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Characteristics of neurologic manifestations in COVID-19 patients at Sanglah Hospital, Denpasar, Indonesia

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ABSTRACT

Background/aim. Coronavirus Disease 2019 (COVID-19) is an infectious disease caused by SARS-CoV-2. Although the main symptoms of this virus are in the respiratory system, neurological clinical manifestations in the form of the central nervous system (CNS), peripheral nervous system (PNS) and musculoskeletal system are often found. This study aims for data on the characteristics of neurological manifestations in COVID-19 patients.

Research methods. A retrospective cohort study with medical record from June 2020 to June 2021 which was analyzed descriptive, Chi-Square test and survival using SPSS program.

Research result. There were 136 patients with PCR swab results (+), 80 (58.8%) male and 56 (41.2%) female, age > 50 years 92 (67.6%), 47 (34.6%) died. Neurological manifestations in the CNS that stroke 72 (52.9%) RR 4.8 (CI 95% 2.1-10.6; p<0.001), seizures 19 (14%) RR 14.7 (95% CI 4-54.3; p <0.001), headache 32 (23.5%) RR 5.7 (95% CI 2, 4-13.4; p<0.001), encephalopathy 35 (25.7%) RR 41.1 (95% CI 12.7-132.7; p<0.001), in the PNS myasthenic crisis 6 (4.4%) RR 10.4 (95% CI 1.2-92.5; p = 0.035) anosmia 73 (53.7%) RR 0.2 (95% CI 0.1-0.5; p<0.001) while musculoskeletal myalgia 25 (18.4%) and low back pain 18 (13.2%) was not significant.

Conclusion. Most neurological clinical manifestations in the CNS (stroke, headache, seizures and encephalopathy) followed by the PNS (myasthenia crisis and anosmia). Neuroinvasive complications are thought to play a role as one of the causes of respiratory failure and death in patients with COVID-19.

Keywords: COVID-19, Manifestations, Neurology, central nervous system, peripheral nervous system, musculoskeletal

INTRODUCTION

Coronavirus Disease 2019 (COVID-19) is an infectious disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) [1]. On December 31, 2019, the WHO China Country Office reported a case of pneumonia of unknown etiology in Wuhan City, Hubei Province, China. On January 7, 2020, China identified the case as a new type of coronavirus. On January 30, 2020, WHO declared the incident a Public Health Emergency of International Concern (PHEIC) and on March 11, 2020, WHO had declared COVID-19 as a pandemic. Indonesia reported its first case on March 2, 2020. Cases are increasing and spreading rapidly throughout Indonesia. As of 9 July 2020, the Ministry of Health reported 70,736 confirmed cases of COVID-19 with 3,417 deaths (CFR 4.8%). The latest WHO data on February 6 obtained globally 103,989,900 confirmed cases of COVID-19, with 2,260. 259 cases died. Data from the Ministry of Health of the Republic of Indonesia recorded 1,134,854 confirmed cases and 31,202 deaths in Indonesia [1–3].

In Indonesia, based on the Guidelines for Prevention and Control of Coronavirus Disease (COV-

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ID-19) of the Ministry of Health of the Republic of Indonesia in July 2020, there are operational definitions of COVID-19 cases, namely Suspected, Probable, Confirmed, Close Contact, Traveller, Discarded, Completed Isolation and Death [1].

Common clinical symptoms that occur in COVID-19 patients include fever, dry cough, dyspnea, fatigue, muscle aches and aches. Based on research conducted by Huang et al., the most common clinical symptoms in COVID-19 patients were fever (98%), cough (76%), and myalgia or weakness (44%). Other symptoms found in patients, but not so often found are sputum production (28%), headache 8%, coughing up blood 5% and diarrhea 3%. As many as 55% of the patients studied had dyspnea. Kumar et al. reported clinical symptoms involving the gastrointestinal tract. Abdominal pain is an indicator of the severity of patients with COVID-19 infection. A total of 2.7% of patients experienced abdominal pain, 7.8% of patients had diarrhea, 5.6% of patients experienced nausea and/or vomiting. Infections in humans are often severe clinical symptoms and high mortality, whereas for COVID-19, several studies have described typical clinical manifestations including fever, cough, diarrhea and fatigue. Coronavirus 2019 also has characteristic laboratory findings and pulmonary Computed Tomography (CT) abnormalities [4,5]. Neurological clinical manifestations are categorized into 3 types, namely the central nervous system, peripheral nervous system and musculoskeletal [6].

