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ORIGINAL RESEARCH PAPER

Neurological symptoms and findings in COVID-19: a prospective clinical study

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ABSTRACT

Objective: We sought to evaluate neurologic symptoms and findings in patients with COVID-19 infection hospitalized in a ward and intensive care unit (ICU).

Methods: This study was designed as a prospective study. Hospitalized COVID-19 rRt-PCR positive patients in the ward and ICU were included in the study. A 54-item questionnaire was used to evaluate the patients. Patients were examined within 3 hours of hospitalization.

Results: A total of 379 patients were included in the study. The mean age of the patients was 56.1 ± 17.8. 89 of the patients were in intensive care. At least one general symptom was recorded in 95.5% of patients. The most common neurologic symptoms were myalgia (48.5%), headache (39.6%), anosmia (34.8%), and dysgeusia (34%). Neurological symptoms in ICU patients were higher than in the ward. 53.6% of patients had comorbidities.

Discussion: This study indicated that the prevalence of neurological symptoms was very high in patients with COVID-19. The percentage of neurological symptoms and findings was higher in patients hospitalized in ICU.

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COVID-19; neurology; neurologic manifestations; hospitalization

Introduction

Emerging in the Chinese city of Wuhan in December 2019 and quickly becoming a pandemic, coronavirus 19 (COVID-19) disease has infected millions of people and resulted in the death of more than 761,000 people [1].

The clinical manifestation of COVID-19 is rather heterogeneous, with a wide variety of symptoms and a broad spectrum of disease severity. Typical symptoms of the disease include fever, cough, malaise, diarrhea, and dyspnea. Symptoms usually appear after an incubation period of 5 days [2]. Although the clinical course is usually mild to moderate, severe cases are frequently observed. Hospitalization with acute respiratory syndrome and frequent intensive care unit (ICU) admissions are required [3].

Studies highlighting the neurological symptoms seen in Covid-19 infection are increasing [4–6]. Headache, myalgia, loss of taste and smell are frequently observed symptoms. Delirium can be detected in patients with COVID-19. There is a case report of an atypical presentation of confusion in the absence of any upper respiratory or constitutional symptoms diagnosed with COVID-19 [7]. In a case series of 58 patients, 49 (84%) developed neuropsychiatric symptoms, including 40 (69%) with agitation, 26 (65%) with positive Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) scores, and 14 (36%) with a dysexecutive syndrome [8]. An article discusses the burden of delirium by identifying potential risk factors and difficulties during challenges associated with SARS-CoV-2 infection [9]. At the same time, especially in hospitalized patients, other more severe neurological impairments such as stroke, Guillain Barre syndrome and status epilepticus may be observed [10–12]. Limited cases of ataxia, ADEM, are reported in COVID-19 patients [13,14]. There is a case report of trigeminal neuralgia as the only neurological sign of COVID-19 disease [15]. Nevertheless, more evidence is needed to support this.

There are only a very limited number of prospective studies that have been reviewed by neurologists [16].

The objective of this study was to determine the symptoms and neurological findings of patients with Covid-19, hospitalized in a ward and intensive care unit.

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Materials and methods

This study was designed as a prospective study. This study included consecutive patients hospitalized in the Covid-19 ward and Covid-19 ICU of Afyonkarahisar University of Health Sciences Medical School Hospital between July 2020 and October 2020. Inclusion criteria were determined to be over 18 years of age and COVID-19 rRt-PCR positive. COVID-19 positivity was identified using real-time reverse transcription-polymerase chain reaction (rRT-PCR) analysis of throat and nose swab samples used for SARS-CoV-2 testing.

Patients hospitalized in the ward after a definitive diagnosis of COVID-19 and patients directly hospitalized in the intensive care unit after a definitive diagnosis of COVID-19, were examined within the first 3 hours of admission. Patients who were taken to the ICU after hospitalization were reexamined during ICU follow-up and were removed from the ward patients and included in the ICU patients.

An evaluation form with 54 parameters was prepared. Demographics (age, sex), comorbidities, smoking, and results of general and neurological examinations were recorded on the assessment form.

General symptoms such as fever, cough, shortness of breath, sore throat, anorexia, abdominal pain, diarrhea, and malaise were questioned. Neurological symptoms such as dizziness, nausea, syncope, myalgia, absence of taste and smell were questioned. During the neurological examination, the level of consciousness (awake, drowsy, stupor, coma), orientation, cooperation, cranial nerve examinations, muscle strength examination, sensory examination, cerebellar examination, extrapyramidal system examinations were assessed. Delirium was identified using the Confusion Assessment in Intensive Care Units (CAM-ICU) method. White blood cell, lymphocyte, C-reactive protein (CRP), and creatine kinase (CK) values were recorded from laboratory results. D-dimer and ferritin values could not be recorded because they were not measured in all patients. The diagnosis of acute polyradiculoneuritis was verified by electromyography.

