facial paralysis (Fig. 3). Despite the fact that patients with neurological symptoms had more comorbidities, there was no significant association between the comorbidities and neurological symptoms.

We also observed that patients had significant sleep disturbances and myalgia. Forty-one percent had sleep disorders, 22 had increased daily sleep time, and

Table 2. The comparisons of neurologic symptoms with sex, smoking, comorbidity, initial symptoms and positive chest CT imaging findings

	Neurological symptoms		Total	P value
	+	-		
Age, Mean ± SD, y	40.2 ±17.02	43.3 ±15.3	41.2 ± 16.4	0.371
Sex				
Female	31%	14%	45%	0.581
Male	35%	20%	55%	
Smoking				
Yes	20%	7%	27%	0.300
No	46%	27%	73%	
Comorbidities				
Yes	35%	18%	53%	0.993
No	31%	16%	47%	
Initial symptoms				
Yes	57%	22%	79%	0.012*
No	9%	12%	21%	
Positive chest CT findings				
Yes	28%	9%	37%	0.118
No	38%	25%	63%	

Table 3. The comparisons of positive chest CT findings and neurological symptoms

	Chest CT findings		Total	P value
	+	-		
Headache				
Yes	18%	31%	49%	0.957
No	19%	32%	51%	
Dizziness				
Yes	9%	9%	18%	0.207
No	28%	54%	82%	
Ataxia				
Yes	1%	3%	4%	0.612
No	36%	60%	96%	
Seiuzure				
Yes	1%	0%	1%	0.190
No	36%	63%	99%	
Impaired consciousness				
Yes	4%	0%	4%	0.008*
No	33%	63%	96%	
Smell impairment				
Yes	18%	15%	33%	0.011*
No	19%	48%	77%	
Taste impairment				
Yes	15%	13%	28%	0.032*
No	22%	50%	72%	
Vision changes				
Yes	2%	1%	3%	0.280
No	35%	62%	97%	
Neuropathic pain				
Yes	5%	5%	10%	0.369
No	32%	58%	90%	
Sleep disturbances				
Yes	20%	21%	41%	0.042*
No	17%	42%	59%	
Myalgia				
Yes	19%	28%	47%	0.504
No	18%	35%	53%	

Abbreviations: CT, Computed tomography; *Significant

19 patients had difficulty either getting to sleep, staying asleep for extended periods, or consolidating their sleep. Forty-seven percent of patients had myalgia.

We investigated the relationship between neurological symptoms and gender, comorbidity, smoking, positive chest CT imaging, and initial symptoms, and neurological symptoms were significantly higher only in patients who had initial symptoms ($p < 0.05$) (Table 2). Thirty-seven patients (37%) had chest CT imaging compatible with COVID-19. We compared chest CT imaging findings with neurological symptoms and sleep disturbances (Table 3), and impaired consciousness, smell and taste impairments, and sleep disturbances were significantly higher in patients with positive chest CT imaging ($p < 0.05$).

Discussion

On December 31, 2019, the discovery of pneumonia cases with unknown etiology was announced by the WHO China Country Office in Wuhan City[10].

The WHO then reported that these cases were associated with a new type of coronavirus originating from a seafood market in Wuhan and could be the cause of a major outbreak. The genomic structure of the new type of coronavirus was revealed in January 2020 by Roujian Lu et al.[11]. The first case was reported in Turkey on March 10, 2020. Herein we report on 100 patients with laboratory-confirmed COVID-19 infection between March 13 and April 27, 2020, in a center in Turkey.

Commonly, patients have typical cold symptoms, such as fever, cough, sore throat, and respiratory system findings. Our study cases had cough (62%), sore throat (56%), fever (39%), and also dyspnea (27%). Patients also had many symptoms related to the other systems, and about 30-36% had neurological symptoms[8,9]. Sixty-six percent of our population had had at least one neurological symptom in the disease process. However, the symptoms in our patients were mild and nonspecific, because the clinical outcomes were better in our cases, and the patients were discharged as healthy. More than half of our patients had an underlying disease, mostly related to the respiratory system, followed by DM, HT, and cardiac diseases. In the literature, cases with neurological symptoms were concomitant with more comorbidities, HT and DM in particular[12].

COVID-19 is thought to affect the nervous system via different pathways. These pathways include 1) the coronavirus invading the nervous system with its neurotrophic effect; 2) secondary inflammation caused by coronavirus damage to the nervous system; 3) brain damage secondary to hypoxia involvement of the respiratory and cardiac system; and 4) development of cerebrovascular events with changes in coagulation parameters due to infection and inflammation caused by the virus[13]. Consistent with previous studies, various neurologic manifestations were observed in our clinic, involving the CNS in particular, more than the PNS.