We report on the characteristics of neurological manifestations in COVID-19 patients treated in the isolation ward of Sanglah Hospital, Denpasar. The purpose of this study was to find data on the characteristics of neurological manifestations in COVID-19 patients treated in the isolation room at Sanglah Hospital for the period June 2020 - June 2021.

METHOD

This research is a research observational analytic retrospective cohort using secondary data and other administrative data from the medical records of Sanglah Hospital, during June 2020 to June 2021. Ethical permission in this study with No. LB.02.01/XIV.2.2.1/13312/2021 from the research ethics commission of the Faculty of Medicine, Udayana University/ Sanglah Central General Hospital Denpasar.

Inclusion criteria included (1) Respondent with confirmed COVID-19 with a PCR swab examination (+) who were treated in the isolation room of Sanglah Hospital, were consulted to the neurology department and had neurological manifestations, central nervous system, peripheral nervous system and musculoskeletal manifestations, with or without comorbidities (2) Signed *informed consent*. Exclusion criteria were patients who were treated in isolation rooms with rapid test results (+) or swab antigens (+) and had no manifestations in the field of neurology.

RESULTS

The research sample came from an affordable population of 136 respondents who met the inclusion criteria. The data are described by percentage, mean value and standard deviation (SD) in Table 1.

TABLE 1. Characteristics of research respondents

Variable		Frequency (N)	Percentage (%)
Age	50 years	44	32.4
	> 50 years	92	67.6
	Mean age ±SD	56.76±13.44	
Gender	Man	80	58.8
	Woman	56	41.2
Comorbid	With comorbid	84	61.8
	No comorbid	52	38.2
Comorbid disease	Hypertension	57	41.9
	Diabetes mellitus	31	22.8
	History of stroke	16	11.8
	History of heart disease	20	14.7
	Dyslipidemia	10	7.4
	Tumor	15	11
	Epilepsy	8	5.9
	Myasthenia Gravis	9	6.6
	Parkinson	5	3.7
Neurological Manifestations			
Central nerve system	stroke	72	52.9
	Seizure	19	14
	Headache	32	23.5
	Vertigo	19	14
	Hypoxic/ metabolic/ septic encephalopathy	35	25.7
Peripheral Nervous System	Myasthenic crisis	6	
	Neuropathy	9	
	Anosmia	73	
Musculoskeletal	Myalgia	25	
	Low back pain	18	
Survival	Life	89	
	Die	47	
Disease free survival	without disease	37	
	With disease	52	

Outcome characteristics of 1 year survival of patients with neurologic manifestations are shown in Table 2, and characteristics of disease free survival are shown in Table 3.

TABLE 2. Outcome of 1 year survival of COVID-19 patients with neurological manifestations

