Original article

UDC: 616.-009.7:578.834
doi:10.5633/amm.2022.0201

NEUROLOGICAL DISORDERS IN PATIENTS WITH CORONAVIRUS DISEASE 2019

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In addition to respiratory symptoms, patients with coronavirus disease 2019 (COVID-19) often have neurological, cardiac, gastroenterological and other symptoms. The most common neurological disorders are headache, myalgia, dizziness, acute cerebrovascular disease, disorders of the senses of taste and smell. We examined clinical symptoms, comorbidities, demographic, hematological, and biochemical parameters of 230 patients who showed neurological symptoms during COVID-19. The diagnosis of COVID-19 was made by rapid antigen or PCR (polymerase chain reaction) test. The diagnosis of neurological disorders was made by neurological examination, computed tomography, electroencephalography, lumbar puncture. The severity of the disease was estimated based on the Australian guidelines for the clinical care of people with COVID-19. The Statistical Package for Social Sciences (SPSS, version 16) was used for statistical data analysis. The probability $P < 0.05$ was considered significant.

The most common age was 51-60 years (mean 52.7 ± 10.3). A significant majority of patients had fatigue/weakness (95.7%), fever (90.9%), cough (75.7%) and chest tightness/pain (65.2%). Comorbidities were present in 69.6% of respondents. The most common were cardiovascular diseases (90.6%) and obesity (82.5%). Other associated diseases were asthma/chronic obstructive pulmonary disease (50.6%), diabetes mellitus (40%), gastrointestinal (26.9%), psychiatric disorders (16.3%). The significant majority of patients had elevated levels of lactate dehydrogenase, creatine kinase and C-reactive protein (95.7%, 82.5% and 79.1%), as well as leukopenia (82.6%). Significant frequency of neurological symptoms included headache (94.3%), loss sense of smell/taste, myalgia (90.9%, 84.8%, 88.7%). Patients with severe disease were significantly more often older than 50 (78.2%), with comorbidities, dizziness and acute cerebrovascular disease.

Acta Medica Medianae 2022;61(2):05-13.

Key words: *COVID-19, severity of disease, neurological disorders*

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Introduction

On January 25, 2020, Chinese scientists announced the identification of a new, seventh member of the coronavirus family with the potential for human infection, soon to be called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (1). Infection with the new virus spread rapidly across the planet. The World Health Organization declared a pandemic of the SARS-CoV-2 virus on March 11, 2020 (2). Despite all the prevention and treatment measures taken, coronavirus disease 2019 (COVID-19) remains a major challenge for physicians and scientists worldwide (3). The number of patients and deaths is still high, despite the vaccine that is used in many countries.

The clinical picture of these patients usually includes general and respiratory symptoms: malaise, weakness, loss of appetite, fever, headache, cough, tightness and chest pain. In addition, patients with COVID-19 may have symptoms of damage to many other organ systems: cardiovascular, gastrointestinal, nervous, hematopoietic, immunological, urinary, reproductive, as well as behavioral changes (4). This is confirmed by pathological biopsy and autopsy findings proving the presence of SARS-CoV-2 virus not only in the lungs but also in other organs - spleen, liver, heart, kidneys and brain (5, 6).

Headache, dizziness, encephalopathy, acute cerebrovascular disease, sensory and taste disturbances, and neuralgia/mialgia are common neurological manifestations of COVID-19 (7). Virus neurotropism has been shown by its identification in brain tissue in 36.4% of autopsied fetuses (8). In addition, replication of the virus has been proven and its particles were detected in the structures and organs of the nervous system of infected persons (9).

The aim

The aim of the study was to analyze the neurological disorders in patients with COVID-19 and their frequency in relation to the severity of COVID-19.

Patients and methods

We examined a total of 230 patients with COVID-19 and neurological disorders who were treated at the Department of Infectious Diseases of the General Hospital Užice in the period from March 1, 2020 to September 1, 2021.

Patients with chronic neurological and malignant diseases were excluded from the study.