Neurological examination was performed at a single center by a single neurologist with personal protective equipment. Verbal informed consent was obtained from the patients. Consent was obtained from the families of patients who were unconscious.

Ethical approval

This study was approved by the local ethics committee (date: 03.07.2020 approval number: 2020/338). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Table 1. Demographic characteristics of COVID-19 patients.

Characteristics	Ward patients (n:290)	ICU Patients (n:89)	Total (n:379)
Age, mean ± SD	52 ± 17.5	68.3 ± 12.3	56.1 ± 17.8
Sex			
Female	170 (58.6%)	22 (24.7%)	192 (50.6%)
Male	120 (41.4%)	67 (75.3%)	187 (49.3%)

ICU: Intensive care unit SD: Standard Deviation

Statistical analysis

During the evaluation of this study, frequency, percentage, arithmetic mean and standard deviation were used as descriptive statistics. The Pearson's chi-squared test was used for evaluation of categorical data and the Mann-Whitney test was used for the evaluation of quantitative data. The significance level was chosen at 0.05. Analyses were performed using the SPSS 20.1 software program.

Results

Demographics

A total of 379 patients were included in this study. The male-to-female ratio was found to be 1.9. The number of male patients followed in the ICU was statistically significantly higher than the number of female patients ($p < 0.0001$). The mean age of patients hospitalized in the ICU was statistically significantly higher ($p < 0.0001$). The demographic characteristics of the patients are summarized in Table 1.

General symptoms

At least one general symptom was observed in 95.5% of all patients. The most frequently observed general symptoms in COVID-19 infection were malaise, followed by cough and fever. The general symptoms are summarized in Table 2.

Neurological symptoms and findings

The frequency of at least one neurologic symptom or outcome was 76% in all patients. The most common neurologic symptoms were myalgia (48.5%) and headache (39.6%). The frequency of neurologic symptoms

Table 2. General symptoms of patients with COVID-19.

Symptoms	Ward Patients (n:290)	ICU Patients (n:89)	Total (n:379)
Fever	113 (38,9%)	40 (44,9%)	153 (40,3%)
Cough	170 (58,6%)	43 (48,3%)	213 (56,2%)
Malaise	179 (61,7%)	71 (79,7%)	250 (65,9%)
Dyspnea	68 (23,4%)	80 (89,8%)	148 (39%)
Sore throat	46 (15,8%)	14 (15,7%)	60 (15,8%)
Anorexia	34 (11,7%)	29 (32,5%)	63 (16,6%)
Stomachache	10 (3,4%)	7 (7,8%)	17 (4,4%)
Diarrhoea	33 (11,3%)	5 (5,6%)	38 (10%)

ICU: Intensive care

Table 3. Neurological symptoms and findings of patients with Covid-19.

Neurological Symptoms and Findings	Ward Patients (n:290)	ICU Patients (n:89)	Total (n:379)
Myalgia	109 (%37,6)	75 (%84,3)	184 (%48,5)
Headache	101 (%34,8)	49 (%55,1)	150 (%39,6)
Anosmia	82 (%28,3)	50 (%56,2)	132 (%34,8)
Dysgeusia	80 (%27,6)	49 (%55,1)	129 (%34)
Nausea	43 (%14,8)	14 (%15,7)	57 (%15)
Sleep Disorder	26 (%9)	13 (%14,6)	39 (%10,3)
Dizziness	24 (%8,3)	4 (%4,5)	28 (%7,4)
Restless Leg Syndrome	4 (%1,4)	2 (%2,2)	6 (%1,6)
Syncope	3 (%1)	2 (%2,2)	5 (%1,3)
Somnolence	1 (%0,3)	12 (%13,5)	13 (%3,4)
Stupor	0	1 (%1,1(	1 (%0,3)
Coma	0	22 (%24,7)	22 (%5,8)
Loss of Orientation	2 (%0,7)	30 (%33,7)	32 (%8,4)
Dysarthria	3 (%1)	1 (%1,1)	4 (%1,1)
Meningeal irritation signs	0	0	0
Ptosis	1 (%0,3)	0	1 (%0,3)
Anisocoria	0	1 (%1,1)	1 (%0,3)
Diplopia	1 (%0,3)	1 (%1,1)	1 (%0,3)
Numbness on the face area	0	1 (%1,1)	1 (%0,3)
Chewing disturbance	5 (%1,7)	0	5 (%1,3)
Facial asymmetry	2 (%0,7)	0	2 (%0,5)
Hearing loss	1 (%0,3)	0	1 (%0,3)
Tinnitus	5 (%1,7)	4 (%4,5)	9 (%2,3)
Dysphagia	1 (%0,3)	0	1 (%0,3)
Dysphonia	1 (%0,3)	0	1 (%0,3)
Neck weakness	1	1 (%1,1)	1 (%0,3)
Tongue weakness	0	1 (%1,1)	1 (%0,3)
Limb weakness	4 (%1,4)	1 (%1,1)	5 (%1,3)
Involuntary movements	0	0	0
Seizure	4 (%1,4)	1 (%1,1)	5 (%1,3)
Sensory deficits	4 (%1,4)	0	4 (%1,1)
Hyperreflexia	3 (%1,0)	4 (%4,5)	7 (%1,8)
Hyporeflexia	8 (%2,8)	18 (%20,2)	26 (%6,9)
Pathologic reflexes	2 (%0,7)	0	2 (%0,5)
Uncoordinated movements	1 (%0,3)	0	1 (%0,3)
Ataxia	1 (%0,3)	1 (%1,1)	2 (%0,5)
Sphincter Disturbances	4 (%1,4)	1 (%1,1)	5 (%1,3)