Variable		1 year overall survival		OR	95% CI	*p-value**	*Rank log*		Average Survival (months)	
		life	die				LRT	df	Month	95% CI
Age	50 years	29	15	1	0.4-2.2	0.937	0.006	1	9	8-10
	> 50 years	60	32						9	8-10
Gender	Man	64	15	0.6	0.3-1.3	0.221	1.1	1	9	8-10
	Woman	25	32						9	8-10
Comorbid	Hypertension	25	32	5.5	2.5-11.7	<0.001†	21.8	1	7	5-8
	Diabetes mellitus	24	7	0.5	0.2-1.2	0.115	3	1	11	9-12
	History of stroke	8	8	2.1	0.7-5.9	0.173	3	1	7	4-9
	History of heart disease	7	13	4.5	1.6-12.2	0.003†	13.1	1	5	3-8
	Dyslipidemia	6	4	1.3	0.3-4.8	0.708	0.3	1	8	4-11
	Tumor	8	7	1.7	0.6-5.2	0.3	0.3	1	8	4-11
	Epilepsy	2	6	6.3	1.2-32.9	0.027†	10.8	1	4	1-7
	Myasthenia Gravis	5	4	1.5	0.4-6.1	0.522	0.8	1	7	4-11
	Parkinson	5	0	N	N	N	N	N	N	N
Central nerve system	stroke	36	36	4.8	2.1-10.6	<0.001†	15.1	1	8	6-9
	Seizure	3	16	14.7	4-54.3	<0.001†	41.3	1	3	1-5
	Headache	11	21	5.7	2.4-13.4	<0.001†	24.8	1	5	3-7
	Vertigo	19	0	N	N	N	N	N	N	N
	Hypoxic/metabolic/ septic encephalopathy	4	31	41.1	12.7-132.7	<0.001†	24.8	1	5	3-7
Peripheral nervous system	Myasthenic crisis	1	5	10.4	1.2-92.5	0.035†	11.3	1	3	1-7
	Neuropathy	9	0	N	N	N	N	N	N	N
	Anosmia	59	14	0.2	0.1-0.5	<0.001†	18.1	1	10	10-11
Musculoskeletal	Myalgia	25	0	N	N	N	N	N	N	N
	Low back pain	18	0	N	N	N	N	N	N	N

*chi-Square
† significant

TABLE 3. Outcome of 1 year disease free survival of COVID-19 patients with neurological manifestations

Variable		1 year disease free survival		OR	95% CI	*p-value**
		without disease	With disease			
Age	50 years	12	16	1.1	0.4-2.8	0.868
	> 50 years	15	36			
Gender	Man	23	26	1.6	0.7-3.9	0.257
	Woman	14	26			
Comorbid	Hypertension	0	25	N	N	N
	Diabetes mellitus	0	24	N	N	N
	History of stroke	0	8	N	N	N
	History of heart disease	0	7	N	N	N
	Dyslipidemia	2	4	1.5	0.3-8.4	0.673
	Tumor	0	8	N	N	N
	Epilepsy	0	2	N	N	N
	Myasthenia Gravis	0	5	N	N	N
	Parkinson	0	5	N	N	N
Central nerve system	stroke	0	35	N	N	N
	Seizure	0	3	N	N	N
	Headache	6	5	0.6	0.2-1.9	0.154
	Vertigo	17	2	0.1	0.1-0.2	<0.001†
	Hypoxic/metabolic/septic encephalopathy	0	4	N	N	N
Peripheral nervous system	Myasthenic crisis	1	0	N	N	N
	Neuropathy	8	1	0.1	0.1-0.6	0.015†
	Anosmia	58	8	0.2	0.1-0.6	0.005†
Musculoskeletal	Myalgia	7	7	0.7	0.2-2.1	0.488
	Low back pain	10	8	0.5	0.2-1.4	0.182

*chi-Square
† significant

DISCUSSION

The cause of COVID-19 is a virus belonging to the coronavirus family. Coronavirus is a positive single-strain RNA virus, encapsulated and unsegmented. There are 4 main protein structures in Coronavirus, namely: protein N (nucleocapsid), glycoprotein M (membrane), spike glycoprotein S (spike), protein E (sheath). Coronavirus belongs to the order Nidovirales, family Coronaviridae. This coronavirus can cause disease in animals or humans. There are 4 genus; α-coronavirus, β-coronavirus, γ-coronavirus, dan δ-coronavirus [7].

