Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Journal of Clinical Neuroscience 86 (2021) 97–102

Contents lists available at ScienceDirect

Journal of Clinical Neuroscience

journal homepage: www.elsevier.com/locate/jocn

Clinical study

Neurological manifestations of COVID-19 in confirmed and probable cases: A descriptive study from a large tertiary care center

Hatice Yuksel [a,*], Gorkem Tutal Gursoy [a], Ebru Bilge Dirik [a], Safiye Gul Kenar [a], Hesna Bektas [a], Levent Yamanel [b], Hatice Rahmet Guner [c]

[a] Department of Neurology, Ankara City Hospital, Turkey
[b] Department of Intensive Care Unit, Gulhane Medical Faculty, Ankara, Turkey
[c] Department of Infectious Diseases and Clinical Microbiology, Ankara City Hospital, Turkey

ARTICLE INFO

Article history:
Received 3 December 2020
Accepted 2 January 2021

Keywords:
SARS-CoV-2
COVID-19
Neurological manifestations
Altered mental status
Seizure

ABSTRACT

During the early phase of the COVID-19 pandemic, it was thought that virus affects only the respiratory system. However, now it is clear that it can affect other systems too, particularly the nervous system. We aimed to identify the most common neurological symptoms and findings of COVID-19 in hospitalized patients and investigate the relationship between these symptoms and clinical, radiological, and laboratory findings. A total of 307 patients, including 125 women and 182 men, were included in the study. They were classified as "confirmed cases" or "probable cases" based on confirmatory tests, including polymerase chain reaction testing of a nasopharyngeal sample or validated antibody test. All medical records, including medical history, clinical course, laboratory data, and radiographic studies, were evaluated by two expert neurologists. Altered mental status (AMS) is the most common neurological finding in both confirmed (68.1%) and probable cases (71.8%). Pre-existing neurological diseases were detected as an independent risk factor for AMS. The mortality rate of patients with AMS was dramatically higher than normal mental status in both confirmed (43.9% vs. 6.2%) and probable cases (47.3% vs. 6.9%) (for both p:0.001). The frequency of seizure attacks was 13.2% in confirmed and 17.5% in probable cases (p:0.321). The mortality rate was higher in patients with a seizure attack in both groups. We conclude that AMS was one of the most common neurological manifestations in this cohort of COVID-19 patients. The development of mental deterioration increases mortality dramatically. Also, the existence of seizure attacks was associated with a high mortality rate.

1. Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was recognized as a serious health problem worldwide after the World Health Organization declared it as a pandemic in March 2020. Although COVID-19 was initially considered as a primary potential threat to the respiratory system, it was recognized that many other organ systems could be significantly affected as the pandemic progressed [1,2]. Patients' clinical patterns vary from asymptomatic cases to acute respiratory distress syndrome (ARDS) requiring intensive care and even multiple organ failure resulting in death [3,4].

In addition to non-specific neurological symptoms such as headache and dizziness at the onset of the pandemic, frequent hyposmia and hypogeusia attracted physicians' attention [4,5]. Recent studies focusing on neurological involvement have shown an increase in the frequency and variety of neurological findings. Central and peripheral nervous system findings can develop due to direct effects of the virus, para-infectious or post-infectious immune-related diseases, and systemic effects of COVID-19 [2,5,6].

Published studies reported that the occurrence of neurological complications in COVID-19 patients was associated with factors such as the severity of infection, age, obesity, metabolic problems, and the presence of comorbid diseases [1,7,8]. The frequency of neurological signs and symptoms was found to be significantly different in various studies [7,9,10].

Pre-existing neurological comorbidities can increase both the frequency and severity of neurological manifestations in patients with COVID-19. However, the available data are inadequate to demonstrate this relationship in detail [4,7,11]. Still, some studies have demonstrated that neurological complications developing during COVID-19 worsen the patient's prognosis and increase mor-

* Corresponding author at: Saklikent Residance, Bestepeler Mahallesi, 33. Cadde No: 4/16, Yenimahalle, Ankara, Turkey.
E-mail address: haticeyuksel73@yahoo.com (H. Yuksel).

https://doi.org/10.1016/j.jocn.2021.01.002
0967-5868/

bidity and mortality. Nevertheless, studies investigating which neurological comorbidities cause poor outcomes are still insufficient [4,7,12].

In this study, we aimed firstly to identify the most common neurological symptoms and findings of COVID-19 in both confirmed and probable cases in hospitalized patients, secondly to investigate the relationship between these symptoms and clinical, radiological, and laboratory findings, and thirdly to assess the impact of neurological manifestations on mortality.

2. Methods

This study was conducted at Ankara Bilkent City Hospital, the largest tertiary care academic center in Ankara. About 11,000 COVID-19 patients were hospitalized between April 2020 and September 2020. We retrospectively reviewed neurology consultations for patients who developed new neurological complaints and symptoms while under care in COVID-19 intensive care units and floors. Two expert neurologists evaluated the results. After these assessments, COVID-19 patients whose examination, laboratory, and imaging findings were sufficient were included in this study. There were a total of 307 patients, including 125 women (68.64 ± 18.21) and 182 men (67.60 ± 13.68). Patients were grouped into two categories based on confirmatory tests. If the patients had a SARS-CoV-2 infection confirmed by a polymerase chain reaction (RT-PCR) testing of a nasopharyngeal sample or validated antibody test, they were classified as ‘‘confirmed cases”. In the case of a negative PCR or antibody test, patients with a severe respiratory disease with clinical and radiographic evidence of pneumonia were categorized as ‘‘probable cases”. All enrolled patients in the study had chest CT.