We analyzed demographic data (sex and age), subjective and objective symptoms (typical and neurological), presence of comorbidities, hematological and biochemical parameters: lactate dehydrogenase (LDH), creatine kinase (CK), C-reactive protein (C-RP).

The diagnosis of COVID-19 was made based on the detection of SARS-CoV-2 virus in the nasopharyngeal swab. Testing was performed in reference laboratories in the Republic of Serbia. A rapid immunochromatographic antigen test and a polymerase chain reaction (PCR) test were used. The tests were registered by the Agency for Medicines and Medical Devices of Serbia.

The diagnosis of acute cerebrovascular diseases (ACVD) was made by computed tomography (CT). All patients with epileptic seizures underwent electroencephalography and CT of the endocranium. Clinical methods - objective status, concentration and memory tests - were used to assess the existence of encephalopathy in our patients. For the purpose of differential diagnosis, computed tomography examinations and examination of cerebrospinal fluid were performed. Cerebrospinal fluid (CSF) was examined cytologically and biochemically. A culture of cerebrospinal fluid was performed. Hematological and biochemical analyses were performed by standard methods used in the Republic of Serbia. Pneumonia was confirmed by radiography or CT.

The severity of the disease was assessed according to Australian guidelines for the clinical care of people with COVID-19:

- Mild illness: no symptoms, or mild upper respiratory tract symptoms, or cough, new myalgia or asthenia without new shortness of breath or a reduction in oxygen saturation;

- Moderate illness: prostration, severe asthenia, fever > 38 ^{O}C or persistent cough, clinical or radiological signs of lung involvement, no clinical or laboratory indicators of clinical severity or respiratory impairment;

- Severe illness: respiratory rate ≥ 30 breaths/min, oxygen saturation ≤ 92% at a rest state arterial partial pressure of oxygen (PaO_2)/ inspired oxygen fraction (FiO_2) ≤ 300 (10).

Patients with critical illness were not included in the study.

All collected data were analyzed retrospectively.

The Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL. USA) version 16.0 was used for statistical analysis with two-side tests and $P < 0.05$ was considered a significance difference.

Results

The investigated patients were aged from 19-85 years (52.7 ± 10.3). The most frequent age group included individuals in the sixth decade, from 50-60 years old.

The main characteristics of our patients with COVID-19 and neurological symptoms are presented in Table 1.

The clinical presentation was significantly dominated by fatigue/weakness, fever and cough in 220, 209 and 174 patients, respectively, as well as chest tightness/pain in 150 individuals.

The presence of comorbidities was statistically significant, most commonly manifested as cardiovascular disease (CVD) (145 patients), followed by obesity (132 patients), diabetes mellitus (DM) type II (91 patients), asthma/chronic obstructive pulmonary disease (COPD) (81 patients) and gastrointestinal disease (GID) (43 patients). The least patients (26) had psychiatric disorders (PD).

Biochemical and hematological findings showed high frequencies of patients for the following parameters: significantly elevated values of CK, LDH and C-RP (192, 220 and 182 patients, respectively) and decreases of leucocyte count (190 patients).

The most common neurological symptom in our patients with COVID-19 was headache (217 patients). A significant number of patients had hyposmia/anosmia and hypogeusia as well as myalgia in 199, 175 and 201 patients, respectively. Fifty-three patients had dizziness. ACVD was diagnosed in 25 patients, of which 16 (64%) patients had ischemic stroke, and 9 (36%) it was hemorrhage. The smallest number of respondents had encephalopathy and epilepsy (11 and 7 patients).

Proteinorachia was present in four patients with CST. Cytological examination of cerebrospinal fluid CSF did not show cells.

Neurological disorders of patients with COVID-19 are presented in Figure 1.

We further compared epidemiological and neurological parameters of patients with COVID-19 according to the severity of the disease.

We further compared epidemiological and neurological parameters of patients with COVID-19 according to the severity of the disease.

Significantly more patients with severe pneumonia were older than 50 years compared to those with mild disease and pneumonia (78.2% vs. 54.3%).