The average incubation period for COVID-19 is 5-6 days, with a range between 1 and 14 days but can be up to 14 days. The highest risk of transmission is obtained in the first days of the disease due to the high concentration of virus in the secretions. Infected persons can be directly infectious up to 48 hours before symptom onset (presymptomatic) and up to 14 days after symptom onset. A Le Bert study, (2020) reported that 12.6% showed presymptomatic transmission [8].

Symptoms are usually mild and appear gradually. Some infected people do not show any symptoms and still feel well. The most common symptoms of COVID-19 are fever, fatigue and a dry cough. Some patients may experience aches and pains, nasal congestion, runny nose, headache, conjunctivitis, sore throat, diarrhea, loss of smell and smell or skin rash. Some patients also present with neurological symptoms and complications including encephalopathy, cerebrovascular disease, seizures, impaired consciousness and musculoskeletal disorders [9]. Neurological clinical manifestations are categorized into 3 types; muscle disorders, central nervous system disorders and peripheral nervous system disorders. Neuroinvasive complications are also thought to play a role as one of the causes of respiratory failure and death in patients with COVID-19 [6,10].

Mechanism of neuroinvasion

The mechanism of neuroinvasion through the spread of the systemic circulation, the virus attacks the nervous tissue because it is neurotropism. This virus binds to and interacts with the angiotensin converting enzyme 2 (ACE2) receptor in endothelial capillaries. This indicates the presence of neurotrophic potential in SARS-CoV-2 which belongs to the -coronavirus subtype. The main target of SARS-CoV-2 is respiratory and gastrointestinal epithelial cells which have an angiotensin converting enzyme-2 (ACE2) component. SARS-CoV-2 has a spike protein surface that has a high affinity for the ACE2 receptor. This ACE2 receptor is also expressed by neurons and glia cells in the brain so that the brain can be a potential target of SARS-CoV-2. The mechanism for the spread of SARS-CoV-2 to the brain is not known with certainty, but there are 2 possible mechanisms for the spread of this virus, namely: (1) hematogenous spread and (2) spread through the cribriform plate and olfactory bulb. SARS-CoV-2 in the systemic circulation can spread to the cerebral circulation where the slowing of blood flow in the microcirculation allows the interaction of the SARS-CoV-2 spike protein with ACE2 which is expressed on the capillary endothelium. Viral particles that develop in the endothelium, damage to the endothelial wall, and damage to the blood-brain barrier facilitate viral entry into the brain [5].

Following central nervous system (CNS) invasion, SARS-CoV-2 infection triggers a massive neuroinflammatory response characterized by reactive astrogliosis and activation of the immune system. microglia. SARS-CoV-2 infection can trigger a cytokine storm that can cause inflammation and injury to CNS tissue [6]. This hypothesis is supported by the results of a study in China which found that levels of interleukin (IL)-6, Granulocytic Colon y-Stimulating Factor (GCSF), Interferon gamma-induced protein *10* (IPIO), Monocate Chemoattractant Proteln-1 (MCPI), Macrophage inflammatory ProtelnS lA (MIPIA) and Tumor Necrosis Factor-a (TNFα) which are part of plasma cytokines and chemokines are positively correlated with the severity of COVID-19 symptoms [11].

Central nervous system manifestations

Reported CNS manifestations include headache, dizziness/vertigo, cerebrovascular disease, loss of consciousness, meningitis, encephalitis, encephalopathy, seizures. Lung damage due to viruses can cause disruption of the ventilation process which eventually triggers the occurrence of hypoxia. Hypoxia in the CNS triggers anaerobic metabolic processes in mitochondria resulting in accumulation of lactic acid which causes vasodilation of cerebral blood vessels, interstitial and brain cell edema, obstruction of cerebral blood flow, and headaches due to ischemia and congestion [12]. ACE2 receptors are expressed in the ventrolateral medulla and nucleus tractus solitarius, which play an important role in cardiovascular and respiratory regulation. Invasion of SARS-CoV-2 into these areas may aggravate or directly cause respiratory failure in patients. The combination of a neuroinflammatory process and severe hypoxia causes damage to the hippocampus and cortical areas that play a role in neuropsychiatric and cognitive function [4].