Two expert neurologists analyzed all electronic medical records, including medical history, hospital admissions, clinical course, neurological status, laboratory data, and radiographic studies. Neurological and radiological findings of patients before COVID-19 infection were excluded from the assessment.

All clinical data were recorded, including the level of consciousness, epileptic seizures, focal neurological findings, dizziness, headache, paresthesia, paresis, and speech impairment.

According to their neurological examinations, both confirmed cases and probable cases were classified into two groups: those with altered mental status (AMS) and those with normal mental status (NMS). If the patient’s level of consciousness and interaction with the environment was normal, this was described as NMS. If somnolence, agitation, delirium, confusion, and coma were present in the neurological examination, this condition was accepted as AMS.

The study was approved by the local ethical committee (Ankara City Hospital Ethics Committee).

All statistical analyses were done using IBM SPSS statistic 22.0 (Chicago, IL, USA). Data were expressed as mean ± SD. Continuous variables were compared using the Student’s *t*-test. Categorical variables were compared using the Chi-Square test. Binary logistic regression analysis was performed to detect independent factors associated with AMS. A p-value <0.05 was considered statistically significant.

3. Results

Age and gender were comparable in both groups (p:0.204 and p:0.633). The intensive care need for probable cases was significantly higher than the confirmed cases (p:0.031). The intubation and mortality rates were similar in both groups (p:0.863 and 0.476) (Table 1).

Table 1
Comparison of the demographics and clinics data of confirmed and probable cases.

	Confirmed Cases n:204	Probable Cases n:103	p
Age (year)	67.22 ± 15.39	69.63 ± 16.15	0.204
Gender			
Female	85 (41.7%)	40 (38.8%)	0.633
Male	119 (58.5%)	63(61.2%)	
Admission in the intensive care unit	121(59.3%)	74 (71.8%)	**0.031**
Intubation required	36 (17.6%)	19 (18.4%)	0.863
Mortality	65 (31.9%)	37 (35.9%)	0.476
Cardiovascular and pulmonary diseases			
Hypertension	131 (64.2%)	74 (71.8%)	0.180
Coronary artery disease	52 (25.5%)	36 (35.0%)	0.083
Hyperlipidemia	50 (24.5%)	27 (26.2%)	0.745
Heart valve replacement	3 (1.5%)	2 (1.9%)	0.758
Coronary artery bypass graft	8 (3.9%)	6 (5.8%)	0.450
Atrial fibrillation	21 (10.3%)	21 (20.4%)	**0.016**
Cardiac pacemaker	6 (2.9%)	5 (4.9%)	0.394
Chronic pulmonary disease	28 (13.7%)	25 (24.3%)	**0.021**
Metabolic diseases and others			
Diabetes mellitus	68 (33.3%)	37 (35.9%)	0.652
Chronic renal failure	9 (4.4%)	13 (12.6%)	**0.017**
Malignancy	15 (7.4%)	10 (9.7%)	0.476
Neurological and psychological diseases			
Stroke	22 (10.8%)	20 (19.4%)	**0.038**
Epilepsy	12 (5.9%)	13 (12.6%)	**0.042**
Parkinson	5 (2.5%)	5 (4.9%)	0.263
Dementia	22 (10.8%)	17 (16.5%)	0.155
Migraine	5 (2.5%)	–	0.109
Multiple Sclerosis	2 (1.0%)	–	0.313
Myasthenia Gravis	2 (1.0%)	–	0.313
Anxiety	17 (8.3%)	12 (11.7%)	0.348
Depression	6 (2.9%)	3 (2.9%)	0.989
Patients with at least one medical comorbidity	167 (81.9%)	93 (90.3%)	0.064
Patients with at least one neurological comorbidity	70 (34.3%)	44 (42.7%)	0.150

The three most common risk factors identified in both groups were hypertension, diabetes mellitus, and coronary artery disease. All other risk factors were shown in Table 1.

Although the frequency of having ‘‘at least one medical comorbidity” and ‘‘at least one neurological comorbidity” in probable cases was higher than the confirmed cases, there were no significant differences between them (p:0.064, p:0.150, respectively). The frequencies of history of stroke, atrial fibrillation, and chronic pulmonary disease were higher in probable cases than in confirmed cases (p:0.038, p:0.016, and p:0.021, respectively) (Table 1).

The most common neurological symptom in both confirmed and probable cases was impaired consciousness (p:0.570). The other neurological symptoms were shown in Table 2.

AMS is the most common neurological findings in both groups. There was no difference between the two groups in terms of the level of consciousness (p:0.171) (Table 2).

On neuroimaging findings, the frequency of infarct, edema, and hemorrhage was higher in probable cases (p:0.003, p:0.001, and p:0.023, respectively). In addition, cerebral venous thrombosis was detected in 4 of the confirmed cases, while brain abscess was observed in one of the probable cases (Table 2).