ICU: Intensive care

and findings in ward and intensive care patients is summarized in Table 3. Neurological symptoms and findings were observed in 96.6% of ICU patients and 70% of ward patients. This difference was found to be statistically significant ($p < 0.0001$).

Comorbidities

115 patients had hypertension (30.3%), 94 patients had diabetes (24.8%), 42 patients had coronary heart disease (11.1%), 25 patients had chronic obstructive pulmonary disease (6.6%), 23 patients had asthma (%.) 6.1), 15 patients had hyperlipidemia (4.0%), 13 patients had malignancy (3.4%), 5 patients had epilepsy (1.3%), 3 patients had multiple sclerosis (0.8%), 13 patients had heart failure (3, 4%), 11 patients had chronic renal failure (2.9%), 4 patients had dementia (1.1%), 7 patients had a history of cerebrovascular disease (1.8%), 15 patients had polyneuropathy (4.0%). The presence of comorbidities was found to be significantly higher in ICU patients than in ward patients ($p < 0.0001$). A significant correlation was found between the presence of comorbidities and death ($p < 0.0001$). A significant correlation was found between the presence of comorbidities and the presence of neurological symptoms and findings ($p = 0.019$). 37 patients were smokers (9.8%); 21 of them were followed in the intensive care unit. A significant correlation was found between smoking and ICU hospitalization and death ($p < 0.0001$). There was no significant relationship between smoking and neurological symptoms and findings ($p = 0.243$).

Neurological diseases that develop during COVID-19 infection

Cerebrovascular disease developed in 7 patients (4 transient ischemic attacks, 2 ischemic cerebrovascular diseases, 1 intracranial hemorrhage). Trigeminal neuralgia developed in 5 patients and occipital neuralgia in 1 patient. Delirium occurred in 2 patients and acute polyradiculoneuritis in 1 patient.

Neurological diseases triggered during COVID-19 infection

Multiple sclerosis attack was triggered in 3 patients. Epileptic seizures were triggered in 5 patients. One patient developed a myasthenic crisis.

Mortality

The mortality rate of patients was found to be 10.6%. All patients who died were hospitalized in the intensive care unit. A statistically significant relationship was found between the presence of neurological symptoms and signs and death ($p < 0.0001$).

Laboratory findings

Leukocytosis was found in 17.2% of patients, lymphopenia in 54.1%, elevated CRP in 88.1% and elevated creatine kinase (CK) in 8.4%. A statistically significant correlation was found between muscle pain and elevated CK ($p < 0.0001$). There was a significant relationship between the presence of leukocytosis and lymphopenia and neurological symptoms and outcomes ($p = 0.006$, $p = 0.026$, respectively), and no significant relationship was found between elevated CRP and neurological outcomes ($p > 0.05$).

Discussion

The result of this study indicates that at least one symptom and neurological finding is found in ¾ of patients with COVID-19 infection in the Turkish population. This indicates that neurological involvement is observed at a very high rate in COVID-19 infection. This high rate also suggests that SARS-CoV-2 may be a neurotropic virus.