Table 1. Characteristics of total patients with COVID-19 with neurological symptoms

Characteristics		Nº (%)
Male gender		132 (57.4)
Years	19 - 30	4
	31 - 40	43 (18.7)
	41 - 50	48 (20.1)
	51 - 60	70 (30.4)
	61 - 70	36 (15.7)
	71 - 80	22 (9.6)
	> 80	7 (3.0)
Symptoms	Fatigue/weakness	220 (95.7)
	Body temperature>37^{0}C	209 (90.9)
	A cough	174 (75.7)
	Chest tightness/pain	150 (65.2)
	Diarrhea	93 (40.4)
	Nausea/vomiting	44 (19.1)
Comorbidities	CVD	145 (90.6)
	Obesity	132 (82.5)
	DM	91 (56.9)
	Asthma/COPD	81 (50.6)
	GID	43 (26.9)
	PD	26 (16.3)
	Total	160 (69.6)
Laboratory date	RBC < 4.1x10^{12} /L	78 (33.9)
	WBC < 4.5x10^9/L	190 (82.6)
	PLT < 150x10^9/L	137 (59.6)
	Hb < 12.5 g/dL	51 (22.2)
	CK > 198 U/L	192 (83.5)
	LDH > 241 U/L	220 (95.7)
	C-RP > 5 mg/L	182 (79.1)

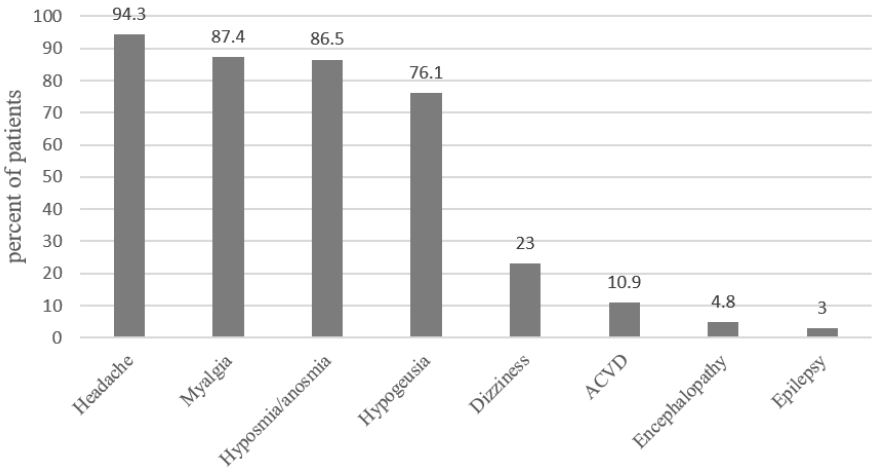

Figure 1. Neurological disorders of patients with COVID-19

The main comparative characteristics of our patients with COVID-19 in relation to the severity of the disease are presented in Table 2.

A cough and chest tightness/pain were significantly more common general symptoms in patients with a more severe clinical course of disease.

ACVD and dizziness were more common neurological disorders in patients with severe disease. The others neurological disorders (headache, encephalopathy, hyposmia, hypogeusia, myalgia) were not significantly different among the groups of respondents.

Comorbidities (obesity, DM, CVD, asthma /COPD, GID and PD) were significantly more frequent in patients with severe disease.

Thrombocytopenia was significantly more common in patients with severe clinical course.

Table 2. Comparative characteristics of the patients with COVID-19 and neurological disorders in relation to the severity of disease