On chest CT findings, bilateral involvement of the lungs in confirmed cases (75.0%) was more common than probable cases (60.2%) (p:0.001).

White blood cell (WBC) count and creatinine level were higher in probable cases than confirmed cases (p:0.001 and p:0.019), whereas hemoglobin was lower (p:0.020). There was no difference between the two groups regarding all other biochemical, hematological, and coagulation parameters (Table 2).

Table 2
Comparison of neurological symptoms, neurological examination, radiology and laboratory of the confirmed and probable cases.

	Confirmed Cases n:204	Probable Cases n:103	p
Symptoms			
Impaired consciousness	132 (65.3%)	70 (68.0%)	0.570
Seizure	27 (13.2%)	18 (17.5%)	0.321
Headache	28 (13.7%)	12 (11.7%)	0.610
Dizziness	32 (15.7%)	9 (8.7%)	0.110
Focal neurological symptoms	52 (22.5%)	40 (38.8%)	**0.016**
Neurological findings			
Level of consciousness			
Normal mental status	65 (31.9%)	29 (28.2%)	
Altered mental status	139 (68.1%)	74 (71.8%)	0.171
Somnolence	*75 (36.8%)*	*31 (30.1%)*	
Confused	*42 (20.6%)*	*23 (22.3%)*	
Coma	*22 (10.8%)*	*20 (19.4%)*	
Speech disorders	71 (34.8%)	35 (34.0%)	0.886
Paresis	42 (20.6%)	35 (34.0%)	**0.011**
Paresthesia	25 (12.3%)	11 (10.7%)	0.685
Brain CT/MRI findings			
No acute changes	124 (65.6%)	35 (37.2%)	**0.001**
Infarct	49 (25.9%)	41 (43.6%)	**0.003**
Hemorrhage	11 (5.8%)	13 (13.8%)	**0.023**
Edema	12 (6.3%)	21 (22.3%)	**0.001**
Cerebral abscess	–	1 (1.1%)	0.332
Cerebral venous thrombosis	4 (2.1%)	–	0.305
Chest CT findings			
Normal	25 (12.3%)	1 (1%)	
Unilateral	26 (12.7%)	40 (38.8%)	**0.001**
Bilateral	153 (75.0%)	62 (60.2%)	
Laboratory tests			
Creatinine mg/dL	1.13 ± 1.02	1.55 ± 1.65	**0.019**
Sodium mmol/L	140.09 ± 6.37	140.59 ± 6.41	0.524
Potassium mmol/L	4.16 ± 0.61	4.20 ± 0.69	0.628
Alanine aminotransferase U/L	55.74 ± 124.86	86.05 ± 408.69	0.332
Aspartate aminotransferase U/L	81.46 ± 447.76	113.91 ± 595.59	0.594
Hemoglobin g/dL	12.31 ± 2.20	11.45 ± 2.44	**0.020**
Platelets 10^9/L	263.47 ± 126.56	255.17 ± 135.01	0.596
White blood cell 10^9/L	7.17 ± 4.86	9.71 ± 8.41	**0.001**
C-reactive protein mg/dL	89.56 ± 201.12	78.98 ± 78.89	0.608
PT	13.96 ± 4.73	15.49 ± 7.15	0.052
aPTT	25.76 ± 8.36	27.54 ± 10.24	0.106
D-dimer mg/L	4.28 ± 7.76	4.81 ± 7.10	0.566

3.1. Confirmed cases

The mean age in the AMS group was higher than the NMS group (p:0.001). AMS and NMS groups were similar in terms of gender (p:0.780) (Table 3).

While the mortality rate in the AMS group was 43.9%, it was only 6.2% in the NMS group (p:0.001). Also, the number of patients requiring intensive care and intubation in the AMS group was higher than in the NMS group (for both p:0.001) (Table 3).

The existence of "at least one medical comorbidity" in the AMS group was substantially more frequent than in the NMS group (p:0.042). Although the presence of "at least one neurological comorbidity" was more common in the AMS group than in the NMS group, the difference was not significant (p:0.173) (Table 3).

On neuroimaging findings, frequencies of infarction, edema and hemorrhage were comparable in the AMS and NMS groups (p:0.104, p:0.107, and p:0.735, respectively) (Table 3).

The AMS group and NMS group were similar in terms of lung involvement on chest CT (p: 0.844).

Biochemical and inflammatory parameters in the AMS and NMS groups are presented in Table3.

Table 3
Comparison of demographic characteristics, clinical data, radiology and laboratory of the NMS and AMS group in confirmed cases.