Most studies of neurological symptoms and signs seen in COVID-19 infection are retrospective studies from medical records [4–6]. In a retrospective study of 214 patients in China, neurologic manifestations were found in 36.4% of patients [4]. In our study, this rate was much higher. This may be due to the prospective and detailed questioning and neurological examination of patients. In a multicenter retrospective cohort study conducted in China, the frequency of neurological manifestations was found to be 3.5% [5]. This rate is quite low. This may be explained by the fact that patients with only nonspecific symptoms such as headache, dizziness, fatigue and myalgia were excluded from the study according to the protocol. This is because, as in our study, the most common symptom in these studies was recorded as myalgia

In a literature review, 177 of 1508 appropriate articles found in databases such as PubMed, Google Scholar, and EBSCO using the keywords 'Coronavirus,' 'COVID-19,' and 'neurology' were evaluated [6]. The reported neurological manifestations were similar to our study, but the observed percentages were not specified. In a retrospective study from China, neurological evaluations were performed on 86 critically ill patients. At least one neurological symptom was detected in 65% of patients [17]. In our study, the frequency of neurological symptoms and findings was found to be higher in patients hospitalized in intensive care.

Recently, the number of prospective studies has increased [16,18–20]. Since April 2020 on the EAN website, a 17-question online questionnaire about a very large study conducted by the European Academy of Neurology has been presented to EAN members and other physicians worldwide. 82% of the 2343 physicians who responded were neurologists. All patients with a diagnosis of COVID-19 hospitalized in the emergency unit, COVID intensive care unit, COVID clinic, and neurology clinic were included in the study. Physicians were asked about the frequency of observed general and neurologic symptoms. The most frequent neurological symptoms were headache (61.9%), myalgia (50.4%), and anosmia (49.2%) [18]. Although the order of these symptoms is different, they are the same most frequent symptoms as in our study.

A very recent prospective study conducted in Turkey evaluated 239 patients, without including intensive care and unconscious patients. Neurological involvement was found in 34.7% of patients. The most common neurological symptoms were headache (27.6%), myalgia (15.1%) and sleep disturbance (12.6%), respectively [16]. In our study, myalgia and headache were more frequent and sleep disturbances were less frequent. In a study from Spain, in which the neurological manifestations of patients hospitalized with Covid-19 were prospectively examined, neurological manifestations were observed in almost 90% of patients. The most common symptoms were anosmia (44%), headache (44%), and myalgia (43%) [19]. The results of this study are similar to those of our study. In a prospective study conducted in Italy, neurological symptoms of 103 cooperative hospitalized patients were evaluated. At least one neurological symptom was detected in 91% of the patients. In contrast to our study and other studies, the most frequent symptom was sleep impairment [20].

In a systematic review on cerebrovascular disease, cerebrovascular disease was reported at a rate of 1.8% in COVID-19 patients [21]. In our study, the incidence of cerebrovascular disease was found to be 1.8%. It is thought that there may be several reasons for the occurrence of cerebrovascular disease in COVID-19 infections. One is the severe inflammatory response elicited by SARS-CoV-2, which may upregulate pro-coagulative factors [22]. Another reason may be the injury of the vascular wall, which leads to the release of tissue factors. Yet another reason is that the cytokine storm precipitates microthrombosis [23].

It has now been shown that SARS-CoV-2, like other human coronaviruses (HCoV) of which SARS-CoV-2 is one, can invade the CNS. SARS-CoV-2 uses angiotensin-converting enzyme-2 (ACE2) as an entry receptor and the cellular transmembrane protease serine 2 (TMPRSS2) for S-protein preparation [24]. Transhuman tissue studies of ACE2- and TMPRSS2-positive cells revealed co-expression of these proteins in oligodendrocytes as well as in nasal and ciliary epithelial cells [25]. Co-expression of ACE2/TMPRSS2 in oligodendrocytes could be a means of CNS infiltration or proliferation [26]. Coronaviruses could invade the CNS via transneuronal or hematogenous routes. Early anosmia, a feature of SARS-CoV-2, may indicate early neuroinvasion through the olfactory bulb, as retrograde transport of HCoV from the nasal epithelium to the olfactory nerve has been demonstrated in CNS mouse models [27].

Several cases of GBS due to SARS-CoV-2 infection have been recorded in the literature, with the onset of GBS symptoms ranging from 1 day before to 3 weeks after the onset of SARS-CoV-2 symptoms [11,28,29]. We recorded one patient with acute polyradiculoneuritis. The symptoms of our cases developed first in the 2nd week as in typical post-viral polyradiculoneuritis and appeared with clinical symptoms in the form of motor-type ascending paraplegia.

Limitations of the study

This is a single-center study. Laboratory values for ferritin, D-dimer, and IL-6 could not be assessed because they were not examined in all patients. Cranial imaging, electroencephalography, and electromyoneurography could not be performed in most patients.

Advantages of the study

This study was prospective and patients underwent a detailed neurological examination by a single experienced neurologist. The number of cases was quite large. A comparison was made by including intensive care patients.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Data availability

Data supporting the results of this study are available upon request from the corresponding author.

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