Characteristics		Mild/moderate illness Nº 138 (%)	Severe illness Nº 92 (%)	P*
Gender	Male	85 (61.6)	47 (51.1)	0.345
	Female	53 (38.4)	45 (48.9)	0.261
Years	19 - 30	4	0	0.00
	31 - 40	36 (26.1)	7 (7.6)	
	41 - 50	35 (25.4)	13 (14.1)	
	51 - 60	47 (34.1)	23 (25.0)	
	61 - 70	9 (6.5)	27 (29.3)	
	71 - 80	5 (3.6)	17 (18.5)	
	> 80	2	5 (5.4)	
Symptoms	Fatigue/weakness	129 (93.4)	91 (98.9)	0.692
	Body temperature > 37 ^{0}C	119 (86.2)	90 (97.8)	0.393
	A cough	82 (59.4)	92(100)	0.001
	Chest tightness/pain	60 (43.5)	90 (97.8)	< 0.001
	Diarrhea	44 (31.9)	49 (53.2)	0.192
	Nausea/vomiting	20 (14.5)	24 (26.1)	0.069
Neurological disorders	Headache	129 (93.5)	88 (95.7)	0.872
	Dizziness	40 (29.0)	53 (57.6)	0.002
	Encephalopathy	4	7 (7.6)	ND
	ACVD	5 (3.6)	20 (21.7)	< 0.001
	Epilepsy	0	7 (7.6)	ND**
	Hyposmia	124 (89.9)	85 (92.4)	0.854
	Hypogeusia	115 (83.3)	80 (87.0)	0.777
	Myalgia	124 (89.9)	80 (87.0)	0.827
Comorbidities	Obesity	51 (37.0)	81 (88.0)	< 0.001
	DM	18 (13.0)	74 (80.4)	0.00
	CVD	60 (43.4)	85 (92.4)	< 0.001
	Asthma/COPD	20 (14.4)	61 (66.3)	< 0.001
	GID	12 (8.7)	31 (33.7)	< 0.001
	PD	9 (6.5)	17 (18.5)	0.016
Laboratory date	RBC < $4.1x10^{12}$ /L	40 (51.2)	38 (48.8)	0.809
	WBC < $4.5x10^9$/L	78 (41.1)	52 (56.5)	0.119
	PLT < $150x10^9$/L	47 (34.1)	90 (97.8)	< 0.001
	Hb < 12.5 g/dL	28 (20.3)	23 (25)	0.485
	CK > 198 U/L	106 (76.8)	86 (93.5)	0.201
	LDH > 241 U/L	104 (75.4)	92 (100)	0.063
	C-RP > 5 mg/L	83 (60.1)	71 (77.1)	0.381

*Statistical analysis performed in five or more patients
** ND, not determined

Discussion

Corona viruses are not primarily neurotropic viruses and their primary target is respiratory epithelium. The target receptor for attachment to cell and subsequent internalization is through the angiotensin converting enzyme-2 receptor (ACE 2). After entry into the cell, the virus RNA is released in the cytoplasm subsequently translated and replicated, after formation of envelope protein and incorporation of RNA into it, the virus is released in the circulation (11).

Epithelial cell damage causes general and respiratory symptoms that were the most common in our patients, in accordance with the already described symptoms of COVID-19 (7, 12). These symptoms are expected to be more common in severe disease. It is also expected that people with comorbidities have a more severe clinical course of the disease.

A significant number of our patients experienced chest tightness/pain. Pulmonary angiography did not indicate pulmonary thromboembolism in these patients. In the vast majority, the pain was short-lived. Often, the pain stopped after admission to the hospital and the application of general therapy. Oliviero et al. have shown that chest pain may be a symptom of increased anxiety present in COVID-19 (13). The same authors describe the occurrence of more frequent gastrointestinal symptoms with increased anxiety (13). Gastrointestinal symptoms were also present in our patients and were probably not just a consequence of the effects of SARS-CoV-2. We cannot draw a reliable conclusion as we did not measure the degree of anxiety of our patients.

A small proportion of people with COVID-19 can experience significant chest pains, which are mostly brought on by breathing deeply, coughing or sneezing. This is likely to be caused by the virus directly affecting their muscles, lungs and peripheral nerve (11).

Myalgia was present in the vast majority of our patients, with no significant difference in the severity of the clinical course. It was accompanied by elevated CK and LDH values. This is expected in relation to other research (7). Mao et al. concluded that it was not clear whether this was due to the direct effect of virus on muscle tissue. The other possible mechanism proposed was the infection-mediated immune response that causing elevated pro-inflammatory cytokines in serum resulting in skeletal muscle damage (7). Lactate levels increased due to surplus cell damage during COVID-19 (14). Lactate and H^+ ion accumulation occur in the cytosol, and the cytosol pH decreases (15). ATP synthesis is reduced due to anaerobic glycolysis. Decreased ATP (adenosine triphosphate) synthesis and low intracellular pH cause pain and fatigue (16, 17). During hypoxic ischemia, the increase of growth factors, cytokines levels, ischemic conditions, and microvascular changes can trigger pain by overexpression in the dorsal root ganglion (18).