	Confirmed Cases		
	NMS n:65	AMS n:139	p
Age (year)	61.91 ± 17.97	70.54 ± 15.85	**0.001**
Gender			
Female	28/65(43.1%)	57/139 (41.0%)	0.780
Male	37/65 (56.9%)	82/139 (59.0%)	
Admission in the intensive care unit	18/65 (27.7%)	103/139 (74.1%)	**0.001**
Intubation required	2/65 (3.1%)	34/139 (24.5%)	**0.001**
Mortality	4/65 (6.2%)	61/139 (43.9%)	**0.001**
Brain CT/MRI findings			
No acute changes	44/60 (73.3%)	80/129 (62%)	0.127
Infarct	11/60 (18.3%)	38/129 (29.5%)	0.104
Hemorrhage	4/60 (6.7%)	7/129 (5.4%)	0.735
Edema	1/60 (1.7%)	11/129 (8.5%)	0.107
Cerebral venous thrombosis	2/60 (3.3%)	2/129 (1.6%)	0.593
Chest CT findings			
Normal	8/65 (12.3%)	17/139 (12.2%)	
Unilateral	7/65 (10.8%)	19/139 (13.7%)	0.844
Bilateral	50/65 (76.9%)	103/139 (74.1%)	
Patients with at least one medical comorbidity	48/63 (73.8%)	119/139 (85.6%)	**0.042**
Patients with at least one neurological comorbidity	18/65 (27.7%)	52/139 (37.4%)	0.173
Laboratory tests			
Creatinine mg/dL	0.87 ± 0.64	1.24 ± 1.14	**0.017**
Alanine aminotransferase U/L	39.12 ± 30.98	63.57 ± 149.48	0.194
Aspartate aminotransferase U/L	35.84 ± 22.36	102.94 ± 542.15	0.320
Sodium mmol/L	137.29 ± 3.63	141.38 ± 6.94	**0.001**
White blood cell 10^9/L	8.07 ± 6.65	9.46 ± 5.48	0.117
Hemoglobin g/dL	12.49 ± 2.06	12.23 ± 2.27	0.437
C-reactive protein mg/dL	50.46 ± 61.86	89.86 ± 70.96	**0.001**
D-dimer mg/L	2.55 ± 5.56	5.09 ± 8.50	**0.029**

AMS: Altered mental status, NMS: Normal mental status.

In binary logistic regression analysis, brain edema, brain hemorrhage, presence of neurological comorbidity, and age were determined as independent risk factors for AMS in the confirmed cases (Table 4).

3.2. Probable cases

The AMS and NMS groups were similar in terms of age (p:0.175). The AMS group included more women than the NMS (p:0.010) (Table5).

The mortality rate, number of patients requiring intensive care, and intubation in the AMS group were higher (p:0.001, p:0.001 and 0.012, respectively) (Table 5).

The frequency of having "at least one neurological comorbidity" in the AMS group was higher than in the NMS group (p:0.005). Although the presence of "at least one medical comorbidity" was more common in the AMS group than in the NMS group, the difference was not significant (p:0.381) (Table 5).

On neuroimaging findings, edema was present more frequently in the AMS group when compared to the NMS group (p:0.006). Infarct in the AMS group was lower than in the NMS group, although the difference was not significant (p: 0.307) (Table 5).

Bilateral lung involvement in the AMS group was higher than the NMS group on chest CT (p:0.021) (Table 5).

Biochemical and inflammatory parameters in the AMS and NMS groups are shown in Table 5.

In binary logistic regression analysis, brain edema, the severity of lung involvement, presence of neurological comorbidity, and gender were determined as independent risk factors for AMS in the probable cases (Table 4).

Table 4
Independent factors associated with altered mental status in binary logistic regression analysis.

	Confirmed Cases			Probable Cases		
	p	Exp(B)	%95 CI	p	Exp(B)	%95 CI
Chest CT findings	0.420	0.868	0.617–1.223	**0.006**	2.832	1.356–5.914
Edema on neuroimaging	**0.011**	24.323	2.079–284.632	**0.005**	31.760	2.768–364.402
Infarct on neuroimaging	0.386	1.436	0.634–3.254	0.384	0.578	0.168–1.987
Hemorrhage on neuroimaging	**0.043**	5.728	1.060–30.950	0.857	1.260	0.103–15.469
Neurological comorbidities	**0.046**	2.297	1.017–5.189	**0.013**	5.003	1.410–17.753
Medical comorbidities	0.654	1.230	0.498–3.039	0.482	2.405	0.208–27.771
Age	**0.001**	1.042	1.018–1.067	0.203	1.029	0.985–1.075
Gender	0.295	0.684	0.335–1.393	**0.005**	9.041	1.957–41.772

Table 5
Comparison of demographic characteristics, clinical data, radiology and laboratory of the NMS and AMS group in probable cases.