In this study, it was found that the age with the most neurological manifestations was over 50 years 92 (67.6%). This is similar to the study of Mao et al., where 124 (57.9%) aged over 50 years were at risk for neurological manifestations than those under 50

years 90 (42.1%) [6]. Tsivgoulis reported that old age is a risk factor for cerebrovascular disease [13]. Several studies have found that COVID-19 patients with cerebrovascular symptoms have characteristics of old age and have other comorbid diseases such as hypertension, diabetes mellitus (DM), which are known risk factors for stroke. The study also reported higher D-dimer laboratory results in severe COVID-19 conditions or COVID-19 with cerebrovascular disorders where these results indicate a disorder of the coagulation system. The mechanism of cerebrovascular disorders without previous vascular risk factors is thought to stem from hypercoagulable conditions that cause thrombus formation in blood vessels. Direct viral infection and hypoxia are thought to play a role in the occurrence of cerebrovascular disease [6,14].

The results showed that respondents with stroke 72 (52.9%) had a significant survival rate where the RR was 4.8 (95% CI 2.1-10.6; p<0.001; mean survival was 8 (95% CI 6-9) months). Stroke is associated with hypercoagulability associated with COVID-19 which is likely a "sepsis-induced coagulopathy" and may predispose to stroke. The SARS-CoV-2 virus binds to the angiotensin-converting enzyme 2 (ACE2) present in smooth muscle and brain endothelial cells. ACE2 is part of the renin-angiotensin system (RAS) and a counterbalance to angiotensin-converting enzyme 1 (ACE1) and angiotensin II. Angiotensin II is proinflammatory, vasoconstrictive and increases organ damage. The decrease in ACE2 by SARS-CoV-2 results in a "dangerous" condition in which the ACE1/angiotensin II axis will cause brain tissue injury that eventually leads to stroke [15].

Hemorrhagic strokes can occur in COVID-19 patients, although they are less common. This situation is thought to be caused by the presence of viral particles that bind to ACE2 in cerebral blood vessels which can increase the intraluminal pressure of blood vessels, causing intracerebral hemorrhage. Blood pressure fluctuations that occur due to SARS-CoV-2 binding to the ACE2 receptor increase the risk of intracranial bleeding. Some COVID-19 patients with severe conditions may have severe thrombocytopenia which may act as a risk factor for intracranial bleeding [16].

The results of encephalopathy 35 (25.7%) with an RR of 41.1 (95% CI 12.7-132.7; p<0.001; survival mean 5 (95% CI 3-7) months means this is in accordance with the study in France where encephalopathy is caused by Acute Respiratory Distress Syndrome (ARDS) with the cause of SARS-CoV-2 and is associated with a state of agitation, confusion, involving the corticospinal tract. MRI examination found several abnormalities in the form of leptomeningeal enhancement, brain perfusion abnormalities and acute ischemic stroke [17].

Seizures can be one of the manifestations of CNS infection by a virus. SARS-CoV-2 can cause severe pneumonia with severe hypoxemia that can lead to brain injury and seizures. Metabolic disorders and septic encephalopathy may also be the cause of acute symptomatic seizures. Patients with pre-existing epilepsy may also experience an increase in the frequency and severity of seizures, mainly because of a decrease in the seizure threshold associated with fever. Some of these things indicate that COVID-19 can cause conditions that can act as risk factors for seizures. Hypoxia is the most common risk factor for seizures [16]. The results in this study were known for seizures 19 (14%) RR 14.7 (95% CI 4-54.3; p < 0.001; mean survival 3 (95% CI 1-5) months).