While many patients experienced common dizziness[9], the most common neurological symptom in our population was headache. When patients were questioned in detail, many characteristics were compatible with a tension-type headache. This symptom was followed by PNS findings, such as smell and taste changes. Many viruses cause inflammation in the nasal mucosa, leading to rhinorrhea and olfactory dysfunction. However, physicians have observed that the complaints about smell and taste in COVID-19 were not related to nasal inflammation or obstruction[14]. Viruses can use peripheral neurons to reach the CNS, and SARS-CoV had been shown to reach the brain in transgenic mice, using an olfactory bulb and spreading rapidly in the brain[15]. SARS-CoV-2 is thought to follow a similar path due to its genetic similarity to SARS-CoV. According to our results, 33% of patients experienced changes to smell, mostly hyposmia, and 28% experienced taste changes. In China, Mao et al. showed 5.6% hypogeusia and 5.1% hyposmia, but in a European study, Lechien et al. showed higher ratios: 85.6% had olfactory dysfunction, and 88.8% had gustatory disorder[9,14].

The reason for this variability is thought to be genetic differences between populations. It is known that SARS-CoV-2 enters the cell using angiotensin-converting enzyme 2 (ACE2), a cell surface receptor, and this receptor is expressed in alveolar epithelial cells, intestinal enterocytes, arterial-venous endothelial cells, glial cells, and neurons. Apart from direct transition from the olfactory bulbus, the neuroinvasive effect of SARS-CoV-2 is thought to be related to the transition to neural tissue as a result of capillary endothelial damage through ACE2 and its expression in the neurons[16]. As a result of all these studies, it was concluded that the expression of ACE2 may be different between Asian and European populations[17], and this may lead to a difference in the clinical findings between ethnic groups.

The general condition of the patients was good, because our study included patients discharged from the hospital. However, the presence of COVID-19-positive chest CT findings in these patients were an indication that the infection had progressed. In these patients, sleep disturbance, impaired consciousness, and smell and taste changes were significantly higher. Liu et al. detected insomnia in 36.1% of patients diagnosed with COVID-19[18]. In our study, we found that half the patients had sleep disorders, which mostly increased their sleep duration.

In previous animal studies, coronavirus was detected in the brainstem of the nucleus of the solitary tract and the nucleus ambiguus. The nucleus of the solitary tract is responsible for the sensory innervation of the respiratory system, mechanoreceptors, and chemoreceptors, and the efferent fibers of the nucleus ambiguus provide innervation to the airway smooth muscle and blood vessels[19]. It is thought that the neuroinvasive effect of SARS-CoV-2 may lead to acute respiratory failure in this way.

Our study had some limitations. First, it was a one-center retrospective study. Second, it consisted of patients who had clinically improved, so our results reflected a population in better health, since we could not inquire about symptoms of patients with more severe clinical conditions. Third, we identified the symptoms from the patients' subjective reports. Finally, because of the outbreak period, advanced neuroimaging (such as magnetic resonance imaging) and diagnostic procedures (such as lumbar puncture and electromyography) were avoided to reduce the risk of cross-infection.

Conclusions

We examined the neurological symptoms of the patients we followed up during an outbreak period caused by a neuroinvasive virus. Although we included patients who had clinically improved, comparing patients' positive chest CT findings with symptoms provided valuable results. In particular, headache, smell-taste impairments, and sleep disturbances were significantly higher in those patients. In line with this information, we hope that our study can contribute to the neurological findings on the novel coronavirus infection and the process of establishing treatment protocols and managing patients appropriately.

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Sažetak

NEUROLOŠKI SIMPTOMI KOJI SU ČESTI U PACIJENATA S COVID-19: RETROSPEKTIVNA OPSERVACIJSKA STUDIJA

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U prosincu 2019. nova epidemija koronavirusa brzo se proširila cijelim svijetom. Poznato je da je virus neuroinvazivan, ali je pun nepoznanica. U ovoj studiji imali smo za cilj predstaviti glavne neurološke simptome kod pacijenata kojima je dijagnosticirana koronavirusna bolest 2019. (COVID-19). Studija je provedena retrospektivno telefoniranjem 156 pacijenata u Turskoj kojima je dijagnosticiran COVID-19 putem lančane reakcije polimeraze u stvarnom vremenu; moglo se doći do samo 100 bolesnika. Prikupljeni su podaci o njihovim demografskim podacima, početnim simptomima, neurološkim simptomima i navikama spavanja. U procesu bolesti, 66% je imalo barem jedan neurološki simptom, 55% je imalo simptome središnjeg živčanog sustava, 42% imalo je simptome perifernog živčanog sustava, a 64% imalo je poremećaje spavanja i mijalgiju. Poremećaji svijesti, mirisa i okusa te poremećaji spavanja bili su značajno veći u bolesnika s pozitivnim slikanjem računalne tomografije u prsima ($p < 0,05$). Neurološki simptomi primijećeni su u COVID-19, kao što su ostali koronavirusi. Posebno je glavobolja najčešći simptom u našoj populaciji. U bolesnika s nalazima dišnog sustava češće je otkrivanje određenih neuroloških simptoma kao što su smetnje okusa mirisa, oslabljena svijest i spavanje. Zaključili smo da s pacijentima s COVID-19 treba postupati na cjelovitiji način, uzimajući u obzir živčani sustav.

Ključne riječi: *COVID-19, SARS-CoV-2, neurologija, neurološki simptom*