	Probable Cases		
	NMS n:29	AMS n:74	p
Age (year)	66.17 ± 16.90	70.98 ± 15.76	0.175
Gender			
Female	5/29 (17.2%)	35/74 (47.3%)	**0.010**
Male	24/29 (82.8%)	39/74 (52.7%)	
Admission in the intensive care unit	14/29 (48.3%)	60/74 (81.1%)	**0.001**
Intubation required	1/29 (3.4%)	18/74 (71.8%)	**0.012**
Mortality	2/29 (6.9%)	35/74 (47.3%)	**0.001**
Brain CT/MRI findings			
No acute changes	12/27 (44.4%)	23/67 (34.3%)	0.359
Infarct	14/27 (51.9%)	27/67 (40.3%)	0.307
Hemorrhage	1/27 (3.7%)	12/67 (17.9%)	0.100
Edema	1/27 (3.7%)	20/67 (29.9%)	**0.006**
Cerebral abscess	–	1/67 (1.5%)	0.523
Chest CT findings			
Normal	1/29 (3.4%)	–	
Unilateral	16/29 (55.2%)	24/74 (32.4%)	**0.021**
Bilateral	12/29 (41.4%)	50/74 (67.6%)	
Patients with at least one medical comorbidity	25/29 (86.2%)	68/74 (91.9%)	0.381
Patients with at least one neurological comorbidity	6/29 (20.7%)	38/74 (51.4%)	**0.005**
Laboratory tests			
Creatinine mg/dL	1.75 ± 2.38	1.47 ± 1.27	0.433
Alanine aminotransferase U/L	27.10 ± 15.25	109.16 ± 481.01	0.362
Aspartate aminotransferase U/L	25.48 ± 15.15	148.56 ± 700.89	0.348
Sodium mmol/L	138.031 ± 4.66	141.48 ± 6.80	**0.023**
White blood cell 10^9/L	8.73 ± 2.75	12.92 ± 9.64	**0.023**
Hemoglobin g/dL	11.90 ± 2.45	11.28 ± 2.42	0.249
C-reactive protein mg/dL	53.27 ± 70.73	89.05 ± 80.07	**0.038**
D-dimer mg/L	2.46 ± 4.34	5.74 ± 7.76	**0.035**

AMS: Altered mental status, NMS: Normal mental status.

3.3. Seizure

Twenty-seven patients (13.2%) in confirmed cases and 18 patients (17.5%) in probable cases had seizure attacks. The characteristics of patients with seizure attacks in confirmed and probable cases are shown in Table 6.

Table 6
Patients with seizure attacks in confirmed cases and probable cases.

	Confirmed Cases n:27	Probable Cases n:18
Seizure type		
Generalized	22 (81.5%)	15 (83.3%)
Focal	5 (18.5%)	3 (16.7%)
History of epilepsy	8 (29.6%)	7 (38.9%)
Admission in the intensive care unit	21 (77.8%)	16 (88.9%)
Intubation required	14 (51.9%)	5 (27.8%)
Mortality	14 (51.9%)	6 (33.3%)
Medical comorbidities	22 (81.5%)	15 (83.3%)
Neurological comorbidities	13 (48.1%)	11 (61.1%)
Brain CT/MRI findings		
Infarct	2 (9.1%)	5 (29.4%)
Hemorrhage	2 (9.1%)	1 (5.9%)
Edema	2 (9.1%)	4 (23.6%)
Abscess	–	1 (5.9%)
Cerebral venous thrombosis	1 (4.5%)	–
Mass	3 (13.6%)	1 (5.9%)
Metabolic disturbance		
Liver failure	–	2 (11.1%)
Hypernatremia	4 (14.8%)	1 (5.5%)
Hyponatremia	1 (3.7%)	–
Acute impairment of kidney function	4 (14.8%)	1 (5.5%)

4. Discussion

Our results demonstrated that the most prominent neurological manifestation in both confirmed and probable cases was altered mental status. Infarct was the most common neuroimaging finding. The mortality rate for confirmed and probable cases was similar. In the case of mental deterioration, the mortality rate was found to increase dramatically. Brain edema, hemorrhage, neurological comorbidity, the severity of lung involvement, and age were independent risk factors for mental deterioration.

The altered mental state has been reported as the most common neurological problem in COVID-19 [4,13]. In accordance with these studies, our findings showed that AMS might be the most common neurological problem in COVID-19. Although current information on COVID-19 infection is insufficient, it is suggested that the main mechanism responsible for manifestations of the central nervous system is not due to direct viral invasion. Given the lack of comprehensive diagnostic neurological investigations due to pandemic limitations, studies could not clearly establish the cause of AMS and encephalopathy [4,7,8]. However, AMS can occur as a result of a wide variety of causes, including toxic-metabolic status, cerebral vascular events, autoimmune mechanisms, encephalitis, and meningitis [2,5,8]. Some of our patients had neuroimaging findings that could explain AMS. Although we cannot clearly identify the reasons for the mental status change in our other cases, we can suggest that it is due to metabolic and hypoxic causes.

Neurological disorders are more common in elderly patients [8,14]. Consistent with this, our patients with AMS were about one decade older than patients with NMS. Pre-existing medical comorbidities play an important role in the development of neurological disorders [11,12]. In our study, pre-existing medical comorbidities were higher in patients with AMS. At the same time, we have demonstrated that pre-existing neurological comorbidities are independent risk factors for AMS.

Given the available information, altered mental status in COVID-19 has been associated with increased mortality and morbidity [4,7,8]. We also observed that the development of mental deterioration increases mortality dramatically.

