

[ORIGINAL ARTICLE]

Neurological Manifestations and Long-term Sequelae in Hospitalized Patients with COVID-19

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Abstract:

Objective Various neurological manifestations have been increasingly reported in coronavirus disease 2019 (COVID-19). We determined the neurological features and long-term sequelae in hospitalized COVID-19 patients.

Methods We retrospectively studied 95 consecutive hospitalized patients with COVID-19 between March 1 and May 13, 2020. Acute neurological presentations (within two weeks of the symptom onset of COVID-19) were compared between 60 non-severe and 35 severely infected patients who required high-flow oxygen. In the 12 ventilated patients (the most severe group), we evaluated neurological complications during admission, subacute neurological presentations, and neurological sequelae (51 and 137 days from the onset [median], respectively).

Results Of the 95 patients (mean age 53 years old; 40% women), 63% had acute neurological presentations, with an increased prevalence in cases of severe infections (83% vs. 52%, $p < 0.001$). Impaired consciousness and limb weakness were more frequent in severe patients than in non-severe ones (0% vs. 49%; $p < 0.001$, and 0% vs. 54%; $p < 0.001$, respectively). In the most severe group (mean age 72 years old; 42% women), 83% of patients had neurological complications [cerebrovascular disease (17%), encephalopathy (82%), and neuropathy (55%)], and 92% had subacute neurological presentations [impaired consciousness (17%), higher brain dysfunction (82%), limb weakness (75%), and tremor (58%)]. Neurological sequelae were found in 83% of cases, including higher brain dysfunction (73%), limb weakness (50%), and tremor (58%).

Conclusions Neurological manifestations are common in COVID-19, with the possibility of long-lasting sequelae.

Key words: COVID-19, neurology, infectious diseases, intensive and critical care

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Introduction

In December 2019, the coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2), rapidly spread around the world, leading to a pandemic (1). As of March 9, 2021, there were over 116 million confirmed cases, including more

than 2.5 million deaths worldwide, and the number continues to grow (2). Japan has one of the lowest number of cases and mortality rate due to COVID-19, despite a large elderly population (3).

Previous studies have reported various neurological manifestations in COVID-19 cases (4-11). Although the neurological complications of COVID-19 are not well-defined, a common spectrum associated neurological diseases has

emerged, including nonspecific symptoms, such as headache or dizziness (4, 8-10), dysosmia and dysgeusia (4, 8-10, 12-14), impaired consciousness (4, 5, 9), cerebrovascular disease (4, 8-11, 15), encephalopathy or meningitis (8, 10, 11), neuropathy (e.g. Guillain-Barré syndrome) (9, 10, 16, 17), and muscle injury (4, 8-10). The presence and prevalence of these complications may be independent of the age, race, and comorbidity of the population, or infection severity (4, 8, 9, 15). Since expert neurological evaluations are absent in many clinical reports because of the pandemic, neurological manifestations may have been underestimated, considering the high prevalence of those reported by trained neurologists in a case series from Spain (8). Furthermore, long-term neurological sequelae have not been established.

In this study, we retrospectively examined the neurological manifestations and long-term sequelae in COVID-19 patients via a detailed evaluation of severely infected patients conducted by board-certified neurologists.

Materials and Methods

Study design, protocol approval, patient consent, and patient recruitment

The present study was a retrospective, single-center observational study. We included 96 consecutive patients hospitalized with COVID-19 between March 1 and May 13, 2020. A confirmed COVID-19 diagnosis was defined as a positive result on polymerase chain reaction (PCR) for SARS-CoV-2 by analyzing nasopharyngeal swab specimens. Detailed genetic information for COVID-19 was not available. Among them, we evaluated 95 patients and excluded 1 patient with severely impaired consciousness pre-infection because a neurological assessment was difficult. We performed the following radiologic examinations according to the clinical necessity for each patient: head CT, head magnetic resonance imaging (MRI), and brain single-photon emission computed tomography (SPECT), or physiological tests, including electroencephalography (EEG) and nerve conduction study (NCS).

The current study was performed in accordance with the principles of the Declaration of Helsinki and approved by the Ethics Committee of Kobe City Medical Center General Hospital, Kobe, Japan, in May 2020. The need for written informed consent was waived because this was a retrospective study without additional invasive procedures or costs to the participants. The patients were provided the opportunity to refuse to participate in the study through a summary of the study on the institute's website.