Headache 32 (23.5%) RR 5.7 (95% CI 2.4-13.4; p<0.001; mean 5 (3-7) months). Nheadache occurs in 8%-12% of 41,000 cases of COVID-19 patients where acute headache caused by systemic viral infection, primary headache, tension-type headache and headache associated with heterophoria may appear in the first phase (phase similar to influenza); and headache associated with hypoxia and headache due to comorbidities, may occur if the second phase (cytokine storm phase) occurs. The symptom of a headache should not be underestimated because it may be a sign of an emergency in a COVID-19 patient [18].

The results of vertigo 19 (14%) of respondents were not statistically significant in survival but had a significance for disease free survival. It was known that from 19 patients, 17 patients were free from this disease, RR 0.1 (95% CI 0.1-0, 2; p<0.001). Vertigo associated with the presence of COVID-19 has been known from several studies although it has non-specific symptoms but should not be ignored.[19] The mechanism of vertigo in SARS-COV-2 may be by viral inflammation or post-viral disorders [20].

Peripheral Nervous System Manifestations

The most commonly reported peripheral nervous system manifestations are anosmia and ageusia. The mechanism of anosmia and ageusia in COVID-19 is not known with certainty. Spread of the virus to the CNS via the olfactory nerves may play a role in anosmia and the inflammatory response may affect taste receptors on the tongue causing ageusia. During the pandemic, new and sudden onset of anosmia and ageusia, without head injury or nasal obstruction should be suspected as COVID-19 infection [17]. The results obtained anosmia 73 (53.7%) RR 0.2 (95% CI 0.1-0.5; p<0.001; survival mean 10 (10-11) months) with the results of 58 respondents recovered and the complaint persisted for 1 year as many as 8 respondents RR 0.2 (95% CI 0.1-0.6; p=0.005)

Patients with myasthenia gravis may be considered at high risk due to chronic immunosuppression. The results showed myasthenia crisis 6 (4.4%) RR 10.4 (95% CI 1.2-92.5; p = 0.035; survival mean 3 (95% CI 1-7) months) this is in accordance with the study Ramaswami et al. reported that myasthenic patients infected with COVID-19 would experience myasthenic crises/exacerbations due to complications of COVID-19 despite undergoing chronic immunomodulatory therapy [21].

The results of neuropathy complaints were found in 9 (6.6%) patients where 100% of patients were alive with 8 respondents who improved and 1 respondent who was still living. Neuropathy is a rare case of COVID-19 so the mechanism is still unknown [22].

Musculoskeletal Manifestations

Neurological manifestations of musculoskeletal in the form of myalgia. Skeletal muscle injury can be characterized by skeletal muscle pain and an increase in serum Creative Kinase (CK) levels of more than 200 U/L. Increased levels of CK in the blood are used as an indicator of muscle damage and the inflammatory response. Patients with muscle injury reported higher neutrophil levels, lower lymphocytes, higher CRP and higher D-dimer [6.23]. In this study, myalgia 25 (18.4%) and low back pain 18 (13.2%) were found.

Prognosis

Neuroinvasive complications are also thought to play a role as one of the causes of respiratory failure and death in patients with COVID-19. Whittaker et al. reported that neurologic involvement in the pathogenesis of SARS-CoV-2 appears to be associated with severe infection and risk of death. However, at present, there is no direct cause and effect associated with nerve damage in patients with SARS-CoV-2 and this association is associated with multi-organ failure [24].

The advantage of this study is that it can determine the characteristics of neurological manifestations observed for 1 year to be able to determine 1 year of overall survival and disease free survival that have been matched by design so that unexpected confounding variables can be minimized.

The limitation of this study is the short duration of the study. This study used subjects in certain populations in certain places; hence, this study's results cannot describe the same conditions in different populations and places. Further research is needed to improve this study's results using a larger sample size involving various types of other neurological manifestation.

CONCLUSION

Most neurological clinical manifestations in the central nervous system (stroke, headache, seizures and encephalopathy) followed by the peripheral nervous system (myasthenia crisis and anosmia). Neuroinvasive complications are thought to play a role as one of the causes of respiratory failure and death in patients with COVID-19.

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