Seizure attack has been reported as one of the central nervous system manifestations of COVID-19. The frequency of seizures reported in the studies was between 0.5% and 4% [4,6–8]. In our study, the frequency of seizure attacks was determined as 13.2% in confirmed and 17.5% in probable cases. Compared to other studies, the frequency of seizure attacks was higher in our study. This high frequency in our cases was that our study population consisted of patients who developed neurological symptoms. Besides, a history of pre-existing epilepsy and comorbidities may be responsible for this high seizure rate. The frequency, causes, and pathogenesis of seizures in COVID-19 infection have not yet been clearly revealed [15]. The virus entering the central nervous system can disrupt the blood–brain barrier. This process may trigger epileptic activity. Also, hypoxia, electrolyte imbalances, mitochondrial dysfunction, thrombotic state, metabolic disorders, and medications can initiate seizure attacks [15,16]. In our study, we detected electrolyte imbalance, deterioration in renal functions, fulminant liver failure, and cerebrovascular events in patients with seizure. Sun et al. reported high mortality in COVID-19 patients with seizure [15]. We also demonstrated that the mortality rate in patients with seizure was very high.

We demonstrated some patients with infrequent neurological disorders, including Myasthenia gravis (MG), Multiple sclerosis (MS), Parkinson's disease (PD), and Guillain-Barré syndrome (GBS) in our study population. Given the lack of well-designed studies, the approach to these diseases in COVID-19 is shaped based on case reports and authors' opinions [17–19].

In the COVID-19 period, the problem of how to approach autoimmune based neurological diseases such as MG has not been clarified yet. MG patients may become at risk for COVID-19 due to immunosuppressive therapy and existing respiratory system problems. On the other hand, COVID-19 can make MG more severe [17,20]. In light of the available data, when immunosuppressives are used carefully, they seem to not increase the risk of COVID-19, and may even have a protective role [17,21,22]. There were two MG patients in our study. Our first patient had a recently diagnosed severe form of MG. The patient did not respond to COVID-19 and MG treatments including IVIG, plasmapheresis, and tocilizumab, and died. The second patient with stable MG developed respiratory distress after COVID-19, and the steroid dose was increased. The patient, whose complaints improved, was discharged.

Disease-modifying drugs (DMDs) used in MS treatment have been associated with an increased risk of infection. [23–25]. Nevertheless, studies have not shown a significant relationship between the use of DMDs and an increased risk of COVID-19 [23,26,27]. Since the clinical worsening of MS patients who are left untreated or not effectively treated would cause poor outcomes, some authors have suggested that MS patients should continue the treatment with the drugs they took before the pandemic [19,27,28]. There were two MS patients in our study. While our first patient was being treated with progressive MS disease, COVID-19 was diagnosed. The patient did not respond to COVID-19 treatment such as steroid, tocilizumab, immune plasma, and cytokine filtration and died. Our second patient developed an MS attack on the 5th day of stopping MS treatment (teriflunomide) after being diagnosed with COVID-19. The patient's complaints regressed with pulse steroid therapy. Our limited findings support the strategy of continuing the treatment of MS patients under close follow-up.

PD is a neurological problem that deserves consideration in the COVID-19 pandemic. Recent studies reported that advanced age and long-term disease increase mortality in advanced PD [18,29]. In one study, it was emphasized that COVID-19 worsened motor symptoms and that the dopaminergic treatment may need to be increased [29]. We had 10 PD patients, and mental deterioration developed in seven, speech impairment in two, and paresthesia in one. All but one of our patients was over 65 years old, and all had concomitant diseases. Two of the patients who presented with AMS died. We adjusted the medication dosage in one patient who developed dyskinesia.

COVID-19 affects the peripheral nervous system as well as the central nervous system. GBS is thought to be the peripheral nervous system manifestation of COVID-19 [12,30]. The first cases demonstrating the relationship between COVID-19 and GBS appeared in the early pandemic period [31,32]. Several valuable, detailed reviews have been published analyzing cases of GBS in COVID-19 patients [33–36]. However, the available information is insufficient to reveal whether COVID-19 is an important risk factor for GBS. More well-designed studies are needed to clarify the relationship between GBS and COVID-19 [33–37]. In our study population of over 300 patients with COVID-19, we only had one newly diagnosed GBS patient.

The strengths of our study were as follows; firstly, our study population included a significant number of confirmed cases, as well as probable cases. In this way, besides evaluating the characteristics and data of two groups separately, it was the first study in the literature comparing the two groups with each other, as far as we know. Secondly, compared to the literature, we had a large number of patients with seizure attacks in both confirmed cases and probable cases, which allowed for the evaluation of the etiology of seizure attacks in COVID-19. Thirdly, we presented the data of patients with rare neurological diseases in our study groups, accompanied by publications in the literature. One of the weak points of the study was that our evaluations were limited to recorded data, as the study was designed retrospectively, and the other was that some detailed neurological investigations could not be performed due to COVID-19 pandemic limitations.

In conclusion, our data showed that one of the most common neurological findings in COVID-19 patients is AMS. Age, the patient's current comorbid diseases, and the severity of infection increase the risk of developing AMS. Mortality increases dramatically in patients who develop AMS. However, one point to keep in mind is that our data reflect moderate and severe COVID-19 disease rather than the entire spectrum of COVID-19 disease, since our study population consists of patients who develop neurological complaints and symptoms while being treated in the hospital. Therefore, prospective studies investigating the effects of COVID-19 in both outpatients and inpatients are required in order to create satisfactory guidelines that allow adequate follow-up and treatment of COVID-19 patients.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Bach I, Surathi P, Montealegre N, Abu-Hadid O, Rubenstein S, Redko S, et al. Stroke in COVID-19: a single-centre initial experience in a hotspot of the pandemic. Stroke Vasc Neurol 2020. https://doi.org/10.1136/svn-2020-000525. svn-2020-000525.