COVID-19 severity rating

We defined patients with severe COVID-19 as those who required mechanical ventilation or the administration of ≥ 5 L/min of oxygen during hospitalization, as determined according to the COVID-19 clinical management protocol described in the World Health Organization (WHO) guide-

lines (18). Among them, we also defined infections requiring ventilation as the most severe cases of COVID-19.

Management of COVID-19 in our institute

Severe COVID-19 patients who required aggressive treatment in the intensive-care unit (ICU) were managed by intensivists, respiratory physicians, and infectious disease specialists. Non-severe COVID-19 patients were treated by physicians from different departments under the direction of an infectious disease specialist. All patients were quarantined until two consecutive negative PCR tests had been confirmed and the minimum required examination was performed. After their release from isolation, some severe COVID-19 patients underwent an evaluation by two trained neurologists as well as a radio-physiological examination, as necessary.

Data collection

We retrospectively reviewed electronic medical information of confirmed COVID-19 patients, including records described by physicians, nurses, and therapists, laboratory data, radiologic examinations, and physiological tests. The following data were collected: patient demographics, general symptoms, systemic complications, neurologic manifestations, radio-physiological examinations, treatment in the acute phase, and death.

Neurological manifestations

Neurological manifestations were divided into acute neurological presentations, neurological complications, subacute neurological presentations, and neurological sequelae. Acute neurological presentations included both neurologic symptoms and deficits that occurred within two weeks of the symptom onset of COVID-19. Neurologic symptoms were provided by patients, their family, or paramedics, and included headache, dysosmia, and dysgeusia. Neurologic deficits were objective findings consisting of a Glasgow Coma Scale (GCS) score and a measurement of limb weakness. Impaired consciousness was defined as a GCS score of ≤ 13 , and limb weakness was defined as a manual muscle testing scale score of ≤ 4 , as evaluated by trained neurologists, intensivists, nurses, or therapists.

Neurological complications, subacute neurological presentations, and sequelae were thoroughly evaluated by trained neurologists in the most severely infected patients, after excluding patients without evaluation and those who died. Neurological complications included cerebrovascular disease, encephalopathy, neuropathy, and muscle injury during hospitalization. Cerebrovascular disease included ischemic stroke and intracranial hemorrhaging regardless of symptoms. Encephalopathy was determined based on the clinical course of impaired consciousness or higher brain dysfunction established by radio-physiological examinations. This category may have included meningoencephalitis cases, but making this distinction was difficult without a cerebrospinal fluid test. Neuropathy was defined as limb weakness with concor-

dant abnormal findings in the NCS. Muscle injury was determined if patients presented with limb weakness and an elevated serum creatinine kinase level (over 5 times the upper limit of normal, 850 U/L in our institute) (19).

We defined subacute neurological presentations as neurologic findings evaluated after quarantine release and at least three weeks after the symptom onset of COVID-19. Neurological sequelae were evaluated at more than two months after the onset by confirming the presence of impaired consciousness, higher brain dysfunction (memory disturbance, impaired verbal fluency, dyscalculia, and apathy), cranial nerve disorders, limb weakness, and ataxia. A Mini-Mental State Examination (MMSE) and frontal assessment battery (FAB) were also conducted. We determined the modified Rankin Scale (mRS) score at the day of the evaluation of neurological sequelae.

All neurological manifestations were reviewed and confirmed by two trained neurologists; any discrepancy was resolved by a third neurologist.

Radio-physiological tests

We reviewed the radio-physiological tests performed for the most severe group. Head CT was performed in the acute phase for patients with suspected stroke or impaired consciousness using a multidetector CT scanner (Optima CT 660; GE Healthcare, Chicago, USA), and the presence of acute intracranial hemorrhaging was evaluated. Head MRI was performed for patients with neurological deficits, which were assumed to be caused by intracranial lesions after release from quarantine, using either a 1.5-Tesla (Magnetom Avanto; Siemens Medical Solutions, Erlangen, Germany) or 3.0-Tesla scanner (Magnetom Skyra; Siemens Medical Solutions). We confirmed whether or not patients had acute ischemic stroke, hemorrhagic stroke, leukoencephalopathy, or multiple cerebral microbleeds (CMBs). Some patients also underwent cerebral blood flow SPECT with N-isopropyl-p-I-123-iodoamphetamine (I-123 IMP), using a dual-headed gamma camera (Infinia Hawkeye 4; GE Healthcare). We evaluated the existence of hypoperfusion or hyperperfusion areas.

EEG was performed in patients with an impaired consciousness or higher brain dysfunction for approximately 20 minutes using the international 10-20 system with 21 electrodes (Neurofax EEG-1200; Nihon Kohden, Tokyo, Japan). We examined the presence of epileptic discharges or abnormal slow waves. An NCS was performed in patients who presented with limb weakness, ataxia, and tremor using standard methods. Electromyography (MEB-2312; Nihon Kohden) was performed with standard filter settings and using a surface stimulator, and the existence of demyelination or axonal degeneration was confirmed.

All radio-physiological evaluations were reviewed by two trained neurologists blinded to the clinical information; disagreements were resolved by a third neurologist.

Statistical analyses

Continuous variables are presented as the mean and standard deviation (SD) and median and interquartile range (IQR) for normally and non-normally distributed data, respectively. Categorical variables are presented as numbers and percentages. To compare background, clinical features and the prognosis between the severe and non-severe groups, Wilcoxon's signed rank tests were used for continuous variables, and chi-square or Fisher's exact tests were used for categorical variables. Two-sided p values of less than 0.05 were considered statistically significant. All statistical analyses were performed using the JMP 12 software program (SAS Institute, Cary, USA).

Results

Baseline characteristics and general manifestations in the acute phase

The characteristics of the 95 participants are described in Table 1. The mean (SD) age was 53 (21) years old, and 38 patients (40%) were women. Among them, 35 (39%) had severe infections, and 60 (61%) had non-severe infections. The severe COVID-19 patients were significantly older [mean (SD) age, 67 (14) vs. 46 (20) years old; $p < 0.001$] and had a higher prevalence of hypertension (54% vs. 18%; $p < 0.001$), diabetes (34% vs. 10%; $p = 0.004$), and chronic kidney disease (CKD) (14% vs. 0%; $p = 0.006$) than the non-severe ones. Ventilator support was provided only to the severe COVID-19 patients [20 (57%)]. Thirty-three patients (35%) required management in the ICU, which included 89% of severe and 3% of non-severe patients. General manifestations are described in Table 2.

Neurological manifestations

• Acute neurological presentations

Acute neurological presentations are described in Table 3. Several neurological presentations were found in 60 (63%) participants in the acute phase, including headache [17 (18%)], dysosmia [21 (22%)], dysgeusia [21 (22%)], impaired consciousness [17 (18%)], and limb weakness [19 (20%)]. Patients with severe COVID-19 presented less frequently with dysosmia [1 (3%) vs. 20 (33%); $p < 0.001$] and dysgeusia [2 (6%) vs. 19 (32%); $p = 0.003$] than those with non-severe disease but conversely had a higher prevalence of impaired consciousness [17 (49%) vs. 0 (0%); $p < 0.001$], lower GCS score [median (IQR), 14 (11-15) vs. 15 (15-15); $p < 0.001$], and higher prevalence of limb weakness [19 (54%) vs. 0 (0%); $p < 0.001$].

• Neurological complications

The most severe group included 12 of 20 patients with severe infections who required ventilation management, after excluding 5 who were discharged before our evaluation and 3 deaths. The mean (SD) age was 72 (11) years old, and 5 patients (42%) were women. Of the 12 patients, 10 (83%)

Table 1. Baseline Characteristics and Treatment in Patients with COVID-19.

	Total (n=95)	Non-severe (n=60)	Severe (n=35)	p value
Profile				
Age, y, mean (SD)	53±21	46±20	67±14	<0.001*
Women, n (%)	38 (40)	26 (43)	12 (34)	0.385
BMI, kg/m ²	23 (20-26)	22 (20-26)	24 (22-27)	0.112
PRE-mRS	0 (0-0)	0 (0-0)	0 (0-1)	0.014*
Alcohol intake, n (%)	42/74 (57)	23/44 (52)	19/30 (63)	0.346
Current smoker, n (%)	6/78 (8)	4/48 (8)	2/30 (7)	1.000
Past medical history				
Hypertension, n (%)	30 (32)	11 (18)	19 (54)	<0.001*
Diabetes, n (%)	18 (19)	6 (10)	12 (34)	0.004*
Dyslipidemia, n (%)	14 (15)	7 (12)	7 (20)	0.269
CKD, n (%)	5 (5)	0 (0)	5 (14)	0.006*
Dialysis, n (%)	4 (4)	0 (0)	4 (11)	0.016*
Cardiovascular disease, n (%)	11 (12)	5 (8)	6 (17)	0.318
Neurological disease, n (%)	3 (3)	1 (2)	2 (6)	0.552
Cerebrovascular disease, n (%)	2 (2)	1 (2)	1 (3)	1.000
Others, n (%)	3 (4)	1 (2)	2 (6)	0.552
Respiratory disease, n (%)	19 (20)	11 (18)	8 (23)	0.595
Asthma, n (%)	8 (8)	6 (10)	2 (6)	0.706
Pneumonia, n (%)	7 (7)	3 (5)	4 (11)	0.417
Others, n (%)	9 (9)	5 (8)	4 (11)	0.721
Malignancy, n (%)	6 (6)	2 (3)	4 (11)	0.189
Medications				
RASI, n (%)	14 (15)	6 (10)	8 (23)	0.088
Hypoglycemic agents, n (%)	13 (14)	6 (10)	7 (20)	0.219
Insulin, n (%)	4 (4)	2 (3)	2 (6)	0.577
NSAIDs, n (%)	8 (8)	2 (3)	6 (17)	0.048*
Antithrombotic drugs, n (%)	9 (9)	2 (3)	7 (20)	0.011*
Immunosuppressants, n (%)	4 (4)	1 (2)	3 (9)	0.140
Treatment in acute phase				
Oxygen administration, n (%)	46 (48)	11 (18)	35 (100)	<0.001*
Ventilator management, n (%)	20 (21)	0 (0)	20 (57)	<0.001*
Sedation, n (%)	20 (21)	0 (0)	20 (21)	<0.001*
Propofol, n (%)	19 (20)	0 (0)	19 (54)	<0.001*
Midazolam, n (%)	12 (13)	0 (0)	12 (34)	<0.001*
Dexmedetomidine, n (%)	10 (11)	0 (0)	10 (29)	<0.001*
Favipiravir, n (%)	38 (40)	10 (17)	28 (80)	<0.001*
Management in the ICU, n (%)	33 (35)	2 (3)	31 (89)	<0.001*
Mortality, n (%)	7 (7)	0 (0)	7 (20)	<0.001*

Data represent median (interquartile range) unless otherwise noted. *p<0.05.

BMI: body mass index, CKD: chronic kidney disease, ICU: intensive care unit, IQR: interquartile range, NSAIDs: non-steroidal anti-inflammatory drugs, PRE-mRS: premorbid modified Rankin scale, RASI: renin-angiotensin system inhibitor

had ≥1 of the following neurological complications: cerebrovascular disease [2 (17%)], ischemic stroke [1 (7%), small cerebellar infarction], intracranial hemorrhaging [1 (7%), slight convexity subarachnoid hemorrhaging], encephalopathy [9 (82%)], neuropathy [1 patient without NCS was excluded; 6 (55%), suspected critical illness polyneuropathy], and muscle injury [2 (17%), rhabdomyolysis or critical illness myopathy].

• Subacute neurological presentations and sequelae

Subacute neurological presentations were evaluated in the most severe group at 51 (38-54) [median (IQR)] days from

the onset. Eleven (92%) patients had ≥1 of the following findings (Table 4): impaired consciousness [2 (17%)], higher brain dysfunction [9 (82%)], memory disturbance [9 (82%)], impaired verbal fluency [9 (82%)], dyscalculia [9 (82%)], apathy [6 (55%)], cranial nerve disorders [6 (50%), including 1 with facial diplegia, 1 with dysarthria, and 4 with dysphagia], limb weakness [9 (75%); 6 due to neuropathy and 3 to disuse], ataxia [3 (27%)], and tremor [7 (58%)]. One patient with severely impaired consciousness was excluded from the evaluation of higher brain dysfunction and ataxia. Ten patients had an MMSE score of 20 (16-25) [me-

Table 2. General Symptoms and Systemic Complications in Patients with COVID-19.

	Total (n=95)	Non-severe (n=60)	Severe (n=35)	p value
General symptoms				
Any, n (%)	88 (93)	54 (90)	34 (97)	0.255
Fever, n (%)	72 (76)	42 (70)	30 (86)	0.085
Cough, n (%)	63 (66)	41 (68)	22 (63)	0.586
Throat pain, n (%)	24 (25)	21 (35)	3 (9)	0.004*
Runny nose, n (%)	11 (12)	8 (13)	3 (9)	0.484
Vomiting, n (%)	3 (3)	2 (3)	1 (3)	1.000
Diarrhea, n (%)	15 (16)	9 (15)	6 (17)	0.782
Systemic complications				
Any, n (%)	37 (39)	13 (22)	24 (69)	<0.001*
Cardiovascular disease, n (%)	4 (4)	0 (0)	4 (11)	0.016*
Venous thromboembolism, n (%)	2 (2)	0 (0)	2 (6)	0.133
Renal failure, n (%)	14 (15)	2 (3)	12 (34)	<0.001*
Liver failure, n (%)	33 (35)	11 (18)	22 (63)	<0.001*

*p<0.05.

Table 3. Acute Neurological Presentations in Patients with COVID-19.

	Total (n=95)	Non-severe (n=60)	Severe (n=35)	p value
Any, n (%)	60 (63)	31 (52)	29 (83)	0.002*
Headache, n (%)	17 (18)	14 (23)	3 (9)	0.059
Dysosmia, n (%)	21 (22)	20 (33)	1 (3)	<0.001*
Dysgeusia, n (%)	21 (22)	19 (32)	2 (6)	0.003*
Impaired consciousness, n (%)	17 (18)	0 (0)	17 (49)	<0.001*
GCS score, median (IQR)	15 (15-15)	15 (15-15)	14 (11-15)	<0.001*
Limb weakness, n (%)	19 (20)	0 (0)	19 (54)	<0.001*

*p<0.05.

GCS: Glasgow coma scale

Table 4. Subacute Neurological Presentations and Neurological Sequelae.

	The most severe group (n=12)	
	Subacute neurological presentations	Neurological sequelae
Evaluation days from onset (days), median (IQR)	51 (38-54)	137 (105-162)
Any, n (%)	11 (92)	10 (83)
Impaired consciousness, n (%)	2 (17)	1 (8)
Higher brain dysfunction, n (%) [†]	9 (82)	8 (73)
Memory disturbance, n (%) [†]	9 (82)	6 (55)
Impaired verbal fluency, n (%) [†]	9 (82)	3 (25)
Dyscalculia, n (%) [†]	9 (82)	5 (45)
Apathy, n (%) [†]	6 (55)	1 (9)
MMSE, median (IQR) [‡]	20 (16-25)	28 (26-29)
FAB, median (IQR) [§]	12 (8-13)	18 (15-18)
Cranial nerve disorders, n (%)	6 (50)	3 (25)
Limb weakness, n (%)	9 (75)	6 (50)
Ataxia, n (%) [†]	3 (27)	0 (0)
Tremor, n (%)	7 (58)	7 (58)

[†]n=11; [‡]n=10; [§]n=8. MMSE: Mini-Mental State Examination, FAB: frontal assessment battery

dian (IQR)], and 8 had a FAB score of 12 (8-13).

We also evaluated the neurological sequelae found in 10 (83%) patients at 137 (105-162) days from the onset (Table 4). Impaired consciousness was found in 1 (9%) of 2 patients in the subacute phase. Higher brain dysfunction was sustained after its initial subacute presentation in 8 (73%) patients, and the prevalence of memory disturbance [6 (55%)], impaired verbal fluency [3 (25%)], dyscalculia [5 (45%)], and apathy [1 (9%)] decreased. Both the MMSE and FAB scores also improved in each patient [28 (26-29) and 18 (15-18), respectively]. Cranial nerve disorders remained in 3 (25%) patients, including facial diplegia, dysarthria, and dysphagia in 1 patient each. Limb weakness persisted in 6 (50%) patients with neuropathy, and tremor remained in all patients in the subacute phase [7 (58%)]. The mRS score was 3 (2-4) [median (IQR)], which was worse than that before the onset [0 (2-4)].

Radio-physiological tests in the most severe group

Of the 6 (50%) patients with head CT findings available, acute intracranial hemorrhaging was found in 1 (17%). Head MRI was performed in 11 (92%) patients with impaired consciousness. Multiple CMBs were found in 4 patients (36%), while acute ischemic stroke, hemorrhagic stroke, and leukoencephalopathy were found in 1 patient (9%) each. Among the 10 (83%) cases with SPECT with I-123 IMP, hypoperfusion was found in all images, and hyperperfusion was detected in 5 (50%).

Of the 8 (67%) EEGs performed in patients with impaired consciousness, epileptic discharge was absent, and abnormal slow waves were found in 4 (50%) patients. Among the 11 (92%) NCSs, demyelination was noted in 4 (36%), axonal degeneration in 5 (45%), and both in 6 (55%).

Individual case characteristics of the most severe group

Table 5 describes the individual case characteristics. Six patients (case 1, 2, 3, 5, 6, 7; 55%) in the most severe group presented with both encephalopathy and axonal neuropathy. All four patients with multiple CMBs (case 1, 3, 5, 7) also suffered from neurological sequelae, such as higher brain dysfunction (case 1, 2, 5, 7), impaired consciousness (case 6), limb weakness, and tremor (all cases).

Discussion

We herein report a retrospective series of neurological manifestations and the prognosis in consecutive patients hospitalized for COVID-19 in Japan. We found a high frequency of neurological symptoms or deficits in the acute phase, as previously reported (4, 8-10). We also demonstrated a high prevalence of neurological presentations, even in the subacute phase, among ventilated patients with severe infections on an evaluation by trained neurologists. Notably, although these findings improved, they often persisted as long-term sequelae.

Of the 95 participants in our series, acute neurological presentations were found in 63% of patients, including 83% of those with severe infections and 52% of those with non-severe infections, which was similar to a study from Wuhan (4). Dysosmia and dysgeusia were less frequent in severe COVID-19 (3% and 6%, respectively) than in non-severe patients (33% and 32%, respectively), which is consistent with a previous report (4, 9). However, whether or not this pattern is reliable is unclear, as one recent report showed that subjective gustatory and olfactory dysfunction might be overestimated when compared with objective findings (20).

Impaired consciousness was observed in 18% of patients with COVID-19 in the acute phase, all of whom had severe infections, and it persisted in 1 patient after recovery. We also found frequent (82%) higher brain dysfunction in the subacute phase of the most severe cases. In a study from Wuhan (4), impaired consciousness was found in 7.5% of participants with a higher prevalence in severe infections compared with non-severe counterparts (14.8% vs. 2.4%). A large Spanish registry showed that 13.9% of patients presented with depressed consciousness with a similar tendency (29.1% vs. 4.1%). In a study examining patients with acute respiratory distress syndrome (ARDS) due to COVID-19 (5), confusion was described in 65% of patients, and 36% of patients presented with dysexecutive syndrome. A surveillance study demonstrated that 31% of hospitalized patients had an altered mental status without providing detailed information on severity (6). The wide prevalence range of impaired consciousness may be due to differences in the definitions of consciousness or infection severity. In addition, our patients with impaired consciousness or brain dysfunction frequently had abnormal slow-wave activities on EEG or perfusion disturbance on SPECT. In a systematic study of EEG in COVID-19, no epileptiform discharges were found, but various non-specific abnormalities were detected, reflecting multifactorial brain dysfunction (21). A case series showed metabolic abnormalities on brain fluorodeoxyglucose positron emission tomography in severe COVID-19 patients with cognitive impairment (22). The radio-physiological abnormalities in this study may therefore indicate functional and metabolic impairment of the central nervous system (CNS), even in the subacute phase.

CNS abnormalities in COVID-19 are thought to be caused by meningitis, encephalitis, encephalopathy, CNS vasculitis, seizure, and cerebrovascular disease (4-6, 8, 23, 24). In the current study, we diagnosed 82% of patients with encephalopathy among the 12 ventilated patients, but encephalitis and meningitis were not detected because of the lack of an extensive examination in the acute phase due to ongoing pandemic restrictions. The mechanisms underlying encephalopathy may be multifactorial, including hypoxia, renal and hepatic dysfunction, systemic inflammation, direct neuroinvasion by SARS-CoV-2, endotheliitis, post-infectious immune-mediated reaction, and drugs (24, 25). As encephalopathy is an independent risk factor for a poor outcome (10), it is

Table 5. Individual Case Characteristics of the Most Severe COVID-19 Group.

Case No.	1	2	3	4	5	6	7	8	9	10	11	12
Age (years)	66	66	69	75	72	75	83	73	83	43	76	78
Gender	M	M	M	M	M	F	F	F	F	M	M	F
Past history	HT, DM	DM	None	HT, DL	HT, DM	HT, PD	HT, DM, DL	HT, DL, CKD, Ca	CHF, IHD	HT, DL, CKD, IHD	HT, Ca	ICH, PD
Neurological complications												
CVD	HS	-	-	-	-	-	-	-	IS	-	-	-
Encephalopathy	+	+	+	+	+	+	+	+	+	-	-	+
Neuropathy	AN	AN Dmy	AN Dmy	-	AN Dmy	AN	AN	-	-	-	-	-
Muscle injury	+	+	-	-	-	-	-	-	-	-	-	-
Radiological findings												
Multiple CMBs	+	-	+	-	+	-	+	-	-	-	-	-
Leukoencephalopathy	-	-	-	-	-	+	-	-	-	-	N/A	-
Brain SPECT	Hypo Hyper	Hypo Hyper	Hypo Hyper	Hypo	Hypo	Hypo Hyper	Hypo	Hypo Hyper	Hypo	N/A	N/A	Hypo
Neurological presentations												
Acute												
Impaired consciousness	+	+	+	-	+	+	-	-	+	-	-	+
Limb weakness	+	+	+	+	+	+	+	+	+	-	-	+
Subacute/Sequelae [†]												
Day of evaluation	50/128	44/98	53/165	54/162	67/124	51/137	47/84	31/73	23/214	36/151	52/160	74/136
Impaired consciousness	-/-	-/-	-/-	-/-	+/-	+/+	-/-	-/-	-/-	-/-	-/-	-/-
Higher brain dysfunction	+/+	+/+	+/-	+/+	+/+	N/A	+/+	+/+	+/+	-/-	-/-	+/+
Memory disturbance	+/+	+/+	+/-	+/+	+/-	N/A	+/+	+/+	+/-	-/-	-/-	+/+
Impaired verbal fluency	+/-	+/-	+/-	+/+	+/+	N/A	+/+	+/-	+/-	-/-	-/-	+/-
Dyscalculia	+/-	+/-	+/-	+/-	+/+	N/A	+/+	+/+	+/+	-/-	-/-	+/+
Apathy	+/-	-/-	+/-	+/-	+/-	N/A	+/+	+/-	-/-	-/-	-/-	-/-
MMSE scores	17/28	21/30	14/30	20/27	13/25	N/A	14/17	19/26	16/28	N/A	30/29	24/26
FAB scores	11/18	13/17	14/18	9/15	8/15	N/A	5/7	13/18	13/18	N/A	N/A	N/A
Cranial nerve disorders	+ [‡] /-	-/-	-/-	-/-	+ [‡] /-	+ [‡] /+ [‡]	+ [§] /+ [§]	-/-	+ [‡] /-	+ [¶] /+ [¶]	-/-	-/-
Limb weakness	+/+	+/+	+/+	+/-	+/+	+/+	+/+	-/-	+/-	-/-	+/-	-/-
Ataxia	+/-	-/-	-/-	+/-	-/-	N/A	-/-	+/-	-/-	-/-	-/-	-/-
Tremor	+/+	+/+	+/+	-/-	+/+	+/+	+/+	+/+	-/-	-/-	-/-	-/-
Modified Rankin Scale												
Premorbid	0	0	0	2	0	4	0	1	0	0	0	3
Discharge	2	2	2	2	4	5	4	2	2	1	3	3

[†]Subacute neurological presentations and sequelae were described at left side of the slash and right side respectively in the Table.

[‡]Dysphagia

[§]Dysarthria

[¶]Facial diplegia

AN: axonal neuropathy, Ca: cancer, CKD: chronic kidney disease, CHF: chronic heart failure, CMBs: cerebral microbleeds, CVD: cerebrovascular disease, DL: dyslipidemia, DM: diabetes mellitus, Dmy: demyelination, FAB: frontal assessment battery, HS: hemorrhagic stroke, HT: hypertension, Hyper: hyperperfusion, Hypo: hypoperfusion, ICH: intracerebral hemorrhage, IHD: ischemic heart disease, IS: ischemic stroke, MMSE: Mini-Mental State Examination, PD: Parkinson's disease

necessary to establish a treatment strategy for each etiology. Seizures were not observed in our study, and epileptic discharges were also not found in the EEG performed in the subacute phase. The prevalence observed in this study is less than that previously reported (4, 8-11, 26); however, it may have been underreported, as EEG data were not available for the acute phase.

Cerebrovascular disease is one of the most important complications in COVID-19, which is found in 0.8-2.9% of

hospitalized patients with a high proportion of ischemic stroke (4, 8-10, 15, 27). Several reports have shown large-vessel occlusion (LVO) and infarction in multivascular territory, which often occur in young patients without risk factors (15, 28-30). Various mechanisms for cerebrovascular events have been proposed, including hypercoagulation caused by a hyperinflammatory state, postinfectious immunoreaction (23), and angiopathic thrombosis due to viral-induced endotheliitis (31). Among the 95 patients in our

study, cerebrovascular disease was found in 2 patients with severe infections but without any focal deficits, and LVO or multiple infarctions were not determined. To our knowledge, symptomatic stroke has not been reported in any institutes in Kobe (32), which is clearly less than the prevalence described in previous reports; this may be due to racial disparity, as a majority of the individuals presenting with COVID-19-associated stroke have been shown to be Black or multi-racial (15).

Limb weakness was found in 20% of our cases in the acute phase, all of whom had severe infections. The etiology was estimated to be axonal neuropathy or demyelination in many of the most severe cases, based on the physiological study performed in the subacute phase. In a large registry from Spain, neuropathy was rarely found in COVID-19 (9). Conversely, a prospective cohort study demonstrated that critical illness-associated axonal polyneuropathy was frequently present in COVID-19 patients, as evaluated by detailed electrophysiological examinations (16). Several reports described Guillain-Barré syndrome in COVID-19, characterized by a high prevalence of demyelination without antiganglioside antibodies (17). In the current series, we performed an electrophysiological evaluation for patients with limb weakness in the subacute phase, showing frequent axonal or demyelinating neuropathy, which indicated the existence of neuropathy in the acute phase.

It was also significant that the most severely infected group presented with frequent (83%) long-lasting neurological sequelae. Although a previous report suggested the potential of long-term neurological sequelae in COVID-19 patients based on the assumed mechanism of neurological damage caused by SARS-CoV-2 (33), few studies have described neurological manifestations in the chronic phase. In the current study, we found a high prevalence of higher brain dysfunction (73%) as sequelae, including memory disturbance (55%). Critically ill patients with ARDS often experience long-lasting cognitive impairment (34), which may account for one aspect of the persistent disturbance of higher brain functions in COVID-19. We also showed that motor symptoms, such as limb weakness (50%) or tremor (58%), frequently persisted in patients with severe infections. This may be associated with ICU-acquired weakness, especially critical illness-associated polyneuropathy, which leads to long-lasting functional limitations caused by weakness and sensory disturbance (35).

Furthermore, individual data in the present study demonstrated that half of the ventilated patients suffered from both encephalopathy and neuropathy, and many of them presented with multiple CMBs. In a large radiological study, 25 of 115 (22%) COVID-19 patients showed CMBs on head MRI (36). One systematic review revealed that CMBs in COVID-19 were typically found in the callosum and juxtacortical brain (37), which is similar to critical illness-associated CMBs (38). Direct viral-induced or immune reactive inflammatory endotheliopathy and microvascular thrombosis were also proposed as etiologies of CMBs (39). Previ-

ous reports showed diffuse petechial hemorrhaging accompanied by perivascular inflammation on a brain autopsy of patients who died from COVID-19 (40). CMBs were reported to be associated with a worse functional outcome (36), and all patients with CMBs in the present study had some neurological sequelae, including both CNS and motor symptoms; however, the relationship between CMBs and neurological manifestations was unclear due to the small number of participants.

The present study has several limitations. First, as all patients were admitted to dedicated wards or the ICU for COVID-19, precise interviews or neurological assessments by neurologists and extensive laboratory or radiophysiological examination could not be performed in the acute phase. However, we performed a thorough evaluation with the help of neurologists after the patients' release from isolation, assessed neurological sequelae, and estimated the etiology in the acute phase. Second, we retrospectively included a very small number of patients from a single center, which may have caused several biases in the observational study. It is necessary to evaluate more patients from multiple centers in Japan. Finally, as our series was a hospital-based study, the true incidence of neurological manifestations in COVID-19 is unclear.

Conclusion

A high prevalence of various neurological manifestations was observed in Japanese patients with COVID-19, and neurological sequelae were frequently found in severely infected patients. As front-line doctors treating COVID-19 often do not recognize frequent potential neurological disturbances, it is important for them to be aware of these issues. We also recommend that neurologists continue to evaluate patients, especially those with impaired consciousness or limb weakness in the acute phase, until after the risk of infection has decreased, as this might lead to an improvement in neurological outcomes. Additional studies will be required to clarify the etiology of each neurological manifestation and follow their long-term outcomes.

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