Although COVID-19 preferentially affects the respiratory and cardiovascular system, up to 84% of patients show neurological symptoms (19).

ACE 2 receptors are also found in glial cells in brain and spinal neurons. During the viremia phase of illness, disruption of blood brain barrier causes the virus to enter the brain directly. Another postulated mechanism is the invasion of peripheral nerve terminals by CoV which then gains entry to the CNS through the synapse connected route (11).

Headache, dizziness, taste and smell dysfunctions were the most frequently reported neurological symptoms in COVID-19, as well as ours (7, 20). In patients with COVID-19 and available data on the severity of disease, headache was reported more frequently in mild or moderate compared to severe or critical disease (20). We do not confirm this conclusion, but our study did not include patients with critical illness. We observed more frequent dizziness in the more severe clinical course of the disease. We also observed a higher incidence of ACVD in patients with severe disease. This can be explained by the conclusion reached by Tehrani et al. that dizziness is more common in people with ACVD (21).

The neuropathogenic effect of SARS-CoV-2 is likely to be achieved by both hypoxic brain damage and immune mediated damage. Severe pneumonia was followed by peripheral vasodilatation, hypercarbia, hypoxia and anaerobic metabolism with accumulation of toxic compounds. These can result in neuronal swelling and brain edema which results in neurological damage (22). Immune mediated injury is mainly due to the cytokine storms with increased levels of inflammatory cytokines and activation of T lymphocytes, macrophages, and endothelial cells (23). Immune-mediated mechanisms of ACVD with consequent dizziness are described (24).

Cerebrovascular disease has been associated with an increased disease severity in patients with COVID-19 (7, 25). We noticed this in our research as well.

Since SARS-CoV-2 binds to ACE2, some patients with underlying hypertension may have unusually high blood pressure and increased risk of intracranial hemorrhage after SARS-CoV-2 infection. Severely low platelets are also an important manifestation of critical SARS-CoV-2 infection, as well as an independent risk factor for acute cerebrovascular events (5).

Our patients also had the progression of thrombocytopenia with the progression of the clinical course. In addition, the most common comorbidity in our patients was CVD. Chinese researchers have also identified CVD as the most common morbidity (7). Their research confirms older age as a risk factor for the progression of the clinical course of the disease, as well as ours.

Some authors describe that the cause of ACVD is more often ischemia than hemorrhage which was confirmed by our examination (26).

This is supported by the conclusions that the hypercoagulability seen in patients with COVID-19 may predispose to a stroke while disseminated intravascular coagulation is more commonly associated with the disease progression (27, 28).

The smell and taste dysfunction was present in a significant majority of our patients. The result corresponds to the order of other authors (29).

Some authors have described a lower incidence of sense of smell loss. Our study included anosmia and hyposmia in a significantly larger sample of patients compared to the mentioned study (7, 30). Mao and Lechien have described higher incidence of taste and smell disorders in mild/moderate clinical forms compared to severe/critical patients (7, 31). In a large Iranian study, taste loss was significantly more common than a loss of smell (32). In our study, no significant difference in the loss of the sense of taste and smell was noticed either in the type of senses or in the severity of the clinical appearance.

Variations among populations infected with different virus mutations were considered. It has been observed that populations infected predominantly with the G614 virus had a much higher prevalence of anosmia compared with the same ethnic populations infected mostly with the D614 virus strain (33).

A smaller number of our respondents had encephalopathy compared to the results of Chinese researchers (34). Encephalopathy can be caused by hypoxia, especially present in patients with asthma/ COPD.

CSF culture ruled out the presence of bacterial diseases. We were not able to diagnose SARS-CoV-2 in CSF. CSF results of our four patients revealed elevated proteins, without pleocytosis. Cases of SARS-CoV-2 in CSF with and without pleocytosis have been reported in the literature (35, 36). It has already been noticed that viral meningoencephalitis may occur frequently in the lack of CSF pleocytosis (37). Proteinorachia in COVID-19 has been described by other authors (38).

Only 3% of our patients had EPI. It is similarly described in the literature with the hypothesis that SARS-CoV-2 could trigger seizures through a neurotropic pathogenic mechanism (39).

Conclusion

SARS-CoV-2 most commonly causes respiratory symptoms, but may infect nervous system.

The most common neurological symptoms are headache, disorders of the senses of taste and smell, and myalgia. Most patients with neurological problems have comorbidities, most commonly cardiovascular disease and obesity. Patients with severe COVID-19 have significantly more neurological manifestations in terms of acute cerebrovascular disease and dizziness.

Careful and timely examination of patients with COVID-19 and neurological symptoms is necessary to avoid delayed diagnosis or misdiagnosis. A multidisciplinary team is needed to carefully monitor multiorgan functions.

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Originalni rad **UDC: 616.-009.7:578.834**
doi:10.5633/amm.2022.0201

NEUROLOŠKI POREMEĆAJI KOD BOLESNIKA SA KORONAVIRUSNOM BOLEŠĆU 2019

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Pored respiratornih simptoma, bolesnici sa bolešću izazvanom korona virusom COVID-19 često imaju neurološke, kardiološke, gastroenterološke i druge simptome. Najčešće neurološke tegobe su glavobolja, mijalgije, vrtoglavica, pojava akutne cerebrovaskularne bolesti, kao i poremećaji čula ukusa i mirisa. Retrogradno, analizirali smo klinički tok, komorbiditete, demografske, hematološke i biohemijske karakteristike 230 bolesnika, koji su u kliničkoj slici COVID-19 virusa ispoljili neurološke simptome. Dijagnoza oboljenja izazvanog virusom COVID-19 postavljena je na osnovu brzog antigenskog i PCR (polimeraza lančane reakcije) testa. U dijagnostici neuroloških poremećaja, osim neurološkog pregleda, primenjivane su kompjuterizovana tomografija, elektroencefalografija, kao i lumbalna punkcija. Težina bolesti procenjena je na osnovu Australijskog vodiča za težinu kliničke slike oboljenja izazvanog virusom COVID-19. Statistička analiza rađena je pomoću Statističkog paketa za društvene nauke (SPSS, verzija 16). Verovatnoća $p < 0,05$ smatrana je značajnom.

Najčešći uzrast ispitanika bio je od 51 godine do 60 godina (prosek 52,7 godina ± 10,3 godine). Značajna većina bolesnika osećala je slabost/malaksalost (95,7%), imala je povišenu telesnu temperaturu (90,9%), kašalj (75,7%) i osećala je stezanje/bol u grudima (65,2%). Komorbiditeti su bili prisutni kod 69,6% ispitanika. Najčešće su bile kardiovaskularne bolesti (90,6%) i gojaznost (82,5%), zatim astma / hronična opstruktivna bolest pluća (50,6%), diabetes mellitus (40%), gastrointestinalne (26,9%) i psihijatrijske bolesti (16,3%). Značajna većina bolesnika imala je u laboratorijskim analizama povišen nivo laktat dehidrogenaze, kreatin kinaze, c-reaktivnog proteina (95,7%; 82,5% i 79,1%) i leukopeniju (82,6%). Značajna učestalost neuroloških simptoma podrazumevala je glavobolju (94,3%), poremećaj čula mirisa i ukusa i mijalgije (90,9%; 84,8%; 88,7%). U odnosu na težinu oboljenja izazvanog COVID-19 virusom, bolesnici sa težom bolešću bili su značajno češće uzrasta preko 50 godina (78,2%), sa prisustvom vrtoglavice i akutne cerebrovaskularne bolesti. Ovi bolesnici značajno češće imali su komorbiditete.

Acta Medica Medianae 2022;61(2):05-13.

Ključne reči: *COVID-19, težina bolesti, neurološki poremećaji*

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