[2] Ellul MA, Benjamin L, Singh B, Lant S, Michael BD, Easton A, et al. Neurological associations of COVID-19. Lancet Neurol 2020;19:767–83. https://doi.org/10.1016/S1474-4422(20)30221-0.

[3] Morassi M, Bagatto D, Cobelli M, D'Agostini S, Gigli GL, Bnà C, et al. Stroke in patients with SARS-CoV-2 infection: case series. J Neurol 2020;267:2185–92. https://doi.org/10.1007/s00415-020-09885-2.

[4] Tyson B, Erdodi L, Ray S, Agarwal P. Altered mental status in 71 deaths due to COVID-19. Int J Neurosci 2020:1–4. https://doi.org/10.1080/00207454.2020.1825422.

[5] Varatharaj A, Thomas N, Ellul MA, Davies NWS, Pollak TA, Tenorio EL, et al. Neurological and neuropsychiatric complications of COVID-19 in 153 patients: a UK-wide surveillance study. Lancet Psychiatry 2020;7:875–82. https://doi.org/10.1016/S2215-0366(20)30287-X.

[6] Whittaker A, Anson M, Harky A. Neurological manifestations of COVID-19: a systematic review and current update. Acta Neurol Scand 2020;142:14–22. https://doi.org/10.1111/ane.v142.110.1111/ane.13266.
[7] Frontera JA, Sabadia S, Lalchan R, Fang T, Flusty B, Millar-Vernetti P, et al. A prospective study of neurologic disorders in hospitalized COVID-19 patients in New York City. Neurology 2020. https://doi.org/10.1212/WNL.0000000000010979.
[8] Liotta EM, Batra A, Clark JR, Shlobin NA, Hoffman SC, Orban ZS, et al. Frequent neurologic manifestations and encephalopathy-associated morbidity in Covid-19 patients. Ann Clin Transl Neurol 2020;7:2221–30. https://doi.org/10.1002/acn3.v7.1110.1002/acn3.51210.
[9] Scullen T, Keen J, Mathkour M, Dumont AS, Kahn L. Coronavirus 2019 (COVID-19)–associated encephalopathies and cerebrovascular disease: the new orleans experience. World Neurosurg 2020;141:e437–46. https://doi.org/10.1016/j.wneu.2020.05.192.
[10] Tan Y-K, Goh C, Leow AST, Tambyah PA, Ang A, Yap E-S, et al. COVID-19 and ischemic stroke: a systematic review and meta-summary of the literature. J Thromb Thrombolysis 2020;50:587–95. https://doi.org/10.1007/s11239-020-02228-y.
[11] García-Azorín D, Martínez-Pías E, Trigo J, Hernández-Pérez I, Valle-Peñacoba G, Talavera B, et al. Neurological comorbidity is a predictor of death in Covid-19 disease: a cohort study on 576 patients. Front Neurol 2020;11. https://doi.org/10.3389/fneur.2020.0078110.3389/fneur.2020.00781.s001.
[12] Azim D, Nasim S, Kumar S, Hussain A, Patel S. Neurological consequences of 2019-nCoV infection: a comprehensive literature review. Cureus 2020. https://doi.org/10.7759/cureus.8790.
[13] Mahammedi A, Saba L, Vagal A, Leali M, Rossi A, Gaskill M, et al. Imaging of neurologic disease in hospitalized patients with COVID-19: an Italian multicenter retrospective observational study. Radiology 2020;297:E270–3. https://doi.org/10.1148/radiol.2020201933.
[14] Jarrahi A, Ahluwalia M, Khodadadi H, da Silva Lopes Salles E, Kolhe R, Hess DC, et al. Neurological consequences of COVID-19: what have we learned and where do we go from here?. J Neuroinflammation 2020;17. https://doi.org/10.1186/s12974-020-01957-4.
[15] Sun M, Ruan X, Li Y, Wang P, Zheng S, Shui G, et al. Clinical characteristics of 30 COVID-19 patients with epilepsy: a retrospective study in Wuhan. Int J Infect Dis 2020. https://doi.org/10.1016/j.ijid.2020.09.1475.
[16] Nikbakht F, Mohammadkhanizadeh A, Mohammadi E. How does the COVID-19 cause seizure and epilepsy in patients? The potential mechanisms. Mult Scler Relat Disord 2020;46:102535. https://doi.org/10.1016/j.msard.2020.102535.
[17] Anand P, Slama MCC, Kaku M, Ong C, Cervantes-Arslanian AM, Zhou L, et al. COVID-19 in patients with myasthenia gravis. Muscle Nerve 2020;62:254–8. https://doi.org/10.1002/mus.26918.
[18] Antonini A, Leta V, Teo J, Chaudhuri KR. Outcome of Parkinson's disease patients affected by COVID-19. Mov Disord 2020;35:905–8. https://doi.org/10.1002/mds.28104.
[19] Ciotti JR, Grebenciucova E, Moss BP, Newsome SD. Multiple sclerosis disease-modifying therapies in the COVID-19 era. Ann Neurol 2020;88:1062–4. https://doi.org/10.1002/ana.v88.610.1002/ana.25907.
[20] Camelo-Filho AE, Silva AMS, Estephan EP, Zambon AA, Mendonça RH, Souza PVS, et al. Myasthenia gravis and COVID-19: clinical characteristics and outcomes. Front Neurol 2020;11. https://doi.org/10.3389/fneur.2020.01053.
[21] Delly F, Syed MJ, Lisak RP, Zutshi D. Myasthenic crisis in COVID-19. J Neurol Sci 2020;414:116888. https://doi.org/10.1016/j.jns.2020.116888.
[22] Jacob S, Muppidi S, Guidon A, Guptill J, Hehir M, Howard JF, et al. Guidance for the management of myasthenia gravis (MG) and Lambert-Eaton myasthenic syndrome (LEMS) during the COVID-19 pandemic. J Neurol Sci 2020;412:116803. https://doi.org/10.1016/j.jns.2020.116803.
[23] Bsteh G, Bitschnau C, Hegen H, Auer M, Di Pauli F, Rommer P, et al. Multiple sclerosis and COVID-19: how many are at risk?. Eur J Neurol 2020. https://doi.org/10.1111/ene.14555.
[24] Dobson R, Giovannoni G. Multiple sclerosis – a review. Eur J Neurol 2019;26:27–40. https://doi.org/10.1111/ene.2019.26.issue-110.1111/ene.13819.
[25] Willis MD, Robertson NP. Multiple sclerosis and the risk of infection: considerations in the threat of the novel coronavirus, COVID-19/SARS-CoV-2. J Neurol 2020;267:1567–9. https://doi.org/10.1007/s00415-020-09822-3.
[26] Chaudhry F, Bulka H, Rathnam AS, Said OM, Lin J, Lorigan H, et al. COVID-19 in multiple sclerosis patients and risk factors for severe infection. J Neurol Sci 2020;418:117147. https://doi.org/10.1016/j.jns.2020.117147.
[27] Crescenzo F, Marastoni D, Bovo C, Calabrese M. Frequency and severity of COVID-19 in multiple sclerosis: a short single-site report from northern Italy. Mult Scler Relat Disord 2020;44:102372. https://doi.org/10.1016/j.msard.2020.102372.
[28] Bowen JD, Brink J, Brown TR, Lucassen EB, Smoot K, Wundes A, et al. COVID-19 in MS: initial observations from the Pacific Northwest. Neurol - Neuroimmunol Neuroinflammation 2020;7:e783. https://doi.org/10.1212/NXI.0000000000000783.
[29] Cilia R, Bonvegna S, Straccia G, Andreasi NG, Elia AE, Romito LM, et al. Effects of COVID-19 on Parkinson's disease clinical features: a community-based case-control study. Mov Disord 2020;35:1287–92. https://doi.org/10.1002/mds.28170.
[30] Ahmad I, Rathore FA. Neurological manifestations and complications of COVID-19: a literature review. J Clin Neurosci 2020;77:8–12. https://doi.org/10.1016/j.jocn.2020.05.017.
[31] Zhao H, Shen D, Zhou H, Liu J, Chen S. Guillain-Barré syndrome associated with SARS-CoV-2 infection: causality or coincidence?. Lancet Neurol 2020;19:383–4. https://doi.org/10.1016/S1474-4422(20)30109-5.
[32] Sedaghat Z, Karimi N. Guillain Barre syndrome associated with COVID-19 infection: a case report. J Clin Neurosci 2020;76:233–5. https://doi.org/10.1016/j.jocn.2020.04.062.
[33] Carrillo-Larco RM, Altez-Fernandez C, Ravaglia S, Vizcarra JA. COVID-19 and Guillain-Barre Syndrome: a systematic review of case reports. Wellcome Open Res 2020;5:107. https://doi.org/10.12688/wellcomeopenres.15987.2.
[34] Abu-Rumeileh S, Abdelhak A, Foschi M, Tumani H, Otto M. Guillain-Barré syndrome spectrum associated with COVID-19: an up-to-date systematic review of 73 cases. J Neurol 2020. https://doi.org/10.1007/s00415-020-10124-x.
[35] Uncini A, Vallat J-M, Jacobs BC. Guillain-Barré syndrome in SARS-CoV-2 infection: an instant systematic review of the first six months of pandemic. J Neurol Neurosurg Psychiatry 2020;91:1105–10. https://doi.org/10.1136/jnnp-2020-324491.
[36] De Sanctis P, Doneddu PE, Viganò L, Selmi C, Nobile-Orazio E. Guillain-Barré syndrome associated with SARS-CoV-2 infection. A systematic review. Eur J Neurol 2020;27:2361–70. https://doi.org/10.1111/ene.v27.1110.1111/ene.14462.
[37] Rahimi K. Guillain-Barre syndrome during COVID-19 pandemic: an overview of the reports. Neurol Sci 2020;41:3149–56. https://doi.org/10.1007/s10072-020-